Anesthesiology Research and Practice

Peripheral Nerve Blockade

Guest Editors: Attila Bondar, Didier Morau, Sridhar Kollipara, and Gabriella Iohom

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Editorial Board

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Editorial
Peripheral Nerve Blockade

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Regional anesthesia has gained significant popularity over the last few decades due to improved efficacy and patient safety. An increasing number of anesthesiologists perform peripheral nerve block (PNB) techniques in their daily clinical practice making the current special issue both timely and practical.

Undoubtedly, PNB is the cornerstone of multimodal analgesia. Effective PNB removes the need for general anaesthesia (and its associated risks and sequelae). Aggressive perioperative analgesia prevents persistent postsurgical pain and may lead to improved clinical outcome. Patients can be discharged from the operating room directly to the ward, bypassing the postanesthesia care unit. Effective pain relief facilitates early physiotherapy, functional recovery, early ambulation, and discharge from the hospital, thus attracting serious cost savings.

Ultrasound guidance has emerged as the "gold standard" in regional anesthesia or it is very close to it! In spite of all visual clues though, ultrasound guidance is incapable of preventing nerve injury or inadvertent intravascular injection; therefore, the usual precautions apply. Current trends in ultrasound-guided regional anesthesia point towards local anesthetic volume reductions. We have learned from recent research that a great deal of nerve stimulation guided blocks were actually intraneural, leading to the known minor, transient, or no neurological symptoms. More than ever before, formal structured training is of paramount importance for the safe practice of regional anesthesia. American Society of Regional Anesthesia and European Society of Regional Anaesthesia Joint Committee guidelines for training in ultrasound-guided regional anesthesia were produced in response to the "dramatic" increase in the use of ultrasound-guided PNBs in recent years.

The current special issue is a representative snapshot of our current understanding of PNB. We believe that the articles are informative and most of all thought provoking.

In "*Perioperative nerve blockade: clues from the bench*" M. R. Suter et al. tease out the effects of nerve blockade on pain-related behaviour and central changes after peripheral tissue injury in animal models. They propose mechanisms for the mitigated results of clinical studies on chronic postoperative pain.

"*Histological consequences of needle-nerve contact following nerve stimulation in a pig model*" by T. Steinfeldt et al. explores an interesting concept, that is, that high threshold current (1.0 mA) is associated with a reduced likelihood of direct needle-nerve contact compared with low threshold current (0.2 mA), thereby reducing the potential for needle-related nerve injury in an open pig brachial plexus model. The authors demonstrated that (i) low current threshold is likely to result in a greater incidence of needle-nerve contact, (ii) needle-nerve contact may result in aseptic neuroinflammation, but (iii) this inflammatory response, although greater following application of low (0.2 mA) compared to high (1 mA) current thresholds, is independent of the presence or absence of current.

Accepting such high current thresholds in clinical practice, in order to avoid needle-nerve contact may result in higher failure rates. The risk-benefit ratio of PNB may be improved when combining blind electrostimulation with ultrasound guidance.

"*Neural blockade anesthesia of the mandibular nerve and its terminal branches: rationale for different anesthetic techniques including their advantages and disadvantages*" by J. Khoury and G. Townsend may seem an outlier at first sight. Although not part of the anesthesiologists' routine armamentarium, mandibular nerve blockade serves as an example of correlating anatomy with different techniques in a clear, unambiguous manner. Inquisitive clinicians will welcome both the approach and the content of this selective review.

The article entitled "*Ultrasound-guided regional anesthesia for procedures of the upper extremity*" by F. Mirza and A. R. Brown describes various approaches to the brachial plexus in terms of their indications and advantages/disadvantages pointing out the value of ultrasound guidance in their performance.

"*Axillary brachial plexus block*" by A. R. Satapathy and D. M. Coventry makes for a comprehensive description of the safest upper limb block, that is, ultrasound-guided axillary approach to brachial plexus blockade including clinical pearls and tricks of the trade.

In "*Ultrasound guidance for deep peripheral nerve blocks: a brief review*," A. Wadhwa et al. review the role of ultrasonography in carrying out deep nerve or plexus blockade, such as infraclavicular, lumbar plexus, and sciatic nerve blocks. The authors highlight technical problems associated with scanning and needling deep structures. They caution that, based on the current literature, ultrasound does not replace experience and knowledge of relevant anatomy, especially for visualising deep structures.

In "*The psoas compartment block for hip surgery the past, present, and future*" M. A. de Leeuw et al. provide an overview of the history, clinical efficacy, and risk profile of the psoas compartment block for hip surgery. While clearly, the block is a valuable adjunct to analgesia following hip surgery, further research is required to optimize the technique for usage as a sole anesthetic technique.

We hope the current selection of peer-reviewed articles will make both an interesting read and a useful reference material. For this, we thank the authors and the reviewers. We also wish to express our gratitude to the extremely supportive editorial staff at Hindawi Publishing Corporation, Ms. Amira Tyseer.

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Review Article

Perioperative Nerve Blockade: Clues from the Bench

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Peripheral and neuraxial nerve blockades are widely used in the perioperative period. Their values to diminish acute postoperative pain are established but other important outcomes such as chronic postoperative pain, or newly, cancer recurrence, or infections could also be influenced. The long-term effects of perioperative nerve blockade are still controversial. We will review current knowledge of the effects of blocking peripheral electrical activity in different animal models of pain. We will first go over the mechanisms of pain development and evaluate which types of fibers are activated after an injury. In the light of experimental results, we will propose some hypotheses explaining the mitigated results obtained in clinical studies on chronic postoperative pain. Finally, we will discuss three major disadvantages of the current blockade: the absence of blockade of myelinated fibers, the inappropriate duration of blockade, and the existence of activity-independent mechanisms.

1. Introduction

The major interest of regional anesthesia (central or peripheral nerve block) in clinical practice remains to replace or supplement general anesthesia for certain types of surgery and to provide efficient pain relief in the postoperative period. Being able to continue the block in the postoperative period allows a more effective pain control and a reduction of opioid-related side effects [1, 2]. While the improved patient comfort is undoubted, an overall improvement in long-term patient outcome is less evident and combining general anesthesia with a regional analgesic technique exposes the patient to the risk of both techniques. Since the concept of pain treatment as a fundamental human right has emerged, the use of invasive pain treatment is warranted already for the improvement of acute postoperative pain treatment [3]. Efficacy of nerve blockade on serious complications in the postoperative period (major morbidity or mortality) is hard to demonstrate because of their low incidence [4]. The possibility of preventing chronic postsurgical pain is becoming a major issue [3, 5, 6]. In the clinical research literature, there are only few reports showing a benefit of regional analgesic techniques on the incidence of chronic postoperative pain states. Two RCT demonstrated a reduction of the incidence of chronic postthoracotomy pain in patients treated with peri- and postoperative epidural analgesia as compared to patients without postoperative epidural analgesia [7, 8]. Further, a single paravertebral block reduced the incidence of postmastectomy pain one year following surgery as compared to a sham puncture [9]. Whereas the incidence of phantom limb pain after amputation was not influenced by epidural analgesia [10]. Surrogate outcomes are studied to increase the indications of regional analgesic techniques: length of hospital stay, improvement on long-term function after surgery (in orthopedics) and, newly, cancer recurrence [11], and reduction in surgical site infection [12]. Experimental research on humans and animals could help to define more clearly the working hypothesis of clinical trials and their design.

Current pain treatment should use a mechanistic-based approach. The best mechanistic knowledge in patient to-date is obtained from quantitative sensory testing (QST) where different modalities of sensation are tested. There is a gap between the sensory testing in human and the cellular and molecular vision offered in an experimental laboratory setting. The experimental setting also allows different types

of blockade, using drugs with specificities on nerve fiber types, longer duration, or motor blockade, all of which cannot be tested on patients unless strong evidence has been gathered beforehand in experimental studies.

This paper is therefore intended to focus on the effect of nerve blockade on pain-related behavior and central changes that occur after peripheral tissue injury in animals (e.g., rats and mice) and build a bridge to clinical practice. We will try to point out some discoveries in bench research that would answer questions or lead to research ideas around the operating room.

2. Pathophysiology of Peripheral Discharges and Central Mechanisms of Persistent Pain

2.1. Peripheral Activity and Central Sensitization: A Potential Contribution to Chronic Postoperative Pain. The potential benefits of regional analgesic techniques rely on the ability of local anesthetics to reduce or abolish the peripheral input electrically transmitted by the nerve. Tissue injury and/or inflammation (with potential nerve lesion) during surgery lead to a massive input of action potentials along the primary afferents. The first relay of the information in the central nervous system (CNS) is the spinal cord dorsal horn. The glutamate release at the synapses in the dorsal horn induces a depolarization in the second-order neuron. If its amplitude is large enough, it triggers an action potential that conducts the information to higher centers. Cumulative afferent inputs gradually sensitize second-order neurons, which become more reactive to subsequent inputs. This global process of signal enhancement in the CNS is called central sensitization and encompasses increased membrane excitability, synaptic efficacy, and reduced inhibition. Central sensitization and its dependency on primary afferent activity has been extensively reviewed by Latremoliere and Woolf [13]. It is often described in 2 temporal phases an early short lasting, transcription-independent phase caused by phosphorylation mechanisms and a late longer lasting phase dependant on transcription and synthesis of new proteins [14]. Central sensitization is triggered by primary afferent release of glutamate which binds on postsynaptic ionotropic (AMPA (amino-3-hydroxy-5-methyl-4-isoxazole propionate), NMDA (N-methyl-D-Aspartate) and kainate), and metabotropic (mGluR 1–8, not all expressed in spinal cord) receptors. Under normal stimulation, the NMDA receptor is blocked by a magnesium (Mg^{++}) ion in a voltage-dependent manner. Following sustained activity as in the case of surgery, the Mg^{++} block is released and glutamate can open the NMDA receptor leading to greater calcium entry in the spinal cord neuron, the first step of central sensitization. This is enhanced by the neuropeptides Substance P and CGRP, also released from primary afferents. The increase in cellular calcium in the dorsal horn neuron appears to be the trigger for the next step of central sensitization implicating activation of kinases (protein kinase A (PKA), C (PKC), or calmodulin kinase II (CaMKII)). These kinases phosphorylate different channels thereby increasing their trafficking to the membrane or changing their biophysical properties globally enhancing their response. Other targets in the later phases of the sensitization phenomenon include mitogen-activating kinases (MAPKs) such as extracellular signal-regulated kinase (ERK) and transcription factors finally leading to changes in gene expression.

2.2. Characterization of Spontaneous Discharges after Nerve Injury. Spontaneous activity occurs from the neuroma (unregulated regeneration of the nerve stump after injury) after nerve section [15, 16], and there have been numerous descriptions of increased peripheral activity after nerve injury, in different neuropathic pain models (Figure 1) and at different timepoints after injury. Most agree that ectopic activity in primary afferent after nerve injury arises from multiple sites (the neuroma, along the nerve, or in the dorsal root ganglion (DRG)) [17, 18]. However, there are still controversies about which type of fibers (injured versus noninjured fibers or myelinated versus unmyelinated fibers) [17]. Since the early recordings following axotomy, different animal models of neuropathic pain (Figure 1) were developed, many consisting of partial nerve lesions. They lead to various configurations between intact and injured nerve fibers. In chronic constriction injuries (CCI, originally described by Bennett and Xie [19] and modified by Mosconi and Kruger [20]), mostly myelinated fibers are injured, leaving neighboring C-fibers relatively undamaged [21]. In the spinal nerve ligation model (SNL) model [22], intact roots are in contact distally with the degenerating fibers of the injured roots and in the spared nerve injury (SNI) model [23] intact fibers are in contact with the proximal part of the injured nerves.

Summarizing all studies on peripheral nerve activity recordings is difficult but we will take out the general ideas. Most researchers consider A-fibers as the principal contributors to peripheral ectopic firing following nerve injury [24–28]. Nevertheless, activity in the unmyelinated C-fibers was recorded either very early, during the first 15 minutes after a nerve lesion [29], or later, after a few days [30]. C-fiber activity was also recorded after spinal nerve ligation in the neighbored intact spinal nerve [31] or after stimulation of a nerve stump with nociceptive mediators [32]. This underlines the importance of uninjured fibers as provider of afferent inputs or of aggravating factors that we could also use as potential therapeutic target [25, 33, 34].

Is pain-related behavior linked to this ectopic firing? Indeed in neuropathic models, onset of activity is strongly related to the generation of pain [17, 31, 35, 36]. Ectopic discharges were even correlated with pain-related behavior at the early phase of nerve injury but not later on [37].

In a translational perspective, a nerve blockade, peripheral or neuraxial, should therefore cover impulse from both myelinated and unmyelinated fibers in the postoperative period. The minimal timeframe until peripheral input is no longer associated with pain-related behavior after surgery still has to be defined. Interestingly, for the clinical setting, Brennan's group recently paralleled guarding behavior in rodents to spontaneous pain in postoperative patient. They were able to show that skin plus deep tissue incision induces

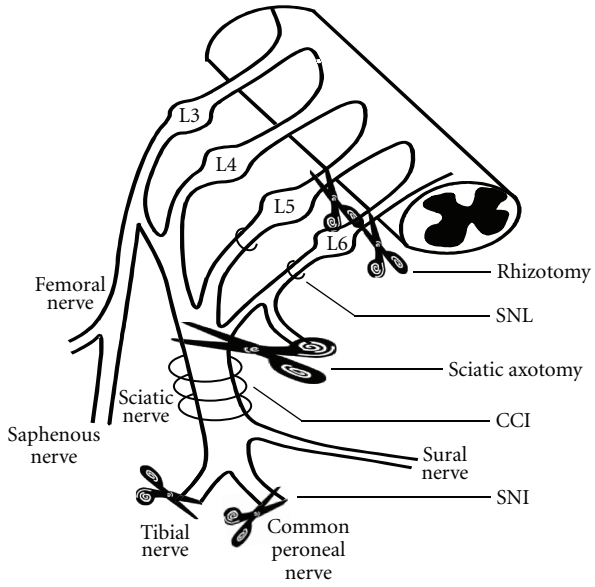

Figure 1: Schematic of the major animal models of nerve injury. Rhizotomy consists of section of dorsal roots; SNL: spinal nerve ligation, usually L5 or L5 and L6; CCI: chronic constriction injury consists of loose ligations of the sciatic nerve; SNI: spared nerve injury, consists of section of the tibial and the peroneal branches leaving the sural intact.

a guarding behavior and increased spontaneous afferent activity which was not present in skin incision alone [38]. This brings to attention that spontaneous activity can appear in an inflammatory model without obvious nerve injury as seen in our daily surgical activity.

3. Advantages and Limits of Animal Research

The necessity of animal models has always been criticized [39, 40]. A few well-known failures to translate research findings into clinical trials, NK-1 antagonists [41], glycine site antagonist [42], or sodium channel blockers [43] remind us of the potential gaps between animals and humans. On the other hand, examples of successful translational research exist such as conotoxin, which revealed a new mechanism in pain development and lead to a new treatment [44]. New compounds are coming to clinical trial, nerve growth factor (NGF) inhibitor [45, 46], or transient receptor potential vanilloid receptor 1 (TRPV1) antagonists [47, 48].

Three current limitations in humans are cited by Mogil [40], (i) single neuron recording which gives valuable information is not obtainable in human, (ii) functional magnetic resonance imaging reaches a ceiling and high activity in neurons cannot be differentiated, and (iii) some regions of interest such as the spinal cord dorsal horn or the DRG are too small to be seen clearly. Therefore, most human studies characterize pain states and do not look at anatomical, biochemical, or physiological mechanisms. We are however able to see an increase in imaging studies which, together with quantitative sensory testing, represent the best mechanistic approach feasible in living patients and with technical improvement some limitations seen above will be overcome.

An obvious advantage of animals is the standardization of the injury and of the genetic and environmental background and avoiding any social factors. Nerve injuries on patients are heterogeneous and, therefore, difficult to study. We will here highlight the advantages and the limits of animal research specifically looking at nerve blockade issues.

3.1. Advantages of Animal Research

(a) Sustained Block. The influence of duration and initiation of epidural nerve blockade to prevent chronic changes after amputation has been studied clinically already 20 years ago with controversial results [10, 49]. For local anesthetics, delivery through slow release polymer is complicated and therefore peripheral or central nerve blockade lasting more than a few hours in patients implies the placement of a catheter. The length of a clinical block will depend on practical issues such as surveillance, costs, risks of catheter infection [50] or ambulatory surgery. In experimental research, slow release devices in development can already be used to block nerves over a few days [35]. By combining a slow release system (microspheres loaded with bupivacaine and a small amount of dexamethasone) with an entrapment (embedding the spheres in fibrin glue inside a silicon tube), we could achieve a complete sciatic nerve block for a week with complete recovery thereafter [51].

(b) Selective Block. As mentioned above, discharges originate in different fiber types depending on the injury model and timing. In clinical setting pain (nociceptive), specific blockade is achieved by reducing the concentration of the local anesthetics. Lots of research is ongoing to discover blockers whose targets are specifically expressed on nociceptors such as TRPV1 or specific isoforms of sodium channels.

TRPV1 can be blocked by an agonist as capsaicin or resiniferatoxin (RTX) which induces a desensitization of the nerve fiber for a longer period. In our hands, RTX directly applied on the sciatic nerve induced a selective block to heat stimulation for 3 days without affecting the response to mechanical stimulation or impairing motor ability. From the 9 voltage-gated sodium channels currently described (Nav1.1–1.9), Nav1.7, 1.8, and 1.9 are almost selectively expressed on nociceptors. No specific blocker of these channels has yet completed clinical trials successfully but compounds are still being tested [52]. These methods of selectively blocking nociceptors are not used in the perioperative setting, yet but in research they are useful tools to study the influence of selective fibers on the mechanisms of pain.

(c) Evaluation during the Blockade. Motor/sensitive block and pain levels can be assessed during peripheral or central

nerve blockade whereas long-term outcomes as chronic pain or functional recovery can be checked later. We know many plastic changes occur in the perioperative period. In animals, tissue can be harvested during the blockade to study which mechanism are changed.

(d) Electrophysiological Recordings. The most important effect of peripheral or central nerve blockade is impeding discharge to pass from periphery to the brain, thereby inhibiting pain. Fundamental research on pathophysiological mechanisms (ectopic electrical activity-dependant or -independent changes, location, and timing of nerve activity) can give hints to clinicians where to block, when, and for how long. Then, clinical trials based on these mechanisms could be designed. Besides observational studies on discharge characteristics in different models, electrophysiological recordings allow to study the effect of blockade on subsequent discharge patterns.

3.2. Limits in Animal Research. Behavioral studies in animals are not an easy task. Subject to interobserver and interindividual variability, they integrate many different aspects of the pain pathways (spinal withdrawal reflexes, spinobulbospinal reflexes as jumping, simple innate behaviors as guarding or licking, or more complicated learned behaviors) depending on the test used. The limits often put forward in animal models are the following: assessment of evoked-pain behavior and not spontaneous pain, no vocalization in the audible range, or no characterization of symptoms. We have to be aware of the limitations when we transfer our results to a clinical application and stay humble when we want to claim the mechanisms in animals and humans are comparable. We hope for mechanistic research in human to improve and to guide our laboratory hypotheses.

4. Clues from the Bench

Detailed effects of blocks on nerve injury models are summarized in Table 1 and the description of the models in Figure 1. We will highlight the general ideas below.

4.1. Effects of Timing and Duration of Block on Behavior.

(i) Effect of Timing. The question of whether a nerve blockade has to be effective before or only after surgery is still unresolved. Few experimental studies compared the exact same treatment given before and after lesion. Fletcher et al. demonstrated a better effect on hyperalgesia when injecting bupivacaine in the paw before than after carrageenan [53]. The difference was even sustained when a second dose of carrageenan was injected a week later [54]. This underlines that priming of the nociceptive or sensitive system can be induced by a first injury without being noticed until it is unraveled by the magnified response to a second insult. In a model of intravesical acrolein injection, the timing of lidocaine injection influenced the referred mechanical hyperalgesia on the hindpaws but not the biochemical changes in the bladder itself [55], which points to activity dependant phenomenon or not. Pain mechanisms also change during development: a nerve blockade was done before or after a paw incision in 2-week or 4-week-old rat pups, the preinjury block was only more effective in the 2 weeks old pups [56]. Short block before injury reduced long-term pain-related behavior in the CCI model [57–59], but not in the partial sciatic nerve ligation (PSNL) [57], SNL [60], or spinal nerve cryoneurolysis models [61]. Sometimes the block only delayed heat hyperalgesia in the CCI [62] or mechanical allodynia in the SNL [63]. In the pain clinic, as opposed to the perioperative setting, preventive block cannot be done and we want to know if nerve blockade is useful once pain is established. This is a fundamental pathophysiological issue to know if peripheral inputs still contribute to maintenance of pain or if pain has become a self-maintained central process. Local anesthetic on the dorsal root or spinal nerve after establishment of neuropathic pain could alleviate transiently mechanical and cold allodynia after SNL [34, 60] and inhibiting distal afferent in the CCI model was effective on heat hyperalgesia [64].

The clinical implication of these results is that it is probably useful to perform a nerve blockade before the surgery rather than only starting after. Even if the pain is already established it is worth to use peripheral nerve blockade to test if peripheral nerve activity still participates to the pain process.

(ii) Effect of Duration. Apart from the question of when to commence the block, the duration of any perioperative nerve blockade is often questioned. To answer, studies compare the same treatment for short versus long period. In animal inflammatory pain models, repeated injections or bupivacaine-microspheres but not a single injection of bupivacaine reduced pain behavior [65–67]. In the paw incision model, which simulates inflammatory postoperative pain, longer block is more effective for relieving primary and secondary hyperalgesia [68]. For neuropathic pain, a one-week-long peripheral nerve blockade in the SNI model did not prevent pain-related behavior [51], whereas slow release bupivacaine placed at the time of lesion could prevent it in the same model and in the CCI [35].

Clinically, the suspicion that a longer block of nociceptive input could possibly prevent the development of chronic pain states has newly been discussed in the context of phantom limb pain after amputation. While older studies never managed to demonstrate a beneficial effect of epidural or peripheral nerve blocks, a recent observational study revealed astonishingly few patients suffering from phantom limb pain one year after lower limb amputation with prolonged peripheral nerve block performed as peri- and postoperative pain treatment (median duration of block 30 days) [69]. There are clinical and experimental arguments in favor of a long-term block but the duration with the best ratio of risk/benefit has yet to be found.

4.2. Biochemical Changes Affected by Blockade. During the period of a regional blockade, behavioral analysis is difficult due to the sensory impairment. Animal research allows

Table 1: Effect of block on animal nerve injury models. Single means one application, local means on the injury site, and pre-emptive: yes: before the injury. SNL: spinal nerve ligation, CCI: chronic constriction injury, SNI: spared nerve injury, Seltzer: partial sciatic nerve ligation, d: day(s), dpi: day(s) postinjury, iv: intravenous, it: intrathecal, ip: intraperitoneal, ttt: treatment, DRG: dorsal root ganglion, SC: spinal cord, RTX: resiniferatoxin, and TTX: tetrodotoxin.

Author	Year	Drug	Duration	Route	Preemptive	Model	Time of effect	Effect
Behavioral changes								
I. Kissin	1999	N-b-tetracaine	single	saphenous	yes	saphenous transection	7 dpi	Prevention early pressure hyperalgesia, caused hyperalgesia alone at 10 d
		Lidocaine	Single	saphenous	yes	saphenous transection	1 dpi	Prevention early pressure hyperalgesia
Y. W. Yoon	1996	Bupivacaine	Single	dorsal root L4/5 5 dpi	no	SNL L5/6	5 dpi	L5: reduction of mechanical + cold allodynia and ongoing pain; L4: reduction of mechanical + cold allodynia
Z. Seltzer	1991	Marcaine	Single	sciatic/ saphenous	yes	sciatic/ saphenous transection		Autotomy is delayed and its magnitude decreased
P. M. Dougherty	1991	Lidocaine	Single	sciatic	yes	CCI	3 and 10 dpi	Reduction in duration and magnitude of thermal hyperalgesia
		Lidocaine	Single	sciatic	yes	Seltzer	3 and 10 dpi	No effect
S. Abdi	2000	Lido/bupivacaine	Single	local before or 4 dpi	yes/no	SNL L5/L6	1 d after ttt	Reduction of mechanical allodynia, no long-term effect
J. M. Zhang	2000	Lidocaine	During 1 or 8 d	DRG following injury	no	DRG compression	1–28 dpi	Reduction of mechanical allodynia and hyperalgesia ipsilaterally with partial effect contralaterally
L. Luo	1995	Lido/tocainide	Single	it	yes	sciatic section	42 d after ttt	No effect on autotomy
S. R. Chaplan	1995	Lidocaine	Single	iv, it, local, 28 dpi	no	L5/L6 ligation	21 d after ttt	Reduction of mechanical allodynia only if plasma concentration was high enough, no long-term effect of local and it
J. Mao	1992	Bupivacaine	Single	sciatic, 3 dpi	no	CCI	1 d after ttt	Reduction of thermal hyperalgesia
J. M. Gonzalez-Darder	1985	Mepivacaine	Single	local	yes	sciatic section	7–70 dpi	Reduction and delay of autotomy
M. L. Sotgiu	1995	Lidocaine	Single	sciatic, iv or iv	yes	CCI	21 dpi	Reduction in paw licking during 2-3 weeks, then no difference
I. Bileviciute-Ljungar	1999	Lidocaine	Repeat	sciatic contra, 6 + 11 dpi	no	CCI	36 dpi	Reduction of thermal hyperalgesia 3-4 d, small effect on pressure stimulation, reduction of autotomy 36 d
T. Yamamoto	1993	Bupivacaine	Single	sciatic	yes	CCI	till 14 dpi	Delaying of thermal hyperalgesia until day 14
		Bupivacaine	Single	sciatic 15 min post	no	CCI	7 dpi	No effect on thermal hyperalgesia

Table 1: Continued.

Author	Year	Drug	Duration	Route	Preemptive	Model	Time of effect	Effect
M. R. Suter	2003	Bupvacaine	Long term	sciatic/spheres	yes	SNI	4 weeks	No effect on mechanical allodynia, thermal hyperalgesia, cold allodynia
Y. S. Lyu	2000	TTX	Single	DRG	no	Chung L5 ligation	2 h after ttt	Reduction of mechanical allodynia, no long-term effect
S. R. Chaplan	2003	ZD7288	Single	ip, 7 dpi	no	SNL L5/6	1 day after ttt	Reduction in mechanical allodynia for 2 h, no effect at 24 h
L. M. Batista	2009	Lidocaine	Single	sciatic	yes	CCI, nylon	over 28 days	Reduction of scratching, thermal hyperalgesia (noxious and non-noxious)
I. Sukhotinsky	2004	Lidocaine	Single	DRG L4 or L5	no	SNL	280 min	Reduction allodynia from 2 to 280 min after ttt, more effective on L5 than on intact L4
S. Eschenfelder	2000	Lidocaine	Single	dorsal root L5 before section	yes	SNL L5	57 dpi	No difference for mechanical hyperalgesia
Biochemical or electrophysiological changes								
J. M. Zhang	2004	Lidocaine	7 d	ip, pump	no	SNL	7 and 14 dpi	Reduction in tyrosine hydroxylase staining
		Lidocaine	14 d	sciatic, pump	yes	sciatic transection	14 dpi	Reduction in tyrosine hydroxylase staining
C. T. Lin	2009	Lidocaine	Single	median nerve	yes	median nerve transection	28 dpi	Dose dependent reduction of injury discharge pre and post electrical stimulation and of NPY and c-fos in cuneate nucleus
I. Omana-Zapata	1997	TTX	Single	intravenoous	no	sciatic transection	4–10 days	Dose dependent reduction of ectopic activity
I. Bileviciute-Ljungar	2001	Lidocaine	Single	contralateral subcutaneous	no	CCI	14 dpi	WDR L4/5 neuron ipsilateral: spontaneous hyperactivity reduced for 60 min
L. A. Colvin	2001	Amethocain	Single	dorsal roots L2–6	no	CCI	10–14 dpi	No effect on neuropeptide Y release in spinal cord (measurement period of 2 h)
J. Scholz	2005	Bupivacaine	7 d	sciatic, spheres	yes	SNI	7 dpi	Delay in apoptosis of inhibitory interneurons in the dorsal horn of spinal cord
Y. R. Wen	2007	Bupvacaine	3 d	sciatic, spheres	yes	SNI	3 dpi	Inhibition of p38MAPK activation in microglia in the spinal cord dorsal horn
W. Xie	2009	Bupivacaine/TTX	Long term	sciatic/DRG pump 7d	no	SNI/SNL	1–10 dpi	TTX: inhibition of NGF increase (DRG, d3) OX-42 (SC, d3) and GFAP (SC, d10); both: inhibition of glial activation (DRG, d1–10)

Table 1: Continued.

Author	Year	Drug	Duration	Route	Preemptive	Model	Time of effect	Effect
S. I. Chi	1993	Local anesthetic		sciatic or systemic	no	sciatic transection	2 and 14 dpi	Reduction in c-fos immunoreactivity in dorsal horn of spinal cord
S. I. Chi	1993	Lidocaine		sciatic or systemic	yes	sciatic transection	2 dpi	Reduction in c-fos immunoreactivity in dorsal horn of spinal cord
M. R. Suter	2009	Bupivacaine/RTX	2 d	sciatic, spheres	yes	SNI	2 dpi	Bupi: inhibition of microglia proliferation and p38MAPK activation in dorsal horn of spinal cord; RTX: no effect
Mixed outcomes								
L. Liang	2010	TTX	Repeat	sciatic, daily	yes	electrical stimulation	up to 35 dpi	Reduction of mechanical allodynia, GFAP-staining on DRG
B. A. Rooney	2007	Lidocaine	Single	dorsal root	yes	bilateral dorsal root L4/5 section	up to 13 days	No increase in excitatory amino acid 10 min post injury, reduction in mechanical allodynia
W. Xie	2005	Bupivacaine	Long term	sciatic, after lesion	no	CCI and SNI	up to 70 d (CCI), 150 d (SNI)	Reduction in mechanical and heat pain for 60 d (CCI + SNI), suppression of hyperactivity at 20–28 dpi in A and C fibers
W. Xie	2005	TTX	Long term	sciatic, TTX (pump 3 or 7 d) just after lesion or 10 d later	no	CCI and SNI	up to 70 d (CCI), 150 d (SNI)	Reduction in mechanical and heat pain for 60 d (CCI + SNI), TTX 10 d effective only during infusion, suppression of hyperactivity at 20–28 dpi in A and C fibers
R. W. Colburn	1997	Bupivacaine	Repeat	spinal nerve before cut + before closure	yes	spinal nerve cryoneurolysis	10 dpi	Reduction of microglial, but only minimal on astrocytic response, no effect on mechanical allodynia
S. Lee	2007	Lidocaine	Single	spinal nerve, it	yes	SNL L5/6	1–4 dpi	Delay in mechanical allodynia by 1–4 d
C. Sato	2008	Ropivacaine	Repeat	epidural, daily 7–17 dpi	no	CCI	since 11 dpi	Relief of thermal hyperalgesia, small reduction of mechanical allodynia, NGF increase in DRG with ropivacaine
W. Xie	2007	TTX	7 d	sciatic, pump	yes	sciatic transection	35–49 dpi	Reduction of hyperexcitability of large and medium cells and sympathetic sprouting. No change in C fiber through TTX

observation of changes occurring along the pain pathways during that period by means of tissue collection and analysis. Early signs of neuronal activation in the spinal cord assessed by increased labeling of c-fos (a transcription factor that leads to expression of proteins) is reduced by nerve blockade in inflammatory [70] and postoperative [71] models of pain. Cyclo-oxygenase 2 (COX2) induction and production of prostaglandin E2 (PGE2) in the CNS is also dependent on peripheral nerve inputs [72, 73]. In the SNI model, we found a sciatic nerve blockade which reduces the apoptotic cell death in the spinal cord dorsal horn. This cell death affects inhibitory interneurons. It participates in the disinhibition process involved in the hyperexcitability of the system leading to pain-related behavior. Sadly, the cell death reduction is not long-lasting but only postponed until the end of the block [74]. Microglia and astrocytes, 2 types of glial cells (nonneuronal cell population of the CNS) have been implicated in pain processing [75, 76]. They are generally said to be activated in the context of pain. This activation was reduced in neuropathic pain model through peripheral nerve blockade [77, 78].

The idea of a magic bullet curing all pain has vanished. Therefore, categorizing specific aspects of sensitization processes into activity-dependent or -independent phenomena is useful to know when to use a blockade. These results also favor the concept of multimodal analgesia combining peripheral or central nerve blockade to systemic drugs on various targets.

4.3. Effects of Specific Block. In clinical postoperative setting, we adjust the concentration of local anesthetic to obtain a selective nociceptive blockade, which does not block nerve activity arising in thicker myelinated fibers. The paralysis of the limb induced by A-β fibers blockade cannot be accepted for a long period due to risk of sore lesions, loss of muscle mass hindering rehabilitation, and masking of complications. Indeed, complications of nerve blockade (nerve injury, hematoma, infection) are suspected when a motor deficit appears or persists [79].

In the SNI model, we compared the effect of complete block (using bupivacaine) to specific nociceptive block with RTX (TRPV1 agonist, inducing desensitization of the receptor). Microglial activation was reduced only by the complete block [80]. Tetrodotoxin (TTX) is a sodium channel blocker. Nociceptive fibers contain TTX-resistant sodium channels, and, therefore, myelinated fibers are preferentially blocked by TTX. TTX could prevent neuropathic pain-related behavior after CCI, SNL, and stimulation-induced pain [35, 81], but failed to reduced flinching in an inflammatory model compared to lidocaine [82]. These examples from animal blockade of specific nerve type highlight the paramount importance of thick myelinated fibers in sensitization processes especially in neuropathic pain. Indeed, we mentioned ectopic activity in myelinated axons after injury coincides with tactile allodynia [37].

We believe partial blockade such as currently performed, especially with an epidural, could be a reason of failure to prevent chronic postoperative pain despite using preemptive long-term block. Older clinical studies already pointed the differential effect of epidural versus spinal intensity of blockade. When both techniques are used at levels were cold and pinprick sensation is abolished, temporal summation is conserved in the epidural group, showing sensitization process might occur in the background of a painless patient [83, 84].

4.4. Other Effects of Nerve Block. Local anesthetics have many systemic or local properties besides impeding nerve conduction through voltage-gated sodium channels inhibition.

(i) The Anti-Inflammatory Effects of Nerve Blockade. The systemic inflammation tested by the levels of cytokines in the blood is reduced by bupivacaine, and this effect is systemic as ipsi, contralateral block and even contralateral intramuscular injection is effective [85]. In a human model of secondary hyperalgesia, local anesthetic had a systemic effect [86] which is clinically relevant as area of hyperalgesia in the acute postoperative period correlates with the incidence of postoperative chronic pain [87–89].

(ii) Axonal Transport. Besides electric discharges axonal transport is another way of signaling a peripheral nerve injury to the CNS. Experimental axonal transport block could influence behavioral and glial changes after nerve injury [90]. Recently bupivacaine has been shown in vivo to inhibit the retrograde transport of TNFα after an inflammatory insult [91].

These less known pharmacologic properties of local anesthetics may contribute to the often observed "therapeutic effect" of local anesthetics injection in interventional pain management of certain chronic pain patients, such as facet joint nerve blocks (a) or epidural infiltrations (b), were local anesthetic administration alone often show the same favorable results as their coadministration with corticosteroids. It is also in this context, that previously performed randomized "placebo" controlled trials with negative results comparing the beneficial effect of the combined administration of corticosteroids and local anesthetics with patients receiving local anesthetics alone, as for example for cervical periradicular injections (c), lacked a real placebo group.

5. Conclusions and Back to Bedside

In clinical practice, nerve blocks are effective for treatment of acute postoperative pain but their impact on the prevention of chronic postoperative pain shows conflicting results. This paper intended to highlight some of the factors found in experimental studies. The main reason is the blockade limited to nociceptors with absence of blockade of myelinated thicker afferents. The latter account for most of the afferent activity after injury and experimental evidence show they participate in pain related behavior. Perioperative block limited to nociceptive fibers reduces the acute pain and we are maybe missing the sensitization phenomena that

occur insidiously at the same time through the myelinated afferents, driving the chronification of the pain process. We mentioned the recent study with long-term block of all fibers [69], although only observational, giving encouraging results on chronic outcomes. For postoperative epidural analgesia, it will not be possible to fully block the inputs over a few days but for peripheral nerve blockade a more intense block can be considered. We have to define the best duration of both peripheral and epidural blockade balancing the advantages of inhibiting some central processes with the risks inherent to these techniques (infection, local anesthetic toxicity, etc.). With regards to the failure of some regional anesthesia techniques we have to keep in mind that some changes might be activity-independent and must, therefore, be addressed by other means. This involves multimodal analgesia combining complementary treatment associating systemic drugs to the regional technique.

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Research Article

Histological Consequences of Needle-Nerve Contact following Nerve Stimulation in a Pig Model

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Background. Nerve stimulation can facilitate correct needle placement in peripheral regional anesthesia. The aim of this study was to determine whether the high threshold current is associated with reduced nerve injury due to fewer needle-nerve contacts compared with low current. *Methods*. In anaesthetized pigs, thirty-two nerves of the brachial plexus underwent needle placement at low (0.2 mA) or high current (1.0 mA). The occurrence of needle-nerve contact was recorded. After 48 hours, the nerves were analyzed for occurrence of histological changes. Nerve injury was scored ranging from 0 (no injury) to 4 (severe injury). *Results*. The frequency of needle-nerve contact was 94% at low compared to 6% at high current. The score was significantly higher at low (median [interquartile range] 2.0 [1.0-2.0]) compared to high current (0.0 [0.0-1.0] $P = .001$). *Conclusions*. Inflammatory responses were directly related to needle-nerve contacts. Hence, posttraumatic inflammation may be diminished using higher current for nerve localization.

1. Background

There is a reported incidence of 3% neurological deficits following peripheral regional blocks; however, most of these seem to regress without functional consequences within some weeks or months [1, 2]. Despite the introduction of insulated needles with short bevel and advances in needle guidance, such as electric nerve stimulation or ultrasound, the incidence of reported nerve injuries remained fairly constant [1].

Of note, causes for neurological deficits subsequent to regional anesthesia remain unknown most of the time. Among putative mechanism, needle-nerve contact leading to direct or indirect nerve injury may be involved. Only few data exist that evaluated causes and consequences of needle-nerve contact or nerve injury related to regional anesthesia [3–6]. Voelckel and coworkers recently reported inflammatory response of target nerves subsequent to needle placement for regional anesthesia in a pig model [7]. Here, marked inflammatory response of the peripheral nerve system was found, notably after needle placement with low current.

The aim of this study was to challenge the hypothesis that high threshold current (1.0 mA) is associated with a reduced likelihood of direct needle-nerve contact compared with low threshold current (0.2 mA), thereby reducing the potential for needle-related nerve injury. Primarily defined outcome variable was an established score representing the presence and magnitude of posttraumatic regional inflammation, occurrence of intraneural hematoma, and signs of myelin damage [6].

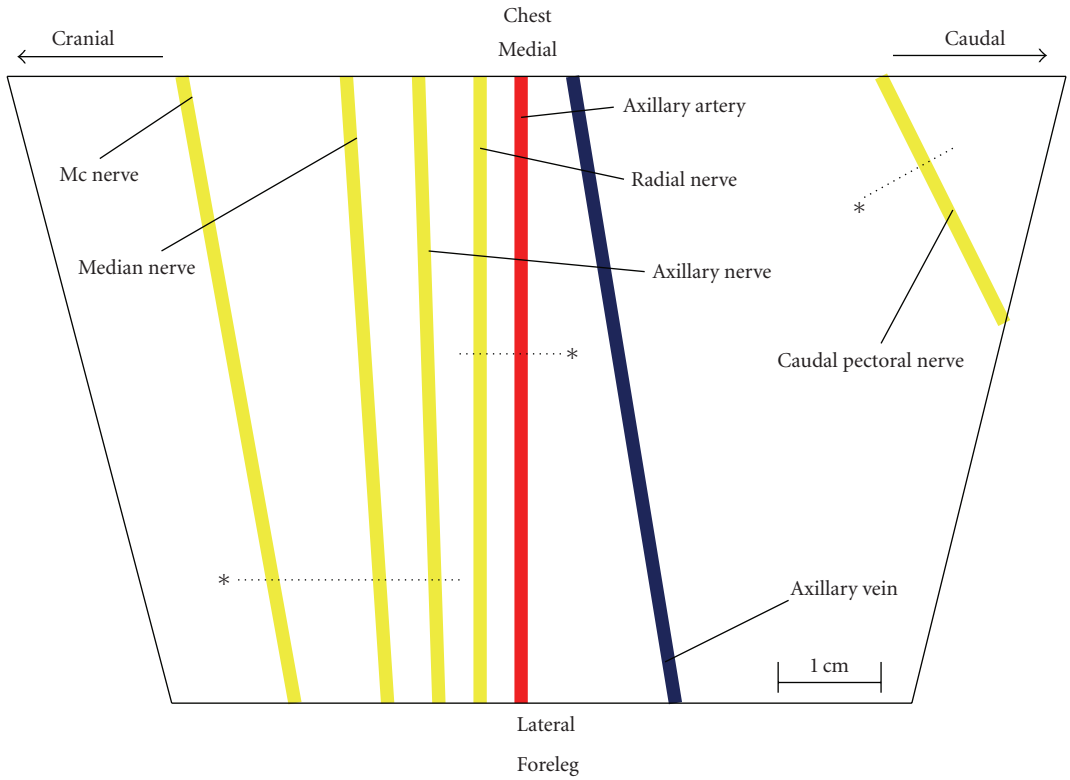


Figure 1: Schematic illustration of the right porcine brachial plexus. *, visual reference (suture); dotted line, imaginary line starting from the visual reference; mc nerve, musculocutaneous nerve. Musculocutaneous, median, radial and caudal pectoral nerve were selected for needle placement with low (0.2 mA) or high (1.0 mA) threshold current on the corresponding imaginary line. For detailed description please refer to Steinfeldt and coworkers [6].

2. Methods

2.1. Animals. The experimental procedures were approved by local authorities (Regional board, Giessen, Hessen, Germany: VI63-19c20/15c MR 20/13-supplement 2006; Ref: 50/2009, Study no. 3), and the study was performed in compliance with the Helsinki convention for the use and care of animals. In this study, 7 female pigs (Deutsche Landrasse) weighing 29–42 kg (mean 34 kg) were used.

2.2. Anesthesia. Following premedication, general anesthesia was induced (propofol: 0.2 mg kg^{-1} min^{-1}, IV; sufentanil: 0.5 μg kg^{-1}h^{-1}, IV) as described recently [6, 8, 9]. All pigs were ventilated with pressure controlled ventilation (Siemens Servo 300; Maquet Critical Care, Darmstadt, Germany). The pigs were kept anesthetized for 48 hours. Adequate anesthesia was ascertained by adapting the dosage of propofol (maximum 0.3 mg kg^{-1} min^{-1}) and sufentanil (maximum 1.5 μg kg^{-1}h^{-1}). Fluid maintenance was with Ringer's lactate solution 3–5 mL kg^{-1}h^{-1}. The body temperature was assessed and kept constant using warming blankets (Bair Hugger Model 540; Arizant Healthcare Inc., Eden Prairie, USA).

2.3. Instruments. An insulated short bevel stimulation needle (Stimuplex A; B. Braun, Melsungen, Germany; 22-gauge; 30° bevel, 5 cm in length) connected to a nerve stimulator (Stimuplex HNS11, B. Braun, Melsungen, Germany) was applied for nerve stimulation. The device delivered a square wave current of 1.0 mA or 0.2 mA, the impulse duration was 0.1 ms with a frequency of 2 Hz. A neutral electrode was placed 30 cm from the site of needle insertion.

2.4. Surgical Preparation. The anesthetized animals were placed in the supine position with both fore limbs slightly abducted. Using an aseptic technique the axillary region was opened carefully by blunt dissection on both sides. The surgical approach was minimized to prevent bleeding related to dissection of muscular tissue or larger vessels. After cautious dissection of the vascular nerve sheath, the brachial plexus were exposed. Contacts by surgical instruments to nerves were prevented. Nerve connective tissue within the vascular nerve sheath was not removed. Subsequent to direct visibility of all plexus nerves, sutures serving as visual references were inserted intramuscularly (Figure 1). All nerves of the brachial plexus were identified, and anatomic landmarks as well as the localization of sutures were documented photographically. The anatomical landmarks of the undertaken approach were illustrated recently (Figure 1) [6].

Cefuroxim 80 mg kg^{-1}d^{-1} IV was administered in all animals, and anesthesia was maintained as described before [6]. After 48 hours, the wound was reopened under

general anesthesia, and the nerves of the brachial plexus were extracted. Photographs and visual references (sutures) guided the removal of treated nerve tissue. All animals were sacrificed at the end of the study period by an intravenous injection of potassium chloride (4 mmol kg^{-1}).

2.5. Needle Placement and Control (Sham) Interventions. Altogether eight needle placements were scheduled for each animal with regard to the brachial plexus: four needle placements were applied using a 0.2 mA current intensity (low-current-treatment group), and another four needle placements utilizing 1.0 mA (high-current-treatment group). During all interventions, the current intensity used on each nerve was only known to the investigator (TW) in control, who was exclusively responsible for the selection of the nerve stimulator setting during needle placement. The operator undertaking the needle placement (TS) was blinded to the current output administered and followed the directives of the investigator in control manipulating the setting of the neurostimulator. Utilizing an internet-based randomization tool (http://www.randomizer.org/), the particular mode of treatment (needle placement with low current (0.2 mA) or high current (1.0 mA)) was allocated to all nerves just prior to the needle placement.

The musculocutaneous, the median, the radial, and the caudal pectoral nerve were selected for needle placement via neurostimulation. All needle placements were executed from cranial to caudal, beginning on the right hand side. The procedure was then continued on the left hand side, again from cranial to caudal.

As a default setting, the needle was initially placed on nerve-connective tissue (muscle fascia and soft tissue) 5 mm lateral of the target nerve. The needle tip was then approaching the target nerve in an angle of 45° to 60°. During this approach, the nerve stimulator continuously delivered a predefined output current intensity of either 0.2 mA or 1.0 mA. The current intensity was not modified during needle positioning. The needle tip was pushed in 1 mm increments towards the target nerve until an adequate neuromuscular response (cloven hoof and lateral thorax) has been achieved. The final needle position was determined based on a minimal but specific neuromuscular response of the preselected target muscle. Subsequently, the needle tip to nerve distance was measured by means of a ruler. The distance was recorded in one millimeter increments. Direct contact of a needle tip with a nerve was documented. Thereafter, the stimulation needle was left in the final position for a period of 40 seconds with ongoing stimulation according to the pre-adjusted output current. All decisions, for example, whether or not an attempt has been accomplished successfully, and all assessments (i.e., measurement of distances and needle-nerve contact) were undertaken by the investigator in control. Following completion of the interventions, the opened tissue around the brachial plexus was carefully closed and sutured.

2.6. Control Groups. The left axillary nerve of each pig was the designated control group (nontreatment-brachial plexus); that is, this nerve was dissected but not exposed to any treatment at all. Thus, histological analysis of this nerve enabled us to determine whether the surgical approach itself had any influence on nerve integrity or associated inflammation. Additionally, the gluteal region was opened, and the left sciatic nerve was resected. The sciatic nerve represented a nerve tissue that was neither exposed to any potential surgical trauma (nontreatment-sciatic nerve), nor any needle placement treatment. Thus, all possibly confounding variables with respect to neuroinflammation such as systemic inflammation following needle placement, surgery, anesthesia, or any other intervention could have been detected. Ligature of a tibial nerve with subsequent histomorphological analysis was considered the control mimicking maximum nerve trauma.

Besides the surgical trauma, placement of the needle or the electric stimulation itself, irrespective of any mechanical alteration, may contribute to nerve injury or inflammation. To control for such current-related injuries, two animals with five nerves each were either exposed to (i) a current of 1.0 mA via direct needle-nerve contact for 40 sec, (ii) needle-nerve contact without application of electrical current, or (iii) close needle-nerve placement (4 mm distance) with application of 1.0 mA. To avoid muscle twitches potentially reducing the needle-nerve distance, a neuromuscular blocking drug (rocuronium, 1 mg kg^{-1}) was given for the latter control group.

2.7. Histology

2.7.1. Tissue Preparation. Each specimen (1–1.5 cm in length) was fixed by immersion in Bouin Hollande for 48 hours. After fixation, all tissue blocks were extensively washed in 70% 2-propanol and processed for paraffin embedding. Series of tissue slices (7 μm) were taken throughout the specimen length.

2.7.2. Histological Examination. Nerve specimens were cut, and every third slice was Giemsa stained. The initial histological analysis by light microscopy focused on the detection of the needle-nerve contact site (i.e., current nerve contact) which was usually characterized by circumscribed accumulation of inflammatory cells or structural damage (hematoma). Within the detected area, the pathologist searched for the most distinctive area of inflammatory response or the combination of inflammation and hematoma or myelin damage to locate the intervention site. Subsequently, at least four adjacent slices in both directions were alternately stained for either macrophages or myelin. Myelin was stained applying the technique by Kluver-Barrera to differentiate vital and avital myelin tissue [11, 12]. CD68 labelling [10] by immunohistochemistry was applied for the identification of macrophages and monocytes representing characteristic target cells with regard to neuroinflammation following nerve injury [13, 14]. As recently described, we developed a specific "injury score" (Table 1), adopting aspects from Hirata and coworkers [6, 15]. This score facilitates the characterization of the grade of inflammatory response

Table 1: Nerve injury score. Slight nerve damage is represented by the score grades 1 and 2. A severe nerve injury with structural damage is described with score grades 3 and 4. For detailed description with histological examples, please refer to Steinfeldt and coworkers [6].

Score value	Definition
0	No signs of neural injury or inflammation
1	Areas with slight accumulation of inflammatory cells
2	Areas with distinctive signs of inflammation
3	Areas with distinctive signs of inflammation *plus* haematoma
4	Areas with distinctive signs of inflammation *plus* myelin damage

(Giemsa staining), the occurrence of hematoma and the presence (or absence) of myelin damage (Table 1).

The relative number of CD68-positive monocytic cells (macrophages and monocytes) in relation to leucocytes was assessed by counting five representative visual fields including intravascular and extravascular areas (×200 magnification).

2.8. Statistical Analysis. The primary outcome measure was any nerve injury after needle placement utilizing low threshold current (0.2 mA) or high threshold current (1.0 mA) according to the grading of the "injury score" (Table 1).

The sample size was chosen to provide a 90% power to detect a score value difference of 1.0 between the nontreatment group of the brachial plexus, the low current group, and high current group. A type-I error of 5% and a standard deviation of 0.5 in each group were assumed. Since most differences were expected between the nontreatment group of the brachial plexus and the current groups (0.2 mA, 1.0 mA), an unequal design with regard to the sample size and the allocation of the nontreatment group and the needle placement groups was executed. A specimen allocation of 1 : 3 : 3 was scheduled (nontreatment group of brachial plexus: high current : low current). The nontreatment sciatic nerve—that is, the control for systemic effects and confounders irrespective of any planned experimental intervention—has not been considered for the sample size calculation as well as the "current controls" and the positive control (nerve ligature).

Using the PASS 2002 statistical package (Numbers Cruncher Statistical Systems, Kaysville, Utah, USA) a total number of at least 35 specimens was calculated. Considering a dropout rate of 20% (hematoma by nerve resection, complications during anesthesia, and accidental specimen destruction during laboratory processing), we planned five pigs to allow at least four intended needle tip placements per current group and animal. Two further pigs were scheduled for "current control" groups (needle-nerve contact with or without current, high current without nerve contact).

Data are presented as median with 25th and 75th percentiles (interquartile range, IQR). Differences among the groups (low current (0.2 mA), high current (1.0 mA), nontreatment brachial plexus) regarding score value were determined by the Kruskal-Wallis test (i.e., global testing). A P value $\leq .05$ was selected as the criterion of significance. A confirmatory post hoc analysis including pairwise comparisons was applied in case of significant differences according to global testing (closed testing). For this, the Wilcoxon-Mann-Whitney test was selected. Statistics were performed using SPSS software for Windows (Release 15.0, SPSS, Chicago, IL).

Only descriptive statistics have been applied with respect to the relative value of monocytic cells to leucocytes (mean ± SD) and needle-nerve distances (mm). However, a score value >1—that is, signs of inflammatory responses—was required for the assessment of monocytic cells.

3. Results

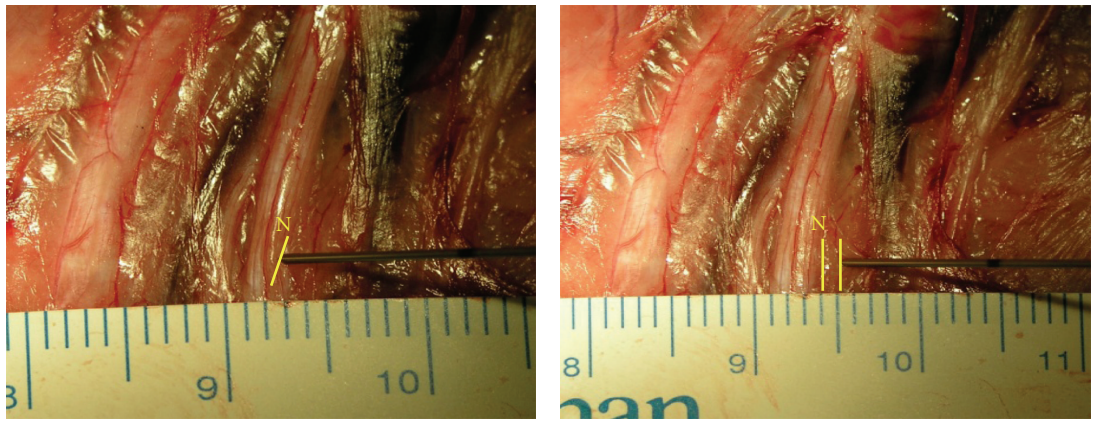
3.1. Animals. None of the 7 animals showed signs of local or systemic infection. Neither fever (>38°C) nor cardiopulmonary complications occurred throughout the experimental period.

3.2. Needle Placement and Immediate Macroscopic Evaluation. In the low current group (0.2 mA), direct needle-nerve contact was required in 15 out of 16 experiments (Figure 2) to elicit minimal twitches of the corresponding muscle. In contrast, in the high current group direct needle-nerve contact was rarely necessary (1 out of 15 cases) to induce a muscular response (Table 2). If needle-nerve contact was required, the needle had to be pushed slightly onto the nerve epineurium. Intraneural needle placement (i.e., nerve penetration) was not required to trigger muscular twitches. A metric evaluation (1 mm increments) of the needle-nerve distance revealed a considerably larger distance in the higher current threshold group (Figure 2) compared with the low current threshold group (Table 2). No (macroscopically) visible residuals were present after needle retraction.

3.3. Resected Nerve Specimens. Accidentally, eight nerves showed a distinctive hematoma, most likely caused during nerve resection (i.e., an iatrogenic lesion independent of the index intervention). Four nerves had undergone low current and four nerves high current stimulation, respectively. These nerves were excluded from further microscopic analysis.

3.4. Assessment of Nerve Injury Score. A variety of artifacts, that is, fascicle destruction, axonal damage in the absence of inflammatory cells, or avital myelin, were found in both the treatment and the control group. Intraneural hematoma with signs of myelin damage and increase of inflammatory cells was observed in the positive control (nerve ligature) only. Nerves with signs of regional inflammation revealed a remarkably high amount of monocytic cells among the leucocytes (Table 2).

3.5. Nerve Injury and Applied Stimulation Threshold Current. Corresponding to the primary outcome in the treatment groups, a difference was found (Figure 5): the median score



(a) (b)

Figure 2: (a) Needle tip to nerve contact following needle placement with low threshold current (0.2 mA). The needle tip is located adjacent to nerve epineurium. (b) Distant needle placement with high threshold current (1.0 mA). A needle tip to nerve proximity of 2 mm was measured. N, radial nerve.

Table 2: Treatment groups and controls. NNC, Needle-nerve contact; NN, needle-nerve; Giemsa, staining according to the Giemsa method; CD68, specific staining of CD68 positive leucocytes (macrophages) applying immunohistochemistry [10]; KB, myelin staining according to the Kluver-Barrera method [11, 12]; SD, standard deviation.

			Controls					
	High current (1.0 mA)	Low current (0.2 mA)	Non-treatment (brachial plexus)	Positive control (ligature)	Non-treatment (sciatic nerve)	Current (1.0 mA) without NNC	NNC with current (1.0mA)	NNC without current
Nerve specimen (n)	16	16	7	5	7	5	5	5
NNC (n)	1	15						
NN distance mean ± SD (mm)	2.9 ± 1.2	0.3 ± 1.0				4		
Slices (n) Giemsa/CD68/KB	2340/80/68	2490/92/71	780/16/16	400/52/48	850/16/16	870/25/45	780/52/48	890/82/94
Hematoma (Giemsa) (n, specimen)	0	0	0	5	0	0	0	0
Avital myelin (KB) (n, specimen)	0	0	0	5	0	0	0	0
Monocytic cells mean ± SD (%)	—	42	—	42	—	—	40	45

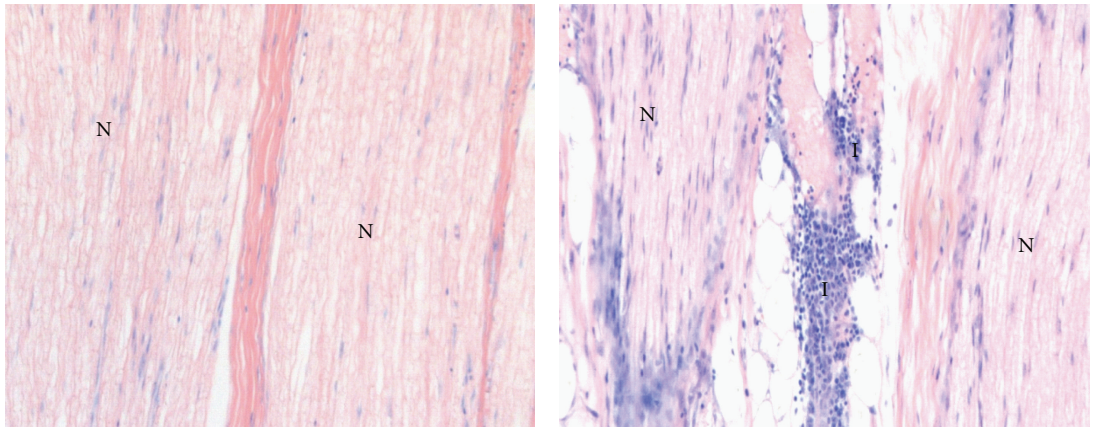
value for nerve injury was higher after needle placement guided with low current (0.2 mA) compared to needle placement with high current threshold (2.0 IQR(1.0-2.0) versus 0.0 IQR(0.0-1.0) (Figures 3, 4, 5). The control group with direct needle-nerve contact revealed no differences with or without current (2.0 (2.0-2.0) versus 2.0 (2.0-2.0)) (Figure 5).

A current intensity of 1 mA applied from a defined distance of 4 mm between needle and nerve did not reveal any signs of axonal injury, damage, or inflammation (Table 2, Figure 5). Herein, the pig was paralyzed to avoid any needle movement or needle-nerve contact.

Corresponding to global comparison (Kruskal-Wallis test) between high current, low current needle placement, and negative control (brachial plexus), a significant difference was found ($P < .01$). Hence, post hoc analysis was executed. Corresponding to the Wilcoxon-Mann-Whitney test without P adjustment, a significant difference ($P < .01$) between low and high current needle placement was observed, whereas no significant difference was found between no treatment brachial plexus and the needle placement with high current ($P = .46$).

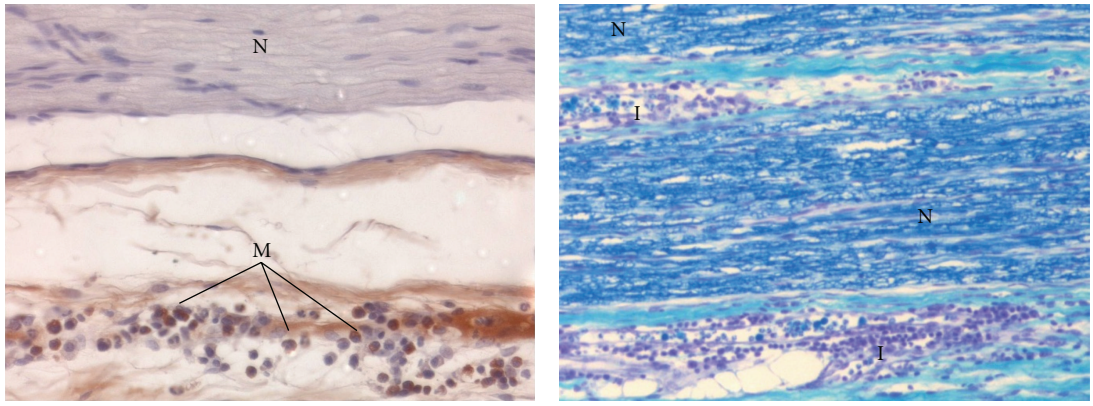
4. Discussion

This study demonstrates (a) a dependency of threshold current and the frequency of needle-nerve contact during experimental regional anesthesia and (b) a pronounced regional inflammatory response subsequent to needle-nerve contact that was independent of the presence or absence



(a) (b)

Figure 3: (a) Longitudinal microscopic view (×200, Giemsa stained) of the radial nerve after needle placement by means of nerve stimulation. A minimal threshold current of 1.0 mA was applied for needle positioning. The needle did not contact the nerve tissue. N, nerve fascicle; I, inflammatory cells. Score value, 0 (b) Longitudinal microscopic view (×200, Giemsa stained) of the median nerve after needle placement by means of nerve stimulation. A minimal threshold current of 0.2 mA was applied for needle positioning. The needle contacted the nerve tissue. N, nerve fascicle; I, inflammatory cells. Score value, 2.0.



(a) (b)

Figure 4: (a) Longitudinal microscopic view (×400, CD68 labeled [10]) of the median nerve after needle placement by means of nerve stimulation. N, nerve fascicle; M, brown, macrophages. Score value, 2.0. A minimal threshold current of 0.2 mA was applied for needle positioning. The needle contacted the nerve tissue. (b) Longitudinal microscopic view (×200, Kluver-Barrera [11, 12]) of the musculocutaneous nerve after needle placement by means of nerve stimulation. A minimal threshold current of 0.2 mA was applied for needle positioning. The needle contacted the nerve tissue. I, inflammatory cells; N, dark blue, myelinated vital nerve tissue. Score value, 2.0.

of current. Interestingly, this posttraumatic inflammatory response was pronounced following needle placement applying low current (0.2 mA) compared to the application of high current threshold (1.0 mA). Regardless of the magnitude of the regional inflammatory response, neither intraneural needle location nor severe nerve injury—that is, structural nerve damage—was observed in either current threshold group.

Recently, Voelckel and coworkers reported signs of inflammation following regional anesthesia in pigs with output currents <0.2 mA [7]. However, a number of methodological issues may limit the applicability of this data: first, the authors selected a time interval of six hours between electric nerve stimulation and nerve removal (i.e., dissection for further analysis). Of note, a pronounced inflammatory response may not occur earlier than 48 hours after nerve trauma [13, 14]. Second, a control group to allow validation of the applied methodology and evaluation of the results in the light of unknown confounders was missing. Third, the exact needle-nerve position subsequent to needle-nerve contact remained unclear: methylen-blue easily penetrates into all areas of the surrounding tissues therefore prohibiting an explicit (metric) assessment of the needle position in relation to the target nerve. Finally, macrophages, serving as important target cells representing posttraumatic inflammation, have not been considered for the description of inflammatory responses.

Our data are in line with the rationale that inflammatory cells accumulate as a response to any kind of nerve trauma

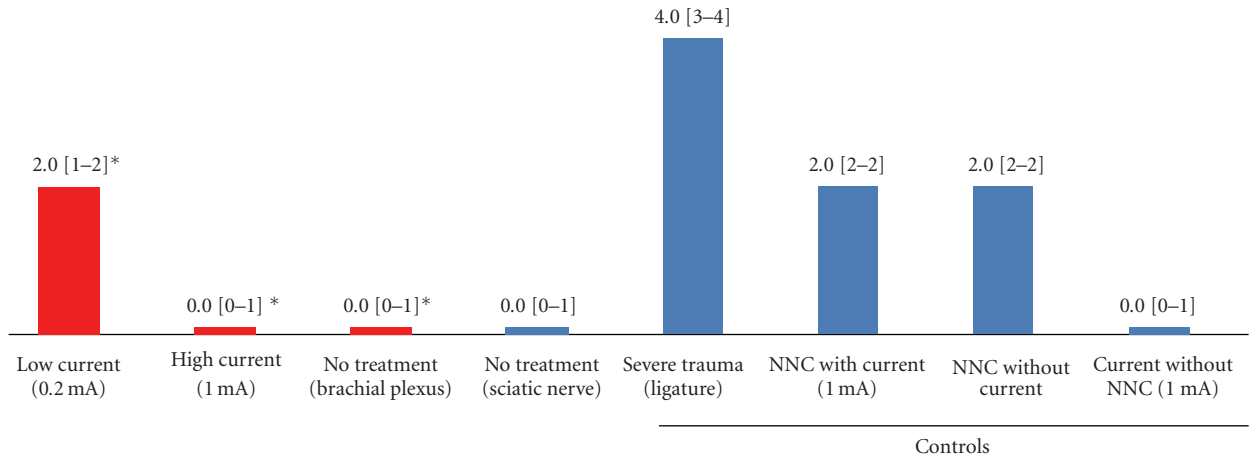


Figure 5: Treatment groups and controls. NNC, Needle-nerve contact; (), interquartile range; *, high current group was compared with low current and none-treatment (brachial plexus) group (Wilcoxon-Mann-Whitney test). The difference of applied nerve injury score values between high and low current treatment was significant ($P < .01$) whereas no significant difference ($P = .46$) was found between the nontreatment group (brachial plexus) and the high current treatment.

[13, 14, 16]. Following nerve ligature mimicking maximum nerve trauma (positive control), massive leukocyte accumulation was found next to hematoma and myelin damage. In contrast, only mild signs of inflammation without structural damage in the nontreatment control were detected. The results of our control groups emphasize both the validity of the undertaken experimental intervention and the construct validity of the applied score [6]: a maximum trauma and a nontraumatic intervention were easily distinguishable and reproducible within the categories of the score. Between the nonintervention control of the brachial plexus and the nonintervention control of the sciatic nerve no differences were found. Therefore, it seems deducible that the surgical trauma (opening and closing of the axilla) did not interfere with the observed results with regard to the "treatment nerves". Thus, relevant bias or unknown confounders may thus be neglected.

The collected data concerning the relationship between needle tip to nerve proximity and electrical current intensity are in accordance with the perception that the level of output current corresponds to needle tip to nerve distance [17, 18]. Tsai and colleagues measured needle-nerve distances dependent on different currents in pigs as well [19]. However, they found a median needle-nerve distance of one millimeter at a minimal current of 1.0 mA, whereas we observed a distance of three millimeters when a minimal current of 1.0 mA was applied. In line with our findings, Tsai and coworkers reported needle-nerve contact in 95% of their experiments at a median current of 0.3 mA [19]. Whether the different anatomical site selected for the experimental setting, Tsai and coworkers used the sciatic nerve, may have contributed to the observed differences remains unknown [19].

Following needle-nerve contact, we found neither axonal nor myelin alterations but signs of regional inflammation. In most cases a gentle needle-nerve contact was sufficient to trigger minimal muscle twitches. In two cases, the nerves had to be stretched slightly during needle-nerve contact. Therefore, we assume that the aseptic inflammation is basically triggered by the needle tip comparable with, for example, a foreign particle reaction. Our control experiments with or without electric stimulation support the notion that inflammation induced via current only is very unlikely.

In contrast to other investigators, we did not limit our assessment of regional inflammation to leucocytes but observed an increased relative number of macrophages and monocytic cells, respectively [7]. Therefore, we are confident that our findings represent a status that may well be termed "*posttraumatic*" inflammation.

According to our experimental setting, there is a paucity of data with regard to sound neurological followup after termination of anesthesia. Therefore, we are unable to relate the observed findings to any clinical manifestation or patient sequelae. Nevertheless, Eliav and coworkers demonstrated in rats that an aseptic inflammation of a peripheral nerve is indeed capable of provoking pain sensation that may be unrelated to apparent axonal damage [20].

The present investigation has a number of methodological limitations that need to be discussed. First, in our experimental setting, we utilized an "open brachial plexus model". Although a percutaneous setup might have been desirable for a variety of reasons (e.g., closer to clinical practice, abdication of surgery, and no doubts with regard to conductance properties), a number of restrictions would have applied. Herein, the challenge to execute and subsequently identify the site of needle-nerve contact illustrates the most important obstacle for a controlled and reproducible experimental setting.

We are confident that no relevant disturbance in electric stimulation and tissue or nerve-related conductance properties occurred for two reasons. (a) The target nerve remained embedded in the surrounding tissue (soft tissue, muscles, and fascia). Accordingly, the current is directed to the target nerve following the lowest impedance thereby passing through the surrounding tissue, which mimicks the

clinically applied percutaneous approach. (b) The applied nerve stimulator provides a circuitry that generates a constant stimulating current despite eventual variability in tissue impedances. Therefore, the target nerve was expected to receive the adjusted current intensity irrespective of an open or closed model.

Second, with respect to the development of local inflammation, data from Mueller and others have demonstrated peak inflammation approximately 72 hours after nerve trauma [13, 14]. Thus, given our experimental setting with an observation period of 48 hours, we may have missed the peak of (post-)traumatic neuroinflammation. However, considering the experimental setting with indwelling catheters, long-term intubation, and mechanical ventilation, the risk for nosocomial infection in our pigs was not negligible. Such occurrence, that is, systemic inflammatory response syndrome, may have interfered with our analyses and was thus avoided. Again, Mueller and coworkers reported significant signs of inflammation following nerve trauma in almost all animals already 48 hours after the insult [13]. Weighing the risks and benefits, we felt comfortable with a setting allowing for insult-related inflammation without carrying a too high potential for nosocomial infection and have, therefore, limited the observation period to 48 hours.

Third, we lack any functional assessment of nerve integrity, for example, electromyography or postinterventional assessment of the animals. However, behavioural assessment is challenging, especially in larger animals such as pigs. In contrary, for rodents, for example, rats and mice, validated and reproducible instruments (i.e., hot plate test, incapacitance meter, von Frey electronic, etc.) are available [20, 21]. Therefore, functional assessment in pigs—as applied recently—should be interpreted with caution [22]. However, we focused on the assessment of morphological and pathophysiological reactions of nerves. Therefore, we used pigs within the applied experimental model, since nerve diameter, anatomic sites, and basic physiology are comparable with human beings, enabling the use of regional anesthesia equipment as applied in clinical routine.

Finally, heterogeneous aspects of different peripheral nerves (i.e., size and ratio of fascicles to connective tissue) could be associated with different needle positions during nerve stimulation with the same threshold current [19, 23].

Future experimental trials in smaller animals may thus, focus on the functional consequences of regional inflammation as described herein. It should be clarified whether regional neuroinflammation is associated with subsequent neurological deficits. Kiefer [16] and Moalem and Tracey [24] reported posttraumatic inflammation capable of inducing an impairment of neurological function, most likely due to the toxic mediators released by macrophages. Thus we cannot rule out that macrophage accumulation itself may lead to a neurological impairment independent from the applied trauma or duration of exposure.

5. Conclusions

We have demonstrated that needle-nerve contact in pigs does not cause axonal damage but may elicit a response denoted as aseptic inflammatory response. We are unable to draw any causal inferences with regard to functional consequences or clinical symptoms. Nevertheless, the present findings point out that needle-nerve contact following needle placement as applied in regional anesthesia may result in aseptic neuroinflammation.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Authors' Contributions

T. Steinfeldt, J. Graf, T. Wiesmann and H. Wulf have made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data. J. Schneider, W. Nimphius, E. Weihe and A. Borgeat have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors have read and approved the paper.

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Review Article

Neural Blockade Anaesthesia of the Mandibular Nerve and Its Terminal Branches: Rationale for Different Anaesthetic Techniques Including Their Advantages and Disadvantages

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Anaesthesia of structures innervated by the mandibular nerve is necessary to provide adequate pain control when performing dental and localised surgical procedures. To date, numerous techniques have been described and, although many of these methods are not used routinely, there are some situations where their application may be indicated. Patient factors as well as anatomical variability of the mandibular nerve and associated structures dictate that no one technique can be universally applied with a 100% success rate. This fact has led to a proliferation of alternative techniques that have appeared in the literature. This selective review of the literature provides a brief description of the different techniques available to the clinician as well as the underlying anatomy which is fundamental to successfully anaesthetising the mandibular nerve.

1. Introduction

Neural blockade anaesthesia is necessary for anaesthesia of much of the mandibular bone as well as lower posterior teeth, which cannot be readily anaesthetised via supraperiosteal deposition of local anaesthetic [1]. Although there is considerable anatomical variation, portions of the mandible consist of dense, thickened bone, making it difficult for externally deposited local anaesthetic to diffuse toward the inferior alveolar nerve (IAN) that lies within the substance of the mandible. Hence, clinicians commonly attempt to anaesthetise this nerve, which supplies all mandibular teeth on the ipsilateral side, before it enters the mandibular canal via blockade anaesthesia. Considering that the peripheral extension of the mandibular nerve, after it leaves the cranial base, is not encased in bone for some distance, there are opportunities to administer blockade anaesthesia at multiple levels. Although many techniques for mandibular blockade anaesthesia are practised, the direct inferior alveolar nerve block (IANB) [2], the indirect IANB [3], the Akinosi closed-mouth technique [4], the Gow-Gates technique [5], and variations thereof are most commonly used internationally, and this paper will focus on these approaches. Some extraoral techniques via the mandibular notch, which are useful in some trauma patients [6], and a recently described intraoral anterior injection technique, a variation of the indirect IANB technique, are also described [7].

2. Anatomy

A thorough knowledge of anatomy is crucial in providing predictable, safe, and effective mandibular anaesthesia. The mandibular nerve is the largest branch of the trigeminal nerve's three main branches which separate at the trigeminal ganglion near the cavernous sinus. It passes through foramen ovale and descends into the infratemporal region for a short distance as a single trunk before dividing into anterior and posterior branches that pass down into the pterygomandibular space. The anterior branch is mostly involved with supplying motor innervation to muscles of mastication, while the posterior branch is predominantly associated with sensory function to the tongue, lower gingivae, mandibular

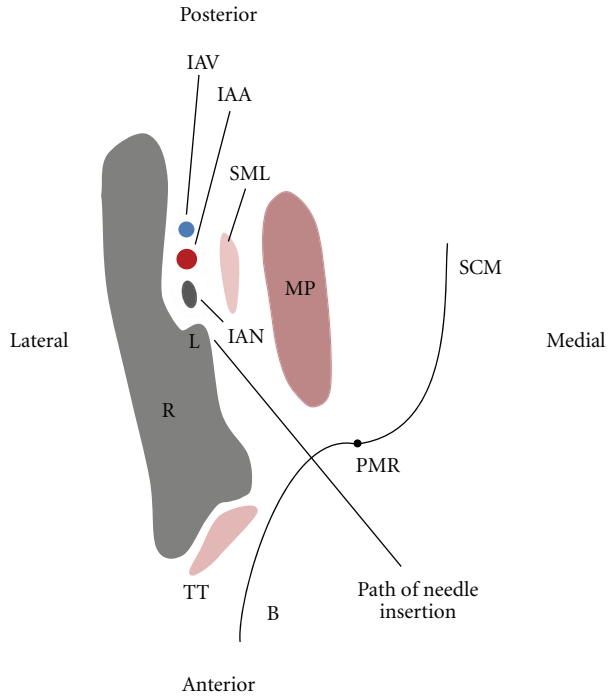

Figure 1: Transverse section of the mandibular ramus at the level just superior to the lingula. (R: Ramus, IAN: inferior alveolar nerve, IAV: inferior alveolar vein, IAA: inferior alveolar artery, SML: sphenomandibular ligament, MP: medial pterygoid muscle, B: buccinator, PMR: pterygomandibular raphe, SCM: superior constrictor muscle, TT: tendon of temporalis L: lingula). The needle is shown passing through the pterygomandibular space where it is directed to an area of bone just superior to the lingula, L. This is the level at which an IANB should be administered.

bone, teeth, and part of the lower lip and chin on the ipsilateral side. The mandibular nerve also provides a route by which post-ganglionic parasympathetic facial nerve fibers can travel to the structures that they supply, such as salivary glands.

The main objective of mandibular blockade anaesthesia is to anaesthetise the posterior branch of the mandibular nerve and its distal branches. The extraosseous course of the mandibular nerve is predominantly within the pterygomandibular space which is a small fascial-lined cleft containing mostly loose areolar tissue (Figure 1) [8]. It is bounded medially and inferiorly by the medial pterygoid muscle and laterally by the medial surface of the mandibular ramus [9]. Posteriorly, parotid glandular tissue curves medially around the back of the mandibular ramus to form a posterior border, while, anteriorly, the buccinator and superior constrictor muscles come together to form a fibrous junction, the pterygomandibular raphe (Figure 1). Most mandibular block procedures involve deposition of local anaesthetic solution within the pterygomandibular space via an intraoral route, namely, by piercing the buccinator muscle anteriorly.

The posterior division of the mandibular nerve gives rise to three nerves as it descends: the lingual, inferior alveolar, and auriculotemporal nerves. Neural blockade anaesthesia of the mandibular nerve may stop pain conduction for any number of these nerves depending on the amount of anaesthetic solution administered, the location in the horizontal plane of drug administration, as well as the height in the vertical plane at which the block is given. All of these nerves have important roles in innervating oral and temporomandibular structures, and anaesthetising them is advantageous before carrying out potentially painful surgical or dental procedures.

In addition to the neural aspects of the pterygomandibular space, there are vascular pathways, fibrous tissue elements, muscular structures, and glandular tissue that need to be considered to improve the predictability, effectiveness, and safety of blockade anaesthesia. Vessels such as the inferior alveolar, maxillary, and external carotid arteries are present within the vicinity of many mandibular block procedures, and damage to these structures may lead to a variety of complications. Similarly, venous components of the vasculature such as the inferior alveolar, retromandibular, and maxillary veins, as well as elements of the pterygoid venous plexus, are also within close proximity to the areas where many mandibular block injections are administered and may be inadvertently damaged, especially if techniques are careless or inappropriate.

Fibrous tissue elements such as the sphenomandibular ligament and interpterygoid fascia have a bearing on diffusion dynamics within the anatomical spaces relevant to mandibular block procedures [10]. In vivo studies involving the radiographic analysis of injected local anaesthetics mixed with contrasting medium have found that local anaesthetic solution diffuses easily through the loose areolar tissue that is present in many anatomical spaces [7, 11]. However, deposition of local anaesthetic in a location where it is separated from its intended target by fibrous tissue may impede its diffusion [10, 12]. This is especially relevant for mandibular block techniques that are administered at a low level, as fibrous tissue converges inferiorly onto the bone, restricting the available area where the needle tip can be placed and not be in a position where it is separated from the intended target (i.e., IAN) by fibrous tissue.

The pterygoid muscles occupy considerable space within the area where needles are directed during mandibular block procedures. The medial pterygoid muscle lies in a position where, if needle placement is too medial during a low block technique such as the direct or indirect IANB, this may result in intramuscular injection, potentially leading to less effective anaesthesia and postoperative trismus [1]. Similarly, for high block techniques such as the Gow-Gates and Akinosi closed mouth techniques, needle placement that is too medial may likewise result in local anaesthetic deposition intramuscularly, within the substance of the lateral pterygoid muscle.

3. Techniques

3.1. Direct IANB. Although there are many techniques described, the direct IANB, also known as the direct thrust approach, remains one of the most commonly used to obtain mandibular anaesthesia [13]. The direct IANB technique

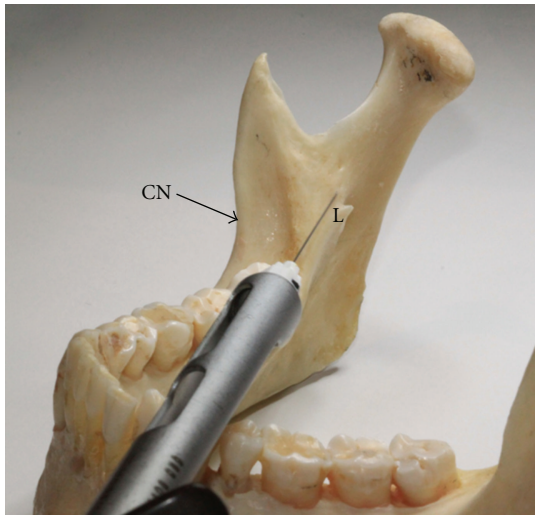

Figure 2: Photograph of the mandible where the needle tip is directed toward the area of bone just superior to the lingula. This positioning of the needle will allow for local anaesthetic deposition in a location in close proximity to the IAN and associated vessels, yet minimising the risk of damaging them. This photograph reflects where local anaesthetic is injected with the direct and indirect IANB (CN: Coronoid notch, L: Lingula).

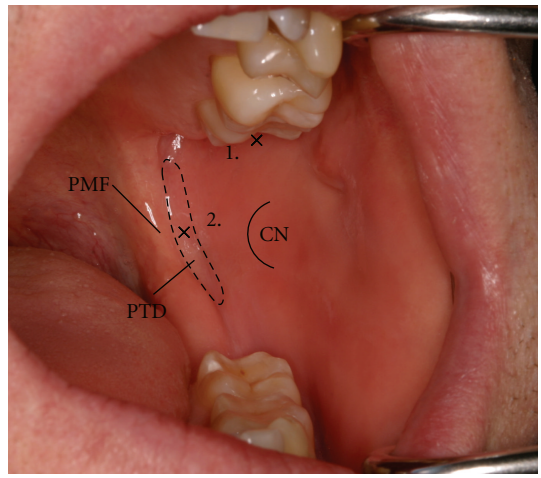

Figure 3: Intraoral photograph of the left side of the oral cavity showing the injection sites for different mandibular block techniques. The pterygotemporal depression exists between the pterygomandibular fold and coronoid notch and represents the area where a direct or indirect IANB is administered in the mediolateral plane. The height at which this block is given is approximately the level of the coronoid notch. In contrast, the Gow-Gates mandibular block is administered at a much higher level. The mesiopalatal cusp of the upper second molar determines the height of the injection while the site in the mediolateral plane is the area of tissue just posterior to the upper second or third molar (PTD: pterygotemporal depression, PMF: pterygomandibular fold, CN: coronoid notch, 1: area where a direct/indirect IANB would be administered, 2: area where a Gow-Gates mandibular block would be administered).

involves needle insertion into the pterygomandibular space by piercing the buccinator muscle, anteriorly. Once in this anatomical space, the objective of this technique is to deposit local anaesthetic solution near the inferior alveolar nerve, just before it enters the mandibular foramen that leads into the mandibular canal. Although the exact location of where the needle tip should be located in relation to the IAN is hard to assess in any one patient due to the required ~20–25 mm depth of tissue penetration [14], it is advantageous to administer the injection so that the tip of the needle contacts bone just superior to the tip of the lingula (Figure 2). This will ensure that local anaesthetic solution is not deposited medial to the sphenomandibular ligament. The lingual nerve lies medial and anterior to the IAN and can be anaesthetised during an IANB by withdrawing the needle and swinging the barrel of the syringe toward the dental midline.

Clinicians use several intraoral landmarks when administering direct IANBs. When the mouth is wide open, the pterygotemporal depression represents the site of injection and is positioned between the raised ridge of mucosa overlying the pterygomandibular raphe medially and the mucosa that overlies the anterior border of the mandibular ramus and tendon of temporalis laterally (Figure 3). The visible intraoral ridge produced by the underlying pterygomandibular raphe is referred to as the pterygomandibular fold (Figure 3).

The level of injection is established by the point of maximum concavity on the anterior border of the mandibular ramus, an area referred to as the coronoid notch. Alternate landmarks for assessing the correct height of needle entry for the IANB includes inserting the needle approximately 10 mm above the lower occlusal plane when the mouth is fully open [1]. Other guidelines include inserting the needle at the midway point between the upper and lower posterior teeth when the mouth is wide open and visualising the apex of the buccal pad of fibrous tissue that forms an apex close to the pterygomandibular fold [10]. The buccal pad is a submucosal fibrous band of tissue separating the overlying mucosa from the underlying buccinator muscle, and it should not be confused with the buccal pad of fat which is an area of adipose tissue between the buccinator muscle and masseter muscle.

The required horizontal angulation of the syringe varies between patients with the morphology of the internal oblique ridge, degree of ramal flaring, shape of the lingula, dental arch type, and alignment of teeth influencing what is appropriate. As a guide, the syringe barrel should extend over the premolars on the contralateral side [1]. This angulation, however, may need to be modified if the needle tip has not made bone contact at the appropriate depth of around 20–25 mm [14]. When the correct depth of needle penetration and angulation has been attained, the needle is then withdrawn one to two millimetres and an aspiration test performed.

Some authors have emphasised the importance of extraoral landmarks in addition to intraoral landmarks to evaluate ideal needle placement and angulation, such as the degree of ramal flaring and the height and width of the mandibular

ramus [8]. This is especially important with the edentulous patient.

Considering the height at which the direct IANB is administered, it only anaesthetises the IAN, LN, and nerve to mylohyoid, in most cases. Generally, anaesthesia of these nerves is all that is required for most dental and local surgical procedures. If, however, other nerves require anaesthesia, or if anatomical variation in an individual results in a disruption in the usual pattern of nerves that a low nerve block would normally anaesthetise, then a higher nerve block technique may be indicated.

3.2. Indirect IANB. The indirect IANB is a variation of the direct technique where the level and site of injection is the same. The fundamental difference, however, lies in the method by which the appropriate depth of needle insertion (~20–25 mm) is obtained. The indirect technique involves the insertion of the needle using the same landmarks to indicate correct height and mediolateral needle placement (Figure 3), but with a significantly greater degree of syringe angulation on the contralateral side [3]. The effect of this is to make early bone contact near the anterior border of the ramus, anterior to the mandibular foramen. Subsequent to this, the needle angulation is slowly altered by swinging the barrel of the syringe toward the midline, thus allowing the needle to penetrate to progressively deeper positions through soft tissue. This process is continued until the appropriate depth of needle insertion (~20–25 mm) is attained [3].

The level at which the indirect IANB is administered is the same as the direct IANB, and, consequently, it has the same advantages and limitations. In addition to this, it is worth noting that the degree of tissue damage sustained to the contents of the pterygomandibular space may be greater than the direct IANB due to the movement of the partially inserted needle as the barrel of the syringe is swung toward the midline.

3.3. Anterior Injection Technique. The anterior injection technique involves the insertion of the needle for approximately 10 mm into the pterygomandibular space where the local anaesthetic is deposited, allowing for the anaesthetic solution to slowly diffuse across the space and toward the IAN [7]. Firstly, the needle insertion site is determined using the same anatomical landmarks as for the direct and indirect IANB (Figure 3). The anterior injection technique also requires a large degree of horizontal needle angulation, similar to the indirect IANB, where the barrel of the syringe lies over the contralateral molars. The fundamental difference between the techniques, however, is that when initial bone contact is made with the needle at ~10 mm (Figure 4), no further insertion of the needle into the pterygomandibular space is attempted. The suggested advantage of this technique over the others is that the risk of vascular and neural damage is said to be reduced as the needle does not penetrate as deeply [7].

3.4. Gow-Gates Mandibular Block Technique. The Gow-Gates mandibular block is often referred to as a true mandibular block as the distribution of its effect is larger than that of lower-level nerve block techniques and it anaesthetises the auriculotemporal and long buccal nerves in most cases [1]. This technique involves the intraoral insertion of a needle through the pterygomandibular space until bony contact is made with the anterolateral condylar neck, under the insertion of the lateral pterygoid muscle, in an area referred to as the processus condyloideus [15] (Figure 5). Although different for every patient, the average depth of needle insertion

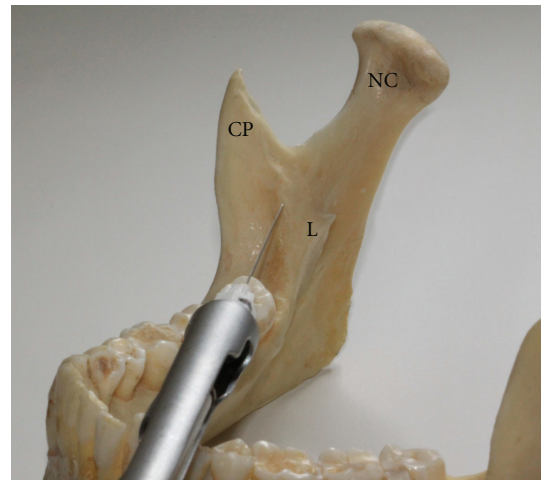

Figure 4: Photograph of the mandible showing the positioning of the needle tip when administering the anterior IANB. Note that the location of the needle tip is a considerable distance from where the IAN would be expected. This technique relies heavily on the ability of local anaesthetic to diffuse throughout the pterygomandibular space (NC: neck of Condyle, CP: coronoid process, L: lingula).

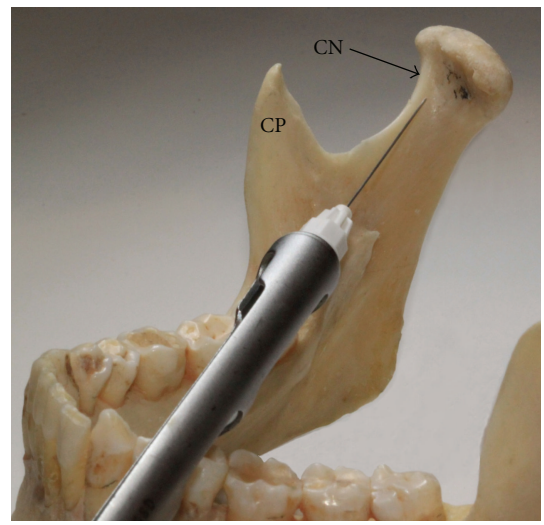

Figure 5: Photograph of the mandible showing the ideal needle tip position when administering the Gow-Gates mandibular block technique. The intended target area for the needle is the lateral condylar neck region, below the insertion of the lateral pterygoid muscle and the attachment of ligaments associated with the temporomandibular capsule (CN: condylar neck, CP: coronoid process).

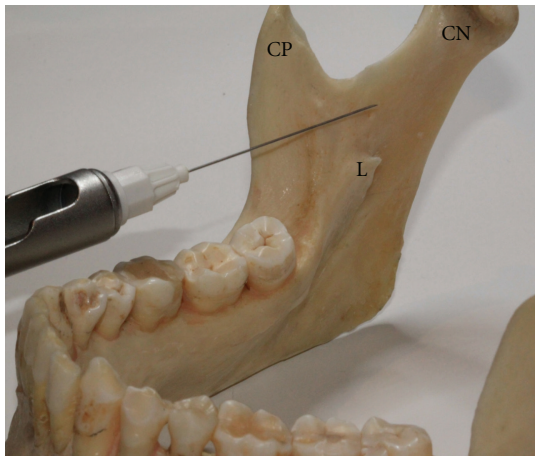

Figure 6: Photograph of the mandibular ramus from a medial view showing the needle tip positioning required for the Akinosi closed mouth mandibular nerve block technique. Note that the needle should not contact bone during needle insertion. The needle tip slips along the medial aspect of the ramus to its intended target area, the loose areolar tissue within the superior reach of the pterygomadibular space (CN: condylar neck, CP: coronoid process, L: lingula).

is ~25 mm, and following needle contact, withdrawal of 1-2 mm, and an aspiration test is required [16]. In addition to this, Malamed has suggested that the patient should keep their mouth open for ~60–90 seconds following injection to allow for more speedy diffusion of local anaesthetic as mandibular opening reduces the distance between where the local anaesthetic is deposited and the mandibular nerve [1].

A combination of intraoral and extraoral landmarks are used for the Gow-Gates mandibular block technique. Firstly, the height of injection is established by the mesiopalatal cusp of the maxillary second molar [1]. Secondly, the site of injection is the tissue immediately distal to the maxillary second molar (or maxillary third molar if present) [1]. The angulation of the syringe in the mediolateral plate involves the barrel of the syringe being approximately in the corner of the mouth, over the contralateral premolars while the orientation of the syringe in the vertical plane requires the alignment of the syringe with the plane that extends between the lower border of the tragus, in the intertragic notch, and the corner of the mouth [17]. As with other techniques, the underlying anatomy may differ between individuals, and due to the significant depth of tissue penetration (~25 mm) required, it is difficult to assess the specific location of the needle tip in any one individual.

The simultaneous visualisation of intraoral and extraoral landmarks required when administering the Gow-Gates mandibular block can be difficult and is often listed by clinicians as a reason why they prefer other mandibular block techniques [13]. Clinical experience with the technique, however, is considered to overcome early difficulties that may be faced when first applying the technique [1]. In addition to this, the time required for onset of anaesthesia is greater than that for the direct IANB due to the greater distance between the site where local anaesthetic is deposited and the mandibular nerve (~5–10 mm), as well as the larger size of the nerve trunk at this relatively higher level [1]. The level at which the injection is given, however, has the advantage of anesthetising more terminal branches of the mandibular nerve than lower-level block techniques, reducing the need for additional injections to supplement the initial block.

3.5. Akinosi Closed-Mouth Technique. The Akinosi closed-mouth mandibular block approach provides an alternate technique for individuals who have limited mouth opening, which is a distinct contraindication for the other block techniques [1, 4]. This technique involves the intraoral insertion of a needle into the pterygomandibular space for ~25–30 mm [18] while the mouth is fully closed. This technique does not involve bony contact, where the desired location of the needle tip should be in the loose areolar tissue medial to the mandibular ramus. As with other block procedures, an aspiration test is performed before deposition of local anaesthetic [18].

The site of injection for this technique is at the level of the mucogingival junction of the maxillary second or third molar [1]. This places the syringe deep in the buccal fornix where the barrel of the syringe needs to be parallel to the maxillary dentition. Ramal flaring should be gauged extraorally, and the path of needle insertion should be parallel to this.

Considering the high level at which this block is administered, it shares the advantages of other high level blocks in the distribution of its anaesthetic effect. Although this technique can be used for anyone, most clinicians reserve it for those who have severe mouth opening deficiencies or are severe gaggers [19]. As no bony contact is made with any structure (Figure 6), the uncertainty surrounding the localisation of the needle tip when the needle is fully inserted in the tissue is a unique disadvantage of this technique [1].

4. Supplementation to Blockade Anaesthesia with Local Supraperiosteal Infiltrations

The success rates of some injection techniques can be quite low, especially with direct and indirect IANBs where the rate of success can be as low as 80% [1]. As a result, supplementation of these injections with local infiltrations has been suggested, and clinical trials have been performed to evaluate their effectiveness. These infiltration injections should not be confused with buccal nerve blocks or infiltrations which are administered following a direct or indirect IANB to anaesthetise the long buccal nerve which innervates the buccal gingivae of lower posterior molars. For example, the long buccal nerve and the lingual nerve must be anaesthetised, in addition to the IAN, if lower posterior teeth are to be extracted.

There are many reasons why anaesthetic failures occur, and they can often be classified into two major categories: poor operator technique and anatomical variation [20]. As it is difficult to determine the anaesthetic outcome in any given patient, the use of supplementary infiltrations from

the outset has been suggested as a safety net for individuals who respond less favourably to IANBs. Most in vivo research demonstrates an increased effectiveness of anaesthesia with supplementary infiltrations [21–23]; however, Foster et al. [24] were not able to observe a statistically significant difference. This may be explained by the type of local anaesthetic formulation used. Foster et al. used 2% Lido-caine HCL with 1 : 100000 adrenaline, and Hasse et al. [22] observed that this preparation did not produce a statistically significant additional effect to mandibular anaesthesia when used as a supplementary infiltration following an IANB, in contrast to the use of 4% Articaine HCL with 1 : 100000 adrenaline as tested in the same research project. Considering that buccal and lingual infiltrations alone when administered to lower first molars in the absence of blockade anaesthesia produce anaesthesia in about 38.7 to 64.5% of individuals with the use of Lidocaine HCL and Articaine HCL, respectively [25], it is likely that supplementary injections will add to the anaesthetic effectiveness of an IANB. However, much more research needs to be conducted in this area to further our understanding of the best approaches to mandibular anaesthesia.

The results of studies used to compare the efficacy of different local anaesthetic agents when given as supplementary infiltrations can be difficult to evaluate due to the different formulation concentrations used, the different volumes injected, the different criteria used for describing profound anaesthesia, and other differences in the research methodology (i.e., which teeth are tested). Most studies indicate that Articaine HCL is more effective than Lidocaine HCL when administered as a supplementary infiltration. However, the concentration of the active ingredient in the former is double that of the latter, 4% and 2%, respectively, making comparisons difficult. More research needs to be conducted to evaluate whether the type of anaesthetic agent used has an impact on the extent and level of anaesthesia attained.

5. Conclusion

Mandibular anaesthesia is an essential part of clinical practice for dental and local surgical procedures in the oral region. Due to various factors, anaesthesia of the mandibular nerve is associated with a high degree of failure, especially with the use of low-level block procedures. Failure of anaesthesia can prove challenging for the clinician to understand. If a mandibular block procedure fails, it is essential that the operator carefully evaluates his/her technique, and considers common anatomical variations, to determine what may have contributed to the problem. If the underlying cause is likely to be due to anatomical variation, then the use of an alternative method is indicated rather than repetition of the same technique.

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Review Article

Ultrasound-Guided Regional Anesthesia for Procedures of the Upper Extremity

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Anesthesia options for upper extremity surgery include general and regional anesthesia. Brachial plexus blockade has several advantages including decreased hemodynamic instability, avoidance of airway instrumentation, and intra-, as well as postoperative analgesia. Prior to the availability of ultrasound the risks of complications and failure of regional anesthesia made general anesthesia a more desirable option for anesthesiologists inexperienced in the practice of regional anesthesia. Ultrasonography has revolutionized the practice of regional anesthesia. By visualizing needle entry throughout the procedure, the relationship between the anatomical structures and the needle can reduce the incidence of complications. In addition, direct visualization of the spread of local anesthesia around the nerves provides instant feedback regarding the likely success of the block. This review article outlines how ultrasound has improved the safety and success of brachial plexus blocks. The advantages that ultrasound guidance provides are only as good as the experience of the anesthesiologist performing the block. For example, in experienced hands, with real time needle visualization, a supraclavicular brachial plexus block has changed from an approach with the highest risk of pneumothorax to a block with minimal risks making it the ideal choice for most upper extremity surgeries.

1. General Anesthesia versus Regional Anesthesia

Anesthesia options for upper extremity surgery include general anesthesia, regional anesthesia, or a combination of the two. In the past general anesthesia was frequently the method of choice for upper extremity surgery due to lack of training and experience with regional anesthesia as well as fear of complications including vascular puncture, local anesthetic toxicity, pneumothorax, and patient discomfort [1]. Needle placement utilizing the paresthesia technique or peripheral nerve stimulator could be a time-consuming process leading to operating room delays and patient discomfort. However, the advantages of general anesthesia, including control of the airway and familiarity of the technique by the majority of anesthesiologists are overshadowed by the clear benefits of regional anesthesia. These include intraoperative, as well as postoperative analgesia [2, 3]. In addition, regional anesthesia results in excellent muscle relaxation during surgery, decreased opioid requirements and their potential side effects, greater hemodynamic stability, increased efficiency in the operating room by avoiding the time required to awaken and extubate the patient, reduced PACU stay, a decrease in unplanned hospital admission for pain control, as well as greater patient satisfaction [2, 3]. The most significant advantage of regional anesthesia for surgery of the upper extremity is the prolonged postoperative analgesia that a nerve block can provide. The pain relief following brachial plexus blockade with long-acting local anesthetics such as bupivacaine, ropivacaine and levobupivacaine has resulted in patients being discharged home on the day of surgery as opposed to a planned or unplanned overnight admission [3, 4].

2. Brachial Plexus Anatomy

Thompson and Rorie performed cadaveric studies to map out the brachial plexus anatomy [5]. The fifth through eighth cervical and first thoracic nerve exit through the

intervertebral foramina and travel along the groove formed by the transverse processes of their corresponding vertebrae. After exiting the transverse processes the roots of the brachial plexus travel between the anterior and the middle scalene muscles, identified as the interscalene groove [1]. The authors reported that the brachial plexus is confined by a continuous fascial sheath formed by the deep cervical fascia and that the fascia is continuous from emergence of the nerve roots to the axilla. Distally the fascia folds inwards to form separate compartments for each nerve. For example, at the cord level, local anesthetic injected around the posterior cord may not spread to include the lateral or medial cords [6–8] whereas an axillary brachial plexus block is performed by identifying the individual nerves and blocking each one separately [9–11]. While an interscalene block is performed by means of a single injection technique, the more distal approach to the brachial plexus, the less likely that a single injection technique will result in complete blockade of the upper extremity [12–14].

3. Basics of Ultrasound

Ultrasound probes (transducers) act as both a transmitter and receiver of sound waves. The probes are classified as either high (10–15 MHz), midrange (5–10 MHz), or low (<5 MHz) frequency. High-frequency probes provide high-resolution images but lack depth of penetration compared to low-frequency probes [15]. Both frequency types are available with a wide or a narrow footprint. High-resolution linear transducers are most suitable for imaging superficial structures such as the brachial plexus in the interscalene, supraclavicular, and axillary regions. The lower frequency curved transducer is preferable when the anatomical structures are deeper than 4 cm, for example, when performing an infraclavicular block [16]. Prior to the use of ultrasound, block needle placement was achieved using a blind approach with the nerve stimulation or paresthesia technique. Ultrasound imaging has revolutionized the practice of regional anesthesia in that the operator can visualize and identify nerves and blood vessels as well as the needle during its passage through the tissues. Abnormal anatomy can also be recognized [17]. In addition, direct visualization of the spread of local anesthetic decreases the risk of intravascular injection, local anesthetic toxicity, pneumothorax, and a failed block [18]. It is important to remember, however, that the success of an ultrasound-guided block is dependent upon the skill and experience of the anesthesiologist. Anesthesiologists performing brachial plexus anesthesia under ultrasound guidance must first become comfortable with identifying anatomical structures as well as visualizing the needle during the block performance. In experienced hands, the benefits of performing a peripheral nerve block with real-time ultrasound imaging of needle placement and local anesthesia spread include decreased performance as well as onset time, a decreased dose of local anesthetic required to achieve a successful block, and an increase in block success rate [19–24]. In a systematic review and meta-analysis of randomized controlled trials comparing ultrasound guidance with electrical neurostimulation for peripheral nerve blocks, Abrahams et al. confirmed these aforementioned benefits of ultrasound. However, the authors concluded that larger studies are needed to determine whether ultrasound can decrease the number of complications [25].

4. Patient Preoperative Evaluation and Education

The success of a regional anesthesia program is dependent on patient education and the support of the surgical team. To put a patient at ease it is desirable for the surgeon to inform the patient about the possibility of receiving a brachial plexus block for his or her surgery prior to the day of surgery. A patient that has been informed beforehand is often more amenable to accepting regional anesthesia. In addition, the training, education, and skill of the individual performing the block are of paramount importance. To this end, both the American as well as the European Society of Regional Anesthesia (ASRA and ESRA) hold annual meetings as well as numerous workshops throughout the year to educate and train individuals in the art of regional anesthesia [26]. There are few absolute contraindications to a brachial plexus block. These include patient refusal, local anesthetic allergy, infection at the site of needle entry, and the presence of infected lymph nodes in the axilla or supraclavicular region [7, 27]. Deep blocks, for example, an infraclavicular approach, as well as blocks in the vicinity of a noncompressible artery (e.g., supraclavicular) should not be performed in coagulopathic patients [6, 7]. A patient that is unable to cooperate secondary to decreased mental status is also an absolute contraindication. Regional anesthesia is not contraindicated in patients that have a pre-existing stable neurological deficit or chronic neurological disease provided that the condition is well documented [28, 29]. It is up to the anesthesiologist to decide, based on each individual patient's risk benefit ratio whether performance of a peripheral nerve block in the presence of pre-existing nerve damage is indicated [30]. An informed cooperative patient is an essential factor in ensuring safe and effective regional anesthesia. Following a brachial plexus block, it is essential that the affected extremity be immobilized and protected until loss of sensation and proprioception have resolved. Patients and family members should receive clear instructions regarding the anticipated duration of the block and how to transition to oral analgesia at home to avoid the sudden onset of pain.

5. Anesthetic Techniques

De Andres and Sala-Blanch state that it is essential to understand both the topographic anatomy and cross-sectional anatomy of each anatomic zone of the brachial plexus [15]. They describe the brachial plexus as being divided into three zones: the supraclavicular region in the posterior triangle of the neck, the infraclavicular region deep to the pectoralis muscles in the anterior chest, and the axillary region. The level of needle entry in one of these zones will determine the

extent, limitations, and potential complications of a brachial plexus block. Prior to the use of ultrasound, the likelihood of encountering the spinal cord, the lung, and major vessels such as the subclavian and vertebral arteries with the more proximal approaches (interscalene and supraclavicular) was a concern [31]. Ultrasound has minimized these risks provided that the needle tip as well as the spread of local anesthetic is constantly visualized throughout performance of the block [20, 32]. The choice of which technique to use is dependent on the surgical procedure, the comfort and expertise of the anesthesiologist, and patient-associated factors such as sepsis in the axilla. In the latter case a more proximal approach is desirable [30].

6. Interscalene Block

The interscalene approach to the brachial plexus is the technique of choice for surgical procedures of the shoulder. It is inappropriate for surgeries involving the medial aspect of the upper extremity due to inconsistent blockade of the lower trunk (C8 and T1) [33, 34]. At the level of the cricoid cartilage the brachial plexus trunks appear as three distinct hypoechoic areas between the anterior and middle scalene muscles [1, 35]. It should be emphasized that the large doses of local anesthetic traditionally used for an interscalene block with the neurostimulation technique result in a 100% incidence of ipsilateral phrenic nerve paralysis due to blockade of the 3rd, 4th, and 5th cervical nerve roots. This may decrease the patient's FRC by 25% [36] and may therefore not be suitable for patients with emphysema and other chronic lung diseases with decreased pulmonary reserve. Ultrasound imaging improves the interscalene approach primarily by being able to visualize the spread of local anesthetic within the fascia surrounding the trunks. This direct visualization decreases the amount of local anesthetic needed to provide surgical anesthesia [37, 38]. Decreasing the volume of local anesthetic to 10 mL or 5 mL resulted in a significant decrease in the incidence of hemidiaphragmatic paresis [37, 39, 40]. Kapral et al. report that ultrasound guidance improves both the quality of the nerve block and shortens the time of onset of sensory blockade [22].

7. Supraclavicular Block

The supraclavicular block was traditionally performed for surgeries of the upper extremity below the shoulder. Liu et al., however, recently reported that ultrasound-guided supraclavicular blocks are effective and safe for shoulder arthroscopy [41]. The supraclavicular approach has several advantages over the more distal approaches including rapid onset of the block, more complete blockade of the nerves supplying the upper extremity (with the exception of the intercostobrachial nerve) due to the compact arrangement of the trunks of the brachial plexus at this level [32, 42]. Prior to the use of ultrasound the supraclavicular approach was frequently avoided, particularly in ambulatory surgeries, due to the increased risk of pneumothorax and, to a lesser extent, direct vascular puncture of the subclavian, superficial (transverse) cervical, suprascapular, or dorsal scapular arteries with subsequent local anesthetic toxicity and cardiovascular collapse [43, 44]. Ultrasound has improved the safety of a supraclavicular block as the anesthesiologist can now visualize the subclavian artery, the first rib, as well as the dome of the lung. Placement of the needle and spread of the local anesthetic can now be seen in real-time resulting in resurgence in the use of this block [17, 45]. Chan et al. examined the supraclavicular region in 40 patients and reported that in all cases the nerves of the brachial plexus appeared as hypoechoic nodules in clusters lateral, posterior, and cephalad to the subclavian artery [46]. The authors also concluded that if the needle is seen at all times and not inserted beyond the first rib, then the risk of a pneumothorax in a supraclavicular block is essentially eliminated. Williams found that supraclavicular nerve blocks were performed faster with ultrasound guidance when compared with nerve stimulation (5 versus 10 min) [20]. Ultrasound guidance has increased the safety profile of the supraclavicular approach so that in experienced hands this may be the block of choice for most upper extremity surgeries below the shoulder.

8. Infraclavicular Block

The infraclavicular approach is indicated for surgeries of the arm and hand. Compared to the supraclavicular approach, the risk of pneumothorax is significantly reduced and is virtually eliminated with the use of ultrasound. In addition, the phrenic nerve is not blocked with this approach [47]. Compared to the axillary approach, the infraclavicular block targets the brachial plexus at the level of the cords which surround the second part of the axillary artery and are proximal to the takeoff of the musculocutaneous, axillary, and medial brachial cutaneous nerves. This may result in a higher success rate of complete blockade with a single injection technique [48]. The infraclavicular anatomy may, however, be more difficult to visualize under ultrasound guidance particularly in obese patients. Perlas et al. found that compared to the interscalene, supraclavicular, axillary, and midhumeral approaches in which the brachial plexus was visualized 100% of the time, in only 27% of patients were they able to visualize the infraclavicular brachial plexus [1, 49]. This difficulty is due to the relative depth of the brachial plexus in the infraclavicular approach compared to all other approaches to the brachial plexus. A low-frequency probe with its greater tissue penetration may facilitate performance of this block [47]. In an ultrasound-guided infraclavicular block the lateral, posterior, and medial cords are seen in close proximity to the axillary artery and vein. The posterior cord is usually blocked first. If the spread of local anesthetic does not surround the lateral and medial cords, then all three cords must be blocked individually to obtain complete blockade of the upper extremity. As with the supraclavicular and axillary approaches, the intercostobrachial nerve will have to be blocked separately in the axilla to achieve anesthesia of the inner aspect of the upper arm.

9. Axillary Block

Axillary blocks are performed for procedures of the elbow, distal arm, and hand. Prior to the use of ultrasound, the axillary approach was the most common approach to the brachial plexus due to the safety of this technique. As with the infraclavicular block, the risk of phrenic nerve paresis is avoided and the risk of pneumothorax is eliminated. The high success rate without respiratory compromise makes this block desirable in patients with reduced lung capacities and chronic pulmonary diseases [50]. Contraindications to the axillary approach include inability to abduct the arm to the position necessary to perform the block, localized infection in the axilla, or enlarged axillary lymph nodes [51]. A major advantage of using ultrasound in an axillary approach is the ability to confirm blockade of the musculocutaneous nerve [52]. Because of the anatomical variance of the musculocutaneous nerve in relation to the axillary artery, failure to block this nerve with a perivascular approach in not uncommon [53]. At the axillary level, the terminal branches of the brachial plexus (median, ulnar, and radial nerves) are situated close to the axillary artery and veins with the two axillary veins situated medial to the artery. There is, however, a great deal of variation in the distribution of these three nerves in relation to the artery [54]. The four nerves are easily visualized utilizing ultrasonography. The ultrasound guided axillary approach has been shown to both decrease block failure rate and time of onset of sensory blockade compared to the transarterial technique [14]. The success of US guided axillary blocks depends on the multiple needle approach in which each nerve is identified individually and spread of local anesthetic is observed around the median, ulnar, radial, and musculocutaneous nerves.

10. Distal Upper Extremity Blocks

Individual terminal nerve blocks can be performed at the midhumeral, elbow, forearm, or wrist either by design or as a rescue block [7]. These more peripheral nerve blocks may be performed to achieve postoperative analgesia while at the same time maintaining more proximal control of the upper extremity.

11. Postoperative Pain Control

Postoperative pain and nausea are the leading causes of unplanned hospital admission after ambulatory surgery [55]. Orthopedic upper extremity surgery is reported as having a high incidence of severe pain [56]. One of the clear benefits of regional anesthesia over general anesthesia for upper extremity surgery is the postoperative pain relief a long-acting local anesthetic can provide. The choice of local anesthetic is determined by the duration of surgery, necessity of motor blockade, urgency of neurological assessment after surgery, and the anticipated requirement for postoperative analgesia. In brachial plexus nerve blocks short-, intermediate-, and long-acting local anesthetics can be chosen. Bupivacaine, ropivacaine, and levobupivacaine are equally effective in surgeries in which extended postoperative analgesia would be beneficial. In comparison to bupivacaine, however, ropivacaine and levobupivacaine are the long-acting local anesthetics of choice due to their decreased cardiotoxicity [57–59]. It is important for the patient to be informed of the anticipated duration of the local anesthetic so that he or she will not be concerned about the length of time it takes for the block to wear off. It is also essential that patients be instructed regarding protection of the extremity until sensation has completely returned. Finally, patients should be instructed to take their prescribed oral analgesics at the earliest sign of pain to mitigate against the analgesic gap that may otherwise develop. Additional methods to improve and or prolong postoperative analgesia include insertion of a brachial plexus catheter to provide continuous regional analgesia [51, 60] as well as the use of multimodal analgesia. In the multimodal approach use of a long-acting peripheral nerve block in combination with acetaminophen, NSAIDs (when not contraindicated), and oral opioid analgesics will minimize the total opioid requirements and their resulting side effects [61, 62].

12. Conclusion

The various approaches to the brachial plexus afford the anesthesiologist the ability to provide both excellent intraoperative anesthesia as well as postoperative analgesia with minimal complications and increased patient satisfaction following upper extremity surgery. The advantages over general anesthesia are numerous when performed in skilled hands. Ultrasound guidance with real-time needle visualization in relation to anatomic structures and target nerves makes regional anesthesia safer and more successful. With ultrasound guidance in experienced hands, brachial plexus blockade can lead to decreased block performance and onset time, increased success rate and decreased rate of complications. These advantages result in increased operating room efficiency, as well as increased patient and surgeon satisfaction.

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Review Article

Axillary Brachial Plexus Block

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The axillary approach to brachial plexus blockade provides satisfactory anaesthesia for elbow, forearm, and hand surgery and also provides reliable cutaneous anaesthesia of the inner upper arm including the medial cutaneous nerve of arm and intercostobrachial nerve, areas often missed with other approaches. In addition, the axillary approach remains the safest of the four main options, as it does not risk blockade of the phrenic nerve, nor does it have the potential to cause pneumothorax, making it an ideal option for day case surgery. Historically, single-injection techniques have not provided reliable blockade in the musculocutaneous and radial nerve territories, but success rates have greatly improved with multiple-injection techniques whether using nerve stimulation or ultrasound guidance. Complete, reliable, rapid, and safe blockade of the arm is now achievable, and the paper summarizes the current position with particular reference to ultrasound guidance.

1. Introduction

The axillary approach to brachial plexus was first demonstrated in 1884 by William Halsted when he injected cocaine under direct vision [1]. In 1911, G. Hirschel performed the first percutaneous axillary block [2]. It was only after Burnham's publication in 1959 [3] that this block gained popularity among anaesthetists. Since then, it has become the most used peripheral nerve block for forearm and hand surgery, especially due the low incidence of complications compared to the more proximal approaches to the brachial plexus.

2. The Brachial Plexus in the Axilla [4]

The brachial plexus supplies the nerve supply to the upper limb and is formed by the ventral rami of the lower four cervical nerves and the first thoracic nerve. It consists of roots, trunks, divisions, and cords. The roots are arranged between the scalenus anterior and medius muscles, and they combine in the posterior triangle to form three trunks: upper, middle, and lower. On approaching the clavicle, each of the three trunks divides into an anterior and posterior division to supply the flexor and extensor compartments of the arm, respectively. Anterior divisions of the upper and middle trunk unite to form the lateral cord, anterior division of the lower trunk continues as the medial cord, and posterior divisions of all the three trunks assemble to from the posterior cord. The three cords enter the axilla at the apex and are arranged, according to the names, around the second and third parts of the axillary artery. In relation to the first part of the artery, however, the lateral and posterior cords are lateral, and the medial cord lies posterior to the artery.

At the lateral border of the pectoralis minor muscle, the cords divide into terminal nerves of the brachial plexus: musculocutaneous, median, ulnar, radial, axillary, medial cutaneous nerve of arm (MCNA), and medial cutaneous nerve of forearm (MCNF), which along with the intercostobrachial nerve (ICB) provide the sensory and motor supply to the whole upper extremity (Figure 1). The cords, the terminal branches, and the vessels lie within an incomplete fascial sheath derived from the scalene fascia, which is in turn derived from the prevertebral fascial layer.

At the level of axilla, the median, radial, and ulnar nerves lie within the neurovascular bundle, whereas the median cutaneous nerve of the arm and forearm may lie either inside or outside the sheath. The musculocutaneous nerve always lies outside the sheath (in the plane between the biceps and

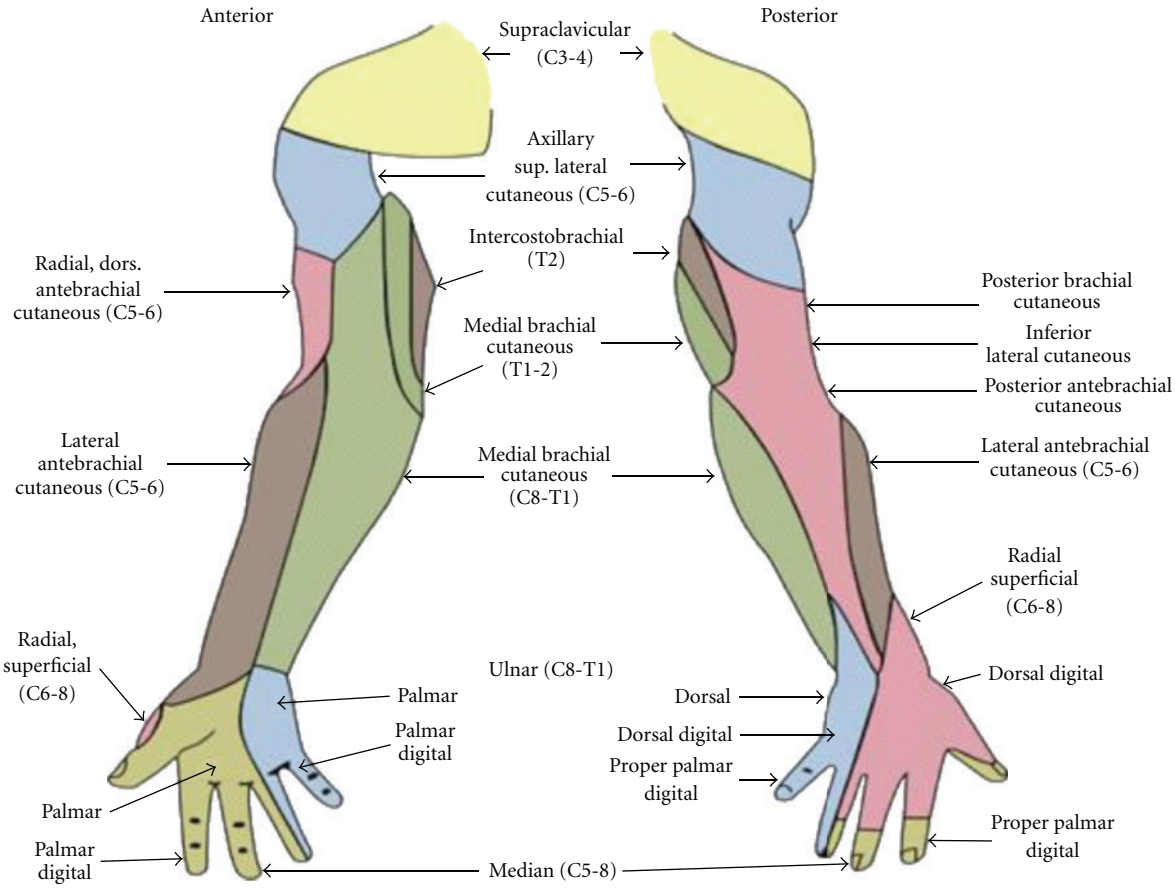

Figure 1: Cutaneous innervation of the upper extremity. Note the significant contributions of the cutaneous branches of the plexus. (Courtesy From Wikimedia Commons, file: Gray's Anatomy 812 and 814.PNG).

coracobrachialis muscle or in the body of coracobrachialis), because it leaves the lateral cord before the cords enter the axilla. Within the fascia, in relation to the axillary artery, the nerves are arranged as follows: (1) median-lateral and anterior, (2) ulnar-medial and anterior, and (3) radial-medial and posterior. The musculocutaneous nerve appears lateral and posterior to the artery.

3. Basic Principles of Brachial Plexus Block

The best approach to brachial plexus is determined by the sensory and motor innervations of the surgical site concerned and the potential adverse effects of each. Hence, for shoulder and proximal humeral procedures, an interscalene block is performed, which reliably blocks C5-C6 nerve roots and proximal branches such as the suprascapular nerve. A supraclavicular approach provides the most widespread surgical anaesthesia for the whole arm, whilst an infraclavicular approach often provides a pattern similar to the axillary approach.

An axillary approach provides good surgical anaesthesia for the elbow, forearm, and hand and also cutaneous anaesthesia of the inner upper arm including the medial cutaneous nerve of arm and intercostobrachial nerve. The axillary approach to the brachial plexus is considered the safest of the four approaches because of reduced risk to surrounding structures such as the risk of phrenic nerve blockade and/or pneumothorax, but the general risks of accidental intravascular and intraneural injection still exists.

4. Axillary Brachial Plexus Block

4.1. Indications

(i) surgical anaesthesia for elbow, forearm, and hand procedures,

(ii) cutaneous anesthesia for superficial procedures of the inner arm, for example, brachiobasilic fistula formation,

(iii) chronic pain treatment.

4.2. Techniques of Axillary Block

(1) peripheral nerve stimulation,

(2) ultrasound guided.

(1) Peripheral Nerve Stimulation. The use of a nerve stimulator for peripheral nerve blockade provided a definite advantage over traditional paraesthesia or transarterial techniques of the 1980s and became the most favoured modality used for peripheral block performance until the advent of ultrasound guidance. A multi-injection technique using a nerve stimulator was found to be associated with a higher success rate [5], as traditional single-injection approaches were limited by lack of circumferential spread of local anaesthetic due to the presence of septa within the axillary sheath, limiting the spread of local anaesthetic [6].

(2) Ultrasound Guided. In 1981, Abramowitz and Cohen described the first use of Doppler ultrasound to identify the axillary artery, thereby aiding the performance of axillary plexus block for upper limb surgery [7]. But it was the use of B-mode ultrasound in 1989 for axillary block performance that heralded the era of ultrasound-guided peripheral nerve block [8]. With the refinement of ultrasound technology and ultrasound-guided block techniques, it is gradually replacing nerve stimulator-based techniques. Ultrasonographic visualisation of target nerve, needle, and local anaesthetic injectate spread has been associated with improved block success rates [9–11], decreased block onset times [9–13], and a decrease in the local anaesthetic dose needed for successful nerve block [14–16].

4.3. Performance of Axillary Block under Ultrasound Guidance. The arm is abducted to 90 degrees and the elbow flexed to 90 degrees. The axilla is prepared aseptically and a high-frequency linear probe scans in a transverse plane at the lateral border of pectoralis major muscle. The pulsating axillary artery is visualized, and the transducer moved to locate the individual nerves around the artery. Easing the pressure off the transducer usually reveals the position of the axillary vein. The nerves at this level have a honeycomb appearance, but their locations relative to the artery are variable. The median nerve usually lies around 9–12 o'clock position, the ulnar nerve often in the corresponding 2 o'clock position, and radial at the 5 o'clock position in relation to the artery [17] (Figure 2). The musculocutaneous nerve usually lies in the plane between the biceps and coracobrachialis muscles or in the body of coracobrachialis and has a flattened appearance with a bright border and often a black, hypoechoic core. As we scan up and down the arm, the musculocutaneous nerve appears to glide in the fascial plane, either moving towards the artery as we scan proximally or away from the artery as we scan distally down the arm. The radial nerve, which lies deeper, below and medial to the artery is the one most difficult to visualise with ultrasound. It is important to exclude postcystic ultrasonographic enhancement beneath the artery, with which the radial nerve is most often confused. Various measures have been tried to obviate this clinical problem including the use of a peripheral nerve stimulator, scanning the radial nerve proximally, beginning from the radial groove on the humerus and tracking proximally into the axilla, and finally employing blind injection of local anesthetic at the 5 o'clock position in relation to the artery. Injection of local anesthetic in a "horse-shoe" pattern underneath the artery, with the needle tip at 5 o'clock position, in our experience, effectively blocks the radial nerve in most cases. A similar "donut" technique has been described by Imasogie et al. [18], where the authors achieved successful block of the median, ulnar, and radial nerves by circumferential deposition of local anaesthetic around the axillary artery, instead of targeting them individually.

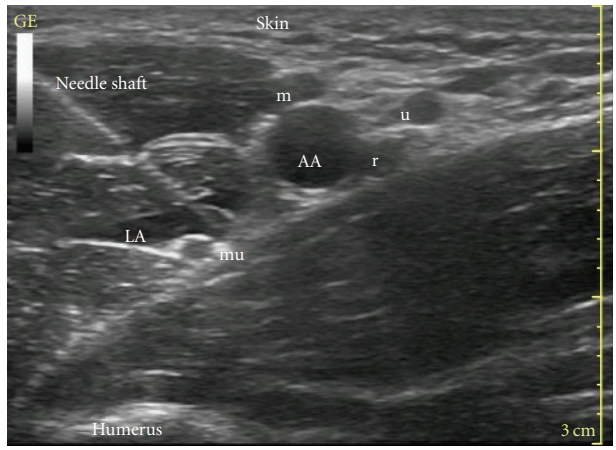

Figure 2: Ultrasound scan of axilla. AA: axillary artery, LA: local anaesthetics, r: radial nerve, mu: musculocutaneous nerve, m: median nerve, and u: ulnar nerve. This is an in-plane approach, with the whole length of the needle shaft visible under ultrasound.

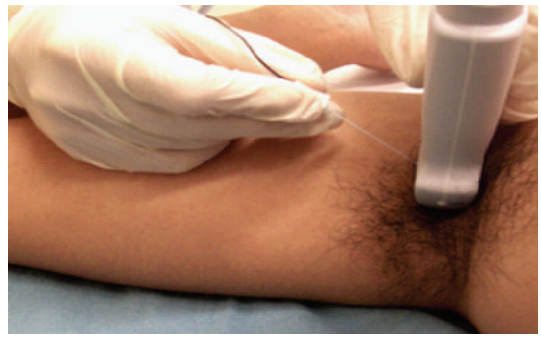

Figure 3: Ultrasound-guided axillary brachial plexus block. This is an example of an out-of-plane approach of the needle with respect to the probe.

After positioning of the probe, we recommend infiltration of local anaesthetic distal to the probe, subcutaneously, to cover the injection site and to block the intercostobrachial nerve. A short-bevelled 5 cm needle can then be inserted either in-plane or out-of-plane (Figure 3) relative to the probe, towards the four nerves and each blocked individually. The in-plane approach to axillary block [11] involves the insertion of the needle along the long axis of the probe, keeping the entire length of the needle in view during the procedure. The out-of-plane approach [19], in contrast, involves insertion of the needle along the short axis of the probe, and hydrolocation of the needle tip may be necessary

to confirm the position of the tip of the needle. In terms of safety, the in-plane approach offers better visualisation of the needle tip [20], but the out-of-plane approach to axillary block has been shown to be more comfortable of the two, for the patient, in a recent study [21]. After careful positioning of needle tip, gentle negative aspiration, and an asymptomatic initial 0.5–1 mL perineural injection, further local anaesthetic is injected in 2 mL aliquots to surround each nerve.

4.4. Choice of Local Anaesthetic. The choice of local anaesthetic is determined by the duration of sensory an-algesia desired. Lidocaine 1.5–2% with adrenaline 5 mcg·mL^{-1}and Mepivacaine 1% provide effective nerve blockade for 2.5–3 hours and are ideal for shorter duration procedures [22, 23]. For longer-duration procedures, it is possible to achieve sensory blockade for 9 hours with Ropivacaine 0.5% and 11 hours with Levobupivacaine 0.33% [24]. When used for surgical anaesthesia decreasing the concentration of both local anaesthetics further would lengthen the onset of block and increase the risk of inadequate blocks [25].

4.5. Volume of Local Anaesthetic. In the past, it was necessary to use large volumes of local anaesthetic to achieve acceptable success rates for peripheral regional anaesthetic techniques. Recent studies have shown that volume of local anaesthetic can be significantly reduced when axillary blocks are performed under ultrasound guidance [22, 23, 26]. An ED95-volume of 0.11 mL/mm^{2}of Mepivacaine has been shown to effective for individual nerves of axillary block, which translates into 0.7–1 mL of local anaesthetic for individual nerves [24]. However, it should be noted that the anatomy of the axillary brachial plexus involves three additional cutaneous nerves (ICB, MCNA, and MCNF) with extensive distribution in the arm and forearm, and the use of such low volumes may risk inadequate block in the distribution of these nerves. Also, it is important to remember that these doses are "adequate" in the hands of very experienced regional anaesthetists, and using such low volumes while learning to perform blocks under ultrasound would reduce success rates and decrease confidence in this technique. It is recommended by the authors to use at least 4-5 mls of local anaesthetic for each nerve during axillary nerve block.

5. Conclusion

Axillary nerve block is a safe and effective regional anaesthetic technique suitable for a wide variety of procedures, for both inpatient and outpatient care [27–32]. Ultrasound guidance has allowed improved efficacy with smaller volumes of local anaesthetic. Direct visualisation of block performance and local anaesthetic injection, though inherently safer, does not completely eliminate the risk of intravascular and intraneural injection, and care should be continually exercised using standard safety precautions of slow, careful, fractionated injections to prevent and minimise the risks associated with the technique.

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Review Article

Ultrasound Guidance for Deep Peripheral Nerve Blocks: A Brief Review

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Nerve stimulation and ultrasound have been introduced to the practice of regional anesthesia mostly in the last two decades. Ultrasound did not gain as much popularity as the nerve stimulation until a decade ago because of the simplicity, accuracy and portability of the nerve stimulator. Ultrasound is now available in most academic centers practicing regional anesthesia and is a popular tool amongst trainees for performance of nerve blocks. This review article specifically discusses the role of ultrasonography for deeply situated nerves or plexuses such as the infraclavicular block for the upper extremity and lumbar plexus and sciatic nerve blocks for the lower extremity. Transitioning from nerve stimulation to ultrasound-guided blocks alone or in combination is beneficial in certain scenarios. However, not every patient undergoing regional anesthesia technique benefits from the use of ultrasound, especially when circumstances resulting in difficult visualization such as deep nerve blocks and/or block performed by inexperienced ultrasonographers. The use of ultrasound does not replace experience and knowledge of relevant anatomy, especially for visualization of deep structures. In certain scenarios, ultrasound may not offer additional value and substantial amount of time may be spent trying to find relevant structures or even provide a false sense of security, especially to an inexperienced operator. We look at available literature on the role of ultrasound for the performance of deep peripheral nerve blocks and its benefits.

1. Introduction

For decades, regional anesthesia has been performed mainly with the help of nerve stimulation [1]. Transitioning from nerve stimulation to ultrasound-guided blocks alone or in combination is beneficial in certain types of regional blocks and scenarios. However, not every patient undergoing a regional anesthesia technique benefits from the use of ultrasound, especially under circumstances resulting in difficult visualization and/or block performed by inexperienced ultrasonographers. The aim of this paper is to specifically discuss the role of ultrasonography for deeply situated nerves or plexuses such as the infraclavicular block for the upper extremity and lumbar plexus and sciatic nerve blocks for the lower extremity. While the authors realize that very few randomized controlled trials (RCTs) have been performed comparing the use of ultrasound with nerve stimulation for performing blocks in deeply located nerves or plexuses, we will attempt to draw conclusions from the existing RCTs.

2. History of Ultrasound Use

About 22 years ago, Ting and Sivagnanaratnam [2] were among the first to utilize ultrasonography to confirm the location of the needle used to perform blocks and observe the spread of local anesthetic while performing axillary nerve blocks. They reported 100% success rate of axillary nerve blocks with no complications during this very first study, and that they were able to visualize the needle tip and axillary anatomy at all times. Subsequently, almost five years later Kapral et al. [3] demonstrated that use of ultrasound for supraclavicular blocks resulted in safe and more effective

Table 1

Study	No. patients	Onset of block time (min)	Time for procedure completion (min)	Success rate (%)	Time to resolution of motor block (min)	Local anesthetic volume	Complications
Dingemans et al. [30]	72	NA	3.1 (US) versus 5.2 (USPNS)	92% (US) versus 74% (USPNS)	NA	Lidocaine 1.5% and Bupivacaine.125% with epi 0.5 mL/kg	NA
Dhir and Ganapathy [31]	66	28 (NS) versus 24 (SC) versus 21(USPNS)	6 (NS) versus 8 (SC) versus 6 (USPNS)	59% (NS) versus 58% (SC) versus 96% (USPNS)	266 (NS) versus 247 (SC) versus 246 (USPNS)	30 mL of Ropivacaine 5 mg/mL with epi 2.5 μg/mL	Secondary catheter failure 9% (US) versus 86% (USPNS)
Sauter et al. [32]	80	13.9 (US) versus 13.7 (USPNS)	4.1 (US) versus 4.3 (USPNS)	95% (US) versus 85% (USPNS)	NA	20 mL Lidocaine 0.5% & 20 mL Bupivacaine, 20 mL Levo-Bupivacaine 0.5% with epi 5 mg/mL	Vascular puncture 6.6%
Brull et al. [33]	103	5 (US) versus 10.5 (USPNS)	5 (US) versus 10.5 (USPNS)	85% (US) versus 65% (USPNS)	NA	Lidocaine 2% 15 mL and 15 mL Bupivacaine 0.5% with epi	No difference in complications in the two groups
Taboada et al. [34]	70	17 (US) versus 19 (USPNS)	3 (US) versus 6 (USPNS)	89% (US) versus 91% (USPNS)	237 (US) versus 247 (USPNS)	NA	NA

US: ultrasound, USPNS: ultrasound plus peripheral nerve stimulation, SC: stimulating catheter.

anesthesia than axillary blocks for the brachial plexus distribution [3]. The same group from Vienna later demonstrated improved success of "three-in-one" lower extremity blocks performed under ultrasound guidance compared with nerve stimulation [4]. They further showed that local anesthetic requirements to produce an effective block were reduced with ultrasound guidance [5]. The use of ultrasound localization of nerves was further advanced when researchers in Toronto demonstrated high quality images of the brachial plexus with ultrasound [6]. They also confirmed the findings by Urmey [7] that contact of a stimulating needle with a nerve does not necessarily elicit a motor response when utilizing nerve stimulation [6, 8].

3. Advantages of Ultrasound Use

Ultrasound guidance makes sense and is intuitive to use for superficial blocks such as supraclavicular, interscalene, axillary, and femoral blocks. These areas are easily visualized with the use of high frequency, linear array transducers that provide very high-resolution images of the brachial plexus. Some of upper extremity blocks like the supraclavicular approach to the brachial plexus have even regained popularity because of the use of ultrasonography in this area. While this has not been proven in randomized controlled trials, visualization of the subclavian artery and the pleura may reduce the incidence of accidental puncture of these structures and consequently reduce the incidence of hematoma and/or pneumothorax. In addition, avoiding blood vessels in general should minimize the chance of local anesthetic toxicity by avoidance of direct injection into the blood stream. Ease of visualization does result in increased success rate in experienced hands and reduced performance time when compared with nerve stimulation alone. Another definite and unique advantage demonstrated with the use of ultrasound guidance is the reduced amount of local anesthetic required to block a variety of nerves and plexuses [5, 9–11]. This is due to the ability to visualize the spread of local anesthetic surrounding a nerve or a plexus, decreasing the need of large amounts of local anesthetic. Although ultrasound has been proven an invaluable tool for regional anesthesia, its use for deep nerve blocks may prove to be more difficult than their superficial counterparts [12, 13]. This is supported by the very few ultrasound studies available for these blocks.

4. Evidence of Use of Ultrasonography for Deep Nerve Blocks

We performed a literature search using Pubmed with each of the three nerve blocks as keywords. We selected published RCTs comparing ultrasound with neurostimulation, for each of the deep peripheral nerve blocks like the sciatic, lumbar plexus, and infraclavicular blocks. Studies were selected from 1993 till present (Table 1). All case series, case reports, and nonrandomized studies were excluded.

4.1. Sciatic Nerve at and above the Subgluteal Level. Nerves can generally be identified by their relationship with other bony landmarks or major blood vessels. The sciatic nerve is recognized by its location between two bony structures: the ischial tuberosity and the greater trochanter. In the gluteal and subgluteal area, the bulk of the gluteus maximus muscle and the adipose tissue make it difficult to identify any deep "soft" structures. In the morbidly obese patients, it may be difficult to recognize even the bony structures. Previous investigators, who have attempted to identify easy and reliable internal ultrasound landmarks for the localization of the sciatic nerve, suggested that locations as much as 7–10 cm

distal to the subgluteal fold may be advantageous for sciatic nerve visualization with ultrasound [12, 14]. Negotiating the sciatic nerve at a level above the subgluteal fold may be difficult with the use of just ultrasound in certain patient populations such as the morbidly obese or patients with positioning issues. Popliteal approach is common for sciatic nerve blocks; this may explain the paucity of studies for ultrasound-guided sciatic nerve block at higher levels. We were able to identify only one study comparing nerve stimulation and ultrasound guidance at the subgluteal level [15]. Using the "up and down" technique, the main outcome parameter was minimal local anesthetic volume necessary to achieve a complete sensory and motor block. Subjects in the ultrasound-guided group were reported to have a 37% reduction in mepivacaine requirements compared with those in the nerve stimulation-guided group. We speculate that the reason for the lack of studies regarding this anatomical approach may be related to the sheer bulk of the gluteus maximus muscle, making sciatic nerve visualization difficult with an ultrasound machine, while nerve stimulation using solid anatomical landmarks reliably provides quick and easy access to the sciatic nerve. Abbas and Brull [16] mentioned their routine use of ultrasound at this level in a letter to the editor; however, it remains to be seen if addition of ultrasound to nerve stimulation offers any advantage to this block.

Given that only one study has been performed comparing the subgluteal sciatic nerve block with the two guidance techniques, it would be reasonable only to comment on the reduced local anesthetic requirement with ultrasound.

4.2. Lumbar Plexus Block. Lumbar plexus blocks are considered advanced blocks by regional anesthesiologists because of the level of difficulty of the block and the potential complications associated with them. Consequently, several case reports of retroperitoneal hematoma and bleeding [17–19], renal subcapsular hematoma [20], and epidural and contralateral spread of local anesthetic have been published [21, 22].

In one of the very first studies, Kirchmair et al. [23] looked at the paravertebral anatomy for ultrasound guided posterior lumbar plexus block. They identified the psoas, quadratus lumborum, and the erector spinae muscles along with the transverse processes at L2–L5 levels. They were able to identify the sono-anatomy in 100% of all volunteers with normal BMI; however, sonography was unfeasible in 20% of patients who were overweight and in 33% of obese volunteers. Thus, ultrasonography may provide no additional benefit over landmarks in overweight patients who may have difficult-to-feel anatomical landmarks. Their subsequent study on cadavers [24] demonstrated good accuracy of ultrasound in reaching the psoas muscle; conversely this study does not give any information about the success rate or efficacy of ultrasound in improving success.

To date, only a single RCT [25] has been reported comparing use of ultrasound versus nerve stimulation guidance for performance of lumbar plexus blocks in patients undergoing total hip replacement. In the ultrasound group, 22% of patients ($n = 23$) and 30% of patients in the nerve stimulation group ($n = 23$) showed incomplete sensory and/or motor block in one of clinically relevant territories of distribution of the lumbar plexus (L2–L4) at 30 minutes after injection of local anesthetic. These patients required an additional bolus of local anesthetic via the lumbar plexus catheter before incision ($P = 0.36$). The average time to readiness for surgery, as defined in the study protocol, was about 7 minutes faster in the ultrasound group ($P = 0.04$). A similar number of patients in both groups required general anesthesia to complete surgery as a result of discomfort referred to pain in the L2-L3 lumbar plexus dermatomes ($P = 0.73$). There were no statistical differences in postoperative pain scores between the two groups at 12 hours (NRS rest = 3 ± 2 in ultrasound group and 3 ± 3 in the nerve stimulation group) and 24 hours (NRS rest = 3 ± 2 in ultrasound group and 2 ± 2 in nerve stimulation group). Average local anesthetic consumption in the first 24 h was also similar between the groups. Thus in patients undergoing primary total hip replacement, ultrasound assistance with nerve stimulation guidance to the lumbar plexus allowed a faster readiness for surgery while often requiring a lower local anesthetic volume than the nerve stimulation technique alone. This may be a result of the reduction of needle redirections that practitioners have to perform to localize the lumbar plexus. The lumbar plexus is located at a depth of 7-8 cm and even deeper in patients with high BMI, and consequently not easily identifiable with ultrasound. High-definition ultrasonography may offer potential advantages in the administration of peripheral nerve blockade. Ilfield et al. [26] provide evidence that prepuncture ultrasound accurately predicts maximal transverse process depth to within 1 cm of its actual location. In addition, the cephalad-caudad location of each transverse process can be estimated with ultrasound to help guide the needle introduction site to either intersect or avoid needle-process contact, whichever the practitioner prefers. Nevertheless, the two techniques seem to be comparable in terms of postoperative local anesthetic consumption and pain scores [25]. Neither of the two techniques seems to offer a clear advantage over the other one. Therefore, we may conclude from the limited data that using a combined prepuncture, ultrasound imaging and neuro-stimulation are likely to reduce the number of needle passes and may position the needle tip closer to the plexus.

Specific complications like retroperitoneal hematoma associated with the lumbar plexus block occur very rarely. Most of them may be explained by either patients being anticoagulated [27] or difficulty during block performance leading to multiple block attempts or by inexperience of the operator [20].

Case reports [13, 28] have attempted to describe the sono-anatomy of location of lumbar plexus between the lumbar transverse processes and the psoas muscle. Some authors have described visualizing the plexus with ultrasound, while others were unable to visualize the plexus itself; but they described the relevant anatomy and the ability to identify the lower pole of kidney [23, 24].

4.3. Infraclavicular Block. Infraclavicular region is particularly suitable for placement of catheters because of the ability to

insert and stabilize the catheter in this area. Compared with the supraclavicular area, where the trunks of the brachial plexus are in close proximity to each other, the brachial plexus divides into divisions/cords below the clavicle. These surround the axillary artery laterally, medially, and posteriorly. Thus, methods that use multiple injection techniques for this block are likely to achieve higher success rates than single injection techniques. Use of hand held Doppler has shown to improve success rate even with a single injection of local anesthetic [29]. We reviewed the available literature to evaluate the usefulness of ultrasound over nerve stimulation in performing these blocks.

In one of the first studies, Wu and colleagues [35] report that ultrasound imaging aided the performance of infraclavicular block and easily blocked the ulnar segment of the medial cord and the intercostobrachial nerves, resulting in enhanced tourniquet pain prevention. However, they mentioned that the distance to the plexus was deeper with this approach, requiring user experience and that the anesthesiologists needed to utilize delicate manipulation when using the anatomical landmark technique. While complete blocks in this investigation were achieved with ultrasound guidance in eight out of nine patients, subclavian artery puncture still occurred on three occasions.

Ootaki et al. [36] used ultrasonography for infraclavicular block in a case series of 60 patients; surgery was successfully performed without supplementation of any other anesthetics or analgesics in 95% of cases. Complete sensory block was obtained in 100% for the musculocutaneous and medial antebrachial cutaneous nerves, 96.7% for the median nerve, and 95% for the ulnar and radial nerves. A complete motor block was achieved in 100% for the musculocutaneous nerve, 96.7% for the median nerve, 90% for the ulnar nerve, and 93.3% for the radial nerve. No complications were identified.

Five randomized controlled studies have compared ultrasound-guided and nerve stimulator-guided infraclavicular blocks in adult patients [32–34, 37]. All studies reported a high success rate with either ultrasound- or with nerve stimulation-guidance, without being able to demonstrate a significant difference between the two modes of nerve identification [32–34, 38]. However, visualization of major anatomic structures by ultrasound appeared to shorten the time to achieve a successful block [33, 34]. While most studies failed to demonstrate a better quality of nerve blockade with one method over the other [38], there was a trend toward a higher success rate in the ultrasound-guided groups [32]. Although limited by sample size, Gurkan demonstrated that the complication rate (e.g., vascular puncture) was lower in the ultrasound-guided than in the nerve stimulator-guided group [38].

In contrast to the previous studies, Dingemans et al. [30] compared the combination of nerve stimulation and ultrasound guidance with ultrasound guidance alone for infraclavicular blocks with residents executing the procedures in all patients. In the "ultrasound only group", a minimum number of injections necessary to visualize local anesthetic spread posterior to and on each side of the axillary artery was performed. The "combined group" received a single injection of local anesthetic after obtaining a distal response to nerve stimulation. They needed one injection for a U-shaped spread around the axillary artery in 76% of patients, two injections in 16% of patients, and three injections in 8% of patients. Dingeman et al. found that infraclavicular nerve blocks were performed faster and with a higher success rate in obtaining a complete block in the ultrasound only group.

In terms of complication avoidance, some case reports have demonstrated that the pressure applied with the ultrasound probe in the infraclavicular area can collapse blood vessels and lead to a negative aspiration test, even when needle position is actually intravascular [39].

5. Conclusions

Although existing studies suggest that the time required to perform peripheral nerve blocks is shortened with the use of ultrasound, the time required to perform an initial ultrasound exam is not included in the total time reported in any of these investigations. Given the limited number of lower extremity studies, it is difficult to comment on the specific advantages of ultrasound with the exemption of a reduced local anesthetic volume required for lumbar plexus blocks. Routine use of ultrasound without the use of a nerve stimulator for deep nerve blocks may give a false sense of security regarding avoidance of complications, as the tip of needle may not be visualized at all times or not at all because of the depth of the neural structures. Consequently, cases of recognized or unrecognized arterial punctures have been reported even with the use of an ultrasound.

Ultrasound offers obvious advantages, but the operator needs to recognize the potential for pitfalls during clinical use related to difficulties with needle visualization and incorrect identification of structures. Even small involuntary movements may lead to insertion into a vascular structure and subsequent local anesthetic toxicity. Visualization of deeper structures may require more pressure to be applied to the probe in order to visualize the target nerve, causing the collapse of blood vessels leading to a false-negative aspiration test.

In summary, without discounting the advantages of adding ultrasound guidance to the armamentarium of regional anesthesia, it would be fair to state that based on the current literature, ultrasound does not replace experience and knowledge of relevant anatomy, especially for visualization of deep structures. In certain scenarios, ultrasound may not offer additional value and substantial amount of time may be spent trying to find relevant structures. In other cases, it may provide a false sense of security, especially to an inexperienced operator. More studies are needed to define the role of ultrasound for the performance of deep peripheral nerve blocks and validate its benefits.

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Review Article

The Psoas Compartment Block for Hip Surgery: The Past, Present, and Future

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A posterior lumbar plexus block or psoas compartment block (PCB) is an effective locoregional anesthetic technique for analgesia and anesthesia of the entire lower extremity including the hip. Since the first description in the early seventies, this technique has been modified based on advanced knowledge of the anatomical localization of the lumbar plexus and the improvement of technical equipment. This paper provides an overview of the history, clinical efficacy, and risk profile of the PCB focused on hip surgery. Current status and future expectations are discussed.

1. History

Although the principles of locoregional anesthesia were invented much earlier, it was Koller, an Austrian intern in ophthalmology, who introduced the first clinical locoregional anesthetic technique in 1884, using topical cocaine to the cornea for a glaucoma operation [1]. Five years later, the German surgeon Bier published [2], and his name became inseparably connected to the introduction of the first central neuraxis block, the spinal anesthesia. It subsequently took more than seven decades before the first description of a proximal lower extremity peripheral nerve block appeared. Winnie described an anterior approach for blocking the lumbar plexus [3]. The needle insertion point was just lateral to the femoral artery and 1 cm below the inguinal ligament. After paresthesia was elicited, more than 20 mL of local anesthetic was injected. Digital pressure below the needle insertion point was used to promote cephalad movement of the local anesthetic (within the femoral nerve sheath) purported to block the *three* main nerves of the lower extremity (femoral nerve, obturator nerve, and lateral femoral cutaneous nerve). In the same paper, the author briefly mentioned the possibility of a *posterior* lumbar paravertebral approach and presented this technique in a separate report one year later [4]. In 1976, Chayen et al. described a posterior approach of the lumbar plexus block named the "*Psoas Compartment Block*" (PCB) [5]. The anatomical compartment, formed by the psoas major muscle and its fascia on the anterior side, the transverse processes on the lateral side and the quadratus lumborum muscle on the posterior side, confines a space in which the lumbar plexus is located. Several years later, studies failed to confirm the existence of this so-called "psoas compartment" [6, 7]. Kirchmair et al. showed in a cadaver study that the lumbar plexus was situated *within* the psoas major muscle in the vast majority of specimens, and not *between* muscle and bony structures [7]. The last 4 decades, different approaches of the PCB have been proposed (Table 1). In 1989, Parkinson et al. described an L3 approach of the PCB (Dekrey's approach) [8] whereas Hanna et al. described an L2-L3 interspace approach of the PCB in 1993 [9]. Capdevila et al. modified the Winnie (L4) approach by a more medial needle insertion point compared to the Winnie approach [10]. Pandin in 2002 modified the Chayen approach with a more medial needle insertion point [11]. There were no significant differences in clinical efficacy between different approaches, but undesired side effects or even serious complications were described more often in the L3 approach and the approaches with a

Table 1: Approaches of the lumbar plexus through the history.

Year	Author	Landmarks	Remarks
1974	Winnie	L4-L5; intersection line parallel spine through posterior superior iliac spine and intercristal line	Too lateral
1976	Chayen	L4-L5; 5 cm lateral and 3 cm caudal from spinous process L4	Too lateral
1989	Parkinson	L3; 3-4 cm lateral	L3 approach enhances the risk of renal puncture
1993	Hanna	L2-L3; 3–5 cm lateral	
2002	Capdevila	L4-L5; junction of lateral one third and medial two thirds of the line L4 and the line passes through posterior superior iliac spine (Modified Winnie approach)	Too lateral
2002	Pandin	L4-L5, 3 cm below intercristal line and 3 cm lateral to the interspinous line (Modified Chayen approach)	Too medial enhancing the risk of epidural spread of local anesthetics

more medial needle insertion point [8, 10, 12–15]. Recently, Heller et al. showed in a cadaver study that except for the Pandin approach, other approaches were too lateral [16].

Parallel with the development of different approaches of the PCB, techniques to locate the lumbar plexus were also evolving. In 1974, Chayen et al. introduced the "loss of resistance" technique with a 20 ml syringe containing air [5]. In recent decades, nerve stimulation using a low-intensity current has become a common practice for locating the lumbar plexus [10–12, 17]. Furthermore, the use of ultrasound guidance has added value to the localization of the lumbar plexus [18–21]. Karmakar et al. described that parts of the lumbar plexus can be identified through the acoustic window of a longitudinal sonogram of the lumbar paravertebral region (Figure 1) [20]. Injected local anesthetics through a needle positioned close to the lumbar plexus could be followed under real-time ultrasound guidance producing an ipsilateral lumbar plexus block. Marhofer et al. described that at the L3–L5 level, the lumbar plexus, although deep, can be visualized using ultrasound [18]. However, the authors suggested the use of nerve stimulation in addition to ultrasound imaging to confirm the correct needle placement and recommended this combined technique as standard practice when performing a lumbar plexus block. Kirchmair et al. concluded that the efficacy of a PCB might be increased by ultasound guidance and that complications such as renal injury, that may occur during blind approaches, should be avoided by this technique [21].

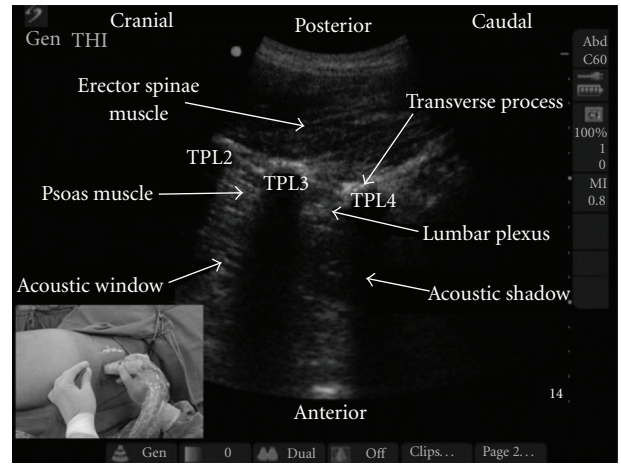

Figure 1: Longitudinal sonogram of the lumbar paravertebral region showing an optimal scan for lumbar plexus block. Picture in the inset shows the orientation of the ultrasound transducer and the direction in which the needle is introduced (long axis) during an ultrasound-guided lumbar plexus block. TP: transverse process. (picture used with permission from [20].

2. Clinical Efficacy

Looking at the clinical efficacy, there is substantial evidence that a posterior approach of the lumbar plexus block has significant advantages compared to the anterior approach (femoral nerve block or "3-in-1 block") of the lumbar plexus block. As the posterior approach is more effective in blocking the obturator nerve (the articular branches innervate the anteromedial capsule of the hip joint), the only real "3-in-1" block actually is the PCB [8, 22–24]. Biboulet et al. described lower visual analogue scale (VAS) scores during the first 4 h postoperative using a PCB compared with a femoral nerve block in patients undergoing a total hip arthroplasty [25]. To provide anesthesia and analgesia to the *entire* leg, a combination of a PCB and a "high" *sciatic nerve block* is necessary [5]. The addition of this sciatic nerve block to a PCB should also be valuable for hip surgery, because the posteromedial section of the hip joint capsule is partially innervated by branches of the sciatic nerve [26]. A PCB, with or without a sciatic nerve block, is of great value for postoperative *analgesia* after hip surgery. Different studies described a reduction of pain scores and a reduced consumption of rescue opioids after hip surgery due to the addition of a PCB [17, 25, 27, 28]. Stevens et al. described significant lower pain scores at $T = 6$ hours after total hip arthroplasty in patients receiving a single-injection posterior lumbar plexus block combined with general anesthesia, compared with patients who did not receive a PCB (VAS 1.4 ± 1.3 versus 2.4 ± 1.4, $P = .007$) [17]. Cumulative postoperative morphine consumption at $T = 6$ hours remained significantly lower as well

Table 2: Undesirable side effects and complications of a PCB.

Epidural spread
Total spinal anesthesia
Mild hypotension
Plexopathy/Neuropathy
Systemic toxicity (central nervous system/cardiac)
Intraperitoneal injection
Retroperitoneal haematoma
Renal puncture

(5.6 ± 4.7 mg versus 12.6 ± 7.5 mg, $P < .0001$) [17]. Biboulet et al. described the analgesic potency of a single-injection PCB compared with patient controlled analgesia (PCA) with intravenous morphine and a femoral nerve block (FNB) in patients undergoing a total hip arthroplasty [25]. At $T = 4$ hours after PCB, both VAS scores (1(0–2), 3(1.5–5.0), 2.5 (2–4) for, resp., PCB, FNB and PCA, data in median (IQR), $P = .001$) as well as morphine consumption (0 mg (0–6), 2 mg (0–16), 9 mg (0–18) for, respectively PCB, FNB, and PCA, data in median (IQR), $P = .002$ PCB versus PCA) were significantly lower in the PCB group [25]. In a meta-analysis, Touray et al. described that the reduction of pain of a single-injection PCB is limited to the first 8 hours after surgery [29]. This analgesic benefit may be extended beyond 8 hours by the use of a continuous infusion. Becchi et al. described the clinical efficacy of a continuous psoas compartment block after a total hip arthroplasty [27]. Low median pain scores at rest and after mobilization and less needed rescue analgesia during the whole study duration (48 hours) were described by the authors in the patients using the psoas catheter. A reduction of rescue opioids by the use of a continuous lumbar plexus block also has been described by Chelly et al. and Siddiqui et al. [30, 31]. Furthermore, Chudinov et al. described a significant reduction of pain scores during 32 hours after surgery by a continuous psoas compartment block in patients undergoing repair of a hip fracture [32]. Türker et al. described no significant differences in analgesic potency between a PCB and epidural analgesia for patients undergoing partial hip replacement surgery [33]. This implies a certain preference for a PCB as a postoperative analgesic strategy for hip surgery, because undesired side effects of epidural analgesia, such as urinary retention, hypotension, and pruritis, are avoided and the possibility of prolonged postoperative analgesia can be maintained [28, 34].

As sole *anaesthetic* technique for hip surgery, the PCB is likely to be insufficient. De Visme et al. described a substantial need for supplement opioids and sedatives for 27% of the patients undergoing hip fracture repair under PCB with an additional sacral plexus block [35]. Buckenmaier III et al. concluded that a lumbar plexus block with perineural catheter and sciatic nerve block with perioperative sedation is an effective alternative to general anesthesia for total hip arthroplasty [36]. However, the concentrations of propofol (50–200 mcg/kg/min) and fentanyl (327 ± 102 mcg) provided by the authors resemble general anesthesia instead of conscious sedation. A possible explanation of the insufficiency of the PCB as a sole anesthetic technique for hip surgery could be the variable innervation of the surgical site from the T12 and L1 dermatome, as described by Mannion et al. [28]. In a clinical efficacy study of PCB for prosthetic hip surgery, De Leeuw et al. concluded that a paravertebral block of L1 should be considered as additional technique to overcome the lack of anesthesia in dermatome L1 by a PCB [37].

3. Undesirable Side Effects and Complications

As with any other locoregional technique, a PCB has undesirable side effects. Seriously, even life threatening complications have been described in different case reports. In Table 2, undesirable side effects and complications of a PCB are pointed out [28].

The most frequently occurring side effect is the epidural diffusion of the injected local anesthetics. Reported incidences vary between 3 and 27% [25, 38]. A medial needle insertion point and a more cephalad lumbar approach (L2-L3) of the PCB seemed to be prognostic risk factors for this undesirable side effect [13, 14]. However, in a more recent publication, Mannion described that a large injected volume is probably the most important prognostic factor for bilateral spread, and not the approach of the PCB [28]. Another important factor which could influence the occurrence of epidural diffusion of local anesthetics after a PCB is the pressure during injection. Gadsden et al. concluded that injection of local anesthetic with high injection pressure (>20 psi) during lumbar plexus block commonly results in unwanted bilateral blockade and is associated with high risk of neuraxial blockade [39]. Retroperitoneal hematoma were described after either the performance of a single-injection PCB or the removal of a perineural psoas catheter [40, 41]. The majority of the hemorrhagic complications of a PCB were described in patients receiving anticoagulant or antiplatelet drugs, used for therapeutic indications or thromboprophylaxis [42]. Based on recent publications of large series of patients undergoing uneventful peripheral nerve blockade in combination with antithrombotic therapy as well as the case reports of hemorrhagic complications after peripheral nerve blocks, the American Society of Regional Anesthesia (ASRA) recommended that guidelines for anticoagulant and neuraxial blocks be applied for "deep" peripheral nerve blocks, like a PCB, including placement and removal of perineural catheters [42]. However, Chelly and Schilling described large series of uneventful continuous and single-injection lumbar plexus blocks, whereby catheters had been removed in anticoagulated patients without hemorrhagic complications, and questioned the evidence of the abovementioned ASRA recommendation [43, 44]. Renal subcapsular hematoma after an L3-PCB has been described by Aida et al. [15]. The inferior renal pole is close to the L3 level, therefore an L4 approach should be safer [13]. A feared complication of PCB is the inadvertent administration of local anesthetics in the intrathecal space leading to a total spinal anaesthesia. However, patients described in case studies by Pousman et al. and Gentili et al., where spinal anesthesia was reported to

occur, were resuscitated without sequelae [45, 46]. The most serious complication of a PCB is the inadvertent intravascular injection of cardiotoxic local anaesthetics, rapidly leading to acute toxic reactions like seizures, cardiac arrest and eventually death [47]. Although false negative results are possible, the best way to prevent these acute toxic reactions remains aspiration prior injection, a negative test dose and a slow fractionated injection [13]. Treatment of a systemic cardiotoxic reaction consists of cardiopulmonary resuscitation and the infusion of intralipid [48]. A relatively highly serious complication rate of the PCB, compared to other lower limb peripheral nerve blocks, was described by Auroy et al. in a major French study [49]. Five serious complications after 394 PCB compared to none after 10309 femoral nerve blocks resulted in a substantial concern about this particular block [49]. These issues, possibly combined with more familiarity with alternative techniques such as neuraxial blocks, could be the reason for reluctance to the routine use of the PCB, leading to an underutilization of the PCB.

4. Conclusions

In conclusion, PCB is proved to be effective as a locoregional technique for *analgesia* after hip surgery. Analgesic potency of a PCB is similar to epidural analgesia for hip surgery without the undesirable side effects. Further research is required to make PCB technique more optimal for anesthesia. In addition, the risk profile of the PCB should be evaluated more extensively. Until now, only one major study concerning complications of locoregional anesthetic techniques and some case reports concluded that a PCB has a relatively high risk profile. More elaborate (inter-)national PCB prospective complication registrations is therefore warranted. To reduce the risk of life-threatening complications, it is important to prevent the injection of large volumes of potentially cardiotoxic local anesthetics into the intrathecal space or into a blood vessel. Ultrasound imaging techniques could be helpful to optimize the needle position of this deep peripheral nerve block. To prevent a bilateral spread of local anesthetics after a PCB (the most frequent adverse effect), dose reduction (and therefore volume reduction), studies would be of great value. With regard to the risks and benefits of the PCB, further studies are required to evaluate the clinical efficacy of PCB in hip surgery and analyze the risk profile of this technique.

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