Review Article

Local Anaesthetic Infiltration in Joint Replacement Surgery: What Is Its Role in Enhanced Recovery?

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The last 10 years has seen the increased use of enhanced recovery pathways across several surgical specialities. A prerequisite of enhanced recovery is the ability to mobilise patients early. This is dependent upon good postoperative pain control. A number of different techniques have been employed in joint replacement surgery to address this issue. This paper focuses upon the current evidence for local infiltration anaesthesia.

1. Introduction

The last decade has seen the growing use of enhanced recovery pathways (also known as “fast-track,” “rapid recovery,” and “accelerated rehabilitation”) across several surgical specialities including orthopaedics. Such techniques, originally described in colorectal surgery, have been shown to both improve patient care and reduce length of stay in general populations undergoing surgery [1–4]. This has huge implications in terms of health care savings.

These pathways focus on optimising every aspect of the patient's journey, promoting the patient as an active participant in their own recovery process and rehabilitation. They involve a multidisciplinary, evidence-based approach and focus on patient education in addition to surgical and anaesthetic techniques [1]. At the core of enhanced recovery is the ability to mobilise patients early. Effective perioperative analgesia is thus an essential component of any enhanced recovery pathway and starts with the choice of anaesthetic. There has been a shift towards the use of regional anaesthesia over general anaesthesia in joint replacement surgery [5]. Whilst general anaesthesia has a lower incidence of hypotension postoperatively, regional anaesthesia is not only associated with reduced nausea postoperatively but may also have the additional benefit of a reduced risk of deep vein thrombosis, pulmonary embolus, myocardial infarction,

pneumonia, and delirium [6–10]. However, this remains an area in which further research is needed. Postoperatively the use of standardised analgesic ladders has been seen to be effective in reducing excessive or inappropriate opiate consumption again aiding early mobilisation.

In order to optimise pain control in the early postoperative period, a number of adjuncts have been tried. These include peripheral nerve blocks (e.g., femoral, combined femoral and sciatic, and lumbar plexus blocks) and local anaesthetic infiltration to the joint or the wound. These techniques may involve single administration of local anaesthetic (possibly combined with other analgesic agents) or continuous infusion/bolus for 24 to 48 hours postoperatively. Variable results have been reported [5, 11–14]. For the purpose of this paper we intend to focus solely on the role of local anaesthetic infiltration in hip and knee replacement surgery. Following a current literature search of the Pubmed and Cochrane databases using the search terms “hip replacement,” “hip arthroplasty,” “knee replacement,” “knee arthroplasty,” and “local anaesthetic,” English language randomised controlled trials were identified from the literature (Tables 1 and 2).

The drive to develop safe and effective opioid-sparing analgesic regimens whilst avoiding the potential complications of peripheral nerve blocks [33] has resulted in increased focus upon the role of local anaesthetic infiltration in joint

TABLE 1: Overview of the literature summarising study design.

Author	Study design	<i>n</i>	Joint replacement	Anaesthesia	Analgesia: study group	Control
Vendittoli et al. [14]	RCT	42	Knee	Spinal	LIA + PCA (275 mg ropivacaine, 30 mg ketorolac, adrenaline) plus 150 mg ropivacaine at 24 hrs	PCA
Kerr and Kohan [15]	Case series	325	Hip and Knee	Majority Spinal	LIA (max 300 mg ropivacaine, 30 mg ketorolac, adrenaline) plus reinjection at 15–20 hrs	N/A
Andersen et al. [16]	RCT	40	Hip	Spinal	LIA + PCA (300 mg ropivacaine, 30 mg ketorolac, adrenaline) plus reinjection next morning	PCA
Busch et al. [17]	RCT	64	Knee	General or regional	LIA + PCA (400 mg ropivacaine, 30 mg ketorolac, 5 mg epimorphine, adrenaline)	PCA
Essving et al. [18]	RCT	48	Knee	General	LIA + PCA (400 mg ropivacaine, 30 mg ketorolac, adrenaline) plus reinjection at 21 hrs	PCA
Gómez-Cardero and Rodríguez-Merchán [19]	RCT	50	Knee	Spinal	LIA (continuous intra-articular infusion 300 mls of 0.2% ropivacaine at 5 ml/hr until empty)	Saline infusion
Krenzel et al. [20]	RCT	66	Knee	Spinal	CFNB + posterior capsule injection + PCA (20 ml 0.2% ropivacaine)	CFNB + PCA
Andersen et al. [21]	RCT	12	Knee (bilateral)	Spinal	LIA + PCA (340 mg ropivacaine, adrenaline) plus reinjection at 8 and 24 hrs	PCA
Zhang et al. [22]	RCT	80	Knee	General	LIA (300 mg ropivacaine, 30 mg ketorolac, adrenaline) plus 48 hrs continuous infusion (ropivacaine, ketorolac)	Control 1: LIA (300 mg ropivacaine, 30 mg ketorolac, adrenaline) plus saline infusion Control 2: saline infusion
Chen et al. [23]	RCT	92	Hip	General	LIA + PCA (24 mls 0.5% bupivacaine) plus continuous infusion 2 ml/hr	PCA
Andersen et al. [24]	RCT	16	Knee (bilateral)	Spinal	LIA + PCA (300 mg ropivacaine, adrenaline) plus reinjection 24 hrs	PCA
Andersen et al. [25]	RCT	32	Knee	Spinal	LIA (170 mls 0.2% ropivacaine and adrenaline) + intra- and extra-articular injection ropivacaine and adrenaline at 24 hrs	LIA (170 mls 0.2% ropivacaine and adrenaline) + intra-articular injection ropivacaine and adrenaline only at 24 hrs
Spreng et al. [26]	RCT	102	Knee	Spinal	LIA + PCA (150 mg ropivacaine and adrenaline), subgroup with 30 mg ketorolac and 5 mg morphine Reinjection 24 hrs	Epidural + PCA
Andersen et al. [27]	RCT	80	Hip	Spinal	LIA (200 mg ropivacaine, 30 mg ketorolac, adrenaline) plus intra-articular injection at 8 hrs	Epidural

TABLE 1: Continued.

Author	Study design	<i>n</i>	Joint replacement	Anaesthesia	Analgesia: study group	Control
Andersen et al. [28]	RCT	40	Knee	Spinal	LIA + PCA (300 mg ropivacaine, 30 mg ketorolac, adrenaline) plus continuous intra-articular infusion (ropivacaine, ketorolac)	Epidural + PCA
Thorsell et al. [29]	RCT	85	Knee	Spinal or epidural	LIA (300 mg ropivacaine, 30 mg ketorolac, adrenaline) plus further injection day 1 (bupivacaine-adrenaline)	Epidural
Toftdahl et al. [30]	RCT	80	Knee	Spinal	LIA (300 mg ropivacaine, 30 mg ketorolac, adrenaline) plus intra-articular injection at 10 pm and 10 am	CFNB
Carli et al. [31]	RCT	40	Knee	Spinal	LIA + PCA (300 mg ropivacaine, 45 mg ketorolac, adrenaline) plus intra-articular injection at 24 hrs	CFNB + PCA
Affas et al. [32]	RCT	40	Knee	Spinal	LIA + PCA (300 mg ropivacaine, 30 mg ketorolac, adrenaline) plus intra-articular infusion at 24 hrs	FNB + PCA

LIA: local infiltration analgesia, RCT: randomized controlled trial, PCA: patient controlled analgesia, (C)FNB: (continuous) femoral nerve block, LOS: length of stay.

replacement surgery. This is a technique that has been developed in part by Kohan and Kerr in Sydney, Australia, and involves the infiltration of the surgical site with a high volume of a long-acting local anaesthetic agent (+/- analgesic agents) with adrenaline [15, 34]. Theoretically, it seems logical to block the pain signal at the site of nociceptive stimulus, that is, the surgical site [35]. This technique has the additional benefits of being simple with a low side effect profile.

There is a growing body of evidence to support the use of local infiltration techniques. Whilst early reports often consisted of case series, the last five years has seen a growing number of randomised controlled trials [14, 16–24, 36]. The majority advocate the use of local infiltration in knee replacement surgery with more limited evidence supporting its use during hip replacement. Most studies observed a reduction in early postoperative pain and opiate use, along with a tendency towards reduced length of stay, without an increased risk of complications. Most studies use a multimodal infiltration approach in which the use of a high volume of long-acting local anaesthetic agent, typically ropivacaine (longer acting than bupivacaine with less cardiac and central nervous system toxicity) is combined with analgesics (NSAIDs and/or opiates) and adrenaline. The use of adrenaline is thought to improve the efficacy of the local anaesthetic and reduces the toxicity, by helping to keep it localised to the injection site. The addition of opiates targets the opioid receptors activated as a result of the surgical trauma [37], and nonsteroidal anti-inflammatory drugs (NSAIDs) also help to reduce local production of inflammatory mediators both acting as adjuncts to the local anaesthetic.

Busch et al. [17] performed a prospective, blinded, randomized, controlled trial on 64 patients undergoing unilateral knee replacement surgery. Patients were randomized to

receive either a multimodal infiltration consisting of ropivacaine, ketorolac, epimorphine, and adrenaline or no injection. In the study group they observed a significant reduction in patient controlled analgesic use over the first 24 hours and improved patient satisfaction. However, no difference in range of motion or length of stay was observed. No adverse events were observed in the study group.

Anderson et al. [16] undertook a prospective randomised, double-blind, controlled trial to investigate the effect of local infiltration followed by continuous intra-articular infusion for 24 hours postoperatively in 37 patients undergoing hip replacement surgery. The study group received local infiltration of ropivacaine, ketorolac, and adrenaline followed by an intra-articular infusion of the same three drugs for 24 hours postoperatively. The control group received saline solution in equal volumes to the study group. The study group reported less pain for the first 2 weeks postoperatively and reduced breakthrough analgesic requirements. This was associated with significantly less joint stiffness and better physical function, but whilst there was a trend towards earlier discharge in the study group, this was not statistically significant. Again, no adverse events were reported in the study group.

However, there are several drawbacks to both these studies and others looking at the role of local anaesthetic infiltration in joint replacement surgery. The sample sizes involved are relatively small, and power analysis was seldom performed. Thus they should be interpreted with caution (Tables 1 and 2). This is especially the case in the nonblinded studies where observational bias may play a role. It also makes drawing negative conclusions difficult, such as “no adverse events,” “no reduction in length of stay,” or “no increased risk of infection” as large study groups are often

TABLE 2: Overview of the literature summarising study outcome measures, results, and conclusions.

Author	Outcome measures	Results	Authors' conclusions
Vendittoli et al. [14]	Morphine consumption, Pain control, Medication-related side effects	Reduced morphine consumption, pain scores, and nausea with LIA	Multimodal approach offers improved pain control with minimal side effects
Kerr and Kohan [15]	Pain scores, Time to mobilisation, LOS	Satisfactory pain control, most walk 5-6 hrs, 71% single overnight stay	Simple, safe, and effective for pain management in hip and knee surgery
Andersen et al. [16]	Opiate consumption, Pain control, Medication-related side effects	Reduced pain (up to 2 weeks) and opiate consumption with LIA, No difference in LOS	Reduces pain and the requirements for analgesics after hip replacement
Busch et al. [17]	PCA consumption, Pain control	Reduced PCA requirements first 24 hrs and pain scores 4 hrs, No difference in LOS	Reduces requirements for PCA and improves satisfaction
Essving et al. [18]	Analgesic consumption, Pain control, LOS	Reduced analgesic consumption and pain scores, Shorter time to home readiness but no difference in LOS	Excellent pain relief, lower morphine consumption and shorter time to home readiness
Gómez-Cardero and Rodríguez-Merchán [19]	Pain scores, Opioid use, Joint function, LOS	Lower pain scores and opioid use first 72 hrs No difference in ROM, Reduced LOS	Effective in treating pain and reducing opioid use and also reduces mean LOS without increased risk of complications
Krenzel et al. [20]	Pain scores, Opioid use	Reduced PCA use at first 12 hrs only	Posterior capsular injection did not improve pain or accelerate recovery after 12 hrs in patients receiving a CFNB
Andersen et al. [21]	Pain in each leg	Significant reduction in pain up to 32 hrs	Effective, and due to simplicity, may be preferable to other analgesic techniques
Zhang et al. [22]	Pain scores, Opioid use, Joint function	Lower pain scores (8–48 hrs) and opiate consumption (24–48 hrs) and improved flexion (days 7 and 90) with LIA and continuous infusion	Continuous LIA provides prolonged superior analgesia. It is associated with more favourable functional recovery
Chen et al. [23]	Pain scores	Longer time to first narcotic rescue, Lower pain scores at first 2 hrs only, No difference in LOS	Continuous intra-articular infusion of bupivacaine does not provide sustained pain relief
Andersen et al. [24]	Pain scores	Reduced pain at first 6 hrs but not at 24 hrs	Effective in early postoperative pain relief but no improved analgesia with 24 hr bolus
Andersen et al. [25]	Pain scores	No significant difference between groups	Optimal site of administration of LA cannot be determined from this study
Spreng et al. [26]	Pain scores, Rehabilitation, Discharge readiness	Lower pain scores initially in the epidural groups. Both LIA groups mobilised faster and were ready for discharge earlier	LIA is effective when compared to epidural analgesia. Ketorolac and morphine are more effective when given locally
Andersen et al. [27]	Pain scores, Time to mobilisation, LOS	LIA group observed reduced pain scores at 20–96 hrs, narcotic consumption, and LOS with increased early mobilisation	LIA combined with intra-articular injection can be recommended in THA

TABLE 2: Continued.

Author	Outcome measures	Results	Authors' conclusions
Andersen et al. [28]	Pain scores, Medication-related side effects, LOS	Reduced morphine consumption and pain scores with LIA. No difference in LOS but ready for discharge earlier with LIA	Provides superior pain relief and reduced morphine consumption compared with continuous epidural infusion and Offers advantages in its simplicity and minimal risk of complications
Thorsell et al. [29]	Pain scores, Time to mobilisation, LOS	Lower pain scores and earlier mobilisation with LIA No difference LOS	LIA is better for postoperative pain relief after TKR then epidural
Toftdahl et al. [30]	Pain scores, Opioid consumption, Time to mobilisation, LOS	Reduced pain scores during physio and opioid consumption on day 1 only, no difference LOS	This technique provides a good quality of analgesia after TKR without increased risk
Carli et al. [31]	Opiate consumption, Functional walking capacity, Physical activity	No difference in pain scores but reduced opiate consumption with FNB. Physical activity and knee function improved at 6 weeks with FNB	FNB is associated with lower opioid consumption and a better recovery at 6 weeks
Affas et al. [32]	Pain scores, opiate consumption	No difference in pain scores or opiate consumption	Both provide good analgesia after TKR. LIA is cheaper and easier to perform

required to make such observations. In addition, the use of different multimodal anaesthetic regimens and different end points makes comparisons across studies difficult.

Thus whilst the growing body of evidence seems to support a role for the routine use of local anaesthetic agents in joint replacement surgery as part of a multimodal infiltration technique, a number of questions remain unclear.

2. Single Dose or Continuous Infusion?

Whilst Busch et al. [17] observed good outcomes using the single infiltration technique other studies have not supported this. Krenzel et al. [20] did not observe any additional benefit beyond 12 hours with a posterior capsular injection of ropivacaine during total knee arthroplasty (with CFNB) when compared with injection of saline. However, these differences may be as a result of the fact that Krenzel et al. [20] used only ropivacaine and infiltrated the posterior capsule alone. These observations may also support the important role of the other drugs used as part of the multimodal infiltration technique.

Concerns regarding the length of duration of action of the local anaesthetic agents have resulted in the use of continuous intra-articular infusions following local infiltration in hip and knee replacement surgery. The rationale being to maximise the benefit of postoperative pain relief in the early post operative period. This technique involves catheter placement by the surgeon at the end of the operation under aseptic conditions and the use of bacterial filters and closed infusion systems [18].

There are now a number of randomised controlled trials supporting the use of the high-volume infiltration combined with intra-articular infusion or further bolus dose [16, 18, 19, 21, 22]. However not all studies support the use of additional bolus doses or infusions [23, 24]. The lack of any significant benefit observed by Chen et al. [23] may be due to the use of bupivacaine rather than ropivacaine. The increased cardiac and CNS toxicity of the former means lower doses must be used. Again, it may also reflect the synergistic action of the other drugs used as part of the multimodal infiltration technique. This is an area that requires further research.

Whilst none of the studies to date are of sufficient sample size to detect a significant difference in infection rates with the use of intra-articular catheters, similar catheter techniques are employed during epidural analgesia for postoperative pain relief in other types of surgery (e.g., abdominal), and infection does not appear to be an issue.

3. What Is the Optimal Infiltration Site?

One of the next stages in the evolution of local infiltration techniques is to try and identify the optimum site of administration of the local anaesthetic. In their randomised study Andersen et al. [36] observed no difference between the use of intracapsular catheters or intra-articular catheters in total knee arthroplasty with ropivacaine infusion. In a randomised, placebo-controlled, double-blind trial investigating the role of subcutaneous wound infiltration (all patients received high volume local infiltration to the deeper layers), the same authors reported a significant reduction in both

static and dynamic pain scores at 24 hours in the group that received intraoperative subcutaneous infiltration [24]. However, bolus administration through a subcutaneously placed catheter at 24 hours was ineffective. These observations support their previously published observations of a tendency (not statistically significant) towards improved pain relief with the addition of local anesthetic in the extra-articular wound space [25].

4. What Is the Most Effective Dose?

The use of ropivacaine instead of bupivacaine enables larger doses of local anaesthetic to be delivered to the joint and the surrounding tissues whilst minimising the risk of toxicity. The addition of adrenaline as part of the multimodal infiltration technique also enables higher doses of local anaesthetic to be used and may also potentiate the duration of action of the local anaesthetic by slowing its release into the vascular system. Only 2 studies were identified in which plasma ropivacaine levels were measured [14, 17]. This gave a combined total of 27 patients. Whilst this number is small, all patients remained below toxic levels.

There are no studies to date looking at the optimal doses for infiltration or infusion/bolus. In general, all of the studies identified adopted a standardised LIA regimen for all patients rather than tailoring doses to individual weights. It is possible that by matching ropivacaine dose to the individual a better response can be achieved. In addition, in the future the use of sustained-release local anaesthetics may negate the need for intra-articular catheters [38].

5. Local Infiltration versus Epidural

Continuous epidural analgesia following hip and knee arthroplasty is an effective method of providing predictable and reliable pain relief in the early postoperative period. However, it is technically demanding and time-consuming and may be associated with an array of side effects that include urinary retention, hypotension, headache, motor blockade, and nausea, all of which may result in delayed mobilisation.

The appeal of local infiltration techniques lies with the fact that they are inexpensive and relatively easy to perform, and have few side effects. Whilst we have reviewed the evidence for the use of such techniques when compared to a placebo (in which one may expect the LIA to perform better), the question remains as to how they compare to epidural infusion.

There have been several studies to date comparing the use of local infiltration techniques to epidural infusion [26–29]. All of these support the use of local infiltration showing equal or better pain relief, earlier mobilisation, and reduced length of stay when compared to epidural infusion. However, as there is no clearly defined gold standard epidural regimen, these results should be interpreted with caution. This is a fact acknowledged by Andersen et al. in their randomised controlled trial of patients undergoing total knee arthroplasty [28].

6. Local Infiltration versus Peripheral Nerve Block

In many institutions femoral nerve block forms part of the standard postoperative pain relief protocols following total knee arthroplasty [30, 39]. So how does local infiltration compare to this? There is little published in the literature comparing these two analgesic modalities. Whilst Toftdahl et al. [30] observed lower pain scores and opioid consumption with earlier mobilisation with intra-articular infiltration in their randomized trial, Carli et al. [31] observed the opposite, concluding that femoral nerve block was the most effective modality. In their randomized trial, Affas et al. [32] observed no significant difference in either pain intensity in the first 24 hours, or opiate consumption, between local infiltration anaesthesia and continuous femoral block. They postulated, however, that LIA may be considered to be superior to femoral nerve block due to the fact that it is both cheaper and less technically demanding. However, it should be noted that in their study Toftdahl et al. [30] observed a couple of adverse events in the LIA group, again highlighting that further research is needed in this area. Also, as with the studies on epidural anaesthesia what constitutes a femoral nerve block varies between studies making comparisons difficult.

7. Summary

There is a growing body of evidence to support the use of local infiltration anaesthesia as part of enhanced recovery pathways in patients undergoing knee replacement surgery. The evidence for its role in hip replacement surgery is less compelling. Despite the growing body of literature, there remain many unanswered questions. These observations are also supported by the recent review by Kehlet and Andersen [40] which approaches the same subject from a different perspective.

Different patients have different responses to analgesia due to their preoperative response to pain [41]. This can be predicted by using preoperative pain tests. The solution may be to use these tests to customise the analgesia for each patient and so achieve enhanced recovery. The goal should be to use the minimum dose for every patient (based on both weight and pain response). This is the area further research needs to focus upon.

Future research should also focus upon standardisation of outcome measures so that different analgesic approaches can be more easily compared. Cost analysis should also be looked at.

References

- [1] H. Kehlet and D. W. Wilmore, "Evidence-based surgical care and the evolution of fast-track surgery," *Annals of Surgery*, vol. 248, no. 2, pp. 189–198, 2008.
- [2] H. Husted and G. Holm, "Fast track in total hip and knee arthroplasty—experiences from Hvidovre University Hospital, Denmark," *Injury*, vol. 37, no. 5, pp. S31–S35, 2006.

- [3] S. O'Brien, L. Ogonda, S. J. Dennison et al., "Day two post operative "fast-track" discharge following primary total hip replacement," *Journal of Orthopaedic Nursing*, vol. 9, no. 3, pp. 140–145, 2005.
- [4] L. Basse, D. H. Jakobsen, P. Billesbølle, M. Werner, and H. Kehlet, "A clinical pathway to accelerate recovery after colonic resection," *Annals of Surgery*, vol. 232, no. 1, pp. 51–57, 2000.
- [5] A. V. Maheshwari, Y. C. Blum, L. Shekhar, A. S. Ranawat, and C. S. Ranawat, "Multimodal pain management after total hip and knee arthroplasty at the ranawat orthopaedic center," *Clinical Orthopaedics and Related Research*, vol. 467, no. 6, pp. 1418–1423, 2009.
- [6] A. Rodgers, N. Walker, S. Schug et al., "Reduction of post-operative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials," *British Medical Journal*, vol. 321, no. 7275, pp. 1493–1497, 2000.
- [7] S. C. Urwin, M. J. Parker, and R. Griffiths, "General versus regional anaesthesia for hip fracture surgery: a meta-analysis of randomized trials," *British Journal of Anaesthesia*, vol. 84, no. 4, pp. 450–455, 2000.
- [8] L. S. Rasmussen, T. Johnson, H. M. Kuipers et al., "Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients," *Acta Anaesthesiologica Scandinavica*, vol. 47, no. 3, pp. 260–266, 2003.
- [9] M. J. Parker, H. H. Handoll, and R. Griffiths, "Anaesthesia for hip fracture surgery in adults," *Cochrane Database of Systematic Reviews*, no. 4, article CD000521, 2004.
- [10] T. J. Luger, C. Kammerlander, M. Gosch et al., "Neuroaxial versus general anaesthesia in geriatric patients for hip fracture surgery: does it matter?" *Osteoporosis International*, vol. 21, no. 4, pp. S555–S572, 2010.
- [11] J. E. Paul, A. Arya, L. Hurlburt et al., "Femoral nerve block improves analgesia outcomes after total knee arthroplasty: a meta-analysis of randomized controlled trials," *Anesthesiology*, vol. 113, no. 5, pp. 1144–1162, 2010.
- [12] E. R. Bogoch, M. Henke, T. Mackenzie, E. Olschewski, and N. N. Mahomed, "Lumbar paravertebral nerve block in the management of pain after total hip and knee arthroplasty: a randomized controlled clinical trial," *Journal of Arthroplasty*, vol. 17, no. 4, pp. 398–401, 2002.
- [13] B. Ben-David, K. Schmalenberger, and J. E. Chelly, "Analgesia after total knee arthroplasty: is continuous sciatic blockade needed in addition to continuous, femoral blockade?" *Anesthesia and Analgesia*, vol. 98, no. 3, pp. 747–749, 2004.
- [14] P. A. Vendittoli, P. Makinen, B. Drolet et al., "A multimodal analgesia protocol for total knee arthroplasty: a randomized, controlled study," *Journal of Bone and Joint Surgery A*, vol. 88, no. 2, pp. 282–289, 2006.
- [15] D. R. Kerr and L. Kohan, "Local infiltration analgesia: a technique for the control of acute postoperative pain following knee and hip surgery—A case study of 325 patients," *Acta Orthopaedica*, vol. 79, no. 2, pp. 174–183, 2008.
- [16] L. J. Anderson, T. Poulsen, B. Krogh, and T. Nielsen, "Post-operative analgesia in total hip arthroplasty: a randomised double-blinded, placebo-controlled study on perioperative and postoperative ropivacaine, ketorolac, and adrenaline wound infiltration," *Acta Orthopaedica*, vol. 78, pp. 187–192, 2007.
- [17] C. A. Busch, B. J. Shore, R. Bhandari et al., "Efficacy of periarticular multimodal drug injection in total knee arthroplasty: a randomized trial," *Journal of Bone and Joint Surgery A*, vol. 88, no. 5, pp. 959–963, 2006.
- [18] P. Essving, K. Axelsson, J. Kjellberg, O. Wallgren, A. Gupta, and A. Lundin, "Reduced morphineconsumption and pain intensity with local infiltration analgesia (LIA) following total knee arthroplasty: a randomized double-blind study involving 48 patients," *Acta Orthopaedica*, vol. 81, no. 3, pp. 354–360, 2010.
- [19] P. Gómez-Cardero and E. C. Rodríguez-Merchán, "Postoperative analgesia in TKA: ropivacaine continuous intraarticular infusion," *Clinical Orthopaedics and Related Research*, vol. 468, no. 5, pp. 1242–1247, 2010.
- [20] B. A. Krenzel, C. Cook, G. N. Martin, T. P. Vail, D. E. Attarian, and M. P. Bolognesi, "Posterior capsular injections of ropivacaine during total knee arthroplasty: a randomized, double-blind, placebo-controlled study," *Journal of Arthroplasty*, vol. 24, no. 6, pp. 138–143, 2009.
- [21] L. O. Andersen, H. Husted, K. S. Otte, B. B. Kristensen, and H. Kehlet, "High-volume infiltration analgesia in total knee arthroplasty: a randomized, double-blind, placebo-controlled trial," *Acta Anaesthesiologica Scandinavica*, vol. 52, no. 10, pp. 1331–1335, 2008.
- [22] S. Zhang, F. Wang, Z. D. Lu, Y. P. Li, L. Zhang, and Q. H. Jin, "Effect of single-injection versus continuous local infiltration analgesia after total knee arthroplasty: a randomized, double-blind, placebocontrolled study," *Journal of International Medical Research*, vol. 39, no. 4, pp. 1369–1380, 2011.
- [23] D. W. Chen, P. H. Hsieh, K. C. Huang, C. C. Hu, Y. H. Chang, and M. S. Lee, "Continuous intra-articular infusion of bupivacaine for post-operative pain relief after total hip arthroplasty: a randomized, placebo-controlled, double-blind study," *European Journal of Pain*, vol. 14, no. 5, pp. 529–534, 2010.
- [24] L. O. Andersen, H. Husted, B. B. Kristensen, K. S. Otte, L. Gaarn-Larsen, and H. Kehlet, "Analgesic efficacy of subcutaneous local anaesthetic wound infiltration in bilateral knee arthroplasty: a randomised, placebo-controlled, double-blind trial," *Acta Anaesthesiologica Scandinavica*, vol. 54, no. 5, pp. 543–548, 2010.
- [25] L. O. Andersen, B. B. Kristensen, H. Husted, K. S. Otte, and H. Kehlet, "Local anesthetics after total knee arthroplasty: intraarticular or extraarticular administration? A randomized, double-blind, placebo-controlled study," *Acta Orthopaedica*, vol. 79, no. 6, pp. 800–805, 2008.
- [26] U. J. Spreng, V. Dahl, A. Hjal, M. W. Fagerland, and J. Ræder, "High-volume local infiltration analgesia combined with intravenous or local ketorolac and morphine compared with epidural analgesia after total knee arthroplasty," *British Journal of Anaesthesia*, vol. 105, no. 5, pp. 675–682, 2010.
- [27] K. V. Andersen, M. Pfeiffer-Jensen, V. Haraldsted, and K. Søballe, "Reduced hospital stay and narcotic consumption, and improved mobilization with local and intraarticular infiltration after hip arthroplasty: a randomized clinical trial of an intraarticular technique versus epidural infusion in 80 patients," *Acta Orthopaedica*, vol. 78, no. 2, pp. 180–186, 2007.
- [28] K. V. Andersen, M. Bak, B. V. Christensen, J. Harazuk, N. A. Pedersen, and K. Søballe, "A randomized, controlled trial comparing local infiltration analgesia with epidural infusion for total knee arthroplasty," *Acta Orthopaedica*, vol. 81, no. 5, pp. 606–610, 2010.
- [29] M. Thorsell, P. Holst, H. C. Hyldahl, and L. Weidenhielm, "Pain control after total knee arthroplasty: a prospective study comparing local infiltration anesthesia and epidural anesthesia," *Orthopedics*, vol. 33, no. 2, pp. 75–80, 2010.
- [30] K. Toftdahl, L. Nikolajsen, V. Haraldsted, F. Madsen, E. K. Tønnesen, and K. Søballe, "Comparison of peri- and intra-articular analgesia with femoral nerve block after total knee arthroplasty: a randomized clinical trial," *Acta Orthopaedica*, vol. 78, no. 2, pp. 172–179, 2007.

- [31] F. Carli, A. Clemente, J. F. Asenjo et al., "Analgesia and functional outcome after total knee arthroplasty: periarticular infiltration vs continuous femoral nerve block," *British Journal of Anaesthesia*, vol. 105, no. 2, pp. 185–195, 2010.
- [32] F. Affas, E.-B. Nygrds, C.-O. Stiller, P. Wretenberg, and C. Olofsson, "Pain control after total knee arthroplasty: a randomized trial comparing local infiltration anesthesia and continuous femoral block," *Acta Orthopaedica*, vol. 82, no. 4, pp. 441–447, 2011.
- [33] S. Sharma, R. Iorio, L. M. Specht, S. Davies-Lepie, and W. L. Healy, "Complications of femoral nerve block for total knee arthroplasty," *Clinical Orthopaedics and Related Research*, vol. 468, no. 1, pp. 135–140, 2010.
- [34] T. Röstlund and H. Kehlet, "High-dose local infiltration analgesia after hip and knee replacement—What is it, why does it work, and what are the future challenges?" *Acta Orthopaedica*, vol. 78, no. 2, pp. 159–161, 2007.
- [35] H. Kehlet and S. S. Liu, "Continuous local anaesthetic wound infusion to improve post-operative outcome: back to the periphery?" *Anesthesiology*, vol. 107, pp. 369–371, 2007.
- [36] L. O. Andersen, H. Husted, B. B. Kristensen, K. S. Otte, L. Gaarn-Larsen, and H. Kehlet, "Analgesic efficacy of intracapsular and intra-articular local anaesthesia for knee arthroplasty," *Anaesthesia*, vol. 65, no. 9, pp. 904–912, 2010.
- [37] C. Stein, K. Comisel, E. Haimerl et al., "Analgesic effect of intraarticular morphine after arthroscopic knee surgery," *New England Journal of Medicine*, vol. 325, no. 16, pp. 1123–1126, 1991.
- [38] J. L. Pedersen, J. Lillesø, N. A. Hammer et al., "Bupivacaine in microcapsules prolongs analgesia after subcutaneous infiltration in humans: a dose-finding study," *Anesthesia and Analgesia*, vol. 99, no. 3, pp. 912–918, 2004.
- [39] T. Wainwright and R. Middleton, "An orthopaedic enhanced recovery pathway," *Current Anaesthesia and Critical Care*, vol. 21, no. 3, pp. 114–120, 2010.
- [40] H. Kehlet and L. O. Andersen, "Local infiltration analgesia in joint replacement: the evidence and recommendations for clinical practice," *Acta Anaesthesiologica Scandinavica*, vol. 55, no. 7, pp. 778–784, 2011.
- [41] M. U. Werner, H. N. Mjöbo, P. R. Nielsen, and Å. Rudin, "Prediction of postoperative pain: a systematic review of predictive experimental pain studies," *Anesthesiology*, vol. 112, no. 6, pp. 1494–1502, 2010.