International Journal of Pediatrics

Pediatric Pain Management and Sedation

Guest Editors: SavitHiri Ratnapalan, Keira P. Mason, and Sharon E. Mace

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Editorial Board

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Hindawi Publishing Corporation
International Journal of Pediatrics
Volume 2010, Article ID 454731, 2 pages
doi:10.1155/2010/454731

Editorial

Pediatric Pain Management and Sedation

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Received 31 October 2010; Accepted 31 October 2010

Our ability to provide analgesia and sedation for children has evolved over the past several years. We have progressed from papoose boards to oral sucrose solutions to soothe babies during procedures. Many procedures that were traditionally performed in the operating room are being performed in remote settings: inpatient wards, satellite units, and emergency rooms. The delivery of pediatric sedation is no longer restricted to a limited group of specialists, but instead is delivered by specialists, and physicians as well as non-physicians, in the field of anesthesia, hospital medicine, pediatrics, intensive care medicine, dental medicine, emergency medicine, and radiology. Some sedatives and analgesics have been introduced to market within the past decade whereas others, still in use, have existed for over a century.

The ability of infants to recognize pain was initially underappreciated. Clinical and bench research, however, have sensitized us to the newborn's capacity to feel pain and has, subsequently, laid the groundwork for ongoing research into the pathophysiology of pain and clinical tools for proper assessment [1, 2]. Acute pain management options for children continue to evolve, encompassing all routes of delivery: oral, rectal, topical, subcutaneous, mucosal, intramuscular, parenteral and recently intranasal. Some of the recent introductions of this century include our appreciation of the analgesic and sedative benefits of oral sucrose in newborns and the use of alternative delivery routes, such as intranasal fentanyl for analgesia [3, 4]. There has also been continued interest comparing the benefits of nonsteroidal anti-inflammatory medications to narcotics [5]. Despite the advances in our knowledge and application of analgesics, patient safety continues to be a concern, particularly as unexpected adverse events, a morphine overdose in breast milk of a mother taking codeine for example, continue to occur [6].

Analgesia and sedation practices are not uniform; guidelines, policies, and protocols differ among professional organizations, provider groups, countries, institutions and among providers within the same institution. The inability to reach a consensus on safe practice and appropriate guidelines threatens our ability to provide safe, consistent care and fuels debate and malcontent amongst and between some specialties.

The magnitude of human and financial cost of jeopardizing patient safety in sedation is large and adverse outcomes should be rare. The numerical value of rare should not be a percentage; for example, a 99.9% probability of having a given outcome or 0.1% (1 in 1000) probability of a serious adverse outcome as a result of sedation is not acceptable. An acceptable aim for pediatric sedation should be "six sigma" which will reduce adverse outcome to 3-4 errors per a million incidents [7].

Ensuring that the practice of pediatric analgesia and sedation follows the same rigorous safety monitoring at all times by all providers, and in any setting across the world is a common responsibility shared by healthcare providers caring for children.

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Hindawi Publishing Corporation
International Journal of Pediatrics
Volume 2010, Article ID 474838, 11 pages
doi:10.1155/2010/474838

Review Article

Pain in Children: Assessment and Nonpharmacological Management

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Received 30 January 2010; Accepted 4 May 2010

Academic Editor: Keira Mason

Pain perception in children is complex, and is often difficult to assess. In addition, pain management in children is not always optimized in various healthcare settings, including emergency departments. A review of pain assessment scales that can be used in children across all ages, and a discussion of the importance of pain in control and distraction techniques during painful procedures are presented. Age specific nonpharmacological interventions used to manage pain in children are most effective when adapted to the developmental level of the child. Distraction techniques are often provided by nurses, parents or child life specialists and help in pain alleviation during procedures.

1. Introduction

For pediatric patients presenting to the emergency department, medical procedures are often painful, unexpected, and heightened by situational stress and anxiety leading to an overall unpleasant experience. Although the principles of pain evaluation and management apply across the human lifespan, infants and children present unique challenges that necessitate consideration of the child's age, developmental level, cognitive and communication skills, previous pain experiences, and associated beliefs [1]. According to the International Association for the Study of Pain, "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage". Perception of pain in pediatrics is complex, and entails physiological, psychological, behavioral, and developmental factors [1]. However, in spite of its frequency, pain in infants, children, and adolescent is often underestimated and under treated [2]. It has also been shown that infants and children, who experience pain in early life, show long-term changes in terms of pain perception and related behaviors [2]. Health care professionals in this setting have a responsibility to reduce pain and anxiety as much as possible while maintaining patient safety.

Pain in infants and children can be difficult to assess which has led to the creation of numerous age-specific pain management tools and scores. Health care workers need to be able to detect the symptoms and signs of pain in different age groups and determine whether these symptoms are caused by pain or other factors [1]. It is difficult for health care professionals to foresee which measurement systems apply to accurately measure pain in the pediatric population [1]. Health care professionals often prefer practical methods, which reliably track the child's pain experience and pain control over time whereas researchers tend to focus on tools, which are meticulously proven for reliability with different observers. Thus a balance may be hard to achieve [1]. Barriers to pain management in children are numerous and include inaccuracies regarding pathophysiological mechanisms of pain with statements such as "children do not feel pain the way adults do" [3], fears regarding the use of pharmacological agents and deficits in knowledge of methods of pain assessment [3, 4]. These myths and other factors such as personal values and beliefs, prevent adequate identification and alleviation of pain for all children [2, 3].

Effective care in pediatrics requires special attention to the developmental stage of the child. Current research does not adequately discuss the effectiveness of certain tools and

measurements used to assess pain in children at various ages [5]. The experience of pain and coping strategies from developmental perspective is also limited. In this paper, our aim is to address potential sources of pain measurement, and responses to pain control and distraction based on pediatric developmental stages. Pharmacological pain management will not be discussed, as it is beyond the intended scope of this article.

2. Pain Assessment Tools

Accurate pain measurements in children are difficult to achieve. Three main methods are currently used to measure pain intensity: self report, behavioral, and physiological measures. Self-report measures are optimal and the most valid [4]. Both verbal and nonverbal reports require a certain level of cognitive and language development for the child to understand and give reliable responses [4]. Children's capability to describe pain increases with age and experience, and changes throughout their developmental stages [4]. Although, observed reports of pain and distress provide helpful information, particularly for younger children, they are reliant on the individuals completing the report [6]. Behavioral measures consist of assessment of crying, facial expressions, body postures, and movements. They are more frequently used with neonates, infants, and younger children where communication is difficult [7]. Physiological measures include assessment of heart rate, blood pressure, respiration, oxygen saturation, palmer sweating, and sometimes neuroendocrine responses [8]. They are however generally used in combination with behavioral and self-report measures, as they are usually valid for short duration acute pain and differ with the general health and maturational age of the infant or child [8]. In addition, similar physiological responses also occur during stress which results in difficulty distinguishing stress versus pain responses. A summary of the following pain assessment tools by age can be found in Table 1.

2.1. Neonates and Infants. Despite early studies, current research supports that infants possess the anatomical and functional requirements to perceive pain [9]. Recent studies also demonstrate that infants elicit certain behavioral responses to pain perception [10]. Pain in infants, despite this data, remains under-treated and often mismanaged [11]. The most common pain measures used for infants are behavioral. These measures include crying, facial expressions, body posture, and movements. The quality of these behaviors depends on the infant's gestational age, and maturity [12]. Preterm or acutely ill infants, for example, do not illicit similar responses to pain due to illness and lack of energy. In addition, interpretation of crying in infants is especially difficult as it may indicate general distress rather than pain. Cry characteristics are also not good indicators in preterm or acutely ill infants, as it is difficult for them to produce a robust cry [12].

Numerous scales are currently available to measure behavioral indicators in infants, the most common being the Neonatal Facial Coding System (NFCS) and the Neonatal Infant Pain Scale (NIPS). Other scales used with infants are composite measurement scales, meaning they use a combination of behavioral and physiological measures. Some scales also take into consideration gestational age and the general behavioral state of the infant [13]. Examples of these scales are The Premature Infant Pain Profile (PIPP), Crying Requires Increased Vital Signs Expression Sleeplessness (CRIES), and the Maximally Discriminate Facial Movement Coding System (MAX) [14–16].

Neonatal Facial Coding System (NFCS). It is used to monitor facial actions in newborns. It was developed at the University of British Columbia, and the British Columbia children's hospital [17]. The system looks at eight indicators to measure pain intensity: brow bulge, eye squeeze, nasolabial furrow, open lips, stretched mouth (horizontal or vertical), lip purse, tout tongue, and chin quiver [17]. The indicators are recorded on videotape, coded, and scored. It has been proven reliable for short duration, acute pain in infants and neonates [18]. Since some facial actions occur in nonpainful situations, while others (horizontal and vertical mouth stretch) are present in less than 50% of painful situations, NFCS is able to discriminate between degrees of distress, but not between pain-related and nonpain-related distress [19]. The system is also difficult to assess in intubated neonates [19].

Neonatal Infant Pain Scale (NIPS). It was developed at the Children's Hospital of Eastern Ontario. It is a behavioral assessment tool to measure pain [20]. The scale takes into account pain measurement before, during and after a painful procedure, scored in one-minute intervals. The indicators include: face, cry, breathing pattern, arms, legs, and state of arousal [20]. Results are obtained by summing up the scores for the six indicators (where 0 indicates no pain, and 2 indicates pain), with a maximum sore of 7 [20]. It is a good system to measure responses to acute painful stimuli. Although it has been fully validated, it is time consuming and hard to interpret in intubated infants.

The Premature Infant Pain Profile (PIPP). It is a 7-indicator composite measure that was developed at the University of Toronto and McGill University to assess acute pain in preterm and term neonates. It has been validated in studies using synchronized videotaping of infants undergoing painful procedures [14, 21]. The indicators include (1) gestational age, (2) behavioral state before painful stimulus, (3) change in heart rate during stimulus, (4) change in oxygen saturation, (5) brow bulge during painful stimulus, (6) eye squeeze during stimulus, and (7) nasolabial furrow during painful stimulus [14]. Gestational age is taken into consideration. Scoring is initially done before the painful procedure. The infant is observed for 15 seconds and vital signs recorded. Infants are then observed for 30 seconds during the procedure where physiological and facial changes are recorded and scored. The score ranges from 0–21, with the higher score indicating more pain [14]. The PIPP is however burdensome and time consuming for clinical

purposes, especially in the emergency department, and its use for intubated neonates remains questionable" [21].

Crying Requires Increased Vital Signs Expression Sleeplessness (CRIES). It is an acronym of five physiological and behavioral variables proven to indicate neonatal pain. It is commonly used in neonates in the first month of life [15]. The scale was developed at the University of Missouri and may be recorded over time to monitor the infant's recovery or response to different interventions [22]. CRIES looks at five parameters: (1) crying, where a high pitched cry is usually associated with pain, (2) increased oxygen requirements, as neonates in pain show decrease oxygen saturation, (3) facial expression where grimacing is the expression most associated with pain, (4) vitals signs, which are usually assessed last as to not awaken or disturb the child, and (5) sleeping patterns where increased sleeplessness is associated with pain [15]. Indicators are scored from 0–2 with the maximum possible score of 10, a higher score indicating a higher pain expression [15].

Maximally Discriminate Facial Movement Coding System (MAX). It is used for infants to assess emotions associated with facial expression. It looks at brow, eye, and mouth movements [16, 23]. MAX provides a system for measuring emotional signals, and identifies nine fundamental emotions: interest, joy, surprise, sadness, anger, disgust, contempt, fear, and physical distress or pain. The scoring entails 68 MAX number codes, each representing a different facial expression. The description of the expression of each number code is based on the anatomically possible movements of the facial muscles and is a description of what the face looks like when the movements have taken place [16]. Critical studies argue that MAX only includes measurements that are said to correspond with emotions and does not differentiate between anatomically distinct facial movements (inner and outer brow raise) [24, 25].

2.2. Toddlers. In toddlers, verbal skills remain limited and quite inconsistent. Pain-related behaviors are still the main indicator for assessments in this age group. Nonverbal behaviors, such as facial expression, limb movement, grasping, holding, and crying, are considered more reliable and objective, measures of pain than self-reports [26]. Most children of this age however are capable of voluntarily producing displays of distress, with older children displaying fewer pain behaviors (e.g., they cry, moan, and groan less often). Most two-year-old children can report the incidence and location of pain, but do not have the adequate cognitive skills to describe its severity [27]. Three-year-old children, however, can start to differentiate the severity of pain, and are able to use a three-level pain intensity scale with simple terms like "no pain, little pain or a lot" [27]. Children in this age group are usually able to participate in simple dialogue and state whether they feel pain and "how bad it is" [27]. The following section describes common scales used for this age group.

The Children's Hospital of Eastern Ontario Pain Scales (CHEOPS). It is one of the earliest tools used to assess and document pain behaviors in young children [28]. It used to assess the efficacy of interventions used in alleviating pain. It includes six categories of behavior: cry, facial, child verbal, torso, touch, and legs. Each is scored separately (ranging from 0–2 or 1–3) and calculated for a pain score ranging from 4–13 [28]. Its length and changeable scoring system among categories makes it complicated and impractical to use compared to other observational scales.

The Faces Legs Activity Cry Consolability Scale (FLACC). It is a behavioral scale for measuring the intensity of postprocedural pain in young children [29]. It includes five indicators (face, legs, activity, cry, and consolability) with each item ranking on a three point scale (0–2) for severity by behavioral descriptions resulting in a total score between 0–10 [29]. FLACC is an easy and practical scale to use in evaluating and measuring pain especially in pre-verbal children from 2 months to 7 years. Numerous studies have proven its validity and reliability [30].

The COMFORT Scale. It is a behavioral scale used to measure distress in critically ill unconscious and ventilated infants, children, and adolescents [31, 32]. This scale is composed of 8 indicators: alertness, calmness/agitation, respiratory response, physical movement, blood pressure, heart rate, muscle tone, and facial tension. Each indicator is given a score between 1 and 5 depending on behaviors displayed by the child and the total score is gathered by adding all indicators (range from 8–40). Patients are monitored for two minutes. The COMFORT scale has been proven to be clinically useful to determine if a child is adequately sedated [32].

The Observational Scale of Behavioral Distress (OSBD). It remains the most frequently used measurement in procedure-related distress studies [33]. It consists of 11 distress behaviors identified by specialists to be associated with paediatric procedure-related distress, anxiety, and pain. Scores are calculated from summing up all 11 distress behaviors. The behaviors are usually organized into categories of growing intensity, considering their level of interference with medical procedures (e.g., moaning, flinching, and disruption of medical materials) [34]. The validity and reliability of the OSBD has been widely reported [35, 36]. Limitations of the OSBD are noted, where the explanations of the different phases of the procedure: anticipatory (when the child is waiting for the procedure), procedural (distress while the procedure is taking place), and recovery (postprocedural distress) are interchangeable among studies [35, 36]. In instances where procedural phases are constant, differences arise in initiating the procedure (e.g., venipunctures) which are frequently independent of the child's behavior, and affect the duration of the procedure and the number of observation intervals. This ultimately increases or decreases the scores [37].

Observational Pain Scale (OPS). It is intended to measure pain in children aged 1 to 4 years, and is used to assess

pain of short or long duration [38]. The scale was primarily produced at the University of Amsterdam in the Netherlands. The scale measures 7 parameters: facial expression, cry, breathing, torso, arms and fingers, legs and toes, and states of arousal [38]. The OPS has a simple scoring system which makes it easy to use by all healthcare professionals to obtain valid and reliable results [39]. The indicators are rated from 0-1 with a maximum score of 7, where the higher score indicates greater discomfort [38].

The Toddler-Preschooler Postoperative Pain Scale (TPPPS). It is used to assess pain in young children during and after a medical or surgical procedure. It is most commonly used for children aged 1–5 years [40]. In order to observe verbal, facial, and bodily movement, the child needs to be awake. This scale relies on behavioral observations, but also includes a self report element. The TPPPS includes seven indicators divided into three pain behavior groups: vocal pain expression, (verbal complaint, cry, moan) facial pain expression (open mouth, squinted eyes, brow bulging and furrowed forehead) and bodily pain expression (restlessness, rubbing touching painful area) [41]. It is a useful tool for evaluating the effectiveness of medication administration in children, but does not measure pain intensity [42]. If a behavior is present during a 5-minute observation period, a score if 1 is given whereas a score of 0 is given if the behavior was not present. The maximum score obtained is 7, which indicates a high pain intensity [40].

2.3. Preschoolers. By the age of four years, most children are usually able to use 4-5 item pain discrimination scales [43]. Their ability to recognize the influence of pain appears around the age of five years when they are able to rate the intensity of pain [44]. Facial expression scales are most commonly used with this age group to obtain self-reports of pain. These scales require children to point to the face that represents how they feel or the amount of pain they are experiencing [45]. The following section describes scales commonly used with this age group.

The Child Facial Coding System (CFCS). It is adapted from the neonatal facial coding system and developed for use with preschool children (aged 2–5 years). It consists of 13 facial actions: brow lower, squint, eye squeeze, blink, flared nostril, nose wrinkle, nasolabial furrow, cheek raiser, open lips, upper lip raise, lip corner puller, vertical mouth stretch, and horizontal mouth stretch [46]. The CFCS has been useful with acute short-duration procedural pain [47].

Poker Chip Tool. It is a tool that was developed for preschoolers to assess "pieces of hurt" [48]. The tool uses four poker chips, where one chip symbolizes "a little hurt" and four chips "the most hurt you could experience". The tool is used to assess pain intensity. Health care professionals align the chips in front of the child on a flat surface, and explain, using simple terms, that the chips are "pieces of hurt". The child is asked "how many pieces of hurt do you have right now?" [49] Although most studies focus on using it in children four to thirteen years old, adolescents have used it successfully as well [50].

Faces Pain Scale. It was developed by Wong and Baker and is recommended for children ages 3 and older [51]. The scale requires health care professionals to point to each face and describe the pain intensity associated with it, and then ask the child to choose the face that most accurately describes his or her pain level [51]. Most pain rating scales using faces that portray degrees of distress are divided into two categories: those starting with neutral face as the "no pain" indicator and those with a smiling face. Results showed that children exposed to smiling scale had considerably higher pain scores in the no pain categories and lower scores for positive pain than children who used the neutral faces scale [52]. A study by Chambers and colleagues indicated that children's pain ratings differ depending on the types of faces scale used, and that faces scales with smiling faces may confuse emotional states with pain ratings [52]. The revised pain scale (FPS-R) is a simplified 6 face adaption of Bieri's validated faces pain scale. It does not contain smiling faces or tears thus avoiding the confounding of affect and pain intensity [45].

The OUCHER Scale. It was developed by Beyer in 1980 [53]. It is an ethnically based self-report scale, which has three versions: Caucasian, African-American, and Hispanic [54, 55]. Even though it covers a wide array of patients, it still has limits. For example, females are not represented, as well as other cultures. It is used for children older than 5 years [55]. The tool has two separate scales: the numeric scale (i.e., 0–100) and the photographic scale usually used for younger children. The photographic scale entails six different pictures of one child, portraying expressions of "no hurt" to "the biggest hurt you can ever have" [56]. Children are asked to choose the picture or number that closely corresponds to the amount of pain they feel [56].

2.4. School-Aged Children. Health care professionals depend more comfortably on self-reports from school-aged children. Although children at this age understand pain, their use of language to report it is different from adults. At roughly 7 to 8 years of age children, begin to understand the quality of pain [57]. Self-report visual analogue and numerical scales are effective in this age group. A few pain questionnaires have also proven effective for this age such as the pediatric pain questionnaire and the adolescent pediatric pain tool [58, 59]. A brief discussion of these tools is presented here.

Visual Analogue Scale (VAS). It is a horizontal line, 100 mm in length, attached to word descriptions at each end, "not hurting" or "no pain" to "hurting a whole lot" or "severe pain". The children are asked to mark on the line the point that they feel represents their pain at this moment [60]. A color analogue scale can also be used, where darker more intense colors (i.e., red) represent more pain [61].

Paediatric Pain Questionnaire. It is a self-report measure to assess children and adolescents coping abilities using 8

subscales "information seeking, problem solving, seeking social support, positive self-statements, behavioral distraction, cognitive distraction, externalizing and internalizing as well as three more complex scales (approach, distraction, and emotion-focused avoidance) [58]. It contains 39 items in total, with scores ranging from 1 ("never") to 5 ("very often"). Children or adolescents are requested to state how often they "say, do, or think" certain items when they hurt or in pain. The questionnaire usually takes about 10–15 minutes to complete [62].

Adolescent Pediatric Pain Tool (APPT). It is a valid all encompassing pain assessment tool used for individual pain assessments and measures intensity, location, and quality of pain in children older than 8 years of age [63]. The APPT is most useful with children and adolescents who are experiencing complex, difficult to manage pain [59]. It consists of a body map drawing to allow children to point to the location of pain on their body and a word graphic scale to measure pain intensity. The word graphic rating scale is a 67 word list describing the different dimension of pain and a horizontal line with words attached that range from "no," "little," "medium," "large," to "worst" possible pain [59, 64–66].

2.5. Adolescents. Adolescents tend to minimize or deny pain, especially in front of friends, so it is important to provide them with privacy and choice. For example, they may or may not choose to have parents present. They expect developmentally appropriate information about procedures and accompanying sensations. Some adolescents regress in behavior under stress [3]. They also need to feel able to accept or refuse strategies and medications to make procedures more tolerable. To assess pain and, specifically chronic pain, the adolescent pediatric pain tool (see above section) or the McGill pain questionnaire are helpful.

The McGill Pain Questionnaire (MPQ). It was developed by Melzack in 1971 [67]. It is an assessment tool that combines a list of questions about the nature and frequency of pain with a body-map diagram to pinpoint its [68]. The questionnaire uses word lists separated into 4 classes to assess the total pain experience. The categories are (1) sensory, which contains words describing pain in terms of time, space, pressure, heat, and brightness, (2) affective category which describes pain in terms of tension, fear, and autonomic properties, (3) evaluative, and (4) miscellaneous. After the patient is done rating their pain words, the administrator allocates a numerical score, called the "Pain Rating Index" [69]. Scores vary from 0–78 with the higher score indicating greater pain [68].

3. Minimizing Pain during Procedures: Nonpharmacologic Methods

Pain is one of the most frequent complaints presented in paediatric emergency settings. The emergency department itself is a very stressful place for children. Thus it is important for health care providers to follow a child centered or individual approach in their assessment and management of pain and painful procedures [70]. This approach promotes the right of the child to be fully involved in the procedure, to choose, associate, and communicate. It allows freedom for children to think, experience, explore, question, and search for answers, and allows them to feel proud for doing things for themselves. It is essential to focus on the child rather than the procedure and avoid statements such as "let's just get it over with" [70]. The child and family should be active participants in the procedure. In fact, allowing parents or family members to act as positive assistants rather than negative restraints helps to reduce stress in both children and parents and minimizes the pain experience [70]. It is also essential to ensure that all procedures are truly necessary, and can be performed safely by experienced personnel. Ideally procedures should be done in a child-friendly environment, using appropriate pharmacologic and nonpharmacologic interventions with routine pain assessment and reassessment [70].

Distraction is the most frequent intervention used in the emergency department to guide children's attention away from the painful stimuli and reduce pain and anxiety. It is most effective when adapted to the developmental level of the child [71]. Distraction techniques are often provided by nurses, parents or child life specialists. Current research has shown that distraction can lead to the reduction in procedure times, and the number of staff required for the procedure [72]. Distraction has also proven to be more economical than using certain analgesics [73]. Distraction is divided into two main categories: passive distraction, which calls for the child to remain quiet while the health care professional is actively distracting the child (i.e., by singing, talking, or reading a book) [74]. Active distraction, on the other hand, encourages the child's participation in the activities during the procedures [74]. Interventions used to minimise pain are classified into three main categories (cognitive, behavioral, or combined) [75].

Cognitive Interventions. They are mostly used with older children to direct attention away from procedure-related pain (e.g., counting, listening to music, non procedure-related talk) [76]. The following are a few examples of cognitive interventions:

(1) *Imagery.* The child is asked to imagine an enjoyable item or experience (e.g., playing on the beach) [77].

(2) *Preparation/Education/Information.* The procedure and feelings associated with the procedure are explained to child in an age appropriate manner. The child is provided with instructions about what he/she will need to do during the procedure to help them understand what to expect [78, 79].

(3) *Coping statements.* The child is taught to repeat a set of positive thoughts (e.g., "I can do this" or "this will be over soon") [80].

(4) *Parental training.* The parents or family members are taught one of the above interventions to decrease

their stress, as decreasing the parent's distress will often lead to a decrease in the child's distress [77].

(5) *Video games and television.* These may be used to distract children from the painful procedures [81].

Behavioral Interventions. They are behavioral methods to guide the child's attention away from procedure-related pain. (e.g., videotapes, games, interactive books). A few examples are:

(1) *Breathing exercises.* The child is taught to concentrate on deep breathing. To engage younger children, health care professionals can use party blowers, or blowing bubbles [82].

(2) *Modeling positive coping behaviors.* The child may watch another child or adult going through the procedure, and rehearse these behaviors [83].

(3) *Desensitization.* This is a step-by-step approach to coping with the painful stimuli. It involves slowly introducing the procedure and tasks involved, and effectively dealing with easier tasks before moving to the next one [77].

(4) *Positive reinforcement.* The child is rewarded with positive statements or concrete gifts, after the painful procedure (e.g., stickers, toys, games, small trophies) [80].

(5) *Parent coaching.* The parents are instructed to enthusiastically encourage the child to use these strategies [84].

Current studies are beginning to take into consideration children's different responses to distraction interventions based on their developmental stage, maturity level, and age. Our goal in this section is to provide various forms of distraction that are proven effective with different age groups.

3.1. Neonates and Infants. When performing painful procedures on infants, it is important to take into consideration the context of the procedure (i.e., is the procedure really necessary, how many painful procedures has the infant had in the past, and what was their previous pain experience) [85]. The procedural environment should also be developmentally sensitive [86]. In fact, reducing noise and lighting, use of soothing smells and clustering procedures to avoid over handling, reduces pain reactions in infants [86].

Distraction techniques used with this age group are mostly passive. Cognitive strategies used to reduce pain perception in infants are either visual or auditory interventions. Visual aids can include pictures, cartoons, mobile phones, and mirrors [87]. Auditory aids include music, lullabies sung by parents or health care professionals [88]. Music is more frequently being used to improve painful outcomes in infants [89]. Studies suggest that music can significantly impact behavioral reactions to pain, but not physiological measures [89]. Behavioral strategies are more common for this age group, and involve either "direct or indirect" interventions that engage the caregivers in handling the infants [90]. The combination of different strategies to provoke different senses has been shown to be more effective [91]. Examples of behavioral strategies include the following.

(1) *Non-nutritive sucking,* an indirect intervention involving insertion of a pacifier or a nonlactating nipple into the infant's mouth to encourage sucking behaviors, was found to stimulate the orotactile and mechano receptors, and decrease cry durations and heart rate [92].

(2) *Skin to skin contact* with the mother (kangaroo care), where the infant is positioned on the mother's exposed chest during, or after the painful procedure [93].

(3) *Rocking and holding the infant,* where the infant is carried by a parent or caregiver during (if possible) and after the painful procedure and gently rocked [94].

(4) *Swaddling the infant* is another similar calming technique where the infant is wrapped with its extremities close to their trunk to prevent him/her from moving around excessively [95].

3.2. Toddlers and Preschoolers. For young children, explaining the procedures with age appropriate information is useful, in addition to providing them with the opportunities to ask questions [70]. Examples for active distraction used with this age group include, allowing them to blow bubbles, providing toys with lots of colour or toys that light up. Initiating distracting conservations (e.g., how many brothers and sisters do you have? What did you do at your birthday party?) and deep breathing methods are also helpful for older children [74]. Passive distraction techniques include: having the parents or child life specialist read age appropriate books, sing songs, and practicing "blowing out birthday candles" with the child [74].

3.3. School-Aged Children. Older children have a better understanding of procedures and why they are being done, thus providing them with age appropriate information is also important [70]. Providing children with a choice (e.g., sit or lie down, choose which hand) helps them feel in control of the situation [70]. Asking parents about their child's previous pain experiences and coping mechanisms helps health care professionals identify appropriate interventions to use with the child. Educating school-aged children about passive and active techniques available will help them cope with the distress and anxiety of the procedure [70]. Active techniques for this age group include blowing bubbles, singing songs, squeeze balls, relaxation breathing and playing with electronic devices [74]. Passive distraction can include watching videos, listening to music on headphones, reading a book to the child or telling them a story [74].

3.4. Adolescents. It is essential to always ensure a private setting for procedures with adolescents especially as they sometimes tend to deny pain in front of friends, and

Table 1: Pain assessment scales.

Ages	Scales	Description/indicators	Websites and references	Validity
Preterm to full-term infants	Premature Infant Pain Profile (PIPP)	Gestational age, behavioral state before painful stimulus, change in heart rate during stimulus, change in oxygen saturation, brow bulge, eye squeeze nasolabial furrow	http://www.cebp.nl/vault_public/filesystem/?ID=1467	Stevens et al., [14, 86]
Preterm to full-term infants	Neonatal Facial Coding System (NFCS)	Brow bulge, eye squeeze, nasolabial furrow, open lips, stretched mouth (horizontal or vertical), lip purse, tout tongue, and chin quiver	http://www.cebp.nl/vault_public/filesystem/?ID=1425	Grunau et al., [18]
Preterm to full-term infants	Neonatal Infant Pain scale (NIPS)	Face, cry, breathing pattern, arms, legs, and state of arousal	http://www.cebp.nl/vault_public/filesystem/?ID=1426	Lawrence et al., [20]
32–60 weeks	Crying Requires Increased vital signs Expression Sleeplessness (CRIES)	Crying, increased oxygen requirements, expression, vitals signs, sleeping	http://www.cebp.nl/vault_public/filesystem/?ID=1295	Krechel and Bildner, [15]
Infants	Maximally discriminate facial movement coding system (MAX)	Brow, eye, and mouth movement	Izard C. Maximally Discriminate Facial Coding System,1983	Izard [23]
1–7 years	Chidren's Hospital of Eastern Ontario Pain Scale (CHEOPS)	Cry, facial, child verbal, torso, touch, legs	http://www.cebp.nl/vault_public/filesystem/?ID=1274.	McGrath et al., [28]
Infancy to 7 years	The Faces Legs Activity Cry Consolability Scale (FLACC)	Face, legs, activity, cry, and consolability	http://www2.massgeneral.org/painrelief/pcs_pain_files/app_d_flacc.pdf.	Merkel et al., [29]
1–4 years	Observational Pain Scale	Facial expression, cry, breathing, torso, arms and fingers, legs and toes, and states of arousal	https://www.cebp.nl/vault_public/filesystem/?ID=1451.	Boelen-Ven der Loo et al., [38]
1–5 years	Toddler-Preschooler Postoperative Pain Scale (TPPPS)	Vocal pain expression, facial pain expression, bodily pain expression	http://www.cebp.nl/vault_public/filesystem/?ID=1490.	Tarbell et al., [40]

Table 1: Continued.

Ages	Scales	Description/indicators	Websites and references	Validity
1–6 years	Child Facial Coding System (CFCS)	Facial actions: brow lower, squint, eye squeeze, blink, flared nostril, nose wrinkle, nasolabial furrow, cheek raiser, open lips, upper lip raise, lip corner puller, vertical mouth stretch, and horizontal mouth stretch.	Manual: Pediatric Pain-Science Helping Children, IWK Grace Health Centre, Dalhousie University & the University of British Columbia C.T. (copyright 1996)	Gilbert et al., [47]
3–7 years	COMFORT Scale	Calmness/agitation, respiratory response, physical movement, blood pressure, heart rate, muscle tone, and facial tension	http://painconsortium.nih.gov/pain_scales/COMFORT_Scale.pdf	Ambuel 1990 [31]
≥3 years	Faces Pain Scale	Pain intensity Faces correspond to pain intensity	http://painconsortium.nih.gov/pain_scles/index.html, http://www.usask.ca/childpain/fpsr/	Wong and Baker, [51], Hicks et al., [45]
3–13 years	The Observational Scale of behavioral Distress (OSBD)	Eleven behaviors related to pain and/or anxiety		Elliot 1987 [34], Tucker et al., [35]
4–13 years	Poker Chip Tool	Pain intensity Poker chips represent "pieces of pain"	http://www.painresearch.utah.edu/cancerpain/attachb7.html	Hester et al., [49]
≥5 years	Oucher Scale	Pain intensityFaces correspond to pain intensity	http://www.oucher.org/the_scales.html	Beyer et al., [56]
7 years	Visual Analogue Scale (VAS)	Pain intensity (numeric, color)	http://www.cebp.nl/vault_public/filesystem/?ID=1478.	
8–17 years	Pediatric Pain Questionnaire	Information seeking, problem solving, seeking social support, positive self-statements, behavioral distraction, cognitive distraction, externalizing, internalizing/	http://www.seattlechildrens.org/pdf/pediatric_pain_questionnaire.pdf	Varni et al., [58]
8–17 years	Adolescent Pediatric Pain Tool (APPT)	Intensity, location, and quality of pain		Savedra et al., [59]
≥12 years	McGill Pain Questionnaire	Sensory and affective pain experience	http://www.cebp.nl/vault_public/filesystem/?ID=1400	Melzack, [68]

family. Giving them the power to choose the type of distraction, or whether they want friends and family present is helpful [70]. Striking conversations, using squeeze balls or having them play with electronic devices are examples of active techniques, while passive distractions include watching videos, training them to breathe deeply (in from the nose, count to 5 and out through the mouth), and listening to music [74].

4. Conclusion

Although there is an overwhelming amount of data regarding effective paediatric pain assessment and management, it is often not being effectively applied. Current studies demonstrate pain management in children remains undertreated. It is the responsibility of health care professionals to educate their peers and advocate for appropriate pain treatment in children. Infants and children present a unique challenge that necessitate consideration of their age, developmental level, cognitive and communication skills, previous pain experiences, and associated beliefs. There is a need for more research to illuminate optimal pain management and strategies that take these special needs into consideration, to improve the treatment of pain in children.

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Hindawi Publishing Corporation
International Journal of Pediatrics
Volume 2010, Article ID 825657, 9 pages
doi:10.1155/2010/825657

Review Article

Management of Pain in Children with Burns

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Received 2 March 2010; Accepted 23 June 2010

Academic Editor: Savithiri Ratnapalan

Burn injuries are common in children under 10 years of age. Thermal injury is the most common mechanism of injury and scalds account for >60% of such injuries. All children with burns will experience pain, regardless of the cause, size, or burn depth. Undertreated pain can result in noncompliance with treatment and, consequently, prolonged healing. It is acknowledged that the monitoring and reporting of pain in children with burns has generally been poor. Due to the adverse physiological and emotional effects secondary to pain, adequate pain control is an integral and requisite component in the management of children with burns. A multidisciplinary approach is frequently necessary to achieve a robust pain relief. Key to successful treatment is the continuous and accurate assessment of pain and the response to therapy. This clinical review article discusses the essential aspects of the pathophysiology of burns in children provides an overview of pain assessment, the salient principles in managing pain, and the essential pharmacodynamics of commonly used drugs in children with burn injuries. Both pharmacological and nonpharmacological treatment options are discussed, although a detailed review of the latter is beyond the scope and remit of this article.

1. Introduction

Children <10 years of age account for approximately 36% of burns seen in Accident and Emergency (A&E) departments [1]. About 44% of all admissions to regional burns units in the United Kingdom (UK) are sustained by those <15 years of age [2]. The aetiology of burns can be broadly divided into: thermal, electrical, and chemical injuries. Thermal injury is the most common in children with electrical and chemical injuries accounting for only 2% and 1%, respectively [2]. Thermal injuries can be further subdivided into scald, flame, contact with a hot surface, and flash burns resulting from ignition of a volatile substance. Scalds account for approximately 61% for injuries in children followed by contact burns at 21% [2] (Figure 1).

Pain and distress are strongly associated with burns in children. Monitoring and reporting of pain in children with burns has been generally poor. For example, the potential for anticipatory pain before procedures, such as dressing changes, is high and little has been reported in the literature about chronic pain following a burn injury. Monitoring of pain is complicated by the traumatic nature of the initial injury and reaction to distress after a burn.

Pain has adverse physiological and emotional effects, and adequate pain control is an important factor in improving outcomes. Key to successful treatment is the continuous and accurate assessment of pain, and the response to therapy. Management of pain should be a multidisciplinary approach involving a range of professionals such as the burn surgeon, paediatrician, pain specialist (usually anaesthetist), nurse, occupational therapist, physiotherapist, psychologist, play therapist, and, importantly, the child's parents/carers. This clinical review article discusses the essential aspects of the pathophysiology of paediatric burns and the effect of associated pain in the management of children with such injuries. The scientific evidence and selection criteria for the salient information and the substantiation of the information provided in this review have been obtained from sources shown in Table 1.

Table 1: Sources of scientific evidence and selection criteria.

The scientific evidence for the preparation of this article was obtained by searching Medline, Ovid, *Burns* and the Cochrane library until June 2010 for randomised controlled trials, systematic reviews, evidence reports, and recent evidence-based guidelines from International Burn and Pain Management Associations.

2. Pathophysiology of Burn Injury

The extent of a burn injury is determined by the degree of heat and duration of exposure of the tissue to the source [3]. The mechanism of injury can provide a useful guide to the possible severity; for example, fat scalds produce a deeper injury than water scalds due to the density. Likewise, children with other comorbidities such as paraplegia secondary to spina bifida suffer worse injury due to lack of sensation or inability to extricate themselves from the source. Local factors, such as inflammatory response and changes in perfusion also influence the final extent of the burn [3].

Coagulation, stasis, and hyperaemia (Figure 2) are the three recognised zones of burn injury (Hettiaratchy and Dziewulski [4]). The zone of coagulation is where irreversible coagulation of tissue protein has occurred and this area is therefore unsalvageable. The zone of stasis is characterised by decreased tissue perfusion. Thus the aim of initial burns management is to improve blood flow to this area to prevent extension of the injury. The third zone of hyperaemia has increased perfusion and therefore is not at risk unless there are added factors such as infection [4].

Systemic response to a burn is associated with those affecting 30% or more of the total body surface area (TBSA) as a result of inflammatory mediator release into the circulation [3, 4]. Consequent upon this, any major system such as the cardiovascular, respiratory, renal, gastrointestinal, metabolic, or immunological can be affected. Tissue and end-organ hypoperfusion is a consequence of hypovolaemia that results from fluid loss and splanchnic and peripheral vasoconstriction. Decreased cardiac contractility and increased capillary permeability, leading to extravasation of protein and fluid into the interstitial space, also contribute to hypotension. Respiratory effects include bronchoconstriction due to inflammatory mediators and may result in respiratory distress syndrome. Basal metabolic rate (BMR) increases three-fold and there is impairment of both humoral and cell-mediated inflammatory responses [3, 4].

3. Burn Depths

The three main categories of burn depth are superficial, partial thickness, and full thickness. [In the US and some parts of the world, the terms 1st degree (superficial), 2nd degree (partial thickness), and 3rd degree (full thickness) are used]. Partial thickness injuries are further subdivided into superficial and deep. Currently in day-to-day clinical practice, the burn depth is assessed based on clinical evaluation using a combination of characteristics such as pain, appearance, colour, blisters (presence or absence), sensation, and capillary refill. Modalities such as Laser Doppler imaging, transcutaneous videomicroscopy (direct visualisation of dermal capillary integrity), and infrared thermography (temperature gradient between burnt and intact skin) have been attempted but are not used in routine clinical practice. Reassessment of burn depth should also be repeated 72 hours postinjury as this can change as a result of management and intervention [5].

Superficial burns are red and painful, only involving the epidermis, and usually heal within seven days [6]. Where there is only erythema and no epidermal loss, this is not included whilst calculating the TBSA. Superficial partial thickness injuries produce blistering and, once debrided, appear pink and wet with brisk capillary refill. These are also painful and will usually heal within 14 days. Deep partial thickness burns are less painful, have a dry and fixed blotchy red appearance, and do not blanch under pressure. Deep partial thickness burns may take longer to heal (about 21 days or more). Full thickness injuries also appear dry but

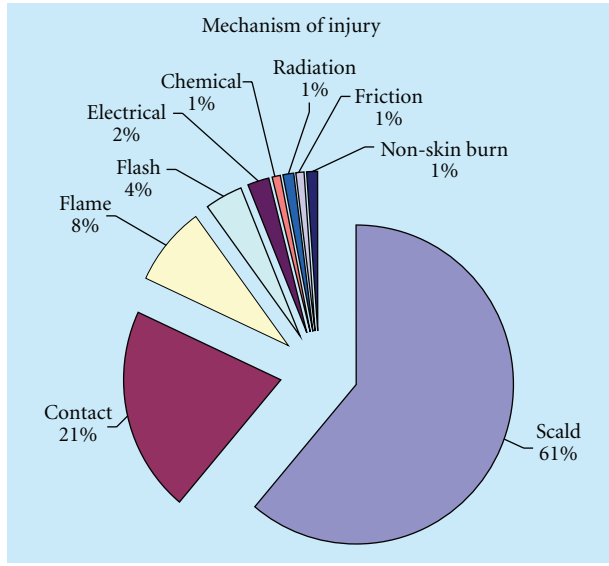

Figure 1: Illustration of various burn aetiologies. Note that scalds in children account for more than 60% of all burn injuries.

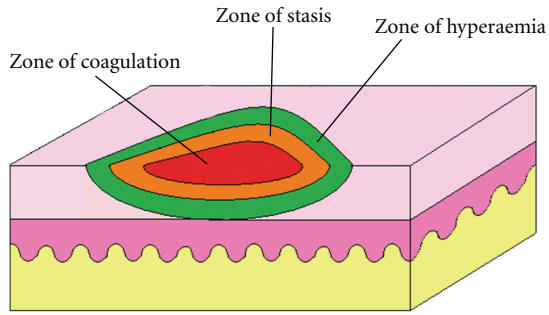

Figure 2: Illustration of zones of burn injury. The centre part (zone of stasis) is the worst affected and the one surrounding it (zone of stasis) is characterised by decreased tissue perfusion. The burn depth in this zone can be prevented from worsening by appropriate first aid and adequate initial fluid resuscitation.

with a white or brown leathery appearance. They are not painful and generally require excision and skin grafting to allow healing [3, 5]. Some of the salient features in burns of different depths are shown in Table 2.

The burn depth may also directly relate to the extent and severity of pain. The initial insult to the skin damages or destroys nerve endings but this initial stimulation causes pain regardless of the depth of burn [7, 8]. In superficial and superficial partial thickness burns, nerve endings remain intact and exposed and therefore stimulation of these, for example, from movement or touch, causes pain. In deep partial thickness injuries, some nerves may be completely destroyed and therefore the pain experienced may be less. However, it needs to be appreciated that surrounding areas (zone of stasis and hyperaemia) of a deep burn can be painful. Exposure of damaged nerve endings to inflammatory mediators, such as bradykinin and histamine, leads to hypersensitivity so that normally nonpainful stimuli cause pain [9]. In addition, the treatment/therapy instituted to treat burns such as debridement, dressing changes, and physiotherapy, leads to continued stimulation of nociceptors and, consequently, pain.

In areas of full thickness burns, all nerve endings have been destroyed and therefore this area should be insensate. Similar to deep partial thickness burns, the surrounding damaged tissue may have intact but damaged nerve endings that are still sensitive to both inflammatory and external stimuli [7–9]. Children with more severe burns are also subjected to more dressing changes, both in frequency and duration, and are also more likely to require operative management. Full thickness injuries often require grafting and donor sites may actually be more painful than the initial burn [7, 8].

4. General Management of Burn

The appropriate first-aid in all forms of thermal burns is to run the burnt area under a cold tap for 20 minutes. Care has to be taken in children to avoid hypothermia; therefore very cold water and ice should be avoided as these can cause vasoconstriction, making the depth of injury worse [10]. In minor burns, the injury is cleaned and blisters debrided to allow full assessment of the wound after appropriate analgesia and sedation if needed. Choice of dressing for superficial partial thickness wounds includes simple nonadherent dressings that can be used in conjunction with antimicrobial agents [6] (e.g., a nonadherent silicone dressing such as Mepitel along with betadine ointment). Tissue-engineered skin substitutes, such as Biobrane, or entirely synthetic equivalent dressings, such as Suprathel, adhere to the wound and gradually peel off as reepithelialisation occurs underneath. The main advantage of these dressings is that it can be left intact until the wound heals (provided there is no underlying infection) and only the outer dressings changed, thus reducing pain [11].

Deep dermal burns initially require daily dressing changes (due to increased exudation from the wound) and as healing progresses the frequency of dressing can be gradually reduced. Full thickness burns re-epithelialise only from the edges due to a lack of skin appendages that harbour epithelial cells. This makes healing very slow and therefore almost all full thickness burns, apart from very small areas (less than about 1%-2%), require excision and grafting. To minimise scarring, the aim should be to re-epithelialise the area within about 21 days of injury and therefore early excision and grafting is strongly recommended [6].

In major burns, management should follow trauma resuscitation guidelines including assessment of potential airway problems, particularly in children with facial or flame burns. Children with a burn >10% of the TBSA require fluid resuscitation, with the most commonly used formula worldwide being the Parkland formula [12]. This is calculated as 4 mL/kg/%TBSA total of Hartmann's solution over 24 hours with half given in the first 8 hours and half in the subsequent 16 hours. This formula should not be considered moralistic but rather as a guide that should be used in conjunction with the patient's physiological parameters and the volume of fluid instituted should be tailored accordingly.

Nutritional support is also vital as the BMR can increase by up to 40% after a significant burn. This catabolic state may last for as long as two years, which is of particular concern in the children as this may affect growth [13]. Although it is generally accepted that nutritional support should be started early postinjury [14], with the enteral route being preferable [15], a recent Cochrane review did not find evidence for, or against, either of these in children [16].

5. Management of Pain

All children with burns will experience pain, regardless of the cause, size, or depth of the burn. Undertreated pain can result in noncompliance with treatment and, consequently, prolonged healing. This can disrupt care and increase the risk of posttraumatic stress disorders. It is possible to ensure better pain management by trying to understand the child's experience rather than just acknowledging the pain. Thus the most fruitful approach would seem to be frequent assessment of pain with readiness to try alternative or additional measure when relief seems inadequate. The general attitude to pain management should be presumptive and preemptive.

Multidisciplinary assessment helps to integrate pharmacological and psychological pain relieving interventions to reduce physical, emotional, and family distress. Special attention should be paid to the child's environmental conditions. For instance, a parent's presence and participation in the procedure can be highly beneficial.

Children with burns have background pain and procedural pain and it is important to differentiate between the two. Background pain, once assessed and evaluated, can be managed pharmacologically with regular analgesia whilst procedural pain requires more intense analgesia. Procedural pain is difficult to assess and is therefore frequently under treated. Poor management of pain can lead to anticipatory anxiety before future procedures and a lower pain tolerance threshold.

Table 2: Some salient features of varying burn depths and their approximate healing times.

Burn depth	Appearance	Blistering	Sensation	Approximate healing time
Epidermal	Red	None	Painful	7 days
Superficial partial thickness	Pink with wet appearance. Brisk capillary refill	Blisters present	Painful	14 days
Deep partial thickness	Pale or fixed red staining. Poor capillary refill	Blisters may be present	Painful usually but can painless	21 days; may require excision and skin grafting
Full thickness	Leathery white or brown	None	None in burnt area	Usually requires excision and skin grafting

Chronic pain has multiple and often unclear origins. Neuropathic pain is one cause for this and develops secondary to nerve damage, abnormalities in nerve regeneration, and reprogramming of the central nervous system [17]. It can be frustratingly unresponsive to conventional treatment modalities. Adjuvant therapies such as clonidine and anticonvulsants are effective in treatment of sympathetically mediated pain. Psychological therapies to boost coping strategies and aid relaxation should be added.

Management of pain is important during all stages of treatment including in the emergency department, during procedures such as dressing changes and after discharge when complex neuropathic pain syndromes may develop [18].

6. Measurement Tools

A major contributing factor to poor pain management is the difficulty children have in expressing their pain and problems that the health professionals may have in interpreting and assessing this information correctly. Hence, it is vital to assess the pain accurately to gauge the severity of pain and the effectiveness of its treatment. The pain experienced by burn children also varies greatly; therefore, analgesia needs to be tailored on an individual basis. In order to achieve this aim it is essential to measure pain in a simple and reproducible manner. Various measurement tools are available for assessment of pain in children. In our institution, we tend to use the "*FLACC tool*" and the "*Faces Ladder Scale*" as these are simple, effective, and quick to use. However, irrespective of the tool adopted, the frequency of measurement should be tailored to the appropriate stage in the burn management. During resuscitation, hourly scores must be recorded to address any breakthrough pain. This schedule can be eased whilst the background pain is monitored, but the frequency of monitoring is increased should any new event occur. Once the immediate need has been controlled with parenteral opiates, a background control primarily with paracetamol and if necessary NSAIDs can be established. The intravenous (IV) route should be used if the oral route is not appropriate (such as due to gastric intolerance or minimum fasting prior to a procedure requiring sedation).

6.1. FLACC Tool (Face, Legs, Activity, Cry, and Consolability). Whenever possible the child's self-report should be used to assess pain. However, there are situations where this may not be possible, for example, in infants or in those with cognitive impairment or language difficulties. In such instances, the FLACC tool [19] should be used (Table 3). FLACC is a behavioural assessment tool with five categories where each category scores on a scale of 0–2, which results in an overall score of between 0–10. The child should be observed for 2–5 minutes and their body activity, face, and cry noted according to the scale. If necessary, the health professional should attempt to console the child. The child's pain score should be assessed and recorded at regular intervals, especially before and after analgesia or after nonpharmacological intervention. The FLACC tool has been adequately validated in areas such as paediatric theatre recovery, and oncology and paediatric intensive care units [20].

6.2. Faces/Ladder Scale. Studies have found that children as young as three years old can communicate and make judgements about their pain [21]. Wong-Baker FACES Pain Rating Scale is recommended for children ≥ 3 years of age [22]. The faces/ladder scale should be explained to the child, that is, that the smiling faces indicates no pain whilst the distressed face indicates severe pain (Figure 3). The wording down the centre of the ladder can be read by the older child. What the child states as their pain score—either from using the numbers or faces on a scale of 0–10—should then be documented.

7. Pharmacological Treatments

The ideal analgesic agent in a child with burn would be the one with the following characteristics: (i) easy to administer, (ii) well tolerated, (iii) produces rapid onset of analgesia with a short duration of action, and (iv) has minimal side-effects to allow rapid resumption of activities and oral intake. Various routes such as parenteral, oral, and intranasal route are available for administration of analgesia. In the acute setting, drugs, preferably, should be given by IV route. However, intranasal route is a sound alternative. Potential

Table 3: Scoring system for infants, young children, cognitively impaired children, anxious children, and any child unable to use faces ladder. Paediatric Pain Assessment: FLACC scale. This pain assessment tool can be used in children <4 years and those with cognitive impairment or unable to use the "FACES" ladder.

	FLACC Scale		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly normal position	Squiring, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or sleep)	Moans and whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractable	Difficult to console or comfort

Each of the five categories Face (F), Legs (L), Activity (A), Cry (C), Consolability (C), is scored from 0–2. This results in a total score of 0–10.

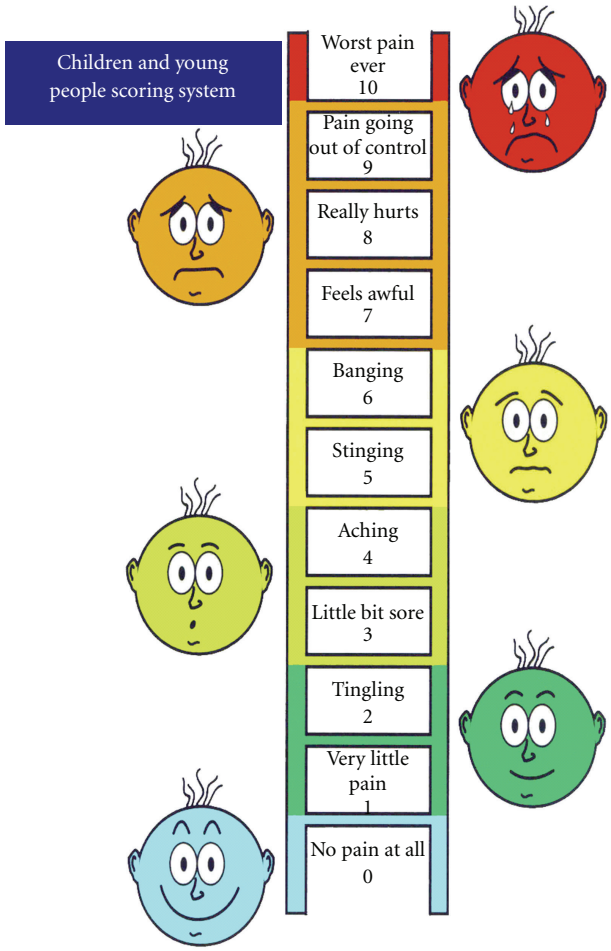

Figure 3: Paediatric Pain Assessment: FACES ladder. Useful in children ≥4 years of age.

advantages of intranasal route compared with parenteral or oral administration include avoidance of painful injection, avoidance of risks associated with IV access, rapid onset and titration to effect, and good bioavailability [23]. Although small trials suggest that intranasal opioids play a useful role in pain management, large clinical trials with Level 1 evidence is required to identify its advantages, safety, and acceptability.

8. Specific Analgesics

Paracetamol (Acetaminophen). continues to be a useful first-line analgesic in minor and superficial burns. Paracetamol, a p-aminophenol derivative that exhibits analgesic and antipyretic activity [24], does not possess anti-inflammatory activity. Paracetamol acts both centrally and peripherally to produce analgesia. The IV route allows rapid passage of paracetamol in the systemic circulation leading to a rapid onset and faster distribution resulting in higher plasma concentration as compared with oral and rectal route. The IV preparation is a good adjunct along with opioids in the acute setting. Used along with opioids, it has a synergistic effect. Meyer et al. [25] described the use of paracetamol in the treatment of background pain in children ($n = 395$) after acute burn injury and found that in 50% of these children, especially the youngest and those with smaller burns, did not require any morphine.

NSAIDs. have analgesic and anti-inflammatory properties. Their mechanism of action is via nonselective inhibition of prostaglandin and thromboxane synthesis via inhibition of the cyclooxygenase enzyme (inhibits platelet aggregation and renal prostaglandin production). Judicious use of NSAIDs can be opioid sparing [26] but their side effects can be a limiting factor [27].

Opioids. provide analgesia via a variety of central and peripheral opioid receptors, particularly via the "mu" and "kappa" receptors.

Morphine. has the lowest lipid solubility of all the opioids, which accounts for its slow entry into the brain and subsequent delayed onset of clinical effect. Its peak analgesic

effect occurs 10–20 minutes after IV administration of a bolus dose of 0.1 mg/kg. While administering morphine as continuous infusion, younger children should be managed in a High Dependency or Intensive Care area. (Dosage for children <6 months of age is 0–12.5 μg/kg/hour and for children >6 months of age is 0–25 μg/kg/hour.) Rate and dosage should be adjusted according to child's pain and sedation scores.

Morphine PCA can be used in children $\geq$5 years who have the ability to understand the workings of a PCA [28]. Bolus dose is usually 20 μg/kg with a lockout interval of five minutes and background infusion of 4 to 8 μg/kg/hour. In children who have difficulty pressing the "demand" button, this modality may be inappropriate. In this instance, it can be delivered by NCA (nurse controlled analgesia)—usually in a high dependency setting. Bolus dose is 20 μg/kg with a background infusion of 0–20 μg/kg/hour and a lock out interval of 20–60 minutes. Criteria for administration of a bolus dose are if the pain score is seven or more on a scale of 0–10 and the sedation score no greater than one. Respiratory rate should be above minimum rate for the age of the child and oxygen saturation must be monitored by continuous pulse oximetry.

Oxycodone. is a new semisynthetic opioid with a better bioavailability than morphine, and thus an effective alternative. Sharar et al. [29] compared oral transmucosal fentanyl citrate (OTFC, 10 μg/kg) and oral Oxycodone (0.2 mg/kg) in 22 paediatric outpatient wound care procedures and concluded that OTFC and oral Oxycodone are safe and effective analgesics in the setting of monitored outpatient wound care in children.

Fentanyl. a synthetic, potent narcotic analgesic with potency up to 100 times that of morphine, is highly lipid soluble and has a rapid onset of action (1-2 min). The duration of analgesia is about 60 minutes. Possible side effects include hypotension, bradycardia, apnoea, chest wall spasm, muscle rigidity, and respiratory depression.

Fentanyl lozenges [30] are a solid formulation of fentanyl citrate on a stick in the form of a lollipop that dissolves slowly in the mouth for transmucosal absorption. Doses around 15–20 μg/kg seem satisfactory and provide rapid onset (10 min) of pain relief [31]. In children, 10 μg/kg is equianalgesic to Oxycodone 0.2 mg/kg [29].

Intranasal fentanyl has been shown to be equivalent to oral morphine in the provision of analgesia for burn wound dressing changes in children. Intranasal fentanyl may be a suitable analgesic agent for use in paediatric burns dressing changes either alone or in combination with oral morphine as a top up agent [23].

Alfentanil. is a short acting opioid with the peak effect reached within a minute. It undergoes hepatic metabolism to inactive metabolites that are excreted via the kidneys; it may thus be a safer option in children with impaired renal function. Change of burn dressings may require strong analgesia for a short duration of time. Studies have shown that Alfentanil can be used for this purpose as target controlled infusion [7, 8] or as a PCA [32].

Remifentanil. is a novel; ultrashort-acting esterase metabolised synthetic opioid. It is a selective "mu" opioid agonist and has an ester linkage rendering it susceptible to rapid metabolism by nonspecific blood and tissue esterases. Adult pharmacokinetic studies have shown a rapid onset of peak effect (blood-brain equilibration time: 1.2–1.4 min), a short duration of action independent of the duration of infusion (context sensitive half time: 3 min), and rapid clearance (40 ml kg^{-1} min^{-1}). Remifentanil has been used for postoperative analgesia in neonates and has been found to have a similar pharmacological profile in neonates to that of older children and adults. Le Floch et al. [33] identified Remifentanil on its own to be a useful agent for undertaking dressing changes in spontaneously breathing, nonintubated burn patients. Due to its pharmacological profile of rapid onset and ultrashort duration of action, it is well suited for procedure related analgesia.

Methadone. is a synthetic opioid that provides analgesia not only as mu-opioid agonist but also acts as antagonist at the N-methyl-D-aspartate (NMDA) receptors. It has got excellent bioavailability and a prolonged duration of action. It has been found both safe and effective in management of paediatric burns [34].

Ketamine. acts both in the central and peripheral nervous system. It exerts strong adjuvant analgesic properties by inhibiting the binding of glutamate to the NMDA-R receptor. This mode of action is different to the action of opioid drugs such as morphine and therefore the use of ketamine in combination with morphine can improve pain relief. Ketamine in combination with morphine reduces the need for high dose of morphine to be used [35] and therefore minimises side effects [36]. Ketamine was extensively used during burn dressing changes [37] but its psychological side-effects have limited its use. All children on ketamine infusion must have a ketamine infusion observation chart and be monitored with continuous pulse oximetry.

8.1. Alpha 2 Adrenergic Antagonists. Maintaining appropriate sedation and analgesia in children with burns can be quite challenging and often requires high doses of analgesics and anxiolytics because tolerance develops quickly. Escalating doses of opioids and benzodiazepines provide little additional benefit while increasing the incidence of side effects. Clonidine acts by augmenting descending inhibitory spinal cord pathways. The dose used in paediatric practice is 1–3 μg/kg three times a day orally or IV [38]. Clonidine is known to reduce the need for morphine in the management of postoperative pain. The addition of clonidine to the pharmacological treatment of burn pain offers a possible adjunct to the standard opioid and benzodiazepines regimen. When clonidine is no longer required the dose must be reduced gradually to avoid withdrawal and rebound hypertension. Dexmedetomidine is a novel alpha 2-adrenergic agonist that

provides sedation, anxiolysis, and analgesia with much less respiratory depression than other sedatives [39].

8.2. Antidepressants and Anticonvulsants. These may be beneficial to improve the sleep patterns. Antidepressants appear to enhance opiate-induced analgesia while anticonvulsants are useful in the treatment of sympathetically maintained pain following burns.

Amitriptyline. a tricyclic antidepressant, acts by augmenting the descending inhibitory pain pathways in the spinal cord. When used in low doses, it has an established role in the management of neuropathic pain [38]. It has been shown to be effective in phantom limb pain in children [40].

Gabapentin. has established efficacy in the reduction of burn-induced hyperalgesia. It binds to presynaptic calcium channels involved in pain hypersensitivity and indirectly inhibits NMDA receptor overactivation [41]. Gabapentin is started at 10 mg/kg and titrated up to 40–50 mg/kg/day [38]. Recent studies have found gabapentin [42] to be useful in the management of neuropathic pain following burn injury but further research is required to define its precise usage. On a different role, Gabapentin has also been found to be effective in the management of itch in children (common after burn injury) unresponsive to simple anti-itch medications such as chlorpheniramine and trimeprazine [43].

Entonox. a homogenous gas made of 50% nitrous oxide and 50% oxygen, is a potent analgesic that may be used for changing the burn dressing in some conscious children [44]. It is self-administered using a demand apparatus that safeguards against inadvertent overdose. Entonox is quick acting due to the insoluble nature of nitrous oxide and wears off rapidly once administration ceases. It can either be used alone or in conjunction with other analgesics. Entonox is contraindicated in situations such as decreased consciousness, pneumothorax or air embolism (where expansion of the air trapped within the body might be dangerous), or gross abdominal distension.

8.3. Local Anaesthetics. These agents act by inhibiting sodium ion flux across the axonal membrane and prevent the nociceptors signalling pain reaching the central nervous system. Addition of adrenaline (1 : 200,000) produces vasoconstriction and decreases systemic absorption, thus leading to prolonged duration of action. Techniques include local infiltration and specific nerve blocks (usually performed under sedation-analgesia). IV infusions of lignocaine have been shown to be effective in alleviating neuropathic pain, especially if there is nerve damage [45]. However, a Cochrane review by Wasiak and Cleland [46] did not demonstrate any conclusive effect in patients with burns.

8.4. Challenges due to Pharmacokinetic and Pharmacodynamic Response to Drugs. Children with burns often show an altered pharmacokinetic and pharmacodynamic response to drugs as a result of physiological/pathological changes due to altered haemodynamics, protein binding and/or increased extracellular fluid volume, and possible changes in glomerular filtration. Hypovolaemia and depressed myocardial function leads to decreased organ and tissue perfusion, delaying absorption of oral drugs. During the hyper metabolic phase, there is increased blood flow with a rapid onset of inhaled and IV agents. Plasma albumin is decreased and this results in an increase in the free fraction of protein bound drugs. Increase in $\alpha 1$ acid glycoprotein leads to a decrease in free fraction of drugs bound to this molecule, for example, muscle relaxants. There is an increased requirement of opioids and sedatives. Tachyphylaxis and tolerance develop quickly.

9. Non Pharmacological Treatments

Various nonpharmacological strategies such as education (understanding of the condition), distraction, relaxation, cutaneous stimulation, acupuncture, bio-feedback, hypnosis, imagery, cognitive, and behavioural techniques can be employed to treat the pain associated with burns. A good understanding of the procedure helps children to control their anxiety cognitively, thus, helping to gain a level of pain relief. This not only corrects misconceptions and decreases anxiety but also allows children to play an active role in the procedure and to benefit fully from pain-reducing strategies. Distraction techniques such as talking, singing, praying, describing photographs, listening to music, and playing games reduces the perception of pain by stimulating the descending control system that leads to painful stimuli being transmitted to the brain [47]. Used in conjunction, these modalities help reduce analgesic requirements [48].

10. Conclusion

The experience of pain varies greatly between children with burn injuries. This may be related to physical factors such as size and depth of burn, as well as to the psychological and emotional support provided by the family. Accurate assessment of pain and an evaluation of the effectiveness of analgesia are vital. Various tools are available to aid in the assessment of pain in children who may have difficulty in communicating their needs. A wide variety of pharmacological interventions exist that range from simple paracetamol to sedating anaesthetic drugs. Many times, a combination of these is required to achieve robust analgesia in treating both background and procedural pain. Non-pharmacological treatments also play a role in reducing analgesic requirements. Psychological strategies should be considered to be helpful adjuncts rather than a substitute to conventional analgesics.

In summary, healthcare professionals need to acknowledge and appreciate the significance of pain associated with burn injuries in children and be aware of the various pharmacological and non-pharmacological options. Judicious use of the drugs tailored to meet the needs of individual children coupled with a multidisciplinary approach is frequently necessary to achieve optimal outcomes.

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Hindawi Publishing Corporation
International Journal of Pediatrics
Volume 2010, Article ID 975313, 4 pages
doi:10.1155/2010/975313

Clinical Study

Development of a Pain Management Protocol for a Paediatric Ward in the Gambia, West Africa

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Received 2 December 2009; Accepted 31 May 2010

Academic Editor: Sharon Elizabeth Mace

Despite recent advances in our understanding of paediatric pain and its management, pain continues to be undertreated globally, particularly in children and in low income countries. This article describes the development of a paediatric analgesia and sedation protocol, tailored to the specific setting of the Medical Research Council (MRC) paediatric ward in the Gambia, West Africa. An iterative process was used throughout development, with inputs from the medical literature, local providers, and pain experts, incorporated to ensure a safe, effective, and locally appropriate protocol. We demonstrate that evidence-based published guidelines, can and should be adapted to allow for optimal pain management given the resources and capabilities of specific health care settings. It is hoped that the process and protocol described here, will not only help to improve care on the MRC ward, but serve as an example to others working toward improving pain management in similar health care settings.

1. Introduction

Despite significant advances in our understanding of paediatric pain and the publication of pain management guidelines by several leading paediatric bodies in recent years, multiple studies and reviews show that pain in children continues to be poorly managed [1]. As MacLean et al. (2007) note, "there remains a gap between what we know to be effective, easily implemented pain management strategies, and what is actually practiced" [2]. Given these findings are based on their review of pain management practices in a paediatric teaching hospital in a high income country, it is perhaps not surprising this gap is larger in low income countries where resources, in their broadest sense, are more constrained.

Some barriers to managing a child's pain are common to a wide variety of health care settings, such as lack of provider training in the recognition, assessment and management of pain, and attitudes and beliefs regarding pain and its management. Other barriers likely play a significant role mainly in low income countries where resources in terms of manpower, equipment, and medications, are in chronic short supply and must be balanced across the competing needs of patients presenting to providers practicing in these settings. Despite these issues, given the current state of knowledge in this area, and the wide variety of options now available for managing paediatric pain, many of these barriers can be overcome through adaptation of published guidelines to address the unique needs and barriers of specific health care settings.

This paper describes the development of a paediatric analgesia and sedation protocol, tailored to the specific setting of the Medical Research Council (MRC) paediatric ward in the Gambia, West Africa. Although a combined paediatric and adult protocol was ultimately developed, only the paediatric portion is reported here. For clarity of presentation, the protocol development process will be described in 3 steps. However, it is important to note, that an iterative process was employed beginning with a recognized need to improve pain management expressed by local clinical staff, and with feedback from local providers sought and incorporated throughout the development process.

2. Methods

2.1. Local Consultation and Capacity Assessment. As noted above, protocol development began with an expressed desire for a pain management protocol tailored to the MRC paediatric ward, to facilitate efforts by clinical staff toward improving pain management. As a first step, key local informants including the senior clinician of the hospital, the matron, and another senior nurse, were interviewed to gain a comprehensive understanding of the hospitals resources, current practices and staff level of training, medication availability, and cost implications. Two important considerations emerged from this consultation process, which were shortage of airway support capabilities and limited staff training in pain assessment and monitoring.

To further assess the airway capabilities on the ward, a survey of equipment was undertaken. During this process, sufficient airway equipment was located to organize two complete airway kits, which included oral airways, bag-valve-masks, intubation medications and equipment. Discussions with physician and nursing staff, revealed both had little training or experience in pain management. For this reason it was felt that a more directive and structured protocol, with a strong educational component to accompany roll out of the protocol was needed.

2.2. Knowledge Gathering. The second step in development of the protocol began with a review of published paediatric analgesia and sedation guidelines, the evidence base for their development where possible, and consultation with experts in paediatric sedation and analgesia. As most published guidelines were developed in and for high income health care settings, during the review process and again in consultation with key local informants a list of issues relevant to paediatric pain management on the MRC ward was identified. Concerns were identified with respect to several unique attributes of the Gambian population, specifically the relative high prevalence of hemoglobinopathies [3, 4] and undernutrition particularly in the first 2 years of life [5]. It was notable that despite the importance of cultural in perceptions and beliefs with respect to pain, no cultural issues were identified as important to pain management efforts in this setting.

Hemoglobinopathies, like sickle cell anemia and glucose-6-phosphatase deficiency (G6PD), are relatively common in the Gambia [3, 4] and present challenges for managing pain. Many established guidelines and experts recommend against sedation in sickle disease patients, and sickle trait patients with low oxygen saturations, unless anaesthesia is in attendance. Given anaesthesia support is not available at the MRC, these were included as absolute contraindications to sedation in the MRC protocol. Of additional concern is the potential for local anaesthetic induced methemoglobinemia. For a variety of reasons, including effectiveness, hemodynamic safety requiring no special monitoring, and availability of inexpensive preparations, local anaesthetics are ideal for management of brief painful procedures. While a variety of local anaesthetics have been reported to induce methemoglobinemia [6], reported cases have occurred mainly in very young infants or where excessive quantities of topical anaesthetic are used [7]. Although an uncommon complication and relatively easily managed in the general population with methylene blue, treatment of methemoglobinemia is significantly more complicated in individuals with G6PD deficiency where methylene blue can cause acute hemolysis and more intensive care, including exchange transfusions, may be required. Given the high incidence of G6PD in the Gambian population, cost and time required for testing, and potential for this serious complication whose treatment is beyond the resource capacity of the setting, use of topical anaesthetics was strictly limited to children at least 6 months of age and within recommended dosing guidelines. Guidelines and experts generally recommend 3 months of age corrected for prematurity; however, given the prevalence of under-nutrition and difficulties in accurately assessing both age of gestation and date of birth in this setting, the age restriction was broadened to ensure minimum safety guidelines were observed.

2.3. Protocol Circulation and Feedback. Based on the findings of the first two stages of protocol development outlined above, a draft protocol was created and circulated to key local informants and an expert in paediatric pain management for feedback and amendment. Perhaps not surprising considering the iterative nature of the development process, with the exception noted below, no major changes were suggested. At this stage the draft appeared as a numbered list of process steps with considerations at each step outlined within the section. For example, within the analgesia section, all available options were listed with their indications, contraindications, and dosages. While this format was modelled after other published protocols, and meant to emphasize options and provider choice, feedback from key local informants suggested that a more limited and algorithmic approach, presented as a flow chart would facilitate adoption of the protocol, particularly early on in the course of the campaign to improve pain management.

Based on this feedback the protocol was reworked into a flow chart (see Figure 1), with the original protocol with small amendments included as a detailed reference or guide. The amended draft was again circulated to key local informants and the pain management expert, with no further revisions suggested.

As a final step in the development of the protocol, the protocol was presented to the physician group at academic rounds, and at a staff meeting to the nursing and health attendant staff, with minor changes to the protocol incorporated as a result of feedback from these sessions.

3. Results and Discussion

In addition to the final product, that is, the paediatric pain management protocol tailored to the MRC ward, other benefits were gained through the process of development. As a result of the equipment survey, two airway kits were created and placed together with other basic resuscitation equipment into a strategic location within the unit for ready access.

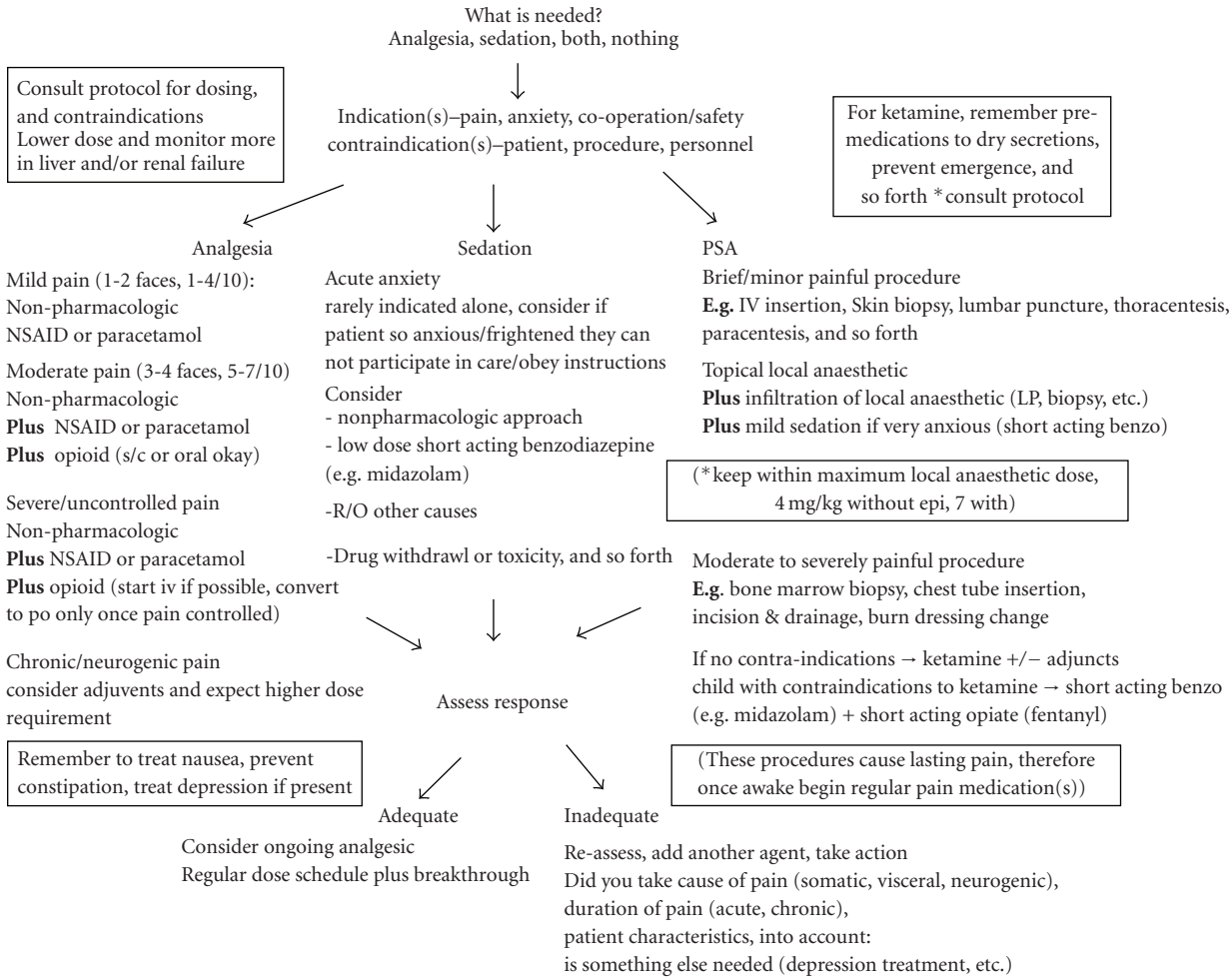

Figure 1: Paediatric pain management flow chart.

Equally important is early evidence that through the educational and feedback sessions, further interest in improving patient care was fostered among clinical staff. As one physician reported "I encountered a case today where I would normally not have considered pain management, but after the session the other day, I decided I better do something." As Clemmer and Spuhler (1998) have argued, "the purpose of creating protocols is greater than reducing practice variation, it also creates new paradigms and changes the culture in which health care is delivered, with the protocol itself designed to be transient, and the development process and the changes it produces, more important than the product itself" [8]. It is hoped this was only the first of many such encounters.

However, to ensure successful implementation of the protocol and ongoing improvements in paediatric pain management, further steps are needed. Ongoing education of clinical staff, particularly early in the implementation process and as new staff are hired, is essential to ensure safe and appropriate pain management procedures. Intermittent reassessment and revision based on experiences in using the protocol is needed to allow for adaptation as the needs of the patients served and the resources and options available change.

4. Conclusion

Despite some progress in recent years, pain continues to be undertreated globally, particularly in children [1], and particularly in low income countries [9]. Published guidelines based on best available evidence, can and should be adapted to allow for optimal pain management given the resources and capabilities of a given health care setting. It is hoped that the development process and protocol described here will not only help to improve care on the MRC ward, but serve as an example to others working toward improving pain management in similar health care settings.

Acknowledgment

The authors thank Dr. S. Ratnapalan for her helpful comments, support, and guidance throughout the process of developing this protocol.

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Hindawi Publishing Corporation
International Journal of Pediatrics
Volume 2010, Article ID 934298, 16 pages
doi:10.1155/2010/934298

Review Article

Professional Skills and Competence for Safe and Effective Procedural Sedation in Children: Recommendations Based on a Systematic Review of the Literature

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Received 30 December 2009; Accepted 7 May 2010

Academic Editor: Keira Mason

Objectives. To investigate which skills and competence are imperative to assure optimal effectiveness and safety of procedural sedation (PS) in children and to analyze the underlying levels of evidence. *Study Design and methods*. Systematic review of literature published between 1993 and March 2009. Selected papers were classified according to their methodological quality and summarized in evidence-based conclusions. Next, conclusions were used to formulate recommendations. *Results*. Although the safety profiles vary among PS drugs, the possibility of potentially serious adverse events and the predictability of depth and duration of sedation define the imperative skills and competence necessary for a timely recognition and appropriate management. The level of effectiveness is mainly determined by the ability to apply titratable PS, including deep sedation using short-acting anesthetics for invasive procedures and nitrous oxide for minor painful procedures, and the implementation of non-pharmacological techniques. *Conclusions*. PS related safety and effectiveness are determined by the circumstances and professional skills rather than by specific pharmacologic characteristics. Evidence based recommendations regarding necessary skills and competence should be used to set up training programs and to define which professionals can and cannot be credentialed for PS in children.

1. Introduction

Invasive diagnostic procedures are a part of daily pediatric practice. Many of these procedures are painful, stressful, and impossible to perform without immobilizing the patient. Therefore, procedural sedation (PS) is required to enable these procedures to be performed. PS can be defined as the use of sedative, analgesic, or dissociative drugs in order to provide anxiolysis, analgesia, sedation, and motor control during painful or unpleasant procedures [1].

Since anesthesiologists cannot cover the growing demand for PS, nonanesthesiologists have organized their own PS strategies [2, 3]. Historically, this resulted in a wide range of drugs and techniques for use in pediatric PS, involving a large variance of sedation levels, sedation level predictability, effectiveness, and associated risks. However, by the end of last century, PS by nonanesthesiologists was increasingly criticized by anesthesiologists for neglecting transparency and standard safety precautions. There are strong indications that within this criticism, a source could be found for PS-related accidents [4, 5]. About a decade ago, dedicated nonanesthesiology specialists, who recognized the urgent need to improve the safety and quality of PS in children, joined the initial criticism by anesthesiologists, pointing at the safety problems of PS by the untrained. In order to prevent PS-related tragedies, guidelines on PS were published [1, 6–10]. In summary, these guidelines specify safety precautions that include the assessment of the risk of sedation prior to PS, informed consent, guidelines on proper fasting status, appropriate monitoring, recovery standards, appropriate rescue facilities, and specific professional skills and competence. Generally recommended skills and

competence are: the ability to perform a preprocedural risk analysis, practical knowledge and experience of applied sedatives, the ability to implement the necessary monitoring and surveillance, the ability to recognize and interpret sedation levels, and the ability to immediately recognize and adequately treat any unwanted side effects or complications, particularly hypoventilation and airway obstruction. These recommendations are mainly based on indirect evidence, expert opinion, "common sense", and widely accepted safety rules for general anesthesia. The adoption of a uniform and systematic practice is associated with a significant reduction in adverse events during anesthesia [11]. Similarly, there is strong evidence that implementation of published guidelines leads to safer and more effective PS [12–15].

However, despite the availability of guidelines, PS practice is still unsafe in many settings and adherence to guidelines among nonanesthesiologists has been reported to be low [16, 17]. It has been argued that guidelines on PS produced by consensus between anesthesiologists (rather than on evidence-based guidelines by the clinicians themselves) have caused confusion and variation in practices [3].

Recent papers focus increasingly on the duty to deliver effective PS, not only from a procedural point of view (i.e., guaranteeing predictable procedural success and timing) but also from a patient's perspective (i.e., achieving optimal procedural comfort and minimizing procedural stress and failure) [18, 19]. Drugs traditionally used for PS (e.g., chloral hydrate, midazolam, barbiturates, and lytic cocktails) are associated with a substantial risk of procedural failure, discomfort, extended sedation times, and deeper sedation levels than intended with associated safety risks [20, 21]. Patient comfort is currently considered a primary goal of procedural sedation [22]. It has been argued that young children who are anticipated to suffer from substantial emotional distress need a titrated form of PS, including deep sedation, in order to have a successfully completed procedure, and to avoid major psychological trauma to the child, the family, and healthcare staff [23, 24]. The application of forced immobilization by physical restraint is increasingly considered as inhumane and unacceptable in nonlifesaving procedures [22, 25].

We searched the literature for available evidence on essential professional skills and competence required for effective and safe PS in children. Results were used to define evidence-based recommendations on the skills and competence a professional entrusted with PS should minimally possess, in order to be able to perform PS in children safely and effectively.

2. Methods

Literature was searched and selected by a multidisciplinary panel of the Dutch Institute for Health Care Improvement CBO, involved in the development of an evidence-based guideline on PS using the Evidence-Based Guideline Development (EBRO) methodology. Systematic searches were done in Medline, Cochrane Library, and Embase, using the Medical Subject Heading (MESH) search terms "Conscious sedation/all", "Moderate sedation/all", and "Deep sedation/all" and the free search-terms "sedation", "pediatric sedation" and "procedural sedation", in title or abstract. The search was limited to papers published between 1993 and March 2009, in 4 languages (Dutch, English, French, and German) and to human subjects aged 0–18 years. Results were systematically and repeatedly combined with the MESH-term "Drug Toxicity" and the MESH-terms of drugs, drug combinations, and drug groups available for PS (chloral hydrate, (lytic) cocktails, promethazine, chlorpromazine, pentobarbital, thiopental, midazolam, fentanyl, meperidine, ketamine, propofol, dexmedetomidine, remifentanil, nitrous oxide, opioids, benzodiazepines, antihistaminic, antipsychotics, barbiturates, nitrous oxide, and anesthetics). For all drugs, specific searches were done using the MESH subheading "*adverse effects*". Additional combined searches were done using search terms for safety, effectiveness, and non-pharmacologic methods (hypnosis, distraction techniques, and play therapy). Textbooks and reference tables were systematically searched for additional papers.

Before inclusion in the pool of studies to be reviewed, all papers obtained were analyzed by the multidisciplinary panel for relevance and accuracy of definitions of safety and effectiveness.

In accordance with the EBRO methodology, selected papers were classified according to their methodological quality and strength of evidence: A1: systematic review including at least two independent A2-level studies, A2: randomized, double blinded comparative clinical trial of good quality and substantial size, B: comparative study, including retrospective cohort study and case-controlled trial, but not having all characteristics of an A2 study, C: noncomparative studies, and D: expert opinion. Findings from literature were summarized in conclusions. These conclusions were classified in 4 levels. Level 1: conclusion based on one A1 study or on at least two independent A2 studies, level 2: conclusion based on one A2 study or on at least two independent B studies, level 3: conclusion based on one B or C study, and level 4: conclusion based on expert opinion only. Finally, on the basis of the conclusions and remaining considerations (nonclassified) recommendations were formulated.

3. Results

3.1. Requisite Skills and Competence to Guarantee Optimal Safety. Many studies were found claiming the safety of all kinds of PS drugs in a variety of settings but usually in a limited series of patients. However, given an estimated incidence of severe adverse events of about 1/10000, the majority of these studies are insufficiently powered to prove such conclusion [18]. Most studies use vague definitions for the adverse reactions they report and consider the absence of directly life-threatening events as synonym for "safe". In more recent observational studies on PS, the study setting is usually a strictly controlled, well-equipped, well-trained,

and dedicated sedation team, which may differ appreciably from common settings in many practices around the world. Finally, well-designed controlled prospective studies in nonanesthesiologists analyzing the relationship between the level of professional skills/competence and the safety of PS are nonexistent. Therefore, evidence on this subject must be gathered in an indirect way. To do so, the following rationale was followed. At first, published critical analysis of PS-related incidents might elucidate the requisite competence and skills for PS. Next, the level of skills and competence professionals must achieve with regard to safety are likely to be determined by (1) the probability that a medicine may have undesirable adverse effects which require specific recognition and treatment, and (2) the predictability of the depth and duration of sedation of a medicine. The latter is important since unexpected deep sedation is associated with a higher rate of adverse events [21]. Out of all retrieved studies reporting PS-related adverse events, only those were selected for this systematic paper that reported the incidence of adverse events in large numbers of patients (>±1000), or that had studied adverse events following the use by nonanesthesiologists of the anesthetics propofol, ketamine, dexmedetomidine, remifentanil, and nitrous oxide.

3.1.1. Retrospective Critical Incident Analysis of PS-Related Adverse Events and Outcomes. In 2000, Coté published, in two separate papers, a retrospective critical incident analysis of adverse sedation events in pediatrics, as reported to the American Food and Drug Administration between 1969 and 1996. 95 incidents were reported, 51 resulting in death, 9 in permanent neurological injury, and 21 in prolonged hospitalization. Significant contributing factors were: "out of hospital" locations, inappropriate monitoring of physiological parameters, inadequate resuscitation skills, inadequate presedation medical evaluation, and inadequate recovery procedures. No particular medication was associated with a higher risk, except that overdosing and drug interactions (particularly when 3 or more drugs were used) were associated with mortality [4, 5]. Although the safety profile and the margins of safety vary among drugs, Coté showed that PS-related safety is determined by circumstances and professional skills, rather than by specific pharmacological characteristics. Professionals who do not have the requisite competence to recognize and treat the potential PS-related complications constitute a significant risk factor for the occurrence of fatal complications or complications causing permanent harm to the patient (*Level 3 conclusion* [4, 5]).

3.1.2. Reported Data on PS-Related Adverse Events. The studies stated below are summarized in Tables 1 and 2.

Adverse Effects of Commonly Used Nontitratable Sedatives. A retrospective study by Sanborn et al. of 16467 sedations during imaging procedures in children using chloral hydrate, midazolam, fentanyl, or pentobarbital found 70 (0.4%) respiratory incidents: desaturation only ($N = 58$), aspiration ($N = 2$), and airway obstruction requiring airway intervention ($N = 10$). The main risk factors were an underlying respiratory problem and the use of more than one sedative [27].

A prospective study by Malviya et al. in 1140 children, of which the majority were sedated with chloral hydrate for diagnostic imaging, showed a 5.5% incidence of respiratory complications leading to oxygen saturation of <90%: respiratory depression (4.7%), airway obstruction (0.6%), and apnea (0.17%). The risk of complications was significantly greater for more seriously ill children and for children less than one year old [28].

A risk analysis by Hofmann et al. based on prospectively collected data of 950 sedations using chloral hydrate, midazolam, fentanyl, pentobarbital, ketamine, or cocktails of 3 or more agents, identified 27 sessions (2.8%) in which a serious adverse event occurred: deep desaturation ($N = 9$), airway obstructions ($N = 5$), apneas ($N = 3$), aspirations ($N = 2$), hypotension, bradycardia ($N = 2$), or excessively deep or prolonged sedations ($N = 6$). Significant risk factors were the absence of a systematic risk assessment, a failure to follow safety guidelines, deep sedation, the simultaneous use of multiple agents, and the use of chloral hydrate [13].

A prospective international multicentre study of 30037 sedations by specifically trained professionals working in dedicated PS teams reported low incidences of major adverse events: desaturation (SatO2 < 90%) 1.57%, stridor 0.04%, laryngospasm 0.04%, apnea 0.24%, excessive airway secretions 0.41%, and vomiting 0.47%. The attending professional could adequately treat all complications. Cardiopulmonary resuscitation was necessary in one case. Anesthesiologists (19%), emergency physicians (28%), and intensivists (28%) administered the sedations. The most frequently used sedatives were propofol (50%), midazolam (27%), ketamine (14%), chloral hydrate (12%), pentobarbital (13%), and opiates (10%) [36].

Mason et al. reported in three separate comparative studies the adverse events of oral and intravenous (IV) pentobarbital used for PS in diagnostic imaging or nuclear medicine. Potentially severe adverse events like oxygen desaturation occurred extremely rare (<1%). Compared to oral chloral hydrate and intravenous pentobarbital, oral pentobarbital is associated with significantly less desaturations (resp., 1.6% versus 0.2% and 0.9% versus 0.2%) [35, 38, 39].

A retrospective study by Roback et al. in 2500 successive children undergoing PS in an emergency department (ED) showed that the incidence of respiratory complications depended on the medication used: 5.8% for midazolam, 6.1% for ketamine, 10% for ketamine + midazolam, and 19.3% for midazolam + fentanyl [33].

A prospective study by Newman et al. of 1341 PS sessions in children in an ED showed an incidence of serious complications of 11.9% (96,2% hypoxia, 1,3% hypotension, and 2,5% stridor). 92% of the complications occurred during the actual procedure, whereas the rest occurred after the procedure up to 40 minutes after the last dose of sedative. The risk of complications depended strongly on the medication used: midazolam 1.4%, ketamine + midazolam + atropine 9.8%, and midazolam + fentanyl 21.5% [34].

Another ED study by Pena and Krauss of 1180 successive children, using intravenous medicines (midazolam +

Table 1: Overall conclusions regarding the relation between professional competence/skills and PS-related safety.

Nr	Conclusion	Quality level
(1)	Serious PS related adverse events occur *more frequently*	
	(I) *In children with an underlying disease.*	Level 1
	(A1) Green et al. 2009 [30]	
	(B) Sanborn et al. 2005 [27], Cravero et al. 2009 [26]	
	(C) Malviya et al. 1997 [28], Vespasiano et al. 2007 [29]	
	(II) *If multiple sedatives are used*	Level 1
	(A1) Green et al. 2009 [30]	
	(B) Hoffman et al. 2002 [13], Pitetti et al. 2003 [32], Sanborn et al. 2005 [27], Cravero et al. 2009 [26]	
	(C) Gall et al. 2001 [31]	
	(III) *In young children*	Level 1
	(A1) Green et al. 2009 (<2 years) [30]	
	(B) Cravero et al. 2009 (<6 months) [26]	
	(C) Malviya et al. 1997 (<1 year) [28], Gall et al. 2001 (<1 year) [31]	
	(IV) *In certain drugs compared to others*:	
	(IV.1) The combination of a benzodiazepine with an opiate (e.g., midazolam + fentanyl) is associated with a higher risk of respiratory complications (21–23%) compared to the use of midazolam alone or ketamine with midazolam.	Level 2
	(A2) Yildizdas et al. 2004 [8]	
	(B) Pitetti et al. 2003 [32], Roback et al. 2005 [33], Newman et al. 2003 [34]	
	(IV.2) Oral pentobarbital is associated with less adverse events compared to oral chloral hydrate	Level 3
	(B) Mason et al. 2004 [35]	
	(IV.3) In comparison with ketamine, midazolam and ketamine + midazolam, midazolam + fentanyl and propofol generate a higher risk of hypoventilation and desaturation.	Level 2
	(A2) Yildizdas et al. 2004 [8]	
(2)	Serious PS-related adverse events occur *less frequently* if specifically trained professionals working in dedicated teams perform sedation according to international guidelines.	Level 2
	(B) Barbi et al. 2003 [12], Hoffman et al. 2002 [13], Cravero et al. 2009 [26]	
	(C) Vespasiano et al. 2007 [29]	

fentanyl $N = 391$, midazolam $N = 67$, fentanyl $N = 21$, ketamine $N = 40$, pentobarbital $N = 93$, lorazepam $N = 9$, or midazolam + morphine $N = 1$), intramuscular ketamine ($N = 180$), oral medicines (midazolam $N = 62$, ketamine $N = 2$, chloral hydrate $N = 122$, diazepam $N = 1$, and lorazepam $N = 1$), rectal chloral hydrate $N = 4$), intranasal medicines (midazolam $N = 3$, midazolam + sufentanil $N = 25$), and nitrous oxide ($N = 168$), showed an overall complication incidence of 2.3% ($N = 27$). The following complications occurred: desaturation < 90% requiring intervention ($N = 10$), apnea ($N = 1$), larynx spasm ($N = 1$), bradycardia ($N = 1$), stridor with vomiting ($N = 1$), and 1 child started to vomit while being ventilated with a mask/bag applied to treat desaturation. There was no significant difference in the incidence of adverse events between the different sedation medicines [37].

A prospective study by Pitetti et al. of 1244 sedations in 1215 children in an ED showed an incidence of adverse events of 17.8% including desaturation ($N = 178$), stridor ($N = 6$), hypotension ($N = 2$), vomiting ($N = 4$), a rash ($N = 7$), agitation ($N = 9$), hiccups ($N = 3$), and dizziness ($N = 3$). An antidote had to be administered 6 times (3 flumazenil, 3 naloxone) and 2 patients sedated with fentanyl + midazolam required respiratory interventions (one with a Mayo cannula and one with mask/bag ventilation). The risk of complications depended heavily on the medication used. Patients sedated with midazolam + fentanyl had a significantly higher risk of adverse events (161/686 = 23.4%), compared to patients who had been treated with midazolam + ketamine + atropine (24/277 = 8.6%) or IV midazolam (1/65 = 1.5%) [32].

In a randomized controlled trial by Yildizdas et al. of 126 children undergoing a PS for painful oncology procedures, patients were randomly assigned for one of five forms of intravenous PS: ketamine (1 mg/kg), midazolam (0.15 mg/kg), ketamine + midazolam (1 mg/kg + 0.1 mg/kg), midazolam + fentanyl (0.1 mg/kg + 2 micrograms/kg), and propofol (2 mg/kg). Patients were monitored through saturation measurement and capnography. Patients sedated with midazolam + fentanyl and with propofol had a significantly more desaturations and hypercapnia compared to the three other groups. Desaturations were observed in 0%, 0%, 8%, 28%, and 52%, respectively, whereas hypercapnia was found in 0%, 0%, 0%, 4%, and 12%, respectively [8].

Table 2: Drug-specific conclusions regarding the relation between professional competence/skills and PS-related safety.

Nr	Conclusion	Quality Level
	Nontitratable drugs intended for moderate to deep sedation	
(1)	During PS, intended to moderate or deep sedation, with the use of benzodiazepines, chloral hydrate, barbiturates, opiates, or combinations of these medicines, and during the subsequent recovery phase, there exists a variable but real risk of potentially serious drug-induced adverse events. Especially the risk for respiratory depression and/or airway obstruction necessitates specific skills and competence from the professionals in charge in terms of recognition and treatment. (B) Hoffman et al. 2002 [13], Pitetti et al. 2003 [32], Sanborn et al. 2005 [27], Cravero et al. 2006 [36], Roback et al. 2005 [33], Newman et al. 2003 [34], Pena et al. 1999 [37], Mason et al. 2001 [38], Mason et al. 2004 [35], Mason et al. 2004 [39] (C) Malviya et al. 1997 [28]	Level 2
	Propofol	
(1)	During PS using propofol, there is a real risk of potentially serious drug-induced adverse events. Especially the risk for respiratory depression and/or airway obstruction necessitates specific skills and competence from the professionals in charge in terms of recognition and treatment. (B) Cravero et al. 2009 [26] (c) Barbi et al. 2003 [12], Hertzog et al. 1999 [40], Hertzog et al. 2000 [41], Pershad and Godambe 2004 [42], Bassett et al. 2003 [43], Guenther et al. 2003 [44], Vespasiano et al. 2007 [29]	Level 3
(2)	PS with propofol, including deep sedation, is equally safe in the hands of anesthesiologists and nonanesthesiologists if the latter are well trained and part of dedicated sedation team. (B) Cravero et al. 2009 [26] (C) Barbi et al. 2003 [12], Vespasiano et al. 2007 [29]	Level 3
(3)	A deep PS using ketamine or propofol for examination of the upper airways, or for endoscopies of the upper gastrointestinal system, carries a real risk of potentially serious complications (i.e., laryngospasm and deep desaturation), which require specific skills and competence from the professionals in charge in terms of recognition and treatment. (C) Barbi et al. 2003 [12], Green et al. 2001 [45]	Level 3
	Ketamine	
(1)	During PS using ketamine, there is a small but real risk of potentially serious drug-induced adverse events. Especially the risk for respiratory depression, airway obstruction and—infrequently—laryngeal spasm necessitates specific skills and competence from the professionals in charge in terms of recognition and treatment. (A1) Green et al. 2009 [30] (C) Green et al. 2001 [45], Evans et al. 2005 [46], Meyer et al. 2003 [47], Cheuk et al. 2005 [48],	Level 1
(2)	Independent risk factors for respiratory adverse events during a PS with the use of ketamine are high intravenous doses, administration to children younger than 2 years or aged 13 years or older, and the coadministration of anticholinergics or benzodiazepines. (A1) Green et al. 2009 [30]	Level 1
	Dexmedetomidine	
(1)	Based on a limited published experience on the use of dexmedetomidine for PS by experienced professionals, there seems to be a very small risk of potentially serious drug-induced adverse events. Respiratory events are extremely rare and hemodynamic adverse events (i.e., bradycardia and hypotension) are mostly clinically insignificant. Specific experience in dosing techniques, individual titration and avoiding dexmedetomidine in those patients who may not tolerate hemodynamic fluctuations seems to be associated with low risks. (A2) Koroglu et al. 2005 [49], Koroglu et al. 2006 [50] (B) Mason et al. 2008 [51], Mason et al. 2008 [52] (C) Berkenbosch et al. 2005 [53], Mason et al. 2006 [54], Ray and Tobias 2008 [55]	Level 1
	Remifentanil	
(2)	During PS using remifentanil, there is a real risk of potentially serious drug-induced adverse events. Especially the risk for respiratory depression and/or airway obstruction necessitates specific skills and competence from the professionals in charge in terms of recognition and treatment. (A2) Keidan et al. 2001 [56] (C) Litman 1999 [57], Litman 2000 [58]	Level 2

Table 2: Continued.

Nr	Conclusion	Quality Level
	Nitrous Oxide	
(1)	PS with nitrous oxide is associated with an extremely low chance of serious adverse events. Instant discontinuation of gas flow in case of respiratory depression is the most important rescue intervention. (B) Babl et al. 2005 [59], Babl et al. 2008 [60] (C) Gall et al. 2001 [31]	Level 2
(2)	Specific risks for adverse events during nitrous oxide administration are: (I) A young age (<1 year old) (C) Gall et al. 2001 [31] II. Simultaneous use of other sedatives (C) Gall et al. 2001 [31]	Level 3
(3)	In patients sedated with nitrous oxide, there exists no significant difference in median fasting time between patients with and without emesis (B) Babl et al. 2005 [59]	Level 3
(4)	Nitrous oxide 70% causes significantly deeper sedation compared to nitrous oxide 50%. However, if embedded in a comprehensive sedation program there exists no significant difference in adverse events rates between both regimens. (B) Babl et al. 2008 [60] (C) Zier et al. 2007 [61]	Level 3

Adverse Effects of Propofol. Barbi et al.'s prospective study concerned deep PS with propofol administered by nonanesthesiologists (1059 procedures in 827 children aged 0–21 years old: gastroscopies ($N = 483$), colonoscopies ($N = 289$), and painful procedures ($N = 173$). All sedating professionals had followed a specific training, including theoretical and practical training on propofol, airway management, mask/bag ventilation, and resuscitation. Of the 1059 patients, 34 (12.6%) had a transient desaturation that resolved spontaneously. Deep desaturation with the need for mask/bag ventilation was required in 4/483 patients (0.8%) undergoing a gastroscopy, in 1/287 patients (0.3%) undergoing a painful intervention, and in 0/289 patients (0.0%) undergoing a colonoscopy. Laryngospasm occurred in 10/483 patients (2.1%) who underwent a gastroscopy. In 24 of the 483 gastroscopies (4.9%), an anesthesiologist was urgently required. In 13/24 cases (54.2%), this concerned assistance with the laryngoscopic insertion of an endoscope, in 10/24 cases (41.7%), the treatment of a laryngospasm and in 1/24 cases (4.2%), assistance to deal with a serious esophageal bleed. The trained professionals were able to manage adequately all adverse events that occurred during colonoscopies and painful interventions [12]. Propofol for PSA in children administered by specifically trained nonanesthesiologists has also been studied in pediatric oncology, radiology, and emergency medicine. A retrospective study by Hertzog et al. found that in 251 propofol sedations by pediatric intensivists hypotension (50%) and respiratory depression requiring transient bag-valve-mask ventilation (6%) were the most important adverse events [40]. A prospective study by the same authors in 28 oncology patients, undergoing 50 sedations, showed similar results: transient hypotension (64%) and partial airway obstruction (12%) were the most important adverse events. Apnea requiring bag-valve-mask ventilation occurred in 2% of procedures [41]. In a retrospective case series by Pershad and Godambe ($N = 52$) of propofol PS in the ED, no patient required assisted ventilation or developed clinically significant hypotension. The incidence of respiratory depression requiring airway repositioning or supplemental oxygen was 5.8% [42].

Bassett et al. analyzed prospectively 293 propofol sedations in children on an ED. Transient decrease in systolic blood pressure without clinical signs of poor perfusion was found in 92% of the patients. Nineteen patients (5%) had hypoxia, 11 patients (3%) required airway repositioning or jaw-thrust maneuvers, and 3 patients (0.8%) required bag-valve-mask ventilation. No patient required endotracheal intubation [43]. In a similar study by the same authors in 87 patients (291 sedation sessions), partial airway obstruction requiring brief jaw-thrust maneuver was noted for 4% of patient sedations. Transient apnea requiring bag-valve-mask ventilation occurred in 1% of patient sedations [44].

Vespasiano et al. reported a prospective study on 7304 propofol sedations outside the operation room in 4464 children, undergoing MRI (42.8%), non-MRI diagnostic imaging (22.5%), hematology/oncology procedures (26.2%), or other procedures (10.5%). All sedations were performed by pediatric intensivists according a sedation program that was in adherence to the American Academy of Pediatrics guidelines. The program was locally governed by a multidisciplinary committee with representation from anesthesiology, critical care, nursing, oncology, cardiology, and emergency medicine. To assess the overall safety profile of propofol a specific quality audit tool was designed. Hypotension (>25 mmHg drop from baseline) occurred in 31.4% of the patients but was mostly without circulatory compromise. High-volume fluid therapy was necessary in only 0.11% of cases. Infrequent respiratory adverse events

were laryngospasm (0.27%), regurgitation without aspiration (0.05%), regurgitation with aspiration (0.01%), and bronchospasm (0.15%). Almost 5% of patients had an oxygen desaturation (1.73% between 85–90%; 2.9% < 85%) while airway obstruction requiring an oral or nasal airway occurred in 2% of cases. Unfortunately, $ETCO_2$ was not evaluated systematically in this study. Only 0.37% of the patients needed bag-valve-mask ventilation because of hypopnea and/or apnea. All side effects could be managed successfully by the sedation team. There were no cardiac arrests. Patients with an abnormal airway (as defined by an airway score) were significantly more likely to develop oxygen desaturation or airway obstruction. None of the intended procedures or sedations had to be aborted [29].

The multicentric Pediatric Sedation Research Consortium (PSRC) collected prospectively data on 49836 propofol sedations in children. The PSRC consists of anesthesiologists, pediatric medical subspecialists, emergency physicians, pediatric intensivists, nurses, physician assistants, and health care research personnel who seek to continuously improve the quality, safety, effectiveness, and cost of pediatric sedation/anesthesia practice. Participants work in 37 different locations, including large children's hospitals, children's hospitals within hospitals and general/community hospitals. Following an initial study, the group meeting in this consortium agreed on a collective mission statement regarding pediatric procedural sedation. Decisions were based on guidelines from the American Academy of Pediatrics, American Society of Anesthesiologists, and American College of Emergency Physicians regarding sedation/anesthesia of pediatric patients, a review of the literature and the consensus of the consortium members. Besides sharing a common mission on PS, the PSRC is a data-sharing group: all participators agree to perform periodic audits of records to assure data and to maintain a prospective registry of all patients receiving PS [36].

Transient O_2 desaturation below 90% for more than 30 seconds occurred 154 times per 10000 propofol administrations (1.5%). Central apnea or airway obstruction occurred 575 times per 10000 administrations (5.8%). Per 10000 encounters stridor occurred 50 times (0.5%), laryngospasm 96 times (0.96%), excessive secretions 341 times (3.4%), and vomiting 49 times (0.49%). Aspiration occurred 4 times during these 10000 sedation/anesthesia encounters (0.04%). There were no deaths. Cardiopulmonary resuscitation was required twice (0.02%). The sedating professionals could manage all adverse events appropriately. In an unadjusted analysis, the rate of pulmonary adverse events was not different for anesthesiologists versus other providers. Young age (<6 months), fasting time <8 hours, ASA classification III or higher and concomitant use of opoids were all significantly related with a higher risk for respiratory adverse events [26].

Adverse Effects of Ketamine. Several authors studied ketamine for PS during oncology procedures (lumbar punctures, bone marrow punctures, and/or bone biopsies), performed by non-anaesthesiologists. Evans et al. reported an incidence of desaturation of 1.7% and no airway obstruction during 119 sedation sessions [46]. Cheuk et al. reported an incidence of desaturations of 8.7% during 369 sedation sessions. These desaturations only required brief treatment with oxygen. No apneas or airway obstructions occurred [48]. In a prospective study by Meyer et al. of 183 PS sessions, potentially serious complications were desaturation <90% (5.4%) and laryngospasm (0.5%) [47]. Both intravenously (IV) and intramuscularly (IM) administered Ketamine were studied for PS in painful ED procedures. In a recent meta-analysis of 8282 children receiving PS with ketamine for procedures in an ED, the overall incidence of respiratory adverse events was 3.9%. Independent risk factors were high intravenous doses, administration to children younger than 2 years or aged 13 years or older, and the concomitant use of anticholinergics or benzodiazepines. Variables without independent association included oropharyngeal procedures, underlying physical illness (American Society of Anesthesiologists class > or =3), and the choice of intravenous versus intramuscular route [30]. A retrospective analysis by Green et al. of a series of cases ($N = 636$) in which sedation with ketamine was administered by pediatric gastroenterologists for gastrocopies in children, showed a high incidence of laryngospasm (13.9% in the age group <6 years; 3.6% in the age group >6 years) [45].

Adverse Effects of Dexmedetomidine. In the last few years, dexmedetomidine has been studied for PS in children undergoing painless procedures. Regarding effectiveness for sedation in diagnostic imaging dexmedetomidine is significantly superior to midazolam and similar to propofol [49, 50]. Berkenbosch et al. published a prospective case series reporting the use of Dexmedetomidine in 48 children. Heart rate, blood pressure, and respiratory rate decreased but remained within normal limits for age. End-tidal CO_2 exceeded 50 mm Hg in seven of 404 measurements (1.7%) [53]. Mason et al. studied dexmedetomidine for sedation for computer tomography imaging (CT) in 62 patients. Heart rate (HR) and mean arterial blood pressure decreased an average of 15% and no significant respiratory changes were observed [54]. In another study ($N = 250$), these authors showed that individual titration of dexmedetomidine for CT imaging is associated with modest fluctuations in HR and blood pressure which were independent of age, required no pharmacologic interventions, and did not result in any adverse events [51]. In a prospective study by the same group, dexmedetomidine as sole agent for pediatric MRI was studied in 747 consecutive patients. Three different dosing groups were analysed. Bradycardia without hypotension occurred in 16% of cases. There were no respiratory adverse events [52]. Ray and Tobias retrospectively reviewed the charts of 42 children with autism pervasive developmental disorders and epilepsy, who received dexmedetomidine for sedation during electroencephalography. No significant hemodynamic or respiratory effects were noted [55]. In two separate randomized controlled trials, Koroglu et al. compared dexmedetomidine with respectively midazolam and propofol for sedation in children undergoing MRI scanning. No relevant adverse events were seen in the

children sedated with dexmedetomidine ($N = 70$) [49, 50].

Adverse Effects of Remifentanil. Remifentanil, a potent ultrashort acting synthetic opioid, has been studied for PS in children undergoing short painful procedures (e.g., lumbar puncture, and bone marrow puncture), both as a sole agent and combined with Midazolam or Propofol. Litman reported a high incidence of potentially life threatening respiratory depression in children undergoing painful procedures with the combination of a benzodiazepine and remifentanil. Out of 31 patients 25 (80.6%) developed an apnea, requiring constant stimulation, and 10 (32.3%) became hypoxemic [58] Keidan et al. published a randomized controlled trial comparing propofol ($N = 36$) and propofol-remifentanil ($N = 41$) for bone marrow aspiration in children. The addition of remifentanil was associated with a decrease in propofol dose and, consequently, recovery time, but with an increased risk of respiratory depression: hypoventilation or hypoxemia were significantly more frequent if remifentanil was added (19.5% versus 11.1%) [56] In a recent randomized controlled trial by Antmen et al.(A2), eighty children undergoing bone marrow aspiration were randomly assigned to one of four sedation regimens: remifentanil 1 mcg/kg ($N = 20$), midazolam 0.05 mg/kg + remifentanil 0.5 mcg/kg/min ($N = 20$), alfentanil 20 mcg/kg ($N = 20$), and midazolam 0.05 mg/kg + alfentanil 20 mcg/kg ($N = 20$). Relevant adverse events occurred in none of the 4 groups [62].

Adverse Effects of Nitrous Oxide. A French multicentric prospective study by Gall et al. of 7,511 sedation sessions with 50% nitrous oxide/50% oxygen premix, investigated the incidence of serious complications (oxygen desaturation, airway obstruction, apnea, bradycardia and/or oversedation). Such complications occurred in 25 sessions (0.3%). In all cases, the problems dissolved instantly after discontinuation of the administration of nitrous oxide, without any need for airway intervention or ventilation. The main risk factors were age (<1 year) and the simultaneous administration of benzodiazepines and opiates [31].

Zier et al. reported a case series of 1018 sedation sessions using nurse-administered nitrous oxide (continuous flow; concentration of 70%) for urinary catheterization. Only minor adverse events (diaphoresis, nausea, and vomiting) were observed in 4% of the sessions. Oversedation without respiratory compromise occurred in 0.8% of cases [61]. Babl et al. studied prospectively the relationship between fasting status and adverse events in 220 patients receiving nitrous oxide in a pediatric ED. Fasting status was obtained in 218 patients (99.1%). Of these, 155 (71.1%) did not meet fasting guidelines for solids. There were no serious adverse events and no episodes of aspiration. Emesis occurred in 7% of cases. There was no significant difference in median fasting time between patients with and without emesis [59].

The same author studied prospectively the safety of high-concentration continuous-flow nitrous oxide (70% versus 50%) in children ($N = 762$, age range 1–17 yrs). Sixty-three (8.3%) patients sustained mild and self-resolving adverse events, most of which were vomiting (5.7%); 2 patients (0.2%) had serious adverse events. Both serious events (1 chest pain and 1 desaturation) occurred in the group of 70% nitrous oxide. There was no significant difference in adverse events rates between nitrous oxide 70% (8.4%) and nitrous oxide 50% (9.9%) [60].

3.1.3. Data from Literature on the Predictability and Controllability of Sedation Depth. It has been shown that unexpected deep sedation is associated with a higher rate of adverse events [13, 21]. The predictability of final sedation levels of a certain drug therefore determines the skills and competence the professionals in charge should possess. A search was made of existing literature on this subject. Results are summarized in Table 3.

Motas et al. published an observational study in 86 children who underwent PS using midazolam, midazolam in combination with fentanyl or pethidine, chloral hydrate, pentobarbital, or ketamine. Sedation depth was assessed by an independent observer, using a validated sedation scale and by bispectral cerebral function monitoring (BIS). These observations were compared to the sedation depth the practitioners set out to achieve. The intended sedation depth was reached in 72% (sedation scale) and in 52% (BIS) of the cases, respectively. In 35% of the cases, the BIS figure present was consistent with general anesthesia. The incidence of airway complications was significantly higher in the group that had been deeply sedated unintentionally [21].

A risk assessment by Hoffman et al. based on prospective collected data of 96 sedations for widely varying procedures with chloral hydrate (15%), midazolam (28%), fentanyl (1%), pentobarbital (28%), ketamine (2.8%), or cocktails of 3 or more of the medicines (5.7%), showed that in 22% of the procedures, a deep sedation level was reached, although deep sedation had only been intended in 7% of the procedures [13].

Malviya et al. studied two different types of discharge criteria in 29 children who had been sedated for an echocardiography (27/29 = 93.1% with chloral hydrate and 2/29 = 6.9% with midazolam + diphenhydramine). Standard criteria (normal vital parameters, normal oxygen saturation, return to original consciousness level, normal cough and swallowing reflexes, and normal movement) were compared with an objective assessment of the consciousness using BIS monitoring and two validated scales of observation. The objective criteria correlated better with being fully awake than the standard criteria but it took significantly more time before those objective criteria were reached [63].

The under 1.2 cited study by Newman et al. (prospective study of 1341 PS sessions in children in an emergency department (ED)) showed an incidence of serious complications of 11.9% of which 92% occurred during the actual procedure, whereas the rest occurred after the procedure up to 40 minutes after the last administered dose of sedative [34].

3.2. Requisite Skills and Competences to Guarantee Optimal Effectiveness. Effectiveness is named as an outcome measure in most of the studies on PS published over the last

Table 3: Conclusions regarding predictability and controllability of nontitratbale drugs intended for PS.

Nr	Conclusion	Quality Level
(1)	For a PS with medicines that are difficult to titrate and/or long-acting (e.g., chloral hydrate, midazolam, barbiturates, opiates or combinations), the eventual depth of sedation, effectiveness and duration of the sedation and timing of adverse events cannot reliably be predicted. Therefore, possible adverse effects of any possible sedation depth should always be anticipated in terms of recognition and treatment.	Level 2
	(B) Hoffman et al. 2002 [13], Newman et al. 2003 [34], Malviya et al. 2004 [63], Motas et al. 2004 [21]	

few decades. Mutual comparisons or combining averages is impossible, because the definition of effectiveness varies considerably for each procedure, or because it is not properly defined at all. No prospective controlled studies were found comparing different levels of professional skills/competence and the effectiveness of PS. Evidence was therefore searched in an indirect way by looking for which PS techniques a professional should master in order to achieve optimal PS effectiveness. We defined that *an optimal PS technique should achieve near 100% predictable procedural success and timing, an optimal match between desired and achieved levels of sedation, minimal induction and recovery times, and an optimal patient comfort by minimizing procedural pain, anxiety and the need for physical immobilization or restraint*. Next, we looked for settings and techniques with published evidence for contributing in reaching this optimal level. Results were classified as conclusions in four different categories of techniques or strategies with a proven effect on PS effectiveness.

3.2.1. Effect of the Introduction of a Dedicated Well-Trained Team for PS on the Effectiveness of PS. Several authors have shown that the introduction of a dedicated PS team that works according to published guidelines results in a significant decrease of procedural failure (*Level 2 conclusion* based on Hoffman et al. 2002(B), Ruess et al. 2002(C), and Sury et al. 1999(C)) [13, 15, 64]. Although it is impossible to deduce from those studies to what extent this result is due to specific professional skills and competence, PS seems to become more effective when specifically trained professionals perform PS in accordance with international guidelines.

3.2.2. The Superiority of Titratable Medicines or Medicines with a Highly Predictable Effectiveness, Including Deep Sedation. In order to achieve an optimal level of effectiveness, each PS should ideally be directed to an individually determined sedation level. This makes the use of short acting drugs (e.g., propofol) that can be titrated to the desired level of sedation (including deep sedation) advantageous over the use of long acting drugs. There is growing evidence for the need for deep sedation for the majority of procedures in pediatrics. A retrospective analysis by Dial et al. of the sedation depth that was eventually required for a category of examinations ($N = 32$) that were not (very) painful and for which immobility was not strictly required turned out to be *deep sedation* after all in 26/32 cases (81.3%). For the category of painful and invasive examinations for which local anesthesia was used, light to moderate sedation turned out to be sufficient in only 4/156 cases (2.6%), whereas deep sedation was necessary in 136/156 cases (87.2%) and even a general anesthesia in 16/156 cases (10.3%) [24]. On the other hand there is good evidence for the superior effectiveness of PS with titratable medicines with a clearly predictable effectiveness. This has been demonstrated in children undergoing very painful procedures (e.g., oncological procedures, procedures in an ED), (protracted) stressful procedures (e.g., endoscopies) and procedures for which patients need to lie still for long periods (e.g., for imaging and radiotherapy). In addition, working with propofol also leads to a significantly shorter induction time and a significantly quicker recovery. Having the requisite competencies and skills to use this sort of sedatives safely therefore seems important to guarantee optimal effectiveness (*Level 1 conclusion* based on Migita et al. 2006(A1), Marx et al. 1997(A2), Pershad et al. 2007(A2), Dalal et al. 2006(B), Seiler et al. 2001(B), Iannalfi et al. 2005(B), Kohsoo et al. 2003(B), and Holdsworth et al. 2003(B)) [65–71].

3.2.3. Deployability of Techniques for Light Sedation. Children often have to be physically forced or restrained for so-called "minor painful procedures" (e.g., blood sampling, inserting an intravenous access, suturing a wound, lumbar puncture, bone marrow puncture, changing a dressing, incision of abscess, resection of naevus or cyst, bladder catheterization, intraarticular injection, and Ear Nose Throat procedures). It has been demonstrated that the level of comfort during such interventions can be considerably improved when nitrous oxide is used. Nitrous oxide in concentrations of up to 70%, when combined with nonpharmacological distraction techniques and adequate topical anesthesia, is a very effective and safe way to suppress procedural pain and stress in children >1 year old. (*Level 3 conclusion* based on Iannalfi et al. 2005(B), Kanagasundaram et al. 2001(C), Burnweit et al. 2004(C), Frampton et al. 2003(C), and Zier et al. 2007(C) [61, 72–75]. For children undergoing reduction of an uncomplicated forearm reduction nitrous oxide in concentrations of 50% in combination with local anesthetics is equally effective as intravenous ketamine but is associated with a significantly shorter recovery time and less respiratory side effects. (*Level 3 conclusion* based on Luhmann et al. 2006(B)) [76]. In children that need to receive sutures, nitrous oxide in concentrations of 50% in combination with local anesthetics controls the procedural pain and stress more effectively than orally taken midazolam or local anesthetics alone (*Level 2 conclusion* based on Luhmann et al. 2001(B) and Bar-Meir et al. 2006(B)) [77, 78]. Inserting a venous access in children who are known to have difficult veins is

easier under sedation with nitrous oxide + topical anesthesia than topical anesthesia alone. (Level 3; Ekbom et al. 2005(B)) [79]. Topical anesthesia and nitrous oxide combined are more effective than topical anesthesia or nitrous oxide alone. (*Level 1 conclusion* based on Paut et al. 2001(A2) and Hee et al. 2003(A2)) [80, 81].

3.2.4. Use of Nonpharmacological Techniques. In literature, good evidence is available for the importance of applying nonpharmacological techniques to improve procedural success and comfort. When a professional takes care over providing good information about the procedure to be followed, this may result in the children feeling less stress during the procedure and being less scared about future procedures (*Level 3 conclusion* based on Claar et al. 2002(C) and Bishop et al. 2002(C)) [82, 83]. Adequate information also helps parents to provide better support for their children during a painful procedure (*Level 3 conclusion* based on Kupietzky and Ram 2002(C) and Cline et al. 2006(D)) [84, 85]. A child (>4 years old) that receives sufficient preparation (e.g., by information, practice, simulation, and play therapy) before an MRI examination, a gastroscopy or nuclear examination will experience less distress during the procedure and will require less sedation or analgesia (*Level 2 conclusion* based on Mahajan et al. 1998(A2), Rosenberg et al. 1997(B), Presdee et al. 1997(C), Awogbemi et al. 2005(C), and de Amorim e Silva et al. 2006(C)) [86–90]. Between 1993 and 2009 3 high-quality Systematic Reviews (SR) of nonpharmacological interventions for procedure-related pain in children have been published, allowing 3 *Level 1 conclusions*. Cepeda et al. (2006; A1 including 51 RCT's of which only 4 addressed procedural pain in children) could not demonstrate evidence for the effectiveness of music therapy during intravenous cannulation and vaccination in children. Although listening to music reduced pain intensity scales in general and opioid requirements in particular, the reported effects are small. Pooling of the 4 studies was impossible due to different quantification methods of pain intensity [91]. Richardson et al. published a SR (2006; A1 including 7 RCTs and 1 non-RCT) on the pain reducing effects of hypnosis in pediatric cancer patients undergoing common painful procedures (infusapost access, venipuncture, lumbar puncture, and bone marrow aspiration). Although 7/8 studies included reported a significant reduction of pain, the authors conclude that due to methodological limitations there is no conclusive evidence for a significant effect of hypnosis on procedure-related pain [92]. Finally, the SR by Uman et al. (2006; A1 including 28 trials) showed a significant effect of distraction and hypnosis on self-reported pain during needle-related procedures (intramuscular injection, vaccination, venipuncture, intravenous cannulation, lumbar punction, and bone marrow aspiration). For other psychologhical techniques no significant effect on procedure-related pain could be concluded [93].

An additional SR by Kleiber and Harper (1999) focused on the effects of distraction on self-reported pain in children during intravenous cannulation, lumbar punction, bone marrow aspiration, injection, venipuncture, dental procedures, and burn treatment. They showed that distraction causes a significant reduction of self-reported pain. An important limitation of this SR is the fact that no details are provided on the methodological quality of the included studies [94]. None of the SR could demonstrate any adverse events of nonpharmacological techniques.

Hypnosis on children reduces procedure-related pain and distress more effectively compared to *local anesthesia* (venipuncture and lumbar puncture; *Level 1 conclusion* based on three independent A2 studies by the same authors: Liossi et al. 2009, Liossi et al. 2006, and Liossi and Hatira 2003), to *cognitive behavioral therapy* or *no therapy* (bone marrow aspiration; *Level 2 conclusion* based on Liossi and Hatira 1999(A2)), and to *standard medical care* including relaxation exercises or play intervention (cystogram; *Level 2 conclusion* based on Butler 2005(A2)) [95–99].

In conclusion, we found that a professional able to use psychological techniques for distraction or hypnosis during painful and/or stressful medical procedures may be able to reduce the child's procedural distress. Furthermore, the use of psychological techniques intended to distract children during a painful and/or stressful medical procedure reduces the need for sedation (*Level 2 conclusion* based on Harned and Strain 2001(B) and Train et al. 2006(B)) [100, 101].

4. Discussion

This paper shows sufficient evidence to support the statement that safety and effectiveness of PS are significantly related to the level of professional skills and competence. Although there are no prospective studies comparing the effect of different levels of skills and competence on PS related safety and effectiveness, this systematic paper identified in the relevant literature which competences and skills a professional should possess or achieve in order to be able to perform PS in children safely and effectively. For that purpose, we systematically summarized the results in conclusions classified according to the strength of evidence of the contributing papers. These conclusions can be translated into recommendations on the general skills and competence any professional entrusted with PS must have in order to achieve optimal safety and effectiveness (Tables 4 and 5).

Besides general recommendations, we formulated additional recommendations depending on the level of sedation. Contrary to the generally accepted division between mild, moderate, and deep sedation in most guidelines, we believe that, based on the evidence, having different levels of monitoring and competence for moderate and deep sedation is arbitrary and potentially dangerous. Ever since the first guideline on PS was published, authors have linked the level of sedation with potential respiratory and cardiovascular side effects and by this with necessary safety precautions, monitoring, and professional skills and competence [10]. Consequently, definitions were made for *mild sedation*, *moderate sedation* (formerly called "conscious sedation"), *deep sedation,* and *anesthesia*. Mild sedation, formerly called "anxiolysis", is typically the result of one standard dose of midazolam or by the breathing of nitrous oxide (inspired concentration up to 50%) [60]. Higher doses, or other drugs,

Table 4: General recommendations on necessary skills and competence for achieving optimal PS related safety and effectiveness in children.

Nr	Recommendations
(1)	Knowledge of the drug dosing, dosing techniques, indications, contraindications, and requisite precautions of the sedation technique used, acquired through specific training or demonstrable relevant experience.
(2)	Regular personal experience of the applied medication or technique*.
(3)	Applying the form of sedation that is most appropriate for the procedure and the patient. This implicates the ability to guarantee the optimally effective sedation level in a predictable manner. An optimal PS technique should achieve near 100% predictable procedural success and timing, an optimal match between desired and achieved levels of sedation, minimal induction, and recovery times and an optimal patient comfort by minimizing procedural pain, anxiety, and the need for physical immobilization or restraint.
(4)	The ability to perform preprocedural screening and a systematic risk analysis.
(5)	The ability to inform the patient, parents or carers about the sedation technique, the effects, potential side effects, and possible alternatives. The information must be given in time and be appropriate for the comprehension level of the patient and parents/carers.
(6)	The ability to guarantee a child-centered approach within a general policy that favors children before, during and after the procedure.
(7)	The ability to apply, or arrange for complementary nonpharmacological techniques like preparation, distraction, combined cognitive-behavioral interventions, and hypnosis.
(8)	The ability to (a) apply effective local or topical anesthesia, if appropriate, and (b) to recognize and intervene with possible toxicity of local anesthetic agents.
(9)	Organizing the necessary monitoring and rescue facilities during and after the procedure for as long as the consciousness level is lowered.
(10)	The ability to organize a supervised recovery phase and to define the discharge criteria.
(11)	The ability to organize the prompt availability of a resuscitation team or a professional trained in Pediatric Life Support.
(12)	Supervising, registering, assessing and optimizing the quality of the sedation in terms of safety and effectiveness.

*It is impossible to derive from literature a more precise definition of "regular personal experience". The authors believe that regular experience means a minimal of 50 PS sessions per year.

either alone or in combination, are likely to cause deeper levels of sedation. Commonly used PS drugs intended for moderate sedation such as chloral hydrate, barbiturates, benzodiazepines with/without opioids, and solely opioids cause wide variations in depth of sedation. If a single dose is given the goal of moderate sedation is not achieved or exceeded in a substantial number of children. Therefore, for individual cases, prediction of the effective sedation end point is unreliable [21]. Multiple doses or combinations of drugs are more likely to cause deep sedation and are associated with hypoventilation, respiratory depression, and serious morbidity. Considering sedation levels as a sliding scale, rather than a step-by-step change in consciousness, the transition from one level to another can be subtle and sudden. It is, therefore, advisable to recommend the same safety precautions and professional skills for all levels of sedation beyond mild sedation, irrespective of the drug used for PS. Consequently, it is wise to formulate separate recommendations regarding professional skills and competence for mild sedation on one hand and for moderate to deep sedation on the other hand (Tables 5(a) and 5(b)). Although the safety profiles of PS drugs are clearly different, the likelihood that potentially serious adverse events may happen and the predictability of depth and duration of sedation are clearly more important. Both issues have a direct impact on the imperative skills and competence, mainly in terms of timely recognition and appropriate management of possible adverse events. PS-related safety is determined by logistics, organization and professional skills rather than by specific pharmacologic characteristics.

In order to achieve an optimal level of effectiveness, each PS should ideally be directed to an individually determined sedation level. This makes the use of short-acting "titratable" drugs advantageous over the use of long-acting drugs. Short-acting drugs can be used to overcome the pain and distress that varies according to the procedures and the patients themselves. It can be concluded from this systematic paper that professionals having the requisite skills and competence to work with titratable anesthetics (e.g., propofol) are able to achieve more optimally an effective PS for children undergoing very painful procedures (e.g., oncological procedures, procedures in an ED), (protracted) stressful procedures (e.g., endoscopies) and procedures for which patients need to lie still for long periods (e.g., diagnostic imaging and radiotherapy). In particular, young children (<6 years) are in need of deep sedation sometimes even for so called "mild" procedures [23, 24]. Although the obvious advantages of titratable deep sedation (e.g.,

Table 5

(a) Recommended specific additional skills and competence for achieving optimal safety during *moderate and deep sedation* in children.

Nr	Recommendations
(1)	In order to guarantee optimal levels of safety and effectiveness during a PS involving (a possibility of) moderate-to-deep sedation, the PS must be carried out by a separate professional that is not involved in the actual procedure.
(2)	During a PS involving (a possibility of) moderate or deep sedation and during the subsequent recovery phase, a professional must be present with at least the following additional competence and skills: (1) The ability to assess and interpret the sedation depth. (2) The ability to guarantee the necessary monitoring of vital parameters, including capnography, and being able to appraise and interpret the monitored information. (3) Having acquired the necessary *knowledge during a specialist course* and by means of *refresher courses* and ability to *manage* the following techniques at APLS* level: (3.1) Techniques intended to guarantee an open airway, including skills to manage larynx spasm and to use Laryngeal Mask Airways. (3.2) Techniques to administer mask/bag ventilation. (3.3) The use of antagonists. (3.4) Heart massage techniques.

*APLS: Advanced Pediatric Life Support.

(b) Specific additional skills and competence for achieving optimal safety during *mild sedation/anxiolysis* in children.

Nr	Recommendations
(1)	During a PS involving mild sedation and during the subsequent recovery phase, a professional must be present with the at least the following additional competence and skills: (1) The ability to assess and interpret the sedation depth. (2) The ability to maintain continuous verbal contact with the patient in the absence of any other form of monitoring. (3) Having acquired the necessary *knowledge through a specialist course* and by means of *refresher courses* and the ability to *manage* the following techniques at BLS* level: (3.1) Techniques intended to guarantee an open airway. (3.2) Techniques to administer mask/bag ventilation.

*BLS: Basic Life Support.

using propofol) over other sedatives for many procedures in children are increasingly emphasized in recent literature, the term *deep sedation* has been under discussion, because it may be indistinguishable from general anesthesia. While this point may be overstated it has led to the widespread recommendation that the same personnel, equipment, and facilities must be available to manage both deep sedation and anesthesia. The most important severe adverse effect of propofol is respiratory depression, which is associated with unexpected deep sedation and can arise suddenly and unexpectedly [1]. As a consequence the question whether nonanesthesiologists can be safely entrusted with the use of this potent drug has been a matter of debate [23]. There is an obvious reluctance by the anesthetic world to entrust trained non-anesthesiologist with highly active anesthetic drugs [23, 102]. However, in many countries, a clear trend is seen to entrust deep sedation to specifically trained non-anesthesia professionals in particular because of the scarcity of anesthesiologists. Emergency physicians, intensivists and gastroenterologists have been prominent in this development [12, 29, 40, 41, 102, 103]. In addition, It has been shown that in optimal safety and monitoring conditions deep sedation using propofol is equally safe irrespective whether it is administered by trained nonanesthesiologists or anesthesiologists [26, 102]. An evidence-based clinical practice advisory for the administration of propofol for PS by nonanesthesiologists was recently published [104].

For minor painful procedures the deployability of short-acting mild sedation using nitrous oxide and ability to apply adequate topical anesthesia are essential skills for optimal effectiveness. In addition, not only the ability to define and apply an individually tailored PS technique but also the ability to implement nonpharmacological techniques, such as distraction, hypnosis and combined cognitive-behavioral interventions, belongs to the essential competence and skills.

Finally, we found evidence that the application of published guidelines within a well organized, well trained, and dedicated PS team will enhance PS related safety and effectiveness.

In conclusion, PS has to be considered as a separate medical act, provided by well-trained, competent, and skilled professionals only, working within a context of transparency, registration, and ongoing quality control. Skills and competence, rather than professional title, are determinants for safe and effective PS. We believe that these evidence-based recommendations regarding necessary skills and competence

should be used to set up training programs and to define which professionals can and cannot be credentialed for PS in children. Much emphasis is needed for adequate and effective implementation strategies for these recommendations.

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Hindawi Publishing Corporation
International Journal of Pediatrics
Volume 2010, Article ID 828347, 5 pages
doi:10.1155/2010/828347

Review Article

Capnography and the Bispectral Index—Their Role in Pediatric Sedation: A Brief Review

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Received 3 December 2009; Revised 5 June 2010; Accepted 20 July 2010

Academic Editor: Savithiri Ratnapalan

Sedation in children is increasingly emerging as a minimally invasive technique that may be associated with local anaesthesia or diagnostic and therapeutic procedures which do not necessarily require general anaesthesia. Standard monitoring requirements are not sufficient to ensure an effective control of pulmonary ventilation and deep sedation. Capnography in pediatric sedation assesses the effect of different drugs on the occurrence of respiratory failure and records early indicators of respiratory impairment. The Bispectral index (BIS) allows the reduction of dose requirements of anaesthetic drugs, the reduction in the time to extubation and eye opening, and the reduction in the time to discharge. In the field of pediatric sedation, capnography should be recommended to prevent respiratory complications, particularly in spontaneous ventilation. The use of the BIS index, however, needs further investigation due to a lack of evidence, especially in infants. In this paper, we will investigate the role of capnography and the BIS index in improving monitoring standards in pediatric sedation.

1. Introduction

Sedation in children is increasingly emerging as a minimally invasive technique that may be associated with local anaesthesia or diagnostic and therapeutic procedures, which do not necessarily require general anaesthesia. During pediatric sedation, the problems to be addressed are linked to a higher risk of upper airway obstruction that can lead to hypoventilation and apnoea. In children who are not always able to cooperate, continuous monitoring of spontaneous ventilation and the "depth" of sedation is therefore essential. In pediatric patients under sedation, standard monitoring requirements, including an electrocardiogram, heart rate, noninvasive blood pressure, pulse oximetry, and respiratory rate, are not sufficient to ensure effective control of pulmonary ventilation and deep sedation. In this review, we will investigate the role of the capnography and the BIS index to improve standards of monitoring in pediatric sedation. Moreover, due to an increasing interindividual variability, maintaining the intended level of sedation is often difficult in children; therefore, the use of cerebral monitoring to indicate the depth of anaesthesia could be particularly useful.

2. Capnography

Respiratory monitoring should include the assessment of two components: oxygenation and ventilation. The pulse oximetry has become standard monitoring for assessing oxygenation in conscious patients. End-expiratory carbon dioxide (End-tidal CO_2) analysis allows assessing of the adequacy of ventilation. The Joint Commission on Accreditation of Healthcare Organizations and The American Academy of Pediatrics [1, 2] have recently recommended capnography monitoring, particularly during sedation. The normal value of End-tidal CO_2 ($EtCO_2$) ranges between 35 and 45 mmHg and indicates the highest concentration of CO_2 in the expiratory breath measured shortly before the next inspiration. Current standards for respiratory monitoring,

including respiratory rate and pulse oximetry, do not always indicate, in real time, the adequacy of alveolar ventilation during spontaneous breathing. In fact, airway obstruction caused by secretions or by the tongue and epiglottis falling back against the posterior wall of the pharynx does not necessarily reduce the respiratory rate. Inspection of the chest, even if performed by an experienced anaesthesiologist, is still a subjective measure and a weak indicator of adequate ventilation. Finally, arterial desaturation due to hypoventilation or obstruction (especially during O_2 administration) may occur later on. One of the pivotal characteristics of the capnography is its early identification of situations that can cause hypoxia. Therefore, in pediatric patients who have a higher risk of early arterial desaturation due to a reduced Functional Residual Capacity (the volume of air present in the lung at the end of passive expiration), the capnography is a particularly important indicator of altered ventilation [3]. The capnography provides not only the numeric value of $EtCO_2$ for each breath, but also a graphical representation of the expiratory phase into its three components (Figure 1). Capnographic Wave A represents the end of the inhalation phase while Wave B represents the beginning of the exhalation phase. Together, A-B indicate Phase I of exhalation and represent an anatomical dead space. Waves B-C represent Phase II: the exhalation of dead space gas mixed with alveolar gas. Wave D indicates the end of exhalation and at the same time the maximum or highest CO_2 concentrations ($EtCO_2$). Phase III corresponds to C-D Waves, that indicates the alveolar gas plateau. Finally, together Waves D-E represent the next inhalation. In Figures 2, 3, 4, and 5, common changes in the trend of the capnographic curve during sedation of a pediatric patient are shown. Recent technological advances have allowed the use of capnography in the management of nonintubated children in spontaneous breathing, even in newborns. In addition, it has also been used in different environments other than in the operating room. Capnography monitors use different types of technology: Mainstream, Sidestream (in use for several years), and the more recently introduced Microstream [4]. In the Mainstream, the sensor is positioned on an airway adapter between the endotracheal tube and the ventilator. In Sidestream monitors, a sample of the gas exhaled by the patient is continuously aspired by a sensor located in the monitor itself. In both types of capnography, humidity and secretions can often occlude the sampling circuit, and the presence of an anesthetic vapor can affect the measurement, especially in pediatric patients because of dilution along the sampling tube. The Microstream system [5] has allowed none of those limitations presented by other systems to be exceeded. In fact, while other capnography systems require a minimum sample of 100–150 ml/min, this system has a sampling chamber of 15 microliters and is reliable even with a capacity of only 50 ml per minute. The Microstream capnography technique can be connected to devices that deliver oxygen through the nose, simultaneously but independently from the sampling of CO_2, consequently avoiding alterations in measurement. The opportunity to sample both nasal and oral exhaled CO_2, which is particularly useful in "mouth breather" subjects, is offered by more recent sampling devices. For specific procedures such as a gastroscopy, special devices, that is, the "smart Bitebloc" have been developed. This device provides protection to the gastroscope, and furthermore, facilitates its introduction. In addition, the "smart Bitebloc" simultaneously supplies O_2 and detects the concentration of exhaled CO_2. Recent capnography systems are compatible with an MRI (Magnetic Resonance Imaging).

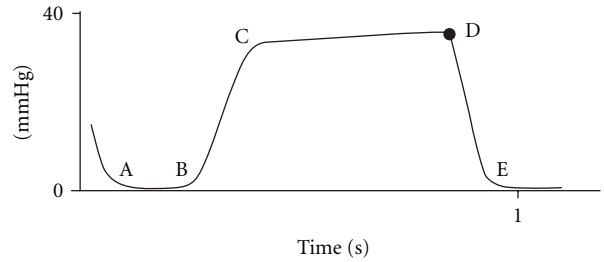

Figure 1: Analysis of the capnograph wave. A: End of inhalation; B: Beginning of exhalation; B–D: Exhalation of alveolar gas; D: End exhalation and point of maximal or highest CO_2 concentration {end-tidal CO_2 ($EtCO_2$)}; D-E: Inhalation.

Recent studies on the use of the capnography in pediatric sedation have assessed the effects of different drugs on the occurrence of respiratory failure. In children sedated in the emergency room for various procedures, opioids combined with midazolam have resulted in a greater increase in $EtCO_2$. This is due to probable synergistic effects of opioids/midazolam on respiratory activity compared to the combination of midazolam/ketamine. However, the midazolam/ketamine combination in turn has caused a greater increase in the values of carbon dioxide compared to the administration of midazolam alone [6]. Tobias shows that in pediatric sedation, midazolam 0.05 mg/kg, associated with ketamine 0.5 mg/kg every 1-2 minutes, has a lower incidence of adverse cardiorespiratory events compared to other schemes proposed in the literature, as demonstrated by the low incidence of hypercapnia [7]. There is no evidence of respiratory depression with the use of ketamine 1.5 mg/kg IV. In fact, $EtCO_2$ values did not exceed 47 mmHg at any time during the procedure performed on pediatric patients [8]. Despite the evidence-based medicine regarding the use of ketamine, hypercapnia resulting from airway obstruction due to increasing secretions was reported. Yldzdas et al. studied 126 sedated children, divided into 5 groups according to the use of ketamine, midazolam, ketamine/midazolam, midazolam/fentanyl, and propofol. After the administration of propofol, 52% of the patients showed an increase in $EtCO_2$ [9]. The authors stressed that hypoxia and hypercapnia were observed in 3.2% of all the patients, whereas hypercapnia alone was found in 16.6%. Therefore, on the basis of the pulse oximetry alone, few patients (4 out of 21) were identified as showing no respiratory depression. Other studies, however, have shown no increase in $EtCO_2$ with continuous infusions of propofol [10]. Another area of interest is the comparison of the Capnography with traditional methods such as the pulse oximetry or the monitoring of thoracic

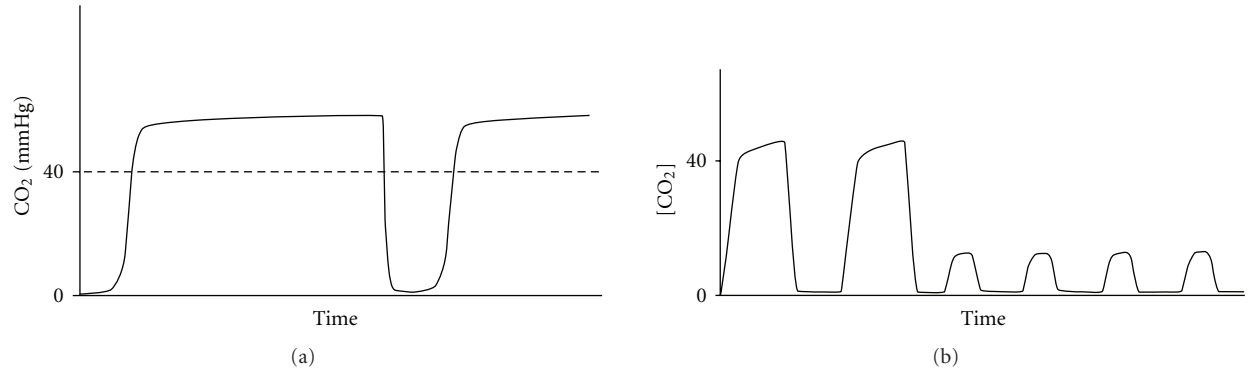

Figure 2: (a) Bradypneic Hypoventilation (type1). (b) Hypopneic Hypoventilation (type2).

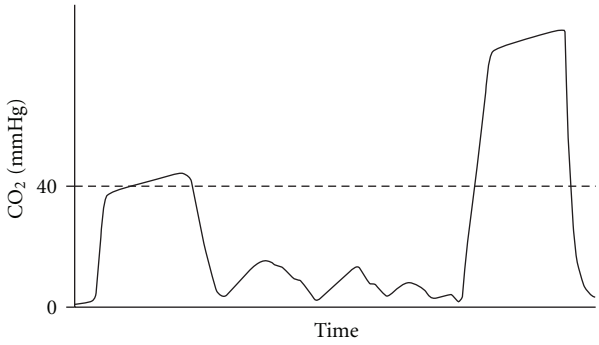

Figure 3: Hypoventilation with a shallow breath followed by a deep breath.

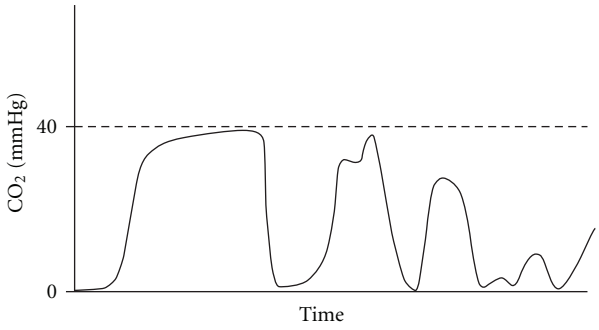

Figure 4: Obstruction of the airways.

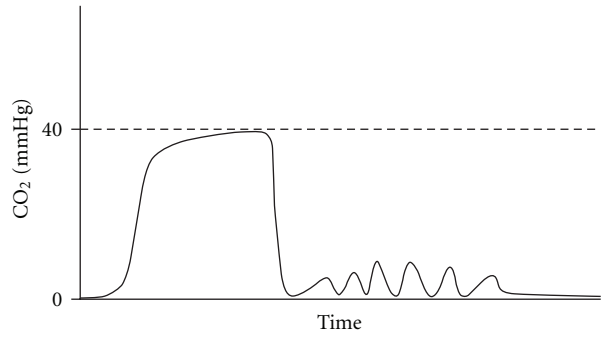

Figure 5: Apnea.

impedance to assess phases of hypoventilation during sedation. There are 2 types of hypoventilation that occur during procedural sedation. Bradypneic hypoventilation (type 1), commonly observed with opioids, is characterized by an increased $EtCO_2$, an increased $PaCO_2$ and a decreased respiratory rate. Bradypneic hypoventilation is graphically represented by a high amplitude and a wide capnogram and can readily be distinguished from hyperventilation which is characterized by increased respiratory rate, low-amplitude, and a narrow capnogram. Hypopneic hypoventilation (type 2) occurs most commonly with sedative hypnotic drugs and is characterized by a normal or decreased $EtCO_2$ and an increased $PaCO_2$. Hypopneic hypoventilation is graphically represented by a low amplitude capnogram. Both capnography and capnometry have been described the early indicators as much as the only indicators of respiratory impairment [11–13]. Moreover, with Microstream detection systems, the simultaneous administration of oxygen does not reduce the effectiveness of the capnography.

Koniaris has demonstrated in his analysis of 600 cases of sedations that capnography monitoring can be useful in proving the absence of a drug overdose during endoscopic procedures. In addition, he reiterates the utility of capnography when the patient's respiratory excursions are not visible to the anesthesiologist [14]. This happens for example in an MRI where verbal stimulation, in order to assess the level of sedation, could affect the quality of the examination.

3. The Bispectral Index

The Bispectral Index (BIS) is based on an integrated analysis of Electroencephalography (EEG) recordings obtained from electrodes placed in the frontal-parietal areas and expressed numerically on a scale from 0 to 100. The numerical values in sedated patients range from 60 (deep sedation) to 90 (conscious sedation) and are related to the "depth" of anesthesia, but not to analgesia. During pediatric sedation, the BIS index may be particularly important to establish the "depth" of anesthesia, because the patient's anaesthetic plane often becomes unexpectedly deeper, associated with breathing depression. Up to now, monitoring of the levels of

anesthesia was evaluated through the use of sedation scales such as the Ramsey and University of Michigan Sedation Scale (UMSS), both during the procedure and in the recovery room. Since these scales use verbal or painful stimuli to assess a response, the BIS index appears to be particularly useful in situations such as MRI, SPECT (Single-Photon Emission Computed Tomography), and in the Emergency Room, where the patient cannot be reached by verbal contact or where stimulation can interfere with the outcome of the procedure (e.g., sudden movements caused by stimulation during an MRI that requires absolute immobility).

As far as the role of the BIS index in children is concerned, the correlation between BIS index and intravenous drugs is valid if propofol, midazolam, thiopental, and fentanyl are used. The correlation is always based on the dose of the drug, the rating scales of sedation and the values of the BIS index [15]. The use of the BIS index in pediatric sedation was proposed when using drugs with long half-life (thiopental, chloral hydrate), either under sedation or in the postoperative period, to avoid dangerous resedation in the recovery room and to achieve a safer discharge [16]. However, this has not been confirmed in recent studies by McDermott and Overly who have shown an insufficient reliability of the use of the BIS index during sedation either with chloral hydrate or with ketamine [17, 18]. Even N_2O does not show any significant correlation with BIS values [19]. The BIS index is also used to guide the titration of intravenous anesthetics such as propofol. During deep sedation, the BIS index can guide the administration of propofol (BIS average 45), avoiding intraoperative awareness or too deep sedation [20]. Sedation with propofol in children is absolutely not a conscious sedation and reiterates the greater utility of the BIS index in guiding the titration of this drug [21]. Other studies have stressed the importance of adjusting the dosage of propofol on the values of the BIS index in order to reduce the incidence of an overdose [22, 23]. The BIS index can be used to guide the administration of anesthesia in children over two years of age. However, in infants under the age of six months, there is no correlation between the values of the BIS index and other measures for assessing the "depth" of anesthesia [24, 25]. The Cochrane review of BIS index monitoring during anaesthesia examined the results of twenty studies. It was found that BIS index-guided anaesthesia reduced the dose requirement of anaesthetic drugs, reduced the time to extubation and eye opening, and reduced the time to discharge. There was a reduction in awareness in high-risk patients. However, all the data regarded the use of the BIS index in the adult population alone [26].

4. Conclusions

In the field of pediatric sedation, performed both inside and outside the operating room, the capnography and the BIS index appear very promising in improving safety and providing guidance during the procedures and during the awakening stage. In fact, the capnography should be recommended for the prevention of respiratory complications during sedation in children, particularly in spontaneous ventilation. The use of the BIS index was the only cerebral monitoring validated by the Cochrane company, at least in adult patients. Data for children is copious and seems comforting, but further developments and investigations are necessary due to the lack of evidence, especially in infants.

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Hindawi Publishing Corporation
International Journal of Pediatrics
Volume 2010, Article ID 701257, 15 pages
doi:10.1155/2010/701257

Review Article

Pediatric Sedation: A Global Challenge

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Received 16 June 2010; Revised 6 August 2010; Accepted 16 August 2010

Academic Editor: Savithiri Ratnapalan

Pediatric sedation is a challenge which spans all continents and has grown to encompass specialties outside of anesthesia, radiology and emergency medicine. All sedatives are not universally available and local and national regulations often limit the sedation practice to specific agents and those with specific credentials. Some specialties have established certification and credentials for sedation delivery whereas most have not. Some of the relevant sedation guidelines and recommendations of specialty organizations worldwide will be explored. The challenge facing sedation care providers moving forward in the 21st century will be to determine how to apply the local, regional and national guidelines to the individual sedation practices. A greater challenge, perhaps impossible, will be to determine whether the sedation community can come together worldwide to develop standards, guidelines and recommendations for safe sedation practice.

1. Introduction

Pediatric sedation is a challenge which spans all continents. Over the past decade, sedation has grown to encompass specialties outside of anesthesia, radiology, and emergency medicine. Until the 1990s, sedation in the United States was limited predominantly to delivery by anesthesiologists, radiologists, dental medicine, and emergency medicine physicians. It now encompasses other specialties which include gastroenterology, intensive care medicine, hospital medicine, pediatric medicine, and nursing [1–3]. Worldwide, however, the majority of pediatric sedation is still administered by anesthesiologists. All sedatives are not universally available and local and national regulations often limit the sedation practice to specific agents and those with specific credentials. Some specialties have established certification and credentials for sedation delivery whereas most have not [4–10]. The challenge is that there is no standardization of sedation practice, guidelines, and credentialing: Many specialties have guidelines and recommendations for their own practice, which may in fact contradict the guidelines set forth by other specialty societies [5, 11–13].

The challenge facing sedation care providers moving forward in the 21st century will be to determine how to apply the local, regional, and national guidelines to the individual sedation practices. A greater challenge, perhaps impossible, will be to determine whether the sedation community can come together worldwide to develop standards, guidelines, and recommendations for safe sedation practice. Some of the relevant sedation guidelines and recommendations of specialty organizations worldwide will be explored. To our knowledge, this will be the first paper to present a comprehensive representation of guidelines across the specialties spanning the globe.

2. Models of Pediatric Sedation: A Global Tour

This paper will explore the existing sedation models, citing examples of sedation care delivered by different individual specialties. Each model and specialty have created their own set of guidelines and models for sedation administration. We have conducted a comprehensive review of the literature to present representative models of sedation delivery directed

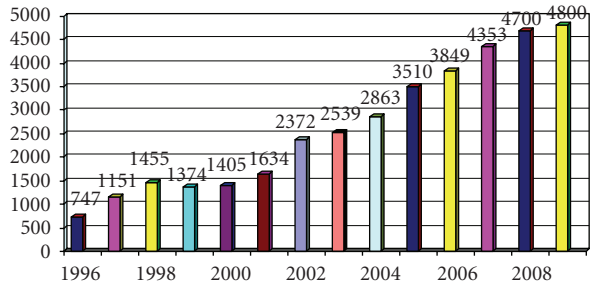

Figure 1: Sedation volume at Hadassah Hospital, Israel.

by different specialties. A summary of the representative models is presented in Table 1.

2.1. Anesthesiologist-Directed Sedation Model [14]. Most common in areas outside the United States, with the exception of countries which have limited anesthesia providers, is the delivery and oversight of sedation by anesthesiologists. The Hadassah University Hospital in Jerusalem was the first hospital in Israel to set up a Sedation Service. This Sedation Service is an example of an anesthesia-directed sedation program and was developed to involve a multispecialty team comprised of specially trained nurses, all with intensive care background, and pediatric anesthesiologists. All sedation is delivered by protocols which were developed by the Department of Anesthesia and approved by the Hospital.

The Sedation Service provides an efficient framework for easing the pain and anxiety in a number of diagnostic or therapeutic procedures performed out of the operating room (OR). As the demand for procedural sedation has increased, so too has the sedation volume. Gradually, the sedation service has evolved to care not only for the pediatric population but also to provide sedation across the age spectrum to even include the elderly. The service has expanded to encompass sedation delivery to over 5000 patients a year, across all specialties in over 40 departments, institutes, and clinics within the Hospital (Figure 1).

The sedation process begins before the patient arrives for the procedure. All patients are carefully screened for preexisting medical illness and appropriateness for sedation before arrival. For outpatients, a few days before the required procedure, a telephone evaluation is performed by the sedation nurse with the child's parents or guardian. For children in hospital, the physician caring for the child relays the pertinent clinical information and also provides the family with informational materials describing the sedation process. Much of the triage is done without the direct involvement of the anesthesiologist, following existing guidelines. Per protocol, however, anesthesiologists are consulted for patients who are American Society of Anesthesiologists (ASA) 3 and 4 [11]. Sedation is delivered in accordance with the American Academy of Pediatrics and American Society of Anesthesiologists guidelines and hospital policy [11, 15].

Sedation delivery is divided between nursing administered and anesthesiologist delivered. Nursing-administered sedation is limited to the oral route with midazolam or chloral hydrate only. Only ASA 1 and 2 patients over the age of one month are allowed to be sedated by nurses who must be able to visualize the patient throughout. Patients who do not meet the above criteria are referred to an anesthesiologist for direct management. A review of outcome supports the screening process in the majority of cases: of all procedures which are under the direct care of a nurse, anesthesiologist assistance is required in 6.5% of the cases. Eighty percent of all procedures are triaged to anesthesiologist management with propofol, and the remaining 20% are sedations that are delivered by nursing.

The most frequent adverse event recorded was a decrease in oxygen saturation, which occurred in 132 cases (1.5% of all cases), all under the care of an anesthesiologist. All these children were sedated either in the oncology clinic (35 patients) (where some refused to accept an oxygen mask before sedation) or for flexible bronchoscopy (97 children), where decreases in oxygen saturation are frequent. All these children had received propofol as the sole sedative agent. The oxygen saturation recovered spontaneously in 74 children and after an increase in oxygen flow in the remaining 58 children. Postsedation vomiting was noted in 6 children (0.07% of all cases) on arousal and resolved spontaneously with no respiratory or other complications and without the need for hospital admission. Finally, cardiac arrhythmia that did not require specific treatment was recorded in 12 children undergoing cardiac angiography.

2.2. Gastroenterologist Directed Sedation Models: From the United States to South America. Gastroenterologists in the United States and Europe have lead the way in establishing guidelines and presenting outcomes for gastroenterologist-administered and/or supervised sedation of adults [6, 16, 17]. The literature on pediatric sedation performed by gastroenterologists for upper and lower endoscopy is limited. In the United States, fentanyl and midazolam remain common agents administered via the intravenous route [18]. The addition of capnography, although not required by the American Society of Gastroenterologists, is recognized as a useful means of identifying and managing alveolar hypoventilation prior to the occurrence of oxygen desaturation [18].

Pediatric gastroenterologists in the United States have described the administration of ketamine as efficacious for gastrointestinal sedation, with an accompanying 9.5% incidence of transient laryngospasm [19]. In Brazil, 78.6% of all pediatric endoscopies at a large hospital described the use of midazolam and meperedine sedation administered under the auspices of pediatricians or gastroenterologists. The remainder of the procedures, approximately 20%, was performed by anesthesiologists under general anesthesia [20].

Nursing-Administered Propofol Sedation (NAPS) or Nonanesthesia-Administered Propofol Sedation (NAAPS) are mnemonics which refer to the administration of propofol by qualified nurse(s) who operate under the direction of a nonanesthesiologist physician. To date, this technique has only been applied for adult sedation. Although

Table 1

	Anesthesia directed	Gastroenterologist directed	Hospital medicine directed	Emergency medicine directed	Critical care directed
Sedation provider	*PHYSICIAN* Anesthesiologist *NURSE* Nurse Anesthetist	*PHYSICIAN* Pediatrician Gastroenterologist Anesthesiologist *NURSE*	*PHYSICIAN* Pediatrician Emergency Medicine Intensive care	*PHYSICIAN* Emergency Medicine	*PHYSICIAN* Intensivist *NURSE*
Training	Sedation course Pediatric Advanced Life Support (PALS)	Sedation course	Sedation course Airway management training	Educational program	No additional training

NAPS/NAAPS is an accepted method of propofol administration by the American Society of Gastroenterologists, its administration by nurses is prohibited or restricted by many State Registries of Nursing within the United States. For example, on October 13, 2005 the Minnesota Board of Nursing issued a statement which supported the administration of propofol by registered nurses but specified that the nurse also has the prerogative to decline delivery should it be perceived as unsafe in the particular circumstance [21].

NAPS is administered via algorithms, all of which were intended for patients over 12 years of age [22, 23]. It is important to recognize that NAPS was not designed with the intent for pediatric application, because most adult sedations are moderate, while most pediatric sedations are deep. Obviously, this difference significantly changes the risk of adverse events. A prospective cohort study of 27,061 adults evaluated the need for airway rescue with NAPS in two ambulatory GI settings which administered propofol consistent with NAAPS guidelines. Propofol was administered by the endoscopy nurse and supervised by the endoscopist. Monitoring consisted of pulse oximetry and clinical assessment. A mean propofol dose of 161 mg (range 50–650 mg) was used for endoscopic gastroduodenoscopy and 116 mg (range 30–500 mg) with 25 mg of meperidine administered for colonoscopy. The target was moderate-to-deep sedation. It is interesting to notice that less propofol was used for "lower" endoscopies, because meperidine was added as an adjuvant. Oxygen saturation fell below 90% in 2.3% of the adults and 6 patients required brief positive pressure ventilation [12, 17]. Only 23% of all the patients had oxygen before the procedure.

A recent study of 498 nurse administered propofol sedations for bronchoscopy (18–86 years of age) reported similar results. 1-2 mg IV midazolam and 25–50 mcg IV fentanyl is administered prior to a 20–40 mg IV propofol bolus. 10–20 mg IV propofol is administered every minute to maintain adequate sedation. The propofol is titrated to the sedation requirements of the procedure. The average propofol dose was 3.13 mg/kg (range 0.12–20 mg/kg). Every patient received supplemental oxygen during the procedure. Overall, there was a 6.6% incidence of sedation related adverse events. 2.8% were reported as major adverse events, which included pulmonary hemorrhage (1.2%), hypoxia/respiratory failure (0.8%), bronchospasm (0.2%), airway obstruction by tumor (0.2%), stridor (0.2%), and pneumothorax (0.2%) [24]. 1.2% of these major events were classified as likely to be sedation-related. There was no sedation-related death. This study was not randomized. The safety of NAPS may have been confounded by the supplemental fentanyl and midazolam.

The worldwide safety experience of endoscopist-administered propofol sedation now exceeds 460,000 patients [25–27]. Additional studies are warranted in order to validate the safety of NAPS in varied clinical settings, for patients of varied ages and medical conditions. To the best of our knowledge, the application of NAPS for pediatric sedation is not being practiced at this time nor is it supported by any specialty society worldwide, for many reasons (deeper sedation is usually required in children, their airways are narrower, and their time to reaction to an adverse event is shorter).

Although the adult literature cites propofol administration by nurses and gastroenterologists, the pediatric literature describes only anesthesiologist-delivered propofol for pediatric gastrointestinal procedures. The risk of respiratory depression, apnea, and cardiovascular instability in addition to the narrow therapeutic window between spontaneous ventilation and apnea has deterred pediatric gastroenterologists and other nonanesthesia care providers from using it for pediatric endoscopy [28–30].

2.3. Hospitalist-Delivered or Supervised Sedation in the United States. Hospital medicine is an evolving specialty which for pediatrics, is represented by pediatricians, emergency medicine or intensive care medicine physicians. The majority of pediatric hospitalists are pediatricians who are committed to a hospital-based practice. Pediatric hospitalists have developed sedation programs in collaboration with their hospital's Department of Anesthesia.

At St. Louis, a pediatrician-delivered propofol sedation program sets the standard for organization, safety, and comprehensive services. Recent oral presentations at the Pediatric Academic Society meeting at Vancouver, May 1–4, 2010 presented the outcomes of their nonanesthesiologist-delivered sedation program (written communication). Under the direction of Dr Doug Carlson, the Chief of Pediatric Hospital Medicine at the Children's Hospital, St. Louis of Washington University, pediatricians undergo rigorous didactic and practical training in sedative administration and airway

management. The hospitalists deliver over 2,000 sedation per year, mostly ketamine based.

At this program, there is a three-tiered system of pediatrician delivered sedation, each tier of which requires specified training. The first tier provides sedation services in the emergency department, primarily utilizing ketamine or nitrous oxide. Training for this tier consists of a two-hour didactic orientation with continuing hands-on experience. The second tier provides sedation throughout the hospital and includes the emergency department, ambulatory areas, and inpatient areas both during the day and as needed overnight. Pediatricians who provide second-tier service may use the agents of the first-tier in addition to pentobarbital and dexmedetomidine. Training for this tier requires a provision of first-tier services for a minimum of a year in addition to five days of operating room (OR) training in sedation administration and airway management with an anesthesiologist. The third-tier sedation service builds upon the 1st and 2nd tier with the additional credentialing to provide deep sedation with propofol. Propofol credentialing requires a three-hour didactic session followed by ten days of OR training under the auspices of an anesthesiologist and the completion of 25 supervised propofol sedations. In order to maintain certification to deliver propofol, the pediatricians must administer a minimum of 50 propofol sedations per year, always with the immediate availability of an anesthesiologist if requested.

2.4. Emergency Medicine-Delivered Sedation Programs. In the United States, pediatric emergency medicine is a specialty of its own. Although not yet a recognized specialty in other countries, the emergency medicine physicians have lead the way in providing pediatric sedation. Historically, as early as the 1980s, the delivery of sedation by emergency medicine physicians was limited to the emergency department (ED) site only [31, 32].

Over the past decade, some of these emergency medicine physicians have established sedation services throughout the hospital, primarily in the Department of Radiology for imaging studies [33–35]. The delivery or supervision of moderate-to-deep sedation by emergency medicine physicians is a growing practice for many reasons: the foremost reason is that these physicians already have sedation skills and are proficient in airway management and cardiovascular resuscitation. Many children's hospitals have established formal sedation training processes for credentialing emergency medicine physicians in pediatric sedation. This training has included an educational program which involves didactics, reading material, and successful completion of a multiple choice test for all emergency medicine physicians and nurses involved in sedation [36–40].

The emergency medicine specialty has made valuable contributions to the sedation literature, particularly with respect to ketamine delivery, the introduction of new sedative agents and sedation outcomes. A meta-analysis of pooled individual-patient data from 32 ED studies examined the clinical variables which predict airway and respiratory adverse events with ketamine administration by emergency medicine physicians. In 8,282 pediatric ketamine sedations, the overall incidence of airway and respiratory adverse events was 3.9%, with the following significant independent predictors: younger than 2 years (odds ratio [OR] 2.00), aged 13 years or older (OR 2.72), high intravenous dosing (initial dose of 2.5 mg/kg or total dose of 5.0 mg/kg; OR 2.18), coadministration of anticholinergic (OR 1.82), and coadministration of a benzodiazepine (OR 1.39). Oropharyngeal procedures, underlying physical illness (American Society of Anesthesiologists class 3), and route of administration (intravenous versus intramuscular) did not predict adverse outcome [41]. In another consecutive case series of 1,022 children, Green et al. report that ketamine at doses of 4 to 5 mg/kg intramuscularly produced adequate sedation in 98% of children. They reported airway complications in 1.4% of patients that included laryngospasm, apnea, and respiratory depression, all of which were quickly identified and treated without intubation or sequela. Emesis occurred in 6.7% without evidence of aspiration [42].

Historically, ketamine, narcotics, nitrous oxide, and benzodiazepines were the agents of choice in the ED. Ketamine has been administered alone or in combination with other sedatives. The published outcomes have been important in establishing the safety of emergency medicine sedation practice. In a randomized controlled trial in 260 children aged 5 to 15 years, Kennedy et al. found that a ketamine and midazolam combination was safer and more efficacious than a fentanyl and midazolam combination for sedation in orthopedic procedures. Hypoxia, while children breathed room air, occurred in 6% of patients receiving ketamine and midazolam versus 20% of patients in the fentanyl and midazolam group [43].

Over the past decade, propofol has been gaining widespread interest. Although propofol is considered by the FDA to be an anesthetic agent, the American College of Emergency Physicians has included it in their sedation guidelines [7]. There is a growing body of evidence supporting the safe use of propofol for procedural sedation by emergency physicians. A review presented adverse events following propofol sedation of children following an opioid premedication, prior to undergoing orthopedic reduction in the emergency department. All children received supplemental oxygen (1 L/minute by nasal cannula) and continuous capnography and had depth of sedation assessed every 2 minutes. Adverse airway or respiratory events with intervention occurred in 14 of the 125 enrolled children (11%): jaw thrust in 4/125, the need for increased supplemental oxygen in 6/125, and bag-valve-mask ventilation in 4/125. All interventions required were brief (<30 seconds). Capnography was successful in detecting apnea before clinical examination or pulse oximetry in all 5 occurrences and similarly first detected airway obstruction in 6 of the 10 occurrences. The median maximal modified Ramsay score was 6 (range 3 to 8), that is, deep sedation [44].

In another prospective observational study performed in the ED, propofol-induced procedural sedation was reported to have the lowest rate of respiratory depression when compared with methohexital, fentanyl/midazolam, and etomidate [45]. There were no significant complications.

Regardless of which agents and which route of delivery are chosen for the delivery of sedation by emergency medicine physicians, the outcomes parallel those of other specialties. A review of a pediatric emergency medicine-staffed sedation service for radiological imaging studies showed that of 923 sedations, overall there was a 10% incidence of adverse events. The majority of the sedations included pentobarbital, fentanyl, midazolam, and/or chloral hydrate. 55 patients received propofol alone. There was a small 0.76% incidence of major adverse events (significant hypoxemia, apnea, laryngospasm, and stridor) which required intervention that may have included repositioning, brief positive pressure ventilation, oral or nasal airway, supplemental oxygen, or vigorous stimulation. Sedation failed to achieve adequate conditions in 17 (1.8%). There was no incidence of endotracheal intubation or cardiopulmonary resuscitation with pharmacologic intervention [33].

In Memphis, Tennessee, a university-affiliated group of pediatric emergency physicians provide sedation services to a radiology department during weekdays at a freestanding urban children's hospital. Of 1285 patient encounters, deep sedation was provided to 1027 children with pentobarbital (midazolam, fentanyl, or both added to pentobarbital if needed) in 65% of cases, propofol in 31%, and ketamine (with or without midazolam) in 4%. 258 children received moderate sedation with chloral hydrate (86%) and 14% received oral diazepam. Procedural sedation times for the most frequently performed imaging studies ranged from 5 to 183 minutes, with a 99.1% incidence of successful imaging studies. The incidence of adverse events was extremely low: 3 children (0,2%) had adverse events which included oxygen desaturation <90% which required in one child brief positive pressure ventilation and hypotension requiring intravenous crystalloids [35]. Other studies support these outcomes and demonstrate that both moderate and deep sedation can be safe and effective when properly administered by experienced emergency physicians [46, 47].

As the emergency department continues to provide sedation services in other areas of the hospital, there may arise a difference of opinion between the emergency medicine physicians and their anesthesia colleagues over a variety of issues. The first issue is that of NPO (nil per os) standards. The emergency medicine physician is frequently accustomed to deliberating the risks versus benefits of providing sedation to children who present in an emergent situation. These situations require balancing the emergent/urgent need to deliver sedation for a procedure against the failure to adhere to ASA and AAP guidelines and the possible aspiration risk associated with a curtailed NPO time [11, 15].

The emergency medicine literature has provided large studies which review the outcome of sedating children outside of the NPO recommendations. The largest study to date reviewed 1014 patients for whom fasting status was available for 905 (89%) patients. Of these 905 patients, 509 (56%) did not meet fasting guidelines as suggested by the American Academy of Pediatrics and the American Society of Anesthesiologists. In this group, there were no episodes of aspiration. Seventy-seven adverse events occurred in 68 (6.7%) of the 1,014 patients. All adverse events were minor and successfully treated. These adverse events occurred in 32 (8.1%) of 396 patients who met and 35 (6.9%) of 509 patients who did not meet fasting guideline Emesis occurred in 15 (1.5%) patients. There were no episodes of aspiration [48]. But much more larger studies are required to accurately validate the incidence of these rare adverse events [42, 49]. Using careful triage and evaluation, including assessment of the urgency of the required procedure, emergency medicine physicians have supported their practice of delivering sedation outside of NPO recommendations when appropriate: they use mostly ketamine which relatively preserves the protective reflexes. Also, there is a lack of airway manipulation with an endotracheal tube. All together, that may reduce the risk of aspiration, compared to general anesthesia. Another factor that can influence their decision, is the administration of opioids, which can delay gastric emptying.

Another area of controversy is the utility of supplemental oxygen delivery during sedation. In a 2007 review of emergency medicine-delivered sedation, the role of supplemental oxygen as a standard was reviewed. Supplemental oxygen did not reduce (or trend toward reducing) the incidence of hypoxia in patients moderately sedated with midazolam and fentanyl. With deep sedation, supplemental oxygen was determined to mask transient desaturation which can occur after a sedative drug bolus [50, 51].

2.5. Critical Care Specialists and Sedation Models. Some sedation models utilize intensive care medicine physicians to administer and provide pediatric procedural sedation out of the intensive care unit. One such model is at the Children's Hospitals and Clinics of Minnesota, Minneapolis. Over a 3-year period, they described the outcome of 7304 propofol elective sedations which were administered by critical care physicians and advanced practice nurses, under the auspices of an anesthesiologist. The most common procedures were diagnostic radiological imaging studies (MRI, CT, and nuclear medicine), short oncologic procedures (lumbar punctures, bone marrow biopsies, and intrathecal chemotherapy) and neurological testing which includes electroencephalograms, evoked potentials and hearing tests. All patients received supplemental oxygen. They report a 2.9% incidence of oxygen desaturation <85%, hypotension in 31.4% (drop of systolic BP of ≥25 mm Hg from baseline), intubation in 0.03%, and the need for brief positive pressure ventilation in 0.37%. There were no failed sedations and no cardiopulmonary resuscitation [52]. The outcomes rivaled those published by Cravero et al. of 49, 836 propofol sedations provided by physician and nurse providers of different specialties. Almost half of the sedation care providers were identified as intensive care physicians. This consortium of sedation care providers from multi-institutions reported brief desaturation <90% in 7.16%, cardiac arrest in .02%, intubation in .53% and positive pressure ventilation in 5.13% [1]. Further studies are needed to determine whether there is a difference in outcome between the different specialists administering propofol, and between fasted and nonfasted patients. Both of these studies

are confounded by different definitions of adverse events, a varied patient population and lack of uniform propofol protocols which would have standardized delivery regimens and provided a more accurate means of comparison.

2.6. Nursing Delivered. A large model of nursing delivered pediatric sedation is at Boston Children's Hospital, within which there are approximately 7,000 nursing-administered sedations performed annually. Half of these sedations are delivered in the Department of Radiology, 25% in the Emergency Department and the remaining 25% are scattered throughout the hospital (oncology, dental, gastroenterology, and cardiology). Within the institution, the Department of Radiology sets the standard for a protocol-driven sedation program, administered by specialized nurses under the direct supervision of sedation-designated anesthesiologists. These anesthesiologists represent a small, core group of physicians who are committed to safe, efficacious sedation delivery as well as to the collection of reliable Quality Assurance (QA) data. The QA data sheets are designed and tailored to each sedation area as well as to the sedation agent. This QA data is reviewed and analyzed monthly and is the essence of the sedation program, guiding the evolution of sedation practice. As the sedation program has evolved, the older sedatives such as pentobarbital and chloral hydrate have been largely replaced with dexmedetomidine and ketamine.

A review of 16,467 elective sedations delivered by radiology nurses at Boston Children's Hospital reported a total of 70 (0.4%) pulmonary adverse events: 58 oxygen desaturations (<5% of baseline for over 60 seconds), 2 pulmonary aspirations (no clinical sequelae), 10 airway resuscitations (brief positive pressure mask ventilation), and 0 (0.0%) cardiovascular events. There was no cardiac arrest and no need for intubation. Single sedation agents were associated with a lower risk than the administration of multiple agents ($P < .001$) [53].

3. Sedation Guidelines and Recommendations: A Global Overview

The challenge facing sedation care providers is the need to balance the delivery of safe and effective sedation while adhering to the sedation guidelines of one's specialty's society. The sedation guidelines are not all consistent between specialty societies. This paper will compare the sedation guidelines of existing specialty organizations as well as of some institutions, highlighting the similarities, differences and opposing views on areas of particular interest.

A global look at sedation guidelines reveals that there is lack of consistency not only between the specialties within a single continent, but also between the continents. These guidelines differ not only with respect to appropriate medications, routes of delivery, NPO status, and physiological monitoring requirements, but also with respect to the appropriate skill sets of the sedation care provider who delivers different levels of sedation. We will review the notable sedation guidelines of notable adult and pediatric specialty societies (anesthesia, dental medicine, emergency medicine, and gastroenterology) both within the United States and abroad. We will identify the important and controversial differences between the guidelines.

3.1. The American Academy of Pediatrics (AAP) [54, 55]

3.1.1. Overview. In 1983, after three children died in a single dental office, the AAP charged the Section on Anesthesiology with the responsibility of developing guidelines for the sedation practice of children by nonanesthesiologists. In 2002, a clarifying addendum to the AAP guideline was published [55]. Subsequently, the ASA revised the document which defined the sedation levels within the sedation continuum, descriptors which were adopted by the Joint Commission of Accreditation of Healthcare Organizations (Joint Commission) [56]. These guidelines were designated for children who received sedation in all in and out of the hospital-venues, including private offices. This addendum retired the phrase "conscious sedation" in preference for depths of "sedation/analgesia" that included minimal, moderate, and deep sedation. They emphasized that sedatives were only to be administered under medical supervision (no home prescriptions) and only by "individuals skilled in airway management and cardiopulmonary resuscitation". These guidelines introduced the important concept of ensuring that sedation care providers were skilled and trained in "patient rescue" [56].

In 2006, the guidelines were again updated to specify that sedation must be administered under appropriate medical supervision throughout all aspects of the sedation and recovery period; after careful presedation evaluation for underlying medical or surgical conditions and after appropriate fasting (NPO) for elective procedures. The NPO status must be considered in context of the need to perform the procedure when sedation is required urgently. Those who require sedation urgently may have NPO status waived after a careful assessment of the risk and benefits associated with delaying the procedure. The importance of a focused airway examination for large tonsils or anatomic airway abnormalities was identified along with the need for providers to have a clear understanding of the pharmacology of the sedatives and appropriate emergency skills, pharamacologic agents, and equipment needed for rescue. An emergency cart must be immediately accessible and stocked with age- and size-appropriate drugs and equipment to resuscitate a child of any size. Monitoring devices should include electrocardiography (ECG) machines, pulse oximeters (appropriate selection of sizes), and defibrillators [55]. End-tidal carbon dioxide monitors are very useful in situations where the child is not directly observed like in the MRI.

3.1.2. Summary of Important Recommendations

NPO Guidelines.

Clear liquids: 2 hours: include water, fruit juices without pulp, carbonated beverages, clear tea, black coffee

Breast milk: 4 hours

Infant formula, Nonhuman milk

Light meal and solid food: 6 hours

Credentials Required to Administer Deep Sedation.

(i) There must be 1 person available whose sole responsibility is to constantly observe the patient's vital signs, airway patency, and adequacy of ventilation and to either administer drugs or direct their administration.

(ii) At least 1 individual, trained and competent to provide advanced pediatric life support, airway management, and cardiopulmonary resuscitation, must be present.

Guidelines for Propofol Administration. There is no statement or recommendations.

Recommendations for Capnography. Not required but encouraged, particularly in situations where other means of assessing the adequacy of ventilation are limited [57–59].

The ASA House of Delegates on October 21, 2009, issued a statement on respiratory monitoring during endoscopic Procedures. The statement advised that capnography be considered when propofol alone or in combination with opioids and/or benzodiazepines be used for sedation [60].

3.2. American Society of Anesthesiologists (ASA) [61]

3.2.1. Overview. The American Society of Anesthesiologists (ASA) has developed "Guidelines for Sedation and Analgesia by Nonanesthesiologists which emphasize the importance of the sedation continuum in following the depths of sedation from minimal sedation to general anesthesia [56].

3.2.2. Summary of Important Recommendations

NPO Guidelines. In emergency situations, when preprocedure fasting is not practical, the target level of sedation should be modified (i.e., less sedation should be administered) for moderate sedation as well as deep.

Clear liquids: 2 h

Breast milk: 4 h

Infant formula: 6 h

Nonhuman milk: 6 h

Light or solid meal: 6 h

Credentials Recommended to Administer Deep Sedation. Privileges to administer deep sedation should be granted only to practitioners who are qualified to administer general anesthesia or to appropriately supervise anesthesia professionals [62]. This individual should have no other responsibilities except to deliver sedation and monitor the patient throughout.

Guidelines for Propofol Administration [63]. All patients who receive propofol (or methohexital) should receive care consistent with deep sedation. Accordingly, practitioners administering these drugs should be qualified to rescue patients from any level of sedation, including general anesthesia.

Recommendations for Capnography. Capnography should be considered, but is not required, for all patients receiving deep sedation and for patients whose ventilation cannot be directly observed during moderate sedation.

Recommendations for Physiologic Monitoring.

(i) Pulse oximetry with appropriate alarms is required.

(ii) Ventilatory function should be continually monitored by observation or auscultation.

(iii) Blood pressure should be determined before sedation/analgesia is initiated and measured at 5-min intervals during the sedation, unless such monitoring interferes with the procedure.

(iv) Electrocardiographic monitoring required with all deep sedation and with those who have cardiovascular disease or are at risk of dysrhythmias.

Recommendations for Oxygen Delivery. Supplemental oxygen should be used during deep sedation to reduce the frequency of hypoxemia.

3.3. Joint Commission of Hospital Accreditation in United States [64, 65]

3.3.1. Overview. The JCAHO 2004 Comprehensive Accreditation Manual for Hospitals was intended to set the standards for sedation and anesthesia care for patients in any setting. Standard PC .03.01.01 requires that a sufficient number of staff, in addition to the person performing the procedure, be present to perform the procedure, monitor, and recover the patient. The person administering the medication must be qualified to monitor the patient as well as manage whatever level of sedation or anesthesia is achieved, either intentionally or unintentionally [64].

These guidelines were meant to be inclusive of all levels of sedation as well as general, spinal, or regional anesthesia. They specified that in order to minimize complications, the appropriate drug(s) and dosages must be chosen, monitored, and administered in the proper setting, and a patient evaluation should be performed before, during, and after their use.

Credentials Recommended to Administer Deep Sedation. The anesthesia care standards require that the individuals who are "permitted" to administer sedation are able to rescue patients, independent of a code team, from whatever level of sedation or anesthesia is achieved either intentionally or unintentionally, for example, when the patient slips from moderate into deep sedation or from deep sedation into

full anesthesia. Each organization is free to define how it will determine that the individuals are able to perform the required types of rescue. The Joint Commission does not specify the training or equipment for proper rescue.

Guidelines for Propofol Administration. The Joint Commission standards do not identify specific medication. Rather, they expect that the appropriate medication be chosen for the intended level of sedation desired.

Expectations for Patient Assessment. Joint Commission standards require that the patient is reevaluated immediately (either on the procedure table or in the moments prior to administering sedation) before administering moderate or deep sedation or before the induction of anesthesia. Typically, the assessment includes vital signs, status of the airway, and response to any preprocedure medications [66].

3.4. American Association of Pediatric Dentistry/American Dental Association [4]

3.4.1. Overview. In 2006, the American Dental Association (ADA) published guidelines for the safe and effective sedation by appropriately educated and trained dentists. For children 12 years of age and under, the ADA supports the use of the American Academy of Pediatrics/American Academy of Pediatric Dentists Guidelines for Monitoring and Management of Pediatric Patients During and After Sedation for Diagnostic and Therapeutic Procedures [55].

These guidelines apply to pediatric dental patients and include two paragraphs which identify areas which are especially challenging: the sedation of the special needs patients and management of emergency situations. These guidelines recognized that if the dental patient undergoing deep sedation or general anesthesia is mentally and/or physically challenged, it may not be possible to have a comprehensive physical examination or appropriate laboratory tests prior to administering care. In these situations, the dentist responsible for administering the deep sedation or general anesthesia should document the reasons preventing the recommended preoperative assessment prior to administering sedation.

These guidelines did not require intravenous access for all patients. Rather, they condoned that in selected circumstances, deep sedation or general anesthesia may be utilized without establishing an indwelling intravenous line. These selected circumstances may include brief procedures or situations in which intravenous access is not possible.

The guidelines also reiterated those of the Joint Commission and AAPD with respect to emergency situations. The dentist responsible for the sedation accepts responsibility for the management of the sedation/anesthetic as well as for the identification and treatment of sedation/anesthesia related emergencies. Most important, this dentist assumes responsibility for ensuring the adequacy of the facility and staff and for providing the equipment, drugs, and protocols for patient rescue.

These guidelines differed from other guidelines in that they specifically identified nitrous oxide as an agent which could be used alone or in combination with other sedatives in order to achieve sedation or anesthesia.

NPO Recommendations. There are no specific recommendations. They advise that preoperative dietary restrictions must be considered based on the intended depth of sedation or anesthesia.

Credentials Recommended to Administer Deep Sedation. A minimum of three individuals must be present: one dentist who is credentialed to administer deep sedation or anesthesia and 2 additional personnel who have current certification of successfully completing a Basic Life Support (BLS) Course for the Healthcare Provider.

The dentist must be qualified to administer the deep sedation or general anesthesia. There are 2 requirements to qualify. The first qualification requires successful completion of an advanced education program on the administration and management of deep sedation or anesthesia, which must be accredited by the ADA Commission on Dental Accreditation. The second requirement is a current certification in both Basic Life Support for Healthcare Providers and Advanced Cardiac Life Support (ACLS) or an appropriate dental sedation/anesthesia emergency management course.

The dentist administering deep sedation or general anesthesia must remain within the facility until the patient meets discharge criteria (or is discharged) and must monitor the patient continuously until the patient meets the criteria for recovery.

These guidelines are unique to the others, in that they allow the dentist to provide the deep sedation/anesthesia to also perform the procedure. In these circumstances, one of the additional appropriately trained team members must be designated for patient monitoring.

Guidelines for Propofol Administration. There is no discussion of propofol in these guidelines.

Recommendations for Capnography.

> Intubated patients: Capnography required.
>
> Nonintubated patients: breath sounds must be assessed via auscultation or capnography must be continually monitored.

3.5. American College of Emergency Physicians (ACEP) [7]

3.5.1. Overview. Similar to the ASA guidelines, the ACEP guidelines apply to all patients, adults and children who receive sedation. They recognize that sedation is a continuum and maintains that practitioners should possess the skills required to rescue a patient from one level beyond the intended level of sedation. These skills are expected to include a competence in cardiovascular resuscitation and airway management which should include a patient who has achieved general anesthesia. The ACEP guidelines consider these skills to be a fundamental part of the emergency medicine training curriculum and inclusive of the training

required of all board-certified emergency physicians. These guidelines are comprehensive and include and update some previously unaddressed issues and recommendations [67].

Credentials Recommended to Administer Deep Sedation. The ACEP guidelines consider that a board-certified emergency physician is qualified to administer deep sedation. Should this physician also be performing the procedure, the guidelines specify that a qualified support person be present for continuous monitoring of the patient.

NPO Recommendations. The guidelines state that although "recent food intake is not a contraindication for administering procedural sedation and analgesia, the emergency physician must weigh the risk of pulmonary aspiration and the benefits of providing procedural sedation and analgesia in accordance with the needs of each individual patient [7]." The NPO recommendations are based upon preliminary, inconclusive or conflicting evidence and state that "recent food intake is not a contraindication for administering procedural sedation and analgesia, but should be considered in choosing the timing and target level of sedation [7]."

Capnography Recommendation. ETCO2 monitoring is not required but may allow more rapid identification of hypoventilation than pulse oximetry alone [58].

Pulse Oximetry Recommendations. The ACEP guidelines are unique in that unlike the ASA or AAP guidelines, pulse oximetry is not mandatory. The guidelines advise that pulse oximetry may not be necessary when the patient's level of consciousness is minimally depressed and verbal communication can be continually monitored. Pulse oximetry is recommended, however, when there is an increased risk of developing hypoxemia, such as when high doses of drugs or multiple drugs are used, or when treating patients with significant comorbidity.

Guidelines for Propofol Administration. The ACEP guidelines specify that propofol can be safely administered for procedural sedation and analgesia in the emergency department.

3.6. American Society of Gastroenterologists [5, 12]

3.6.1. Overview. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) prepared these guidelines in conjunction with a search of the medical literature using MEDLINE and PubMed databases. These guidelines apply to all patients, both adults and children, who receive sedation. The ASGE has approved the ASA guidelines for sedation by nonanesthesiologists and assert that an anesthesia specialist is not cost effective for average-risk patients undergoing routine upper and lower endoscopic procedures.

The guidelines recommend that with an intravenous benzodiazepine and opioid combination, adequate and safe sedation can be achieved in most patients undergoing routine esophagogastroduodenoscopy and colonoscopy. Others drugs such as droperidol can be used.

Credentials Recommended to Administer Deep Sedation. Deeper levels of sedation may be considered for longer and more complex procedures or for those who have been difficult to manage with moderate sedation and are anticipated to be poorly responsive to sedatives. Indications may include those patients who have had long-term use of narcotics, benzodiazepines, and alcohol. Deep sedation requires at least 1 person who is dedicated to the uninterrupted monitoring of the patient and is qualified in advanced life support skills needed to rescue a patient who becomes unresponsive, unable to protect the airway, or who loses spontaneous respiratory or cardiovascular function.

Recommendations for Pulse Oximetry. The ASGE follows the recommendations of the ASA and recommends that pulse oximetry be used during all endoscopic procedures [61, 68].

Recommendations for Propofol Administration. Propofol can be safely and effectively given by nonanesthesiologist physicians and nurses provided they have undergone appropriate training and credentialing in administration and rescue from potential pulmonary and cardiovascular complications. The guidelines state that clinically important benefits of propofol in average-risk patients undergoing upper endoscopy and colonoscopy have not been consistently demonstrated with regard to patient satisfaction and safety.

NPO Guidelines. The ASGE follows the ASA guidelines:

(i) NPO 2 hours clear liquids.

(ii) NPO 6 hours after light meals.

Recommendations for Capnography. Capnography is not required, although the ASGE indicates that integrating it into patient monitoring protocols may improve safety, acknowledging that there is insufficient evidence to support its use during routine upper and lower endoscopic sedation [69–72].

The ASGE guidelines cite the ASA guidelines in stating that capnography "should be considered for all patients receiving deep sedation and for patients whose ventilation cannot be observed directly during moderate sedation [61]."

3.7. The Scottish National Guidelines [9]

3.7.1. Overview. In Scotland, the sedation guidelines are meant to encompass minimal and moderate sedation only. Nonanesthesiologist delivered sedation is restricted and nurse administered sedation is only condoned with strict protocols, comprehensive backup and a comprehensive clinical governance and risk management framework. Deep sedation is given the same considerations as a general anesthetic and requires an identical standard of care.

These guidelines specify that children be sedated as proximal as possible to the procedure location and never at home. Patient assessment is important for these Guidelines in that they guide the choice of sedation care provider. Specifically, abnormal airway, sleep apnea, or respiratory tract infection are contraindications for sedation by nonanesthesiologist personnel, and require an anesthesiologist. Precautions are recommended with neonates, premature babies, emergency cases, or for children who are receiving narcotics.

Sedation practice in Scotland offers a unique viewpoint on the role of the child and parent in the sedation process. In 1995, the Child Scotland Act specified that an informed consent be obtained from the child when appropriate. The presence of the parents is recommended during the sedation, in hopes of providing emotional support.

NPO Guidelines.

Clear fluids: 2 hours

Breast milk: 4 hours

Formula or bottle milk: 6 hours

Nitrous Oxide, if used alone, does not require any NPO status

Emergency Procedures: if NPO status is unable to be met, general anesthesia recommended.

Guidelines for Administration of Deep Sedation. In the United Kingdom, deep sedation is considered to be a part of the spectrum of general anesthesia and administration should be limited to anesthesiologists. Those who administer deep sedation should not be performing the procedure.

Recommendations for Propofol Administration. Propofol is considered to be a general anesthetic and administration should be restricted to anesthesiologists.

Recommendations for Capnography. Capnography is recommended but not compulsory.

3.8. South African Society of Anaesthesiologists [10]. In South Africa, separate adult and pediatric sedation guidelines exist for the South African Society of Anaesthesiologists. The pediatric guidelines were written by Dr A. Reed, Dr R. Gray, Dr M. de Kock, Prof J. Thomas, Dr J. Piercy, and Prof J. Roelofse and shared with the authors (written correspondence).

3.8.1. Overview. The South African Society of Anaesthesiologists will publish in 2010 the Paediatric Procedural Sedation and Analgesia (PSA) Guidelines. These guidelines are intended for painful and nonpainful procedures but are not meant for sedation of children in the intensive care unit, under conditions of palliative care, for sedation at home, for "night sedation" or for preoperative sedation. These guidelines distinguish sedation in the hospital setting from sedation outside the hospital setting. The airway exam is identified as an essential requirement of the presedation evaluation and is used to differentiate those children who are appropriate for sedation in settings outside of the hospital from those who require sedation in a hospital. Specific airway factors which include but are not limited to retropharyngeal masses, Mallampati >2, stridor, large tonsils, obstructive sleep apnea, syndromic features (large tongue, micrognathia and abnormal ears) and limited neck mobility should exclude a patient from receiving sedation outside of the hospital setting.

These guidelines identify two different sedation techniques—"simple" and "advanced". Simple/basic sedation uses a single agent (not a combination of single agents), typically an oral/transmucosal/rectal drug (e.g. small dose oral benzodiazepine) or inhalation of nitrous oxide (N_2O) in at least 50% oxygen. It requires appropriate NPO status and cannot progress beyond the administration of one sedative agent. Advanced sedation encompasses a technique which administers multiple sedatives, uses the intravenous route or an inhalation anesthetic or nitrous oxide in a concentration of greater than 50%.

NPO Guidelines.

Clear fluids: 2 hours

Breast milk: 4 hours

Formula and solid food: 6 hours

When N_2O is used alone (50%), no fasting is necessary.

In urgent cases, when NPO guidelines are not met, a general anesthetic with rapid sequence induction is encouraged.

Recommendations for Deep Sedation. Considered to be part of the spectrum of general anesthesia and should be administered only by trained anesthesiologist.

Recommendations for Propofol Administration. Propofol should only be administered by experienced seditionist skilled in airway management of children. Capnography is highly recommended with propofol. Targeted controlled infusions are highly recommended with propofol in order to avoid the risk of respiratory depression with repeat bolus injections and infusions.

Recommendations for Capnography. Capnography is recommended for advanced sedation. If capnography is not available, a precordial stethoscope is recommended.

3.9. Saudi Arabia (National Guards Health Affairs) [8]

3.9.1. Overview. The pediatric sedation guidelines In Saudi Arabia are based upon the American Society of Anesthesiologists guidelines. These guidelines apply to sedation by non anesthesiologists in areas of dental medicine, pediatrics, cardiology, obstetrics and gynecology, oncology, and gastrointestinal medicine. These guidelines indicate that future consideration will be given to permit non-anesthesiologsts to deliver fos-propofol.

NPO Guidelines. All patients

Clear fluids: 2 hours

Breast milk: 4 hours

Formula and bovine milk: 6 hours

Meal: 8 hours

Recommendations for Deep Sedation. The sedation provider will be solely responsible for the monitoring and care of the patient, and not for performing the procedure.

The process of credentialing requires:

(i) documented attendance at an approved sedation by nonanesthesiologist course and

(ii) a minimum current certification in BLS, or preferably ACLS, issued by National Guard Health Affairs, the Saudi Heart Association or the American Heart Association. For pediatric sedation, a current PALS certification is required.

Recommendations for Propofol. Propofol administration is restricted to anesthesiologists when used for procedural sedation in nonintubated children.

Recommendations for Capnography. No specific recommendations.

Oxygen saturation, heart rate, blood pressure, respiratory rate, and level of consciousness are required data elements.

4. Discussion

The need for pediatric sedation has increased over the past decade, likely paralleling the increasing volume of procedures which are being performed by different specialists in areas outside of the operating room. The delivery of sedation has evolved from the traditional narcotic, benziodiazepine, ketamine, and hypnotic agents to now include broader option of agents and routes of administration. As the choices have expanded, so also has the complexity of the challenges which face sedation care providers and, in many cases, the specialty societies which they represent. Sedation policies, procedures, and guidelines are now presented not only by specialty societies and institutions, but now also by countries themselves.

Sedation is largely performed in areas remote from the operating room. The delivery of sedation and anesthesia in these remote areas presents risks and challenges which are unique to those of the operating room environment. In the USA, the American Society of Anesthesiologists has recognized this risk by establishing a closed claims database which collects the medicolegal outcomes of sedation or anesthesia-related events in areas outside of the operating room setting. In 2009, data from the ASA closed claims database suggests that sedation in remote locations (unfamiliar environment, inadequate anesthesia support, deficit resources, dark, small rooms, and variability of monitoring modalities) contributes to injuries and liability [73]. A review of 8496 claims concluded that sedation in remote locations is associated with a significant risk of adverse effects and a growing area of liability for the anesthesiologist [73].

Although specialty societies may not agree on all aspects of sedation, they all are unified by their primary interest in providing safe care. Outcome data is important in order to be able to evolve the sedation practice. To this end, the foremost challenge facing sedation care providers is the lack of universal consensus on the terminology and definition of adverse events, both minor and major. Hypoxia, oxygen desaturation, airway interventions, aspiration, and respiratory depression, for example, are all terms that are used in the literature without a universal definition. For example, some define oxygen desaturation as a drop of 10% from baseline, while others define it as an oxygen saturation less than 95% or in some cases, 90% or below. Furthermore, the duration of the desaturation often distinguishes a brief event from one which is noteworthy of being recognized as an adverse event. This duration of this desaturation is arbitrary and has not been defined or standardized. Thus, the limitations of all literature on sedation outcome is that it is based on definitions which have been established by the authors.

In order to advance the safety of pediatric sedation, through clinical studies and dedicated research, all sedation providers would benefit from having standardized descriptors of adverse events. To date, our lack of universal definitions has limited our ability to compare outcome data between different studies. Varied sedation practice and lack of consistent adverse outcome definitions have hampered our ability to evaluate the data and apply outcomes to improving sedation delivery [46, 48, 49, 74–79]. Using the same definitions to describe sedation practices, interventions, adverse events, and time intervals is an important first step to facilitate comparisons between studies and the aggregation of data from multiple studies [80–83]. The so-called "Quebec Guidelines" represented an effort to present a set of definitions which could be adopted by all sedation providers. This was a joint project between emergency medicine physicians and anesthesiologists in the United States and Canada (Consensus Panel on Sedation Research of Pediatric Emergency Research Canada (PERC) and the Pediatric Emergency Care Applied Research Network (PECARN).

These Guidelines represented a monumental achievement-collaboration between two specialties with a consensus on terminology. Furthermore, these guidelines changed the fundamental approach to identifying and defining adverse events: they were based on the need for interventions rather than on the actual event itself [84]. This represented an important first step in establishing universally accepted terminology.

The next step will be to reach a consensus between all specialists and their societies all over the world on the definition of adverse events. To date, these providers have operated independently, generally following the guidelines of their representing society. The Pediatric Sedation Research Consortium represents a group of institutions that voluntarily, for an enrollment fee, collect sedation data [85]. A

limitation of the existing research efforts is that they are limited to those who enroll, are not large scale, and do not represent the full spectrum of specialists and sedation practice worldwide. This year, the World Society of Intravenous Anesthesia (http://www.worldsiva.org/) recognized the need to unite these specialists by establishing the International Sedation Task Force (http://www.internationalsedationtaskforce.com/). Members of this Task force share a common goal: to advance the practice of safe sedation throughout the world.

The International Sedation Task Force represents a group of recognized sedation experts collected from around the world amongst different specialties. The members of this Task Force include sedation experts, for both adults and pediatrics: dental, hospital, emergency, gastroenterology, and intensive care medicine, as well as anesthesiology. Task force members from around the world with research and clinical expertise in sedation practice from all the major disciplines, continents and specialties are represented. The Task Force, led by Chairman and cochairman, Keira Mason, MD and Steve Green, MD, will first work to establish globally accepted definitions of adverse events which are objective, reproducible, applicable to all settings worldwide, and focused upon events which are of clinical significance.

By establishing a common "vocabulary" to define adverse events and outcomes, sedation practice will ultimately benefit. Data will be presented in a uniform fashion which will facilitate comparison between practices globally. For example, a review of the sedation policies confirms that there are areas of disagreement: currently, the major areas of discrepancy and disagreement amongst institutions, countries, and specialty societies involves the necessary qualifications requisite of providers who deliver deep sedation and propofol. Additional discrepancies between policies involves the necessity of physiologic monitors and supplemental oxygen during sedation. To date, there is no data to support a standard which would apply across specialties.

Establishing universal definitions will lay the foundation for someday establishing guidelines, policies and sedation boundaries: who should deliver deep sedation? Currently, many of the disagreements revolve around the debate on the whether nonanesthesiologists should deliver deep sedation or propofol. Ironically, however, the definitions of deep sedation are subjective. The sedation continuum which was established by the American Academy of Pediatrics and National Institute of Health in 1985 defines the depths of sedation using subjective criteria based on an observer's evaluation of a patient's response to tactile, verbal, and painful stimulation [54, 86].

The sedation continuum is an imprecise measure of sedation depth: when an emergency medicine physician or interventional radiologist provides sedation for a painful procedure, what demarcates deep sedation from general anesthesia? [87, 88] Universal definitions of adverse events will enable sedation providers to one day determine the incidence of respiratory and cardiac compromise between these levels in a step towards establishing the necessary resuscitation skills necessary for the providers of deep sedation. Furthermore, outcome data will lay the framework for reconfiguring the sedation continuum to represent an objective means of expressing depth of sedation and the associated, validated risks [89].

Acknowledgments

The authors would like to thank Mythili Srinivasan, MD, PhD, Michael P. Turmelle, MD, Douglas Carlson, MD, Neil Morton, MBChB, FRCA, FRCPCH, FFPMRCA, Professor James Roelofse, and Samir Haddad MD for sharing their expertise, protocols, and guidelines for inclusion in this paper. Special thanks to Ms. Amanda Buckley for the preparation and support of this paper.

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Hindawi Publishing Corporation
International Journal of Pediatrics
Volume 2010, Article ID 870921, 9 pages
doi:10.1155/2010/870921

Review Article

Sedation and Anesthesia Options for Pediatric Patients in the Radiation Oncology Suite

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Received 29 November 2009; Accepted 21 February 2010

Academic Editor: Keira Mason

External beam radiation therapy (XRT) has become one of the cornerstones in the management of pediatric oncology cases. While the procedure itself is painless, the anxiety it causes may necessitate the provision of sedation or anesthesia for the patient. This review paper will briefly review the XRT procedure itself so that the anesthesia provider has an understanding of what is occurring during the simulation and treatment phases. We will then examine several currently used regimens for the provision of pediatric sedation in the XRT suite as well as a discussion of when and how general anesthesia should be performed if deemed necessary. Standards of care with respect to patient monitoring will be addressed. We will conclude with a survey of the developing field of radiation-based therapy administered outside of the XRT suite.

1. Introduction

Cancer continues to be a leading cause of pediatric mortality in the developed world, with physicians and scientists constantly developing new weapons to combat it. Chemotherapy, surgery, nutrition, and holistic medicine all have a place in the multimodal approach that can prolong longevity and ameliorate quality of life. As part of this armamentarium, external beam radiation therapy (XRT) has proven to be a safe and effective technique for the management of various malignant (and occasionally nonmalignant) lesions. XRT can be used for both curative and palliative purposes; in the latter case, children benefit from decreased pain, preserved organ function, and the maintenance of lumen patency in hollow organs [1]. The medical team, led by a radiation oncologist, often includes a physicist, a dosimetrist, several radiation therapists (technologists), the patient's primary care pediatrician, and often an anesthesiologist to direct the sedation and ensure patient safety [2].

Since radiation therapy is a painless procedure, many older patients can complete their treatment without the use of anesthesia or sedation. Parental reassurance, and possibly the promise of a small reward afterward, is enough motivation for many children to remain still. Clearly babies and younger toddlers are not receptive to such enticement, and these are the patients that make up the vast majority of XRT anesthesia cases. Older children may be distressed by the absence of a parent next to them, but they often respond well to pictures attached to the ceiling within their field of view or the presence of music in the room. Indicators that suggest the need for anesthesia include young age, anxiety, treatment complexity (e.g., prone position), emotional immaturity for age, and a history of noncompliance [3].

2. Alternate Site Anesthesiology

The provision of anesthesia for patients undergoing radiotherapy procedures may present a deceptively simple challenge to the anesthesiologist. These cases are often very short in duration, sometimes lasting no more than ten minutes, and can usually be accomplished without the use of general anesthesia. The patients are often healthy from a cardiopulmonary standpoint although some malignancies may be associated with other medical conditions (e.g., Trisomy 21) which increase the likelihood of cardiac anomalies, such as endocardial cushion defects. Furthermore, there is essentially no blood loss or fluid shift present. How then can we explain

Figure 1: The linear accelerator.

the discomfort that anesthesia providers experience when faced with performing cases in the radiation therapy suite?

In general, many clinicians experience a palpable sense of angst when asked to do cases anywhere outside of the "*comfort zone*" of the operating room. The personnel employed in the XRT suite are well trained in their field of expertise; unfortunately for us, that field has little to do with anesthesiology. Assistance with lines, difficult airways, or anesthetic emergencies may be delayed or completely unavailable. Your colleagues and the anesthesia technicians might not be familiar with the location of the XRT suite, making it difficult and time-consuming to acquire personnel support, extra drugs, or equipment. However, the greatest source of concern seems to be the physical distance that must be maintained from the patients. While many alternate-site anesthetizing locations force the anesthesiologist to be at a considerable distance from the patient, perhaps even in a different room (CT scanner, MRI suite), the XRT area is unique in that there is no means of directly viewing the patient or the monitors. Instead, once the procedure has begun, we must rely solely upon the use of closed circuit television monitoring. While "*teleanesthsia*" has long been postulated as being a possible future direction of the field, few practitioners are excited about being the mavericks forced to incorporate this technology into their current practice.

3. Fundamentals of XRT

Before anesthesiologists can feel more comfortable providing anesthesia in the XRT suite, they must first have a basic understanding of what is accomplished there. When the actual treatment room is first entered, the most obvious piece of equipment you will notice is the linear accelerator (Figure 1). Inside of this machine, electrons are accelerated to very high energy states within a vacuum. The electrons are then forced to collide with a material such as tungsten, which releases energy in the form of X-rays [4]. This energy is then focused at specific sites within the patient in an effort to degrade the genetic material within the tumor cells. The energy absorbed by the tissues is measured in terms of gray (Gy), which has replaced the more antiquated unit of rad. 1 Gy is equal to the deposition of 1 J/kg and is equivalent to 100 rad units [5]. While most patients receive this type of X-ray therapy, other types of lesions respond better to bombardment with electron, proton, or neutron beam therapy. In any event, the anesthetic considerations are essentially identical despite the type of subatomic particle that is utilized.

4. Simulation

When a child is accepted as a candidate for XRT, he or she must first undergo a treatment planning session, referred to as a simulation. The physical set-up of the simulation suite is very similar to the XRT therapy room (Figure 2). However, the simulation machine is incapable of delivering therapeutic doses of radiation. Instead, it is used to provide radiographs of each treatment field which will aid the radiation therapy team in planning radiation doses and points of entry. Simulation serves several functions at the outset of therapy.

(1) Simulation allows the radiation oncologist to prescribe the proper treatment by reproducing the exact conditions that will be encountered during the weeks of therapy. The number and location of anatomic fields that will need treatment will be decided; the radiation therapy team may typically treat anywhere from one to four fields, depending upon the type and size of the lesion. Ideal patient positioning will be also determined. Most patients can be treated in the supine position; however, craniospinal axis radiotherapy will necessitate the patient remaining in the prone position throughout therapy, while two lateral whole brain fields are supplemented with a posterior field of the spine [6]. This adds another layer of challenge to the anesthetic management.

(2) Once these sites are determined, the therapist will mark the skin with ink to denote targets for future treatment. These markings will remain on the patient for the duration of the therapy and may be reapplied by the therapist as necessary. The markings increase accuracy and greatly enhance the speed of the future therapy sessions.

(3) Plaster immobilization casts of the head (Aquaplast RT™, Q-Fix, Avondale PA, Figure 3) and/or body (Alpha Cradle, Smithers Medical Products Inc., North Canton OH, Figure 4) are made, depending upon the sites that are to be treated. These casts make certain that the child will not move during the treatment sessions, ensuring that the radiation is directed at its target and not at normal surrounding tissue. Inadequate immobilization can result in treatment failure [7, 8] as well as damage to normal tissue [9].

Figure 2: The simulation machine.

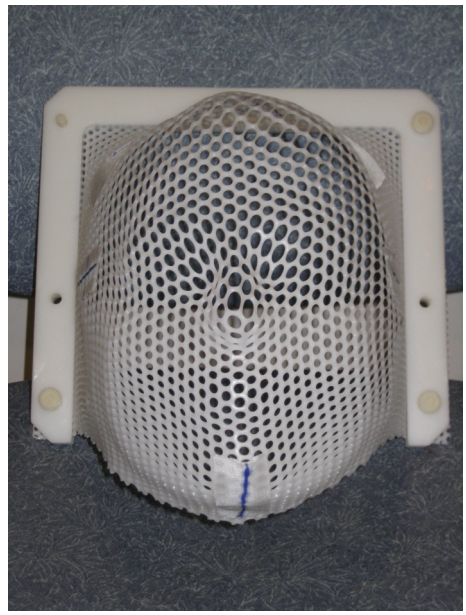

Figure 3: A premolded aquaplast.

(4) The radiation oncologist will determine if blocks will be necessary during the treatment period. Blocks are radio-opaque shields that are attached to the linear accelerator (Figure 5) to shield radiosensitive organs (e.g., kidneys and eyes) from the ionizing radiation.

(5) If the team is still questioning the need for anesthesia, the simulation offers an ideal trial without the risk of radiation to see if the child will be cooperative and can remain immobile during the session.

The simulation session takes place anywhere from 20 to 90 minutes, depending upon the level of cooperation of the patient and the number and location of the fields that need to be marked. Most patients who will require anesthesia intervention for XRT will do well during the simulation with monitored anesthesia care (MAC). Since therapeutic radiation is not used, the anesthesia team can remain with the patient during the majority of the simulation. When conventional radiographs are taken, the anesthesia and radiation oncology teams can remain in the room while wearing lead shielding or safely observe the patient through a panel of leaded glass from an adjacent room. Medications can be given freely throughout the procedure as dictated by patient anxiety and motion. If general anesthesia is required, the anesthesia machine must be placed in a location that will not interfere with the lateral X-ray fields. Circuit hose extensions may be needed to place the machine at an appropriate distance from the patient. At the conclusion of the simulation patients may be recovered in the XRT suite, provided there is adequate nursing supervision. Alternatively, the patient can recover in the main postanesthesia care unit.

The simulation phase may immediately be followed by the first treatment, but it is more common for the family

Figure 4: A premolded alpha cradle.

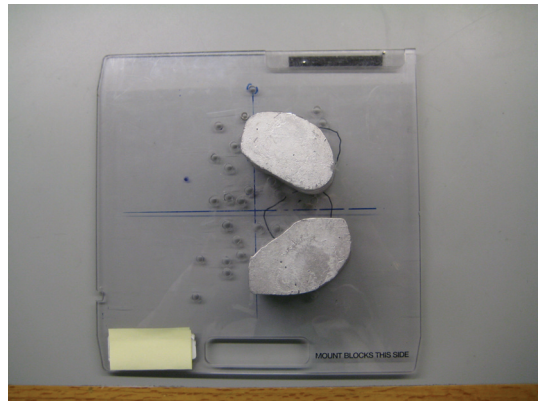

Figure 5: Blocks used to shield radiosensitive organs.

to return within the next day or two to begin the actual radiation therapy. This gives the team adequate time to map the coordinates of the sites that will be irradiated and decide upon dose and duration parameters. Total dose varies between 25 and 80 Gy, with a median value of 60 Gy. Lower doses are used for hematological cancers (leukemia and lymphoma) and seminomas; higher doses are reserved for solid tumors such as sarcomas and gliomas. The total dose of radiation is typically divided into 30 equal portions and administered once daily, five days per week over a 6-week period. Certain patients may benefit from hyperfractionated irradiation or the administration of XRT more than once daily [10]. Each field requires up to 90 seconds of irradiation; after this is completed, the radiation therapists must adjust the couch, reset the coordinates of the linear accelerator, and change the blocks so that the next field can be treated. Depending upon the number of fields (typically no more than four), the entire process can be completed in anywhere from 5 to 20 minutes. At specified time intervals (usually once per week), the therapists will repeat the radiographs to ensure that the anatomic targeting of the radiation beam is still accurate. This should add no more than another 5 minutes to the procedure.

5. Anesthetic Management of XRT Treatment

The majority of children who require anesthetic intervention can tolerate the daily therapeutic regimen with only MAC. Even patients who may have required general anesthesia for the simulation typically do well with moderate sedation (as defined by the ASA Task Force, Table 1) during the therapy phase, due to the brief time required for treatment. One significant exception is the child being treated for retinoblastoma; in this case, the globe must be kept completely immobile. MAC sedation, especially if ketamine is used (with a resultant lateral nystagmus), cannot accomplish this [11]. The room will be evacuated during the treatment period; however, it is safe to reenter in between doses, and therefore it is unusual to be away from the patient for more than 3 minutes. Of course, any reasonable request to reenter the room at any time should be honored by the radiation therapist; the treatment can be aborted before it is completed to allow safe entry into the room.

Parents are advised to follow fasting guidelines typical for all ambulatory surgical cases. If the tumor or medical condition is impairing gastric emptying, stricter guidelines may need to be enforced. Parents are encouraged to allow infants and children to ingest solid food and breast milk up to 4 hours before the procedure, and clear liquids are generally permitted up to 2 hours beforehand [13, 14]. Since fasting guidelines vary by institution, it is suggested that the practitioners follow the recommendations established by their own department.

The intravenous route is the preferred method of administering medication to these patients. While intramuscular drugs such as ketamine are effective, the repeated trauma of a painful injection daily for six weeks is often worse than the prospect of the XRT therapy. A large majority of these children have either recently completed a course of chemotherapy or are receiving it concomitant with the XRT and will therefore have an intravascular port present. Typically the port can be accessed with a Huber needle (Figure 6) prior to the first treatment, and the access can be left in place throughout the week and removed after the week's final treatment. The port remains dormant over the weekend, and the cycle repeats the following week. Parents can apply EMLA cream (AstraZeneca, London UK) to the site one hour before arriving Monday morning to make the access less traumatic. Alternatively, if the patient does not have a port, intravenous access via a peripheral vein can be obtained Monday morning, left in throughout the week, and removed on Friday, thereby following the same schedule [15]. Again, EMLA can greatly facilitate the process. In either case, the port or catheter should be flushed with a heparin flush solution (typically 300 units of heparin in 3 cc of normal saline) at the conclusion of each treatment to ensure continued patency throughout the week.

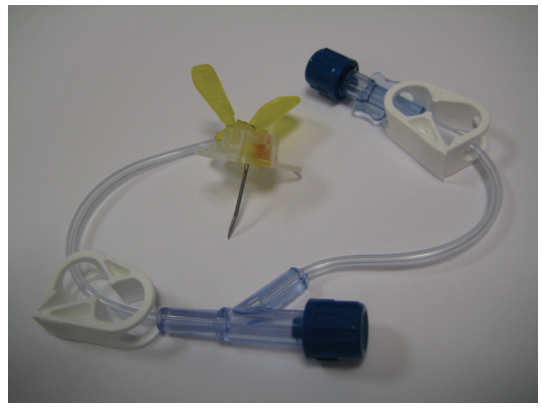

Figure 6: A Huber needle used to access an intravascular port.

Aseptic technique is imperative when accessing a port or placing an intravenous catheter. These children are typically neutropenic from the XRT and/or chemotherapy, as well as their disease state, and cannot tolerate the threat of bacterial infection. Large case series estimate the risk of sepsis between 7% [3] and up to 15% [16]. The use of propofol, which can act as a potent culture medium for bacteria, may enhance the risk [17].

Fortunately, the advent of short-acting sedative agents has decreased the prevalence of such pediatric favorites as rectal methohexital [18], chloral hydrate, and the DPT cocktail (meperidine, promethazine, and chlorpromazine [19]). Intravenous midazolam has been the cornerstone of pediatric sedation since its introduction into clinical practice. The anxiolytic and amnestic profile is so good that many patients can complete their entire series of treatments with the aid of only this drug. If this is the case, participation of an anesthesiologist is rarely warranted [20]. The safety record of intravenous midazolam used in the absence of other sedative drugs is extensive. Since XRT is a painless procedure, it is unnecessary to supplement the benzodiazepine with narcotics. Therefore, with adequate monitoring of vital signs, the sedation can typically be managed by a registered nurse credentialed/trained in sedation, as per institutional protocol.

Table 1: Definitions of clinical states of sedation as proposed by the American Society of Anesthesiologist's task force on sedation and analgesia by nonanesthesiologists [12].

Sedation level	Characteristics
Minimal sedation/anxiolysis	A drug-induced state during which patients respond normally to verbal commands
	Cognitive function and coordination may be impaired
	Ventilatory and cardiovascular functions are unaffected
Moderate sedation/analgesia	A drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation
	No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate
	Cardiovascular function is usually maintained
Deep sedation/analgesia	A drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation
	Ability to independently maintain ventilatory function may be impaired
	Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate
	Cardiovascular function is usually maintained
General anesthesia	A drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation
	Ability to independently maintain ventilatory function is often impaired
	Patients often require assistance in maintaining a patent airway and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function
	Cardiovascular function may be impaired

Patients who require more extensive therapy often still benefit from the use of midazolam. An initial dose of 0.05 mg/kg IV often provides enough sedation to allow for the placement of monitors. If ketamine is to be used, midazolam may decrease the incidence of postprocedure delirium [21]. After this initial dose of midazolam, the child should be dosed with a more potent agent to allow for transfer to the treatment couch and placement of therapeutic restraining devices. If necessary, midazolam can be readministered; cumulative doses greater than 0.2 mg/kg are rarely necessary. Of course, flumazenil must be readily available whenever benzodiazepines are being administered.

When benzodiazepine therapy is insufficient due to continued patient agitation, propofol is usually the preferred drug of choice for most anesthesiologists in the XRT suite, especially when dealing with children. After benzodiazepine pretreatment as previously described, an initial propofol bolus in the range of 0.5–0.8 mg/kg has been shown to provide adequate sedation for positioning and manipulation on the XRT couch while still allowing for spontaneous respiration and airway control [22]. This is followed by a continuous propofol infusion in the range from 7.4 mg/kg/hr [23] to 10 mg/kg/hr [24] throughout the treatment phase. Spontaneous eye opening was noted within 4 minutes of discontinuing the infusion [23]. Initial concerns about tachyphylaxis to propofol [25] have been disproved by more recent studies [26–28]. Thus propofol, combined with midazolam, provides excellent therapeutic conditions throughout the entire course of treatment [29]. Propofol has also been cited as being an excellent *stand-alone* drug to use in XRT without the need for benzodiazepine premedication. If the patient has a centrally accessed port, the likelihood of burning during propofol administration is highly unlikely.

The infusion of the α-2 agonist dexmedetomidine in the XRT suite has been described [30] although it has not been widely adopted. The most likely reasons for its infrequent use are the prolonged time needed to administer the initial bolus (which can be as long as the entire case itself), and the fact that pediatric administration of the drug constitutes an off-label usage.

Ketamine is another drug that is also used successfully, following midazolam pretreatment [31], to manage patients in the XRT suite [32, 33]. Ketamine can be given as a continuous infusion (25 mg/kg/hr) [34], but the α-phase serum half-life of 11 minutes [35] and the short duration of these cases often make this unnecessary. An initial dose of 0.5–0.75 mg/kg given at the start of therapy is often all that is required to accomplish the procedure. If the patient becomes agitated during the treatment, a supplemental dose of 0.25 mg/kg can be given to extend the period of cooperation. At some institutions, the use of ketamine has become so standardized that it is used in the XRT suite in the absence of an anesthesiologist [36].

Unlike propofol, it is not uncommon to witness tachyphylaxis develops to the effects of ketamine. By the fifth or sixth week of therapy the child may require twice the dosage to obtain the same effect as seen during the first or second week. Clinical experience has shown that recovery time is not prolonged in the latter phases of treatment, suggesting that the metabolism of the drug is also enhanced.

Fospropofol, a prodrug of the induction agent propofol, has recently been approved by the FDA for use as a sedative

agent, to be administered by practitioners trained in the provision of anesthesia [37]. Like dexmedetomidine, its use in the pediatric population is currently considered an off-label usage. Fospropofol is converted in vivo by alkaline phosphatase to release propofol, formaldehyde, and phosphate [38]. Clinical studies suggest that an initial dose of 6.5 mg/kg, followed by a redose of 1.5–2 mg/kg if needed four minutes later, provides adequate sedation for minimally painful procedures with statistically insignificant incidence of side effects (desaturation below 92%, hypotension 20% below baseline [39, 40]). Burning on injection was not reported with fospropofol, but almost all patients report a tingling or burning sensation in the genital and perianal area [41, 42]. While fospropofol has not yet been widely marketed in the United States, it will be produced by the Esai Corporation under the trade name Lusedra [43]. Future clinical studies will determine its suitability in the XRT suite although its pharmacodynamic profile seems ideal for pediatric oncology cases.

When general anesthesia is required, the brevity of the procedure must be kept in mind when choosing an induction agent. A muscle relaxant may not be necessary (the exception, as stated before, is XRT for retinoblastoma, which requires paralysis of the extraocular muscles). The subglottic swelling that may develop with repeated daily intubations can be obviated by the use of a supraglottic airway such as the LMA (LMA North America Inc., San Diego, CA), [44, 45].

Antiemetic therapy is suggested at the conclusion of each day's treatment. The emetic effects of XRT can exacerbate the nausea from chemotherapy and stress and result in vomiting in the recovery area. Ondansetron 0.1 mg/kg is perhaps the agent of choice for most practitioners, but others report the use of steroids or phenothiazines with good results. Haloperidol, while showing some promise for the relief of postoperative nausea and vomiting, has been shown to be of little value in the XRT suite [46].

6. Nonpharmacological Methods of Anxiolysis

Some practitioners use psychosocial methods either in lieu of or as a supplement to pharmacologic sedation. These interventions may begin before the child enters the XRT suite. One center constructed an imitation linear accelerator in the children's playroom, complete with a large doll who received mock treatments. The children were allowed to act as the physicians and via transference were able to quell some of their apprehensions [47]. Other reports describe the use of music and videos [48], gradually immersing the patient by slowly introducing him/her to what is expected, rewarding each successful step [49], and using an interactive Barney character [50] in an attempt to keep patients calm and motionless. While the last study showed a statistically significant decrease in patients' heart rates, there was no difference in the incidence of observed behavioral distress or the need for sedation. Therefore, it is difficult to draw firm conclusions about the utility of these techniques. Furthermore, a busy XRT service might not be able to devote the necessary time and patience to foster the atmosphere necessary for such methods.

Figure 7: A remote monitor bank.

7. Monitoring during XRT

Remote monitoring of the patient receiving XRT therapy has progressed to the point where it is on par with technology found in the operating room. The days of rigging together makeshift monitoring devices [51] have been supplanted by the use of crystal clear closed circuit monitoring. The typical configuration (Figure 7) uses two cameras to provide visual monitoring. Each camera is controlled by switches next to the television screens, allowing individual control of zoom and focus [52]. One camera is directed at the patient to observe for consistent breathing and the absence of other movements. The other camera is focused upon the monitors, which typically include (at minimum) the ASA standards of EKG, NIBP, and pulse oximetry and qualitative end-tidal CO_2. If the patient is receiving general anesthesia, the field of vision can be widened to include the ventilator and anesthesia machine as well. A microphone is also present to transmit the pulse oximeter tone. Remote audio monitoring of an esophageal stethoscope has been reported [53] but is not widely practiced. Documentation, either electronic or manual, should be completed from the initiation of sedation until the patient is transferred to a postanesthesia care provider.

8. XRT in Alternate Sites

The provision of radiation therapy is not limited solely to the XRT suite; indeed, it has begun to make inroads into the operating room. Brachytherapy or the intracavity implantation of radiotherapeutic material (e.g., radioactive prostate seeds and intrauterine isotopes) has been used successfully for years. Patient fears about "*becoming radioactive*" are largely exaggerated; because the radioactive material is sealed, only a small area around the site will be radioactive. The body as a whole will not emit radioactivity and it is generally safe for the patient to resume contact with others. In contrast, a patient receiving external beam XRT will emit no radioactivity whatsoever. Patients who receive intravenous radioactive isotopes, however, will continue to discharge radioactive material in their saliva, sweat, and

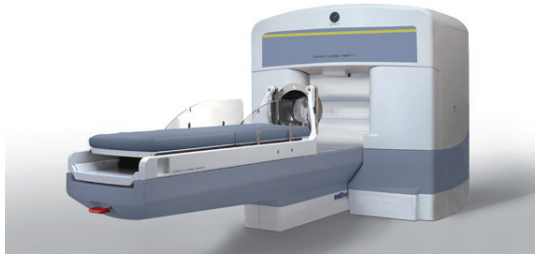

Figure 8: The gamma knife machine (courtesy of Elekta).

urine. The duration of this is dependent upon the half-life of the agent used [54].

Surgeons, radiation oncologists, and anesthesiologists can also work as a team to provide intraoperative radiation therapy (IORT) [55]. This is especially useful for tumors which cannot be fully resected or have a high probability of local recurrence. In these cases, the treatment begins in the operating room, where surgical exposure and debulking of the tumor occurs. The wound is then covered, and the patient is then transported to the XRT suite to receive high-dose external beam radiation directly to the exposed tissue. The child is then returned to the operating room for closure of the surgical site. These cases, typically performed under general anesthesia, require a great degree of coordination between all parties involved. Transport of the patient with an open surgical site requires careful attention to maintaining a sterile field as well as continued provision of anesthesia and analgesia. The patient should be stable from a cardiovascular standpoint prior to leaving the operating room, and full monitoring, airway, and PALS supplies should accompany the patient during the transit phase [56].

Stereotactic radiosurgery is another radiation therapy venue where anesthesiology services may be necessary. This procedure is used to treat conditions as diverse as malignancies, arteriovenous malformations, acoustic neuromas, and trigeminal neuralgia. The most widely used device, the Gamma Knife (Elekta Instruments Inc., Stockholm, Sweden), focuses 201 beams of gamma radiation (derived from cobalt-60) upon the lesion [57] (Figure 8). In contrast to XRT derived from a linear accelerator, only a single session of radiotherapy is needed to treat the disease. However, the patient may require several doses administered consecutively, each targeted to a different surface of the lesion.

Anesthetic management is much like what has been described for traditional XRT. MAC usually provides sufficient anesthesia although general may be required for very young patients and other special circumstances. The patient must first have the stereotactic frame placed which involves having four anchoring screws placed into the soft tissue of the head. The neurosurgeon or oncologist applying the frame will use local anesthesia to numb the areas; however, a small dose of ketamine or propofol immediately beforehand will make the procedure less traumatic. The child will then proceed to the MRI suite, where scans will be taken of the patient's brain with the external frame in place. It is imperative that all practitioners are aware of the hospital's protocols for MRI safety. The patient will likely be transferred to an MRI compatible stretcher, and all monitoring devices will be replaced with appropriate alternatives. Oxygen cylinders must be removed from the vicinity of the magnet. The patient's caregivers must be interrogated about the presence of any metallic implants, and the medical staff must remove any objects that may become a projectile hazard. Since the frame will limit access to the patient's airway, it is imperative that the patient is transported with the appropriate tools to quickly remove the frame in case airway access is necessary. If a vascular lesion is present, the child may also be taken to the neuroangiography suite for a diagnostic cerebral angiogram to further elucidate the anatomy. Afterward, the patient is permitted to rest while the physicians and physicists perform a 3D reconstruction of the MRI, plotting the coordinates that will most effectively target the intracranial pathology. The child is then placed into the Gamma Knife unit where several doses of radiation are administered (each lasting from 4 to 10 minutes). Upon completion, the stereotactic frame is removed, antibiotic ointment is applied to the puncture sites left by the screws, and the patient is transported to the recovery area.

The Cyberknife Robotic Radiosurgery System (Accuray Inc., Sunyvale CA) offers the clinical advantage of being able to treat tumors in any part of the body, freeing it from the intracranial restrictions of the Gamma Knife unit. Other enhancements include the Synchrony Respiratory Tracking System, a tracking software program that compensates for target movement caused by normal respiration. This obviates the need for a restrictive stereotactic device to be attached to the child, the primary reason anesthesia assistance is often requested for these patients. Thus, the absence of the frame and the freedom to relax and breathe normally mean older children can often tolerate this procedure with no pharmacological sedation.

9. Conclusion

Alternate-site anesthesiology has become more routine over the last decade as hospitals realize they can reduce costs and increase efficiency by "*outsourcing*" some types of cases out of the operating room. While some clinicians still feel uncomfortable emerging from the "protection" of the OR, others have embraced the chance to expand their practice beyond its traditional borders. XRT offers the anesthesiologist both a physical layout and a patient population that can be challenging initially but ultimately extremely rewarding.

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Hindawi Publishing Corporation
International Journal of Pediatrics
Volume 2010, Article ID 748564, 6 pages
doi:10.1155/2010/748564

Clinical Study

Clinical Effectiveness of an Anesthesiologist-Administered Intravenous Sedation Outside of the Main Operating Room for Pediatric Upper Gastrointestinal Endoscopy in Thailand

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Received 1 February 2010; Revised 23 June 2010; Accepted 23 June 2010

Academic Editor: Savithiri Ratnapalan

Objectives. To review our sedation practice and to evaluate the clinical effectiveness of an anesthesiologist-administered intravenous sedation outside of the main operating room for pediatric upper gastrointestinal endoscopy (UGIE) in Thailand. *Subjects and Methods*. We undertook a retrospective review of the sedation service records of pediatric patients who underwent UGIE. All endoscopies were performed by a pediatric gastroenterologist. All sedation was administered by staff anesthesiologist or anesthetic personnel. *Results*. A total of 168 patients (94 boys and 74 girls), with age from 4 months to 12 years, underwent 176 UGIE procedures. Of these, 142 UGIE procedures were performed with intravenous sedation (IVS). The mean sedation time was 23.2 ± 10.0 minutes. Propofol was the most common sedative drugs used. Mean dose of propofol, midazolam and fentanyl was 10.0 ± 7.5 mg/kg/hr, 0.2 ± 0.2 mg/kg/hr, and 2.5 ± 1.2 mcg/kg/hr, respectively. Complications relatively occurred frequently. All sedations were successful. However, two patients became more deeply than intended and required unplanned endotracheal intubation. *Conclusion*. The study shows the clinical effectiveness of an anesthesiologist-administered IVS outside of the main operating room for pediatric UGIE in Thailand. All complications are relatively high. We recommend the use of more sensitive equipments such as end tidal CO_2 and carefully select more appropriate patients.

1. Introduction

With the availability of newer and smaller endoscopes, the utilization of endoscopy to diagnose gastrointestinal disorders in children is increasing. Pediatric upper gastrointestinal endoscopy (UGIE) can be completed without sedation, by using intravenous sedation, or with general anesthesia [1–4]. However, the ideal method for sedating children for UGIE remains controversial.

Various medication combinations have been used for pediatric sedation, including intravenous ketamine, propofol, midazolam, fentanyl, and pethidine [2]. The standard sedation practice at our institution dependeds on the staff anesthesiologist. The goals of sedation are to ensure patient safety, provide analgesia and amnesia, control behavior during the procedure, enable successful completion of the procedure, and quickly return the patient to pretreatment level of consciousness.

In a developing country like Thailand, pediatric UGIE is being performed at increasing rate [5–7]. In addition, in provincial or community hospitals, general anesthesia in the main operating room remains the sedation plan of choice for pediatric UGIE. At Siriraj hospital, a World Gastroenterology Organization (WGO) Endoscopy Training Center, there is a dedicated gastrointestinal endoscopy unit and dedicated anesthesiology service for the unit. Over the years, we have observed a change in the trend of sedation for pediatric UGIE towards intravenous sedation

(IVS) technique [5–7]. This study, therefore, is done to review our sedation practice and to evaluate the clinical effectiveness of an anesthesiologist-administered intravenous sedation outside of the main operating room for pediatric upper gastrointestinal endoscopy in Thailand.

2. Subjects and Methods

This retrospective study was approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University. All pediatric patients scheduled for UGIE procedures consecutively from March 2006 to October 2009 at the WGO Endoscopy Training Center in Siriraj Hospital were included. Due to hospital policy, all children undergoing GIE were admitted prior to the procedure. All patients who underwent UGIE procedures with IVS were included for analysis. Exclusion criteria were the patients who had hemodynamic instabilities and the patients who needed endotracheal intubation. All sedations for UGIE were clinically titrated to either moderate or deep sedation as defined according to American Academy of Pediatrics and American Academy of Pediatric Dentistry [4].

For all patients who underwent IVS, appropriate monitoring was used. Cardiovascular monitoring included continuous electrocardiogram, heart rate, oxygen saturation measurements and five-minute interval noninvasive blood pressure measurements from blood pressure cuff device. All patients received supplemental oxygenation at 2 L/minute through nasal canula. Ventilation monitoring included continuous respiratory rate measurements and interval observation of patterns of respiration, chest movement, and signs and symptoms of airway obstruction. Level of consciousness was also periodically assessed. End-tidal carbon dioxide (CO_2) monitoring with capnography or precordial stethoscope was not used during sedation.

The following data was obtained: age, gender, weight, ASA physical status, indications, presedation problems, successful completion of the procedure, sedation time, type of intervention, and sedative agents. The presedation problems were defined as the underlying diseases such as cardiovascular disease, hematologic disease and liver disease. The effectiveness of intravenous sedation was defined as successful completion of the procedure at the target sedation level as intended. The secondary outcome variables were complications during and immediately after the procedure. Complications were recorded including: hypotension (defined as a decrease of blood pressure by 20% from baseline and below normal for age), hypertension (defined as an increase of blood pressure by 20% from baseline and above normal for age), bradycardia (defined as a decrease in heart rate by 30% from baseline and below normal for age), and hypoxia (defined as oxygen desaturation with $SpO_2 < 90\%$). Serious complication is any adverse event not easily treated or managed with medication and/or maintenance of the patient's airway resulting in endotracheal intubation including apnea and/or laryngospasm.

Results with variable data were expressed as mean ± SD. Results with categorical data were expressed as percentage (%). Comparison of adverse events by ASA physical status or different medication groups was done by using Student *t*-test. The statistical software package SPSS for Window Version 11 (SPSS Inc., Chicago, IL) was used to analyze the data. A significance level of 5% was used throughout the study.

3. Results

During the study period, a total of 168 patients (94 boys and 74 girls), with age ranging from 4 months to 12 years, underwent 176 GIE procedures with IVS. Of these, 26 UGIE procedures were performed with general anesthesia (GA), and 142 UGIE procedures were performed with intravenous sedation (IVS) and reviewed. All sedation was given by a staff anesthesiologist or the anesthetic personnel directly supervised by a staff anesthesiologist physically present in the endoscopy room. Anesthetic personnel included second-year residents in the Anesthesiology residency program and anesthetic nurses who are well-trained in general anesthesia, intravenous sedation, airway management including intubation, and cardiopulmonary resuscitation. There were no premedications prior to the procedure. A single anesthesiologist sedated or supervised the sedation of the patients throughout the study. The equipment used for the procedures included appropriate standard pediatric endoscopes, depending on patient age and size. All endoscopic procedures were performed by a pediatric gastroenterologist.

Patient characteristics, duration of sedation, indication of procedure, and the type of interventions are listed in Table 1. Hematologic disease, mild to moderate anemia (40.1%), liver disease, cirrhosis, portal hypertension (37.9%), and electrolyte imbalances, hypo/hyperkalemia and/or hyponatremia (12.4%) were the most common presedation problems. A total of 142 procedures, anesthesiology residents involved in 74 procedures (52.1%), and anesthetic nurses involved in 68 procedures (47.9%).

Table 2 showed the intravenous sedative agents used by age and ASA physical status. Propofol was the most common sedative drugs used in all age and ASA physical status groups. Mean dose of propofol (mg/kg) used in all age groups was significantly different ($P = .032$). However, mean dose of propofol (mg/kg) used in both ASA physical groups was not significantly different ($P = .365$). Additionally, mean dose of fentanyl (mcg/kg), midazolam (mg/kg) and ketamine (mg/kg) in all age and ASA physical status groups was not significantly different. However, the number of fentanyl used in the 0–2.99 years-old group (60.0%) was relatively lower than in the other groups (86.5% and 87.5%). Nevertheless, the number of ketamine used in the 0–2.99 years-old group (75.0%) was significantly higher than in the other groups (39.2% and 16.7%). According to ASA physical status, there were no significant differences in the number of propofol, fentanyl, midazolam and ketamine used.

There were no failures of sedation. However, two patients became more deeply than intended and required unplanned endotracheal intubation. These two patients were 5-month

Table 1: Patient characteristics, duration of sedation, and indication of procedure.

Variable	Overall ($n = 142$)
Age (yr) (mean, SD; range)	7.2 (3.7); 0.04–12.0
Gender (Male/Female; %)	80/62 (56.3/43.7)
Weight (kg) (mean, SD; range)	23.5 (11.3); 2.7–55
ASA physical status (I/II/III/IV; %)	43/47/50/2 (30.3/33.1/35.2/1.4)
Duration of sedation (min) (mean, SD; range)	23.2 (10.0); 5.0–60.0
Indication of procedure	
Variceal screening	40 (28.2)
Abdominal pain	27 (19.0)
History of upper gastrointestinal hemorrhage	16 (11.3)
Chronic vomiting	10 (7.0)
Anemia	9 (6.3)
Others	40 (28.2)
Type of intervention	
Diagnostic procedure	99 (69.7)
Therapeutic procedure	43 (30.3)
Variceal banding	24 (16.9)
Sclerosing injection	16 (11.3)
Esophageal dilatation	2 (1.4)
Remove foreign body	1 (0.7)

and 7-month old. They were then intubated. After the patient's status had improved, the procedure was completed with GA.

Table 3 showed the sedation related-complications comparing ASA physical status groups. Overall, 36 patients (25.4%) experienced sedation related complications. Respiratory complications with hypoxia occurred in seven patients (4.9%), and upper airway obstruction occurred in six patients (4.2%). Cardiovascular complications arose in 23 patients (16.2%) and mainly consisted of hypotension (14 patients) and bradycardia (9 patients). If only serious complications are included, the complication rate is none. All complications were easily treated and managed with medication and/or maintenance of the patient's airway by the staff anesthesiologist or anesthetic personnel under direct supervision of a staff anesthesiologist who was physically present in the room. There was no difference in the incidence of complications when sedated by trainees, anesthetic nurses, or anesthesiologist.

The overall complications in children who had ASA physical status I-II as compared to ASA physical status III-IV were not significantly different ($P = .202$). Similarly the respiratory and cardiovascular complications between these two groups were not statistically different. In addition, one patient in ASA physical status I-II and one patient in ASA physical status III-IV developed hypoxia and hypotension. Two patients in ASA physical status I-II and one patient in ASA physical status III-IV developed upper airway obstruction and bradycardia. The emergence reactions or hallucinations, increased salivation or laryngospasm were not seen in patients receiving ketamine as part of IVS.

4. Discussion

This retrospective study demonstrates the clinical effectiveness of an anesthesiologist-administered intravenous sedation outside of the main operating room for pediatric upper gastrointestinal endoscopy in a developing country. The complication rate of our study is relatively high. However, the serious complications were none. IVS for pediatric UGIE procedure in children 12 years of age and younger is challenge and requires an experienced anesthesiologist as well as appropriate monitoring. Anesthetic personnel should remind themselves to use more sensitive equipments to detect potential complication such as end tidal CO_2 and carefully select more appropriate patients.

UGIE procedure in children is an important and effective tool for the diagnosis and treatment of upper digestive tract diseases. The indications for upper endoscopy in the pediatric age group are similar to those for adult endoscopy [8]. These procedures are generally performed either with IVS in the endoscopy room, or under GA in the operating room [9]. The decision to use GA is usually based on the patients' parameters such as age, diagnosis, respiratory compromise and severity of disease. In some centers, GA is used on all infants, children and adolescents [3, 10, 11]. However, in other centers, IVS is used for the procedures. With IVS, several medication combinations have been used successfully [9, 12–15].

In a developing country where pediatric UGIE performed at increasing rates, the majority of cases are performed under general anesthesia in the operating room (OR). At Siriraj Hospital, there is a dedicated endoscopy unit with dedicated anesthesia service. Over the last two years, 2006 to 2008, we performed most pediatric UGIE with IVS [5–7]. We followed the guidelines provided by the American Academy of Pediatrics and American Academy of Pediatric Dentistry and ASA standards for sedation providers [4, 16]. Our previous reviews of IVS practice in pediatric population showed that it can be done safely with various sedative combinations with proper monitoring and anesthesiology service supervision.

Majority of children received propofol in combination with other sedatives. Propofol has gained wide acceptance among adult gastroenterologist. Its use in pediatric population has been shown to be safe, effective and reliable [10–15]. In Thailand, sedation with propofol is administered by anesthesiologist. The drug combination provides synergistic action while lowering the doses of each agent. Our practice reflects this where many different combination regimens were used [5–7]. Propofol is the most common agent used in combination with midazolam and fentanyl in this study. Additionally, we did not observe hemodynamic instability, emergence reactions, hallucinations, increased salivation or laryngospasm with the use of ketamine combining regimen. This observation was similar in the previous studies [17–19].

Table 2: Intravenous sedative agents used by age and ASA physical status.

	0–2.99 yr (20)	3–9.99 yr (74)	>9.99 yr (48)	*P*-value	ASA I-II (90)	ASA III-IV (52)	*P*-value
Propofol				.032[(a)]			.365
n (%)	19 (95.0)	72 (97.3)	46 (95.8)		88 (97.8)	49 (94.2)	
mg/kg (mean, SD)	2.28 (2.29)	3.50 (2.99)	4.43 (3.36)		3.65 (3.44)	3.63 (2.37)	
Fentanyl				.896			.276
n (%)	12 (60.0)	64 (86.5)	42 (87.5)		76 (84.4)	42 (80.8)	
mcg/kg (SD, range)	0.96 (0.16)	0.95 (0.20)	0.97 (0.27)		0.96 (0.21)	0.96 (0.25)	
Midazolam				.657			.578
n (%)	17 (85.0)	57 (77.0)	38 (79.2)		68 (75.6)	44 (84.6)	
mg/kg (SD, range)	0.05 (0.05)	0.06 (0.07)	0.06 (0.04)		0.06 (0.06)	0.06 (0.04)	
Ketamine				.082			.564
n (%)	15 (75.0)	29 (39.2)	8 (16.7)		29 (32.2)	23 (44.2)	
mg/kg (SD, range)	2.68 (4.44)	1.05 (0.24)	0.85 (0.33)		1.10 (0.35)	1.98 (3.66)	

[(a)]considered statistically significant.

Table 3: Complications comparing ASA physical status groups.

Complications (36)	ASA I-II (90) *n* (%)	ASA III-IV (52) *n* (%)	*P*-value
Overall	26 (28.9)	10 (19.2)	.202
Respiratory	10 (11.1)	3 (5.8)	.288
Hypoxia (SpO_2 < 90%)	5 (5.6)	2 (3.8)	.650
Upper airway Obstruction	5 (5.6)	1 (1.9)	.300
Cardiovascular	16 (17.8)	7 (13.5)	.501
Hypotension	9 (10.0)	5 (9.6)	.941
Bradycardia	7 (7.8)	2 (3.8)	.354

Cardiopulmonary complications account for more than half of the major complications during endoscopy, and are often related to hypoxia, especially in children less than 1 year old [20, 21]. In our study, the overall adverse event was relatively high (25.4%). Cardiovascular complications accounted for the majority (16.2%) followed by respiratory complications (9.2%). However, all complications were transient and easily treated with no adverse sequelae. Many previous studies involving the use of propofol and other combination sedative drugs have reported slightly higher adverse events [22–24]. In our study, there was significant difference in the mean dose of propofol between the three aged groups.

In a study by Barbi and colleagues, major desaturation was noted in 0.7% of all the children, and transient desaturation that resolved sponstaneously occurred in 12% of all the procedures [22]. Additionally, the study by Yildizdaş et al. demonstrated that the use of propofol and midazolam/fentanyl in 126 children had 16.6% incidence of respiratory depression as shown by high end-tidal carbon dioxide (>50 mmHg) [23]. The high incidence of respiratory depression reflected the better detection of respiratory depression by the use of end-tidal carbon dioxide. In our study, complication rate is comparable to studies that did not use end-tidal carbon dioxide monitoring [22, 24]. ASA physical status III-IV has been shown to be a predictor of increased risk for sedation-related complications [24]. There is also a concern for increased respiratory complication in patients undergoing UGIE procedures. Endoscope can potentially compress and obstruct airway.

Several publications described the use of propofol for sedation by physicians or providers other than anesthesiologists [24–27]. Consequently, there was a difference in outcomes once nonanesthesiologists use propofol. When a dedicated pediatric sedation team involving an anesthesiologist was utilized, the reported successful sedation rates were 100%, and adverse events ranged from 1.7 to 5% [28]. There was no failure of sedation in this study. However, two patients became more deeply than intended and required unplanned endotracheal intubation. Finally, all procedures were completed as intended. A high success rate in our study is due to the procedure is performed by an experienced endoscopist and is sedated by an experienced anesthesiologist. Consequently, our center had a dedicated anesthesia service involved with sedation and the use of basic noninvasive monitoring, which includes noninvasive blood

pressure monitoring, pulse oximetry, and electrocardiogram. Additionally, the safe and successful sedation is also dependent on proper preparation, evaluation, monitoring, and appropriate skills to rescue the patient, and proper recovery [27].

Our study has several limitations. This is a retrospective paper of a cohort of patients undergoing pediatric UGIE with IVS. We accept that there are limitations with chart review in regards to proper and complete documentation. We also realized that with this review, the study is reflected in the variety of regimen and sedative drugs used for IVS. In addition our cohort varied widely in age range. Therefore, the drug requirement, drug doses, and side effects varied as well. According to the design of study, we defined an alteration of blood pressure by 20% from baseline, and a decrease in heart rate by 30% from baseline as the complication. The complication rate in this paper was also relatively high. Moreover, we did not use the end tidal CO_2 monitoring. Overall, even with these limitations, we believe that the study findings are applicable to the sedation practice and to remind the physicians for sedation the pediatric patients for UGIE procedures.

In summary, this study shows the clinical effectiveness of an anesthesiologist-administered intravenous sedation outside of the main operating room for pediatric upper gastrointestinal endoscopy in a developing country. Although, the complication rate of our study is relatively high. All complications were transient and easily treated with no adverse sequelae. We also recommend the use of more sensitive equipments to detect potential complication such as end tidal CO_2 and carefully select more appropriate patients for pediatric UGIE.

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Hindawi Publishing Corporation
International Journal of Pediatrics
Volume 2010, Article ID 189142, 9 pages
doi:10.1155/2010/189142

Review Article

Sedation and Analgesia in Children with Developmental Disabilities and Neurologic Disorders

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Received 2 December 2009; Revised 15 June 2010; Accepted 20 June 2010

Academic Editor: Savithiri Ratnapalan

Sedation and analgesia performed by the pediatrician and pediatric subspecialists are becoming increasingly common for diagnostic and therapeutic purposes in children with developmental disabilities and neurologic disorders (autism, epilepsy, stroke, obstructive hydrocephalus, traumatic brain injury, intracranial hemorrhage, and hypoxic-ischemic encephalopathy). The overall objectives of this paper are (1) to provide an overview on recent studies that highlight the *increased* risk for respiratory complications following sedation and analgesia in children with developmental disabilities and neurologic disorders, (2) to provide a better understanding of sedatives and analgesic medications which are commonly used in children with developmental disabilities and neurologic disorders on the *central nervous system.*

1. Introduction

With advances in health care, many children with developmental disabilities and neurologic disorders are living longer lives, and increasingly require diagnostic and therapeutic interventions. Pediatricians and pediatric subspecialists are increasing being called upon to safely sedate and provide analgesia for these children for diagnostic procedures (CT, MRI, angiogram, endoscopy, and bronchoscopy) and for therapeutic interventions (interventional radiology, intracranial injury, and emergency stabilization). This paper will focus on children with developmental disabilities and neurologic injury, and will highlight the risks involved with these patients, and the effects of common sedatives and analgesic agents on the central nervous system. The purpose of this paper is to provide the pediatrician and pediatric subspecialist a better understanding on the neurologic effects of different sedative and analgesic medications so that rational and safe choices can be used in children with developmental disabilities and neurologic disorders without causing further "neurologic" compromise.

2. Materials and Methods

We performed an extensive review of the medical literature regarding sedation analgesia in children with developmental disability and neurologic disorders utilizing Pubmed. Search terms included "sedation", and "analgesia", "pediatric", "child", "neonate", "brain", "developmental disabilities", "neurologic", "autism", "epilepsy", "seizure", "stroke", "hydrocephalus", "traumatic brain injury", "intracranial hemorrhage", "hypoxia-ischemia", and "encephalopathy" and the period of search was from 1960–2010. The authors are pediatric neurocritical care specialists and have extensive clinical experience caring for pediatric patients with developmental disabilities and neurologic disorders and research experience in experimental animal models of pediatric neurologic injury.

3. Results and Discussion

3.1. Overview—Increased Risk for Respiratory Complications following Sedation in Children with Developmental Disabilities and Neurologic Disorders. Sedation and analgesia for

the pediatric patient with developmental disabilities and neurologic disorder require a thorough understanding of potential adverse events, and the knowledge and skill to avoid potentially life-threatening complications from the administration of sedative and analgesic medications. In addition, the practitioner must focus particular attention on the entire periprocedural period including presedation evaluation, sedation/analgesia administration, and recovery. The American Academy of Pediatrics, Section on Anesthesiology has published *Guidelines for the Pediatric Perioperative Anesthesia Environment,* which includes suggestions for age categorization, need for intensive care following sedation for recovery, and presence of coexisting disease [1].

Since these guidelines were published, sedation outside of the operating room continues to increase, along with the varied practitioner's disciplines that are delivering sedation. With this practice increasing, the debate about safety and the practitioner core competency requirements to provide sedation and/or analgesia to the complex pediatric patient with developmental disabilities and neurologic disorders has also increased and several policy statements have been published by different professional societies [2], with no clear evidence of practice standards and incidence of adverse outcomes. To aid in the investigation of the practice and potential adverse outcomes associated with the delivery of sedation outside the operating room, the Pediatric Sedation Research Consortium (PSRC), a collection of 37 institutions that share information on sedation practices within their individual institutions, has created a self-reporting prospective, observational database. This database has provided vital information to define the frequency and nature of adverse events during pediatric sedation from a multispecialty perspective [3]. Large PSRC studies have shown a relatively low risk to pediatric sedation by practitioners other than anesthesiologists [4]. However, despite zero deaths in the 49,836 sedation encounters, one in 65 of these sedation encounters was associated with stridor, wheezing, airway obstruction, laryngospasm, or central apnea, conditions that all have the potential to deteriorate to respiratory failure and death. Airway obstruction and pulmonary complications were the most frequently cited adverse event. In subsequent analysis, factors that related to higher rates of pulmonary complications were young patients, use of adjunctive opiates, and patients with a higher American Society of Anesthesiology (ASA) status ($\geq$III), a large proportion with *neurologic conditions* [5]. This continues to emphasize that pediatric patients with neurologic disorder and developmental disabilities receiving sedation continue to be at increased risk for adverse events with the most prevalent concerns for airway obstruction and altered respiratory mechanics. Unfortunately, extensive studies have not been performed to identify specific patients at risk and aid in the development of evidence-based clinical protocols for patients with neurologic pathology and developmental disabilities. Most reported experience refers to scattered case reports of specific syndromes (Butler et al. has an excellent review of sedation complications related to many specific syndromes [6]).

So what are the actual added risks associated with sedation of the pediatric patient with developmental disabilities or neurologic disorders? Brain MRI has become an important diagnostic and management tool for these children and is being increasingly used in many pediatric centers [7]. Kannikeswaran and colleagues recently published a retrospective review of children, 1–18 years of age, sedated for brain MRI with and without developmental disability [8]. Developmental disability is defined by these investigators as delay in one of the following: fine/gross motor, cognitive, speech/language, social/personal, and activities of daily living. Pentobarbital and fentanyl were the two most common medications used with no difference in mean dosages between children classified as "normal" or "developmental disability". However, the patients classified as having developmental disability had a threefold increased incidence of hypoxia (11.9% versus 4.9%; $P < .01$). These findings seem to recapitulate the findings described in the PSRC studies: an increase in adverse events, most notably airway compromise, for children with developmental disabilities and those with neurologic disorders. In this study, the most common diagnosis for the cause of developmental disability was autism (36%). In addition, the authors included patients with attention deficit hyperactivity disorder (20%) as a diagnosis for developmental disability.

In another study, a small observational chart review performed by Elwood et al. suggests that the anteroposterior oropharyngeal airway diameter was smaller in children with developmental delay than in those without developmental delay, in static MRI images [9]. The limitations in this study were the varied diagnoses within groups of patients diagnosed with developmental delay without specific recommendations for certain patient populations. However, it does reinforce the idea that sedation practitioners need to exhibit marked vigilance for airway patency in patients with developmental disabilities. In addition to a baseline risk for airway compromise in patients with developmental disability, Cortellazzi and colleagues showed that the risk for airway obstruction significantly increased in neurologically impaired children undergoing MRI who were administered a combination of sedative medications [10]. Thus, as practitioners escalate pharmacologic intervention a patient with developmental disabilities or neurologic disorders is at increased risk for airway obstruction and may need higher level of care, including the potential need for a pediatric emergency medicine specialist, anesthesiologist, or intensivist.

The choice of sedation plan varies by institution, practitioner credentials, and experience. Protocols are based on agent pharmacokinetic and pharmacodynamic profiles, with an attempt to maintain a proper plane of sedation and analgesia without respiratory and hemodynamic compromise. However, virtually no protocol exists on the use of different sedatives and analgesic medications with the focus on preventing "neurologic" compromise. While there is not enough evidence-based data to support specific clinical guidelines for sedation and analgesia in children with developmental disabilities and neurologic disorders, the authors' hope is that the sedating practitioner will have a better understanding to safely administer these medications without promoting "further" neuronal injury.

3.2. The Central Nervous System Effects of Different Sedative and Analgesic Medications Commonly Used in Children with Developmental Disabilities and Neurologic Disorders. The practitioner must have a well-developed understanding of the effects that different sedative and analgesic agents will have on cerebral vasculature, metabolism, autoregulation (maintaining constant cerebral blood flow despite changes in perfusion pressure), intracranial pressure (ICP), and cerebral perfusion pressure (the perfusion pressure that causes blood flow to the brain); see Table 1 that provides the route and dosages of the different sedative and analgesic medications that are commonly administered.

3.2.1. Opioids. Opioids, such as morphine, fentanyl, and remifentanil, have long been considered effective adjuvant medications for analgesia of patients with developmental disabilities and neurologic disorders. Opioids are very useful in the treatment of nociceptive pain, and are crucial in developing a balanced sedation plan when analgesia is a concern, for example, intubation and comorbid injuries. Higher doses of opioids can also have some degree of sedation and even hypnosis; however, sedation is a side effect and not the intended pharmacodynamic purpose. Furthermore, opioids lack amnestic properties, and therefore are rarely used as sole agents for sedation in children. Opioids are commonly coadministered with benzodiazepines, because of their ability to provide sedation, amnesia, and hypnosis. Side effects of all opioids are similar, and include: constipation, urinary retention, sedation, nausea, vomiting, respiratory depression, bradycardia, hypotension, and pruritis.

Opioid pharmacology can have effects on the central nervous system. Cerebral metabolic oxygen rate, cerebral blood flow (CBF), and ICP all decrease with the administration of opioids if a patient's arterial carbon dioxide ($PaCO_2$) remains unchanged. An increase in $PaCO_2$ relaxes smooth muscle, dilates cerebral vessels, decreases cerebrovascular resistance, and increases CBF [11]. However, opioids have minimal effects on cerebral hemodynamics in adequately resuscitated patients with controlled ventilation [12]. The use of short-acting and ultra-short acting IV narcotics (fentanyl, sufentanil, and remifentanil) via bolus infusion and/or continuous infusion reported conflicting data on ICP effects [13–15]. Opioids have a direct effect on the respiratory centers in the medulla, and decrease minute ventilation by decreasing respiratory rate and produce a dose-dependent depression of ventilatory response to carbon dioxide levels; therefore, opioids decrease the apneic threshold which may lead to hypoxia and respiratory failure. This side effect may be exacerbated in children with developmental disabilities and neurologic disorders, who commonly have hypotonia, central apnea, and inadequate airway reflexes.

Morphine, like most narcotics tend to decrease heart rate, depending on the level of sympathetic output, through central vagal stimulation. In addition to a negative chronotropic effect, morphine can lower mean arterial blood pressure via arterial and venous dilation. Venodilation lasts longer than arterial dilation and at increasing dosages will decrease cardiac output and lower myocardial oxygen demands. Because of these properties morphine is commonly administered in adults with myocardial ischemia; however, in patients with traumatic brain injury a substantial decrease in cardiac output and cerebral perfusion pressure may lead to cerebral ischemia. Morphine administration results in elevated histamine levels released from non-IgE-mediated stimulation of mast cells. Histamine can result in decreased systemic vascular resistance and an increased incidence of pruritis in children. In children with developmental disabilities and neurologic disorders it may be difficult to differentiate between increasing levels of agitation due to pain or pruritis, and other side effects. The terminal half-life of morphine is higher in neonates, especially preterm neonates, and decreases with age; however, there is significant individual variability in children. On average the terminal half-life ($t_{1/2}$) is approximately 9 hours in preterm infants, 6.5 hours in full-term neonates, and 2 hours in infants and children.

Fentanyl has several advantages over morphine as an adjuvant medication for analgesia in children with developmental disabilities and neurologic disorders. Fentanyl crosses the blood brain barrier quickly and has a rapid onset and relatively short offset. In lower doses, fentanyl has minimal effects on cardiac output or respiratory depression unless used in combination with other medications such as benzodiazepines. Fentanyl is highly lipophilic and can be administered by intranasal, transmucosal, or transdermal routes. One of the major side effects of fentanyl is that *rapid* IV bolus can cause chest wall rigidity. In our intensive care unit, fentanyl is the most common opioid used to provide analgesia in postoperative patients with developmental disabilities and neurologic disorders and is administered over 3 to 5 minutes when administered by the IV route. We also commonly administer fentanyl in combination with midazolam to provide sedation and analgesia for intubation and mechanical ventilation.

Remifentanil is a potent ultra-short acting synthetic opioid that has become a common component of total intravenous anesthetics (TIVAs) especially for procedures requiring neuromonitoring of somatosensory evoked potentials (SSEP) and motor evoked potentials (MEP) in children for neurosurgery and spinal surgery. The half life is 4 minutes, and unlike other synthetic opioids which are metabolized by hepatic elimination, remifentanil is metabolized by nonspecific tissue and plasma esterases, thereby eliminating accumulation. Remifentanil is also commonly used in combination with other sedatives such as propofol or midazolam for short painful procedures [16]. Significant dose-dependent bradycardia can be associated with remifentanil administration. Due to the lack of effect on neuromonitoring, lack of accumulation, and short half life, remifentanil can be used with great success by allowing the practitioner the ability to quickly adjust the depth of sedation for patients with neurologic disorders [17].

3.2.2. Benzodiazepines. Benzodiazepines are particularly useful for sedation in pediatric patients with developmental disabilities and neurologic disorders because of their pleiotropic

Table 1

Agent	Type	Route	Dosage Induction	Sedation/Analgesia
Thiopental	Barbiturate	*IV* *Rectal*	3–8 mg/kg 15–25 mg/kg	
Pentobarbital	Barbiturate	*IV* Oral		2–6 mg/kg (150 mg max) 2–6 mg/kg
Ketamine	*N*-methyl-*D*-aspartate (NMDA) antagonist	*IV* *IM*	2–4 mg/kg	0.5–1 mg/kg titrated to effect 3–7 mg/kg
Propofol	Hypnotic, Amnestic	*IV*	2–4 mg/kg (Lower dose for critically ill)	Initial: 200–300 mcg/kg/min Maintenance Infusion: 125–200 mcg/kg/min (Infants/younger children may require higher dosages)
Etomidate	Hypnotic, Carboxylated imidazole derivative	*IV*	0.3–0.5 mg/kg	
Dexmedetomidine	Central Acting α-2 Agonist	*IV*		Loading Dose: 0.5–2 mcg/kg Maintenance Infusion: 0.2–0.7 mcg/kg/hour
Morphine	Opioid	*IV* *Oral*		Bolus: Neonate 25–50 mcg/kg Infants and Children 15–30 mcg/kg Infusion: Neonate 2–10 mcg/kg/hour Infants and Children 15–30 mcg/kg/hour Infants and Children 0.25–0.5 mg/kg
Fentanyl	Opioid	*IV* *Oral* *Intranasal*	1–3 mcg/kg	Bolus: 0.5–1 mcg/kg Infusion: 0.5–3 mcg/kg/hour 10–15 mcg/kg 1-2 mcg/kg
Remifentanil	Opioid	*IV*		0.1–0.5 mcg/kg/min
Midazolam	Benzodiazepine	*IV* *IM* *Oral*	0.1-0.2 mg/kg	Bolus: 0.1-0.2 mg/kg Infusion 0.1–0.3 mg/kg/hour 0.2–0.5 mg/kg 0.2–1 mg/kg (max 10 mg)

IV: Intravenous, IM: Intramuscular.

effects: sedation, anxiolysis, muscle relaxation, and anterograde amnesia. Benzodiazepines also have anticonvulsant effects by enhancing the effect of the neurotransmitter gamma-aminobutyric acid (GABA) and is ideal for sedating children with epilepsy. Significant effects on organ systems include: decrease in blood pressure, depressed ventilation (transient apnea, especially in combination with opioids), and a decrease in cerebral metabolic rate. It is very interesting to note that basic science research continues to try to elucidate the effect of anesthetics, including benzodiazepines, on the developing brain and neurocognitive function [18]. No traumatic brain injury studies, solely involving pediatric patients, exist on the administration of commonly used benzodiazepines (midazolam, lorazepam, diazepam). One case series studied the effects of diazepam in 7 adults and 1 adolescent with severe traumatic brain injury and revealed a reduction in cerebral blood flow and cerebral metabolic rate with no effect on blood pressure [19]. In our ICU, if the fentanyl fails to control intracranial hypertension, and as long as the hemodynamics are adequate, we will then commonly administer a bolus IV dose of midazolam and start a continuous IV infusion in a critically ill patient who is intubated and mechanically ventilated.

Midazolam is a short-acting (unlike lorazepam and diazepam), water-soluble benzodiazepine commonly used for sedation in children with developmental disabilities and neurologic disorders. Midazolam does not cause local irritation after injection (unlike diazepam) and can be readily mixed with other medications for intravenous, intramuscular, oral, intranasal, or rectal administration. Rapid redistribution from the brain to other tissues, and rapid metabolism by the liver, accounts for a short duration of action and an elimination half life of 1 to 2 hours [20].

3.2.3. Barbiturates. Barbiturates, such as thiopental and pentobarbital, have long been considered effective sedatives for patients with neurologic disorders. Barbiturates decrease cerebral blood flow (CBF) and cerebral metabolic rate ($CMRO_2$) in a dose-dependent fashion but preserves autoregulation [21]. Reductions in CBF and $CMRO_2$ result in a reduction in ICP which can be useful for traumatic brain injury patients as well as acute stroke or intracranial hemorrhage patients with intracranial hypertension. In animal studies, barbiturates have been observed to reduce infarct size following focal cerebral ischemia [22]. Barbiturates' neuroprotective characteristics are also related to reductions in ischemia-induced glutamate release and inhibition of intracellular calcium release [23, 24]. Barbiturates have anticonvulsant properties and are ideal for sedating children with seizure disorders.

Pentobarbital is a commonly used barbiturate for sedation in children undergoing diagnostic radiologic imaging. It can be administered orally or intravenously. Recovery time can be prolonged following administration which may be a concern if subtle changes in neurologic exam need to be detected such as in the acute pediatric stroke patient. Some pediatric patients may also experience severe agitation during recovery which can confound sequential neurologic examinations [25]. High-dose pentobarbital is also used as a third tiered therapy to control intracranial hypertension following severe traumatic brain injury in children but the practitioner must be aware of the association with hemodynamic instability and the need for blood pressure support with intravenous fluids and inotropic infusions [26].

Besides myocardial depression and hypotension, barbiturates also have the side effect of respiratory depression which can lead to hypoxia. This side effect may be exacerbated in children with developmental disabilities. In a retrospective study, 260 children with developmental disabilities and 226 children without developmental disabilities undergoing brain MRI with sedation were reviewed. No difference in dosages of pentobarbital were observed between the two groups but there was a threefold increased incidence of hypoxia in children with developmental disability (11.9% versus 4.9%) [8]. In summary, pentobarbital is commonly used for sedation in children undergoing diagnostic radiologic procedures such as MRI or CT scan, but in the child with developmental disabilities or neurologic disorders the practitioner must be aware of the important side effects of systemic hypotension and respiratory depression and be prepared to respond to them quickly to avoid further neurologic injury.

Thiopental is an ultrashort-acting barbiturate which in its IV form is commonly used as an induction agent for intubation. The fast onset for induction and short duration of effect make it an attractive agent for rapid sequence intubation in pediatrics. It still poses some of the risks associated with barbiturates including myocardial depression and hypotension. The use of rectal thiopental (15–25 mg/kg) for sedation of pediatric patients undergoing diagnostic CT imaging of the head has been reported to be effective [27]. Due to the short duration of action, thiopental is generally not used for sedation during MRI imaging due to longer scan times.

3.2.4. Etomidate. Etomidate is a short-acting IV drug that produces sedation, anxiolysis, and amnesia. Side effects include respiratory depression, hypotension, myoclonus, and adrenal suppression. Etomidate has the benefits of decreasing ICP by reductions in CBF and $CMRO_2$ and has the advantage of producing less cardiovascular depression than barbiturates or propofol, and preserving cerebral perfusion pressure [28, 29]. These neuroprotective qualities are counterbalanced by its ability to increase cerebral vascular resistance by a greater magnitude than its reduction of $CMRO_2$ resulting in an increased metabolic deficit [30, 31]. The increased metabolic deficit has the potential to expand the ischemic core and penumbra in brain-injured tissue. This increase in cerebrovascular tone is thought to be attributed to etomidate's inhibition of nitric oxide synthase [32].

Previous reports on the efficacy of etomidate for pediatric sedation during diagnostic imaging have been mixed. Kienstra et al. performed a prospective randomized trial comparing etomidate versus pentobarbital for head and neck CT imaging in children 6 months to 6 years [33]. Sedation success rate was significantly lower in the etomidate group

(57%–76% versus 97%) but the duration of sedation was not surprisingly shorter in the etomidate group. Prospective data collected from the PSRC also compared sedation with pentobarbital versus etomidate for diagnostic CT [34]. Only 1 of 446 children sedated with etomidate was deemed "not ideal sedation" compared to 11 of the 396 children who received pentobarbital and duration of sedation was shorter with etomidate (34 versus 144 minutes). Etomidate may have a role for sedation during diagnostic CT imaging but etomidate's short duration of sedation is disadvantageous for the longer scan times required for MRI. Of further note, etomidate's role in the sedation of the pediatric stroke and intracranial hemorrhage patient may be limited and caution should be used to avoid further expansion of the penumbra and ischemic core.

3.2.5. Ketamine. Ketamine is a phenylcyclidine derivative typically formulated as a mixture of two enantiomers in a hydrochloride salt form. It possess low pH of around 4 which can produce pain at the injection site when administered intramuscularly or intravenously. Ketamine can provide both sedation and analgesia. Ketamine is a *N*-methyl-*D*-aspartate (NMDA) antagonist which produces increases in CBF and $CMRO_2$ [35, 36]. Early studies in patients with obstructed CSF pathways reported ketamine administration increased ICP with reductions in cerebral perfusion pressure [37, 38]. More recent studies in adult patients with severe head injury have demonstrated improvements in cerebral perfusion pressure and minimal increases in ICP with ketamine [39–41]. One recent report of 30 intubated pediatric head injury patients observed that single doses of ketamine lowered ICP without producing decreases in blood pressure or cerebral perfusion pressure [42]. However, it is still unclear regarding the effect of ketamine on ICP in patients where ventilation is not being tightly controlled. At the present time, there is not enough data to recommend the use of ketamine in the pediatric population at risk for intracranial hypertension, but further studies to assess the role of ketamine in this patient population are warranted. Ketamine is sometimes used as a continuous infusion in intubated patients as an anti-convulsant for children with refractory epilepsy. While ketamine is also a bronchodilator and is helpful in children with asthma, it increases oropharyngeal and airway secretions which may be problematic in children with neurologic disorders who have difficulty handling respiratory secretions. As a result, pretreatment with an antisialogogue such as glycopyrrolate or atropine before the administration of ketamine may be beneficial. In older children and adolescents, hallucinations and delirium can occur; these patients are often premedicated with a short-acting benzodiazepine such as midazolam.

3.2.6. Propofol. Propofol is a short-acting sedative-hypnotic IV agent that can be used to provide moderate or deep sedation. Propofol can induce a deep state of sedation rapidly, provide a short duration of effect, and have a pleasant recovery phase [43]. Propofol is a very popular agent for sedating pediatric patients with neurologic conditions for noninvasive diagnostic imaging, such as a CT scan or MRI. Due to the fast onset and recovery following administration, repeated neurologic examinations are easy to assess such as a child with sickle cell disease who comes in with altered mental status due to a stroke. Propofol also has anticonvulsant properties and reduces ICP which can be advantageous in sedating a patient with epilepsy or a patient with concerns for obstructive hydrocephalus due to a malfunctioning ventriculoperitoneal shunt to obtain diagnostic neuroradiologic imaging [44–46]. While there have been cases of propofol providing adequate sedation and successfully treating intracranial hypertension [47, 48], several pediatric traumatic brain injury case reports have reported metabolic acidosis and death in patients on prolonged (24 hrs) continuous infusion of propofol [49–53]. In the 2003 published guidelines for the care of severe pediatric traumatic brain-injured patients, "continuous infusion of propofol is not recommended" [54].

Adverse effects of propofol include pain at the injection site, apnea or respiratory depression, hypotension, and bradycardia which can be detrimental in a patient at risk for brain ischemia. Propofol does not provide any analgesia. As already discussed, a rare but potentially fatal "propofol infusion syndrome", associated with lactic acidosis, hyperlipidemia and multiorgan system failure was first described in pediatric patients who received prolonged (24 hours) continuous infusion and at higher dosages (>4.5 mg/kg/hr) [51, 55, 56].

3.2.7. Dexmedetomidine. Dexmedetomidine, a centrally acting α_2-adrenergic agonist, is a recently FDA approved agent used for short term (<24 hours) continuous IV sedation of adults who are tracheally intubated. Like propofol, it has a rapid onset and a relatively rapid elimination half life and is administered as a loading dose followed by continuous IV infusion. One of the advantages is that it provides sedation with a lower risk of respiratory depression than many other sedative medications [57]. There is increased interest with this agent as a sedative during non-invasive neuroradiologic imaging studies in children who are not intubated. In one study, dexmedetomidine was compared to propofol in children undergoing MRI studies. While the onset of sedation and recovery time were significantly shorter in the children that received propofol, hypotension, respiratory depression and desaturation were more common compared to the children receiving dexmedetomidine [58].

There is increased interest in the use of dexmedetomidine as a sedative and potential neuroprotective agent in both adults and children, as animal studies revealed neuroprotection from hypoxia-ischemia and decreased apoptosis and adult human studies in healthy volunteers demonstrated parallel decrease in $CMRO_2$ and CBF, which may temporarily be helpful in briefly sedating patients who are at risk for intracranial hypertension such as head trauma, brain tumor, and obstructive hydrocephalus [59, 60]. In pediatric traumatic brain injury case reports, no detrimental effects on their ICP was observed. However, systemic hypertension was observed in one child who were receiving dexmedetomidine

with other sedatives, while bradycardia was observed in 2 other children who was receiving dexmedetomidine, other sedatives, and therapeutic hypothermia [59, 60]. Further studies are warranted on the potential use and side effects of this agent in children at risk for intracranial hypertension.

The most common adverse side effects of dexmedetomidine appear to be cardiovascular. Bradycardia with rare reports of sinus pause or cardiac arrest has been reported. Hypotension has been reported as well as hypertension, the latter thought to be due to peripheral α_{2B} agonism with peripheral vasoconstriction. There are conflicting reports on the effects of ventilatory function, with some studies suggesting mild respiratory depression, while others show no effect. While ICP does not appear to increase, cerebral perfusion pressure and CBF have been shown to decrease. The effects on seizure threshold appear to be mixed [61]. Further studies are warranted on the use of this agent in pediatrics.

4. Conclusions

While a variety of sedative and analgesic medications have been used in pediatric patients with developmental disabilities and neurologic disorders, it is clear that further studies are needed to determine the optimal agent(s) that will maximize good outcome and will minimize or prevent respiratory, circulatory, and further neurologic compromise.

Acknowledgments

J. Huh is supported by NINDS Grant K08-NS053651, NICHD Grant R01-HD01963, and the Endowed Chair of Critical Care Medicine at Children's Hospital of Philadelphia. R. Raghupathi is supported by NICHD Grant R01-HD01963, NICHD Grant R01-HD41699, and VA Merit Review. S. Friess is supported by NINDS Grant K08-NS064051.

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Hindawi Publishing Corporation
International Journal of Pediatrics
Volume 2010, Article ID 825079, 6 pages
doi:10.1155/2010/825079

Case Report

Extended Infusion of Dexmedetomidine to an Infant at Sixty Times the Intended Rate

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Received 30 June 2010; Accepted 6 August 2010

Academic Editor: Savithiri Ratnapalan

Dexmedetomidine is an $\alpha 2$ adrenergic agonist which has recently been approved in the United States for procedural sedation in adults. This report describes an infant who inadvertently received an intravenous infusion of dexmedetomidine at a rate which was 60 times greater than intended. We describe the hemodynamic, respiratory, and sedative effects of this overdose.

1. Introduction

Infants and children frequently require sedation in order to ensure motionless conditions for radiological imaging studies. At our institution, dexmedetomidine (Precedex; Hospira, Lake Forest, IL) is the standard sedative, approved by the Hospital Sedation Committee and Pharmacy and therapeutics Committee for MRI studies. Dexmedetomidine is a highly selective $\alpha 2$ adrenoceptor agonist that possesses both sedative and analgesic effects [1]. Recently approved by the Food and Drug Administration (FDA) for procedural sedation, dexmedetomidine approval is still limited to adults only. In children, when dexmedetomidine is used as a sole agent for sedation, the doses needed to achieve adequate sedation have been shown to be remarkably high and exceed those approved for use by the FDA [2].

The potential hemodynamic effects of dexmedetomidine, notably sympatholysis due to $\alpha 2$ agonism at sympathetic ganglia, have been well described in healthy adults [3]. Bradycardia, hypotension, and the potential for hypertension have all been described when dexmedetomidine is administered to adults [4, 5]. The hemodynamic effects of dexmedetomidine in children, particularly when administered in greater than approved dosages, still remain to be clearly defined. Some series have reported that at higher dosages there is bradycardia and a tendency towards blood pressure variability [2, 6, 7]. The dosages required to accomplish MRI sedation with dexmedetomidine range from 2 to 3 mc/kg bolus and an infusion of 1-2 mcg/kg/hr [2, 6, 8].

The only case report in the literature of a dexmedetomidine overdosage in a child describes an elevated blood pressure and an extended recovery period [9]. Our case report describes a different sedative and hemodynamic response when an infant received an inadvertent administration of dexmedetomidine at an infusion rate of 60 times that prescribed for 20 minutes.

2. Case Report

A 21-month-old female with recent history of two febrile seizures (30 minutes apart) presented for an outpatient MR imaging study of the brain to complete the neurological evaluation. The infant was an otherwise healthy, full-term baby, and with an unremarkable medical history and review of systems. Upon presentation, the patient was not taking any medications although her mother carried Diastat (Acudial. Diazepam, Valeant Pharmaceuticals. Costa Mesa, CA) in the event the seizure recurred. The 9.9 kg infant presented in a calm, nonagitated state with a heart rate (HR) of 110 beats/minute, respiratory rate (RR) of 20 breaths/minute, and noninvasive brachial blood pressure

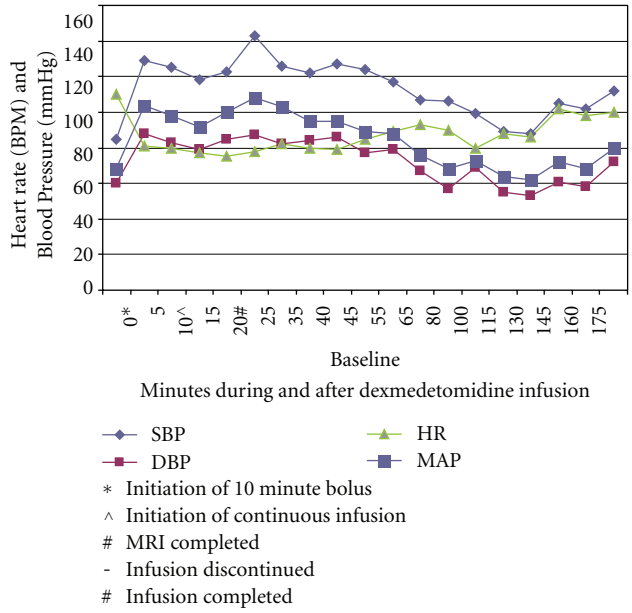

Figure 1

(NIBP) measurement of 85/60 with a mean arterial pressure (MAP) of 68 and a room air oxygen saturation of 100%.

After careful review of the infant, discussion with the mother, and a physical examination, the dexmedetomidine was ordered per protocol by the pediatric nurse practitioner under the supervision of an anesthesiologist. Written, informed consent was obtained from the mother for the dexmedetomidine sedation. A 24-gauge intravenous catheter was initiated and dexmedetomidine was ordered per protocol, specifying a bolus of 2 mcg/kg over 10 minutes and a subsequent infusion of 1 mcg/kg/hr. The bolus was administered at the ordered rate of 2 mcg/kg over a period of 10 minutes using an Iradimed 3850 mRidium MR IV pump (Iradimed Corp, Winter Park, Fla). Vital signs (NIBP, MAP, 3-lead EKG, pulse oximeter, and HR) were monitored continuously using an Invivo Precess monitor (Invivo Corp, Orlando, and Fla) and documented every five minutes. The patient achieved successful sedation conditions (Ramsay Sedation Score = 4) by the completion of the bolus. Upon completion of this 10-minute bolus, NIBP was 118/79 (MAP 92), HR 77 (normal sinus), RR 17, and oxygen saturation of 97% on 2 liters/min oxygen via nasal canula (see Figure 1). Sedation guidelines at our institution specify supplemental oxygen delivery throughout the sedation and recovery period until discharge criteria are met. Following the bolus, the infusion pump initiated delivery of the dexmedetomidine infusion at the rate that had been programmed in at the initiation of the sedation. The dexmedetomidine infusion was continued throughout the sedation until the MRI scan was complete. The patient remained hemodynamically stable throughout Vital signs were documented at five-minute intervals per our hospital standard for sedation, following initiation of this dexmedetomidine infusion (Table 1).

At the termination of the study, the radiology nurse noted that the dexmedetomidine remaining in the syringe was less than anticipated and medication reconciliation was immediately initiated with a second nurse. Reconciliation revealed that the 9.9-kg infant had received 196 mcg more dexmedetomidine than had been ordered. Review of the intravenous infusion pump revealed that the pump had been misprogrammed to deliver the infusion at a rate of mcg/kg/min rather than mcg/kg/hr. Thus, instead of delivering the usual 1 mcg/kg/hour as ordered, the infusion pump delivered the dose at 1 mcg/kg/minute (equivalent to 60 mcg/kg/hr). Because this error was not identified during the mandatory institutional nursing "double check" when the infusion pump was programmed, the error was not identified, and the dexmedetomidine infusion was continued for the 20 minutes.

Following the imaging study, the patient was transferred uneventfully to the radiology recovery room at which time monitoring was continued. The patient arrived in the recovery room deeply sedated with an RSS 4. Per recovery room policy, NIBP, MAP, EKG, HR, O2 Sat, and RR are documented every 5 minutes until modified Aldrete discharge criteria are met [10]. A minimum Aldrete score for discharge from the recovery room is 9. Although documented every 5 minutes, pulse oximetry is monitored continuously. Throughout the recovery room course, all physiologic parameters remained within age-adjusted normal values. 20 minutes after the discontinuation of the dexmedetomidine, the infant had achieved a modified Aldrete score of 9 and maintained an Aldrete of 9-10 throughout the remainder of the recovery room stay. No cardiac arrhythmias were noted at any time, both during the sedation as well as in the recovery room period. As soon as the error in dosing was identified, Risk Management was notified and the parents were debriefed and all questions answered by the Risk Management team as well as the supervising anesthesiologist. The parents were informed that the intravenous infusion pump had been misprogrammed and that the child had received an infusion of 60 times that which was ordered and intended. The effects of such a high dosage of dexmedetomidine delivery to an infant had not to date been described nor documented. In adults, the distribution half-life (t1/2) is approximately 6 minutes and the terminal elimination half-life (t1/2) is approximately 2 hours [11].

The infant returned to baseline neurological status, an Aldrete Score of 10, after a 2-hour recovery room period. Although the half-life of dexmedetomidine is relatively short, and the child met discharge criteria with a modified Aldrete Score of 10 within hours of discontinuing the dexmedetomidine, the physicians chose to admit her to the hospital for overnight, continuous cardiorespiratory monitoring. Subsequently, the patient was admitted to the intensive care unit (ICU) for overnight monitoring of EKG as well as pulse oximetry, blood pressure, and neurological status. The child remained hemodynamically and neurologically stable in the ICU throughout the night. There were no arrhythmias, no change in neurologic status nor any deviation in heart rate or blood pressure outside of age-adjusted anticipated normal values. The next morning, after reassessment by neurology and the intensive care unit service, the infant was discharged home with no subsequent sequela.

Table 1: Vital Signs at time points (minutes) prior to, during, and following initiation of the dexmedetomidine bolus and infusion.

	Presedation/Baseline	0	5	10	15	20	25	30	35	40	45
NIBP	85/60	118/79	123/85	143/87	126/82	122/84	127/86	124/72	117/79	107/67	106/57
MAP (mmHg)	68	92	100	108	103	95	95	89	88	76	68
Heart Rate (BPM)	110	77	75	78	82	85	79	85	89	93	90
RR (breaths/min)	20	17	13	24	13	14	14	16	18	18	18
O2 Saturation	100%	97%	96%	96%	96%	97%	97%	98%	98%	99%	99%
EKG	NSR	NSR	NSR	NSR	NSR	NSR	NSR	NSR	NSR	NSR	NSR

NSR: Normal Sinus Rhythm
MAP: noninvasive mean arterial blood pressure
RR: Respiratory rate
0–10 minutes: The dexmedetomidine bolus administered
10–20 minutes: The dexmedetomidine infusion initiated and completed
20–45 minutes: The recovery room period until discharge criteria, defined as a minimum modified Aldrete Score 9, are achieved.

3. Discussion

Dexmedetomidine (Precedex) is a relatively selective $\alpha 2$-adrenergic agonist with sedative properties. As an imidazole, dexmedetomidine has an $\alpha 2 : \alpha 1$ activity ratio of $1620 : 1$, compared to $220 : 1$ with clonidine [12]. It is known that spinal and supraspinal $\alpha 2$-adrenoreceptors mediate and modulate nociception. These receptors are widely distributed throughout the peripheral and central nervous systems and a variety of organs, including liver, kidney, and pancreas. $\alpha 2$-adrenoreceptors have been located at presynaptic, postsynaptic, and extrasynaptic sites. Of these, the presynaptic and postsynaptic receptors may be the more clinically important in analgesia. In general, activation of $\alpha 2$-presynaptic receptors inhibits norepinephrine release and possibly substance P release, thereby inhibiting pain signal transmission. Postsynaptic activation in the central nervous system inhibits sympathetic activity, thus moderating heart rate and blood pressure [13–18]. Together, these effects produce analgesia, sedation, and anxiolysis.

Recently approved (October 2008) for procedural sedation outside of the intensive care unit setting, Dexmedetomidine is still not approved by the Food and Drug Administration (FDA) for pediatric use. Although not approved in children, its use has been described for pediatric sedation in the intensive care unit, for radiology, gastroenterology, and dental procedures, as well as for electroencephalograms [19–28]. The dosages required to achieve sedation in infants and children tend to be higher than for adults. The need for higher dosages in children as compared to adults is confirmed in a recent pharmacokinetic study [29].

In adults, dexmedetomidine can produce varying depths of sedation which have been compared to states of natural sleep with respect to cardiovascular and respiratory effects [1]. When administered to adults within clinical dosing guidelines, there are no demonstrated significant accompanying changes in resting ventilation [3, 30, 31]. In fact, there is an evidence to support that dexmedetomidine actually mimics some aspects of natural sleep in both children and adults [30, 32].

Our concern with this infant following the overdosage was the potential for hemodynamic compromise. In both adults and children, there may be an increased incidence of clinically significant bradycardia with hypotension and possibly even cardiac arrest with dexmedetomidine, especially when administered with other medications which possess negative inotropic or chronotropic effects [33]. The potential hemodynamic effects of dexmedetomidine, notably sympatholysis, have shown a biphasic physiologic response characterized by an initial increase in systolic blood pressure and a reflex-induced decrease in heart rate followed by stabilization of heart rate and blood pressure below baseline values. The initial increase in MAP reportedly lasts for 5–10 minutes with a subsequent decrease in MAP of approximately 10%–20% below baseline with an HR that usually stabilizes below baseline values. These effects have been attributed to an inhibition of the central sympathetic outflow [30, 34]. Hemodynamic variability with dexmedetomidine has been described in case reports of severe bradycardia in a child with digoxin, hypertension in a child with traumatic brain injury, and hypertension in a child with acute transverse myelitis [5, 35, 36]. Children who received dexmedetomidine (3 mcg/kg bolus and 2 mcg/kg infusion) are more likely to manifest hypertension if they are less than one year of age and have received more than one bolus of dexmedetomidine [7].

At our institution, radiology sedation is administered by nurses under the direct supervision of a pediatric nurse practitioner and supervising anesthesiologist. All children must be medically appropriate to receive dexmedetomidine sedation and cannot have any conditions which our institutional Hospital Sedation Committee considers to be a contraindication to dexmedetomidine [2, 6, 8] (Table 2). Dexmedetomidine sedation is administered following protocols which are on preprinted, templated order sheets approved by the Pharmacy and Therapeutics Committee. The order sheet specifies the following. A bolus of dexmedetomidine is administered at a specified dose in mcg/kg over 10 minutes. The goal of the bolus is to achieve a minimum Ramsay Sedation Score (RSS) 4 [37]. An RSS 4 or RSS 5 is a clinically derived scoring system that is generally accepted as the depth of sedation adequate to facilitate diagnostic imaging studies [8, 38]. This bolus may be repeated at the same dosage and time interval if the patient

Table 2: Medical Conditions Which Contraindicate Dexmedetomidine Sedation.

Active, uncontrolled gastroesophageal reflux—an aspiration risk
Active, uncontrolled vomiting—an aspiration risk
Current (or within past 3 months) history of apnea requiring an apnea monitor
Active, current respiratory issues that are different from the baseline status (pneumonia, exacerbation of asthma, bronchiolitis, and respiratory synctitial virus)
Unstable cardiac status (life threatening arrhythmias, abnormal cardiac anatomy, and significant cardiac dysfunction)
Craniofacial anomaly, which could make it difficult to effectively establish a mask airway for positive pressure ventilation if needed
Current use of digoxin
Uncontrolled hypertension
Moya Moya Disease
New-onset stroke

fails to achieve or maintain the minimum RSS 4, at any time during the sedation. Following completion of the bolus, and confirmation of adequate sedation, an infusion at a specified dosage in mcg/kg/hr is immediately started and continued until completion of the study. Following completion of the MR scan, the dexmedetomidine is discontinued, the patient is transported to the radiology recovery room and monitored with documentation of vital signs every 5 minutes until discharge criteria are met. Per our institutional guidelines, discharge criteria require a minimum Aldrete Score of 9 points [10].

In summary, this report describes the outcome during and following a substantial, inadvertent overdosage of dexmedetomidine to an infant. The overdosage represents a continuous dexmedetomidine infusion for 20 minutes at a rate which was almost 80 times that was recommended by the Food and Drug Administration for adults. To date, most of the reports of inadvertent overdosage are in adults, with the degree of overmedication substantially less than cited in our report [39]. The child received 60 mcg/kg/hour for 20 minutes and maintained cardiovascular and respiratory stability. Our experience differs from a previous overdose report which described an increase in blood pressure [9]. The absence of a significant hypertensive response suggests that infants may not demonstrate the biphasic hemodynamic response for blood pressure and vascular resistance as is reported in the adult literature [40]. This report is important because it demonstrates that even in excessive dosages, dexmedetomidine may not elicit an extreme hemodynamic or respiratory effect. This child exhibited a prolonged recovery and somnolence, with almost 2 hours to meet Aldrete discharge criteria. This prolonged recovery period is longer than the average 30 minutes recovery time, when the prescribed dosage is administered [2].

Although the infant in this report did not suffer any noticeable short- or long-term adverse sequela, our experience, however, identifies a serious and important mishap; Dexmedetomidine is unusual in that it is administered as an infusion with an hourly rate rather than a rate expressed per minutes. Both nursing and physicians are more commonly habituated to administer infusions per minute. Thus, careful double checks of the programmed rate must be followed in order to ensure accurate delivery of dexmedetomidine. There are no clear guidelines from the Joint Commission for the programming and delivery of intravenous medication. Rather, standard practice in our institution requires that the accurate programming of the infusion pump be independently verified by two separate nurses. Even with this process in place and documentation by two separate nurses that each had independently performed and verified the drug concentration, bolus and infusion dosage, and rate of administration, the error occurred. As a result of this incident, our institution has added an additional safety measure. The dexmedetomidine program in the infusion pump has been restricted to deliver infusions in units of mcg/kg/hour and a bolus in units of mcg/kg. The ability to deliver dexmedetomidine at a mcg/kg/minute rate or mg/kg dosage has been lockedout.

In conclusion, despite a large overdose of dexmedetomidine, this infant demonstrated hemodynamic stability throughout without incidence of hypotension or hypertension. Aside from the prolonged sedation for up to 2 hours following discontinuation of the infusion, she suffered no additional sequela. This report reveals the need for continued study of dexmedetomidine in order to determine the optimal dosing to ensure successful sedation conditions, hemodynamic stability, and a safe recovery period.

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