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### Surgical site infiltration: A neuroanatomical approach



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Local anaesthetic administration into a surgical wound blocks the noxious stimuli that result from surgical insult at the site of origin. Surgical site infiltration (also known as local infiltration analgesia) is easy to perform, safe and inexpensive. In addition, it avoids motor blockade, which is particularly relevant for lower limb surgery. The best approach to surgical site infiltration includes meticulous, systematic and extensive surgical site local anaesthetic infiltration in the various tissue planes under direct visualisation before closure of the surgical wound. Local anaesthetic solutions that could be used include bupivacaine HCl, ropivacaine or liposomal bupivacaine diluted with preservative-free normal (0.9%) saline to a total volume depending on the size of the incision. Bupivacaine and ropivacaine are sometimes combined with additives, which have controversial benefits. Continuous wound infusion with preperitoneal wound catheters is an effective pain modality in abdominal surgery and can be used as an alternative for neuraxial analgesia. It is essential that surgical site infiltration is combined with other non-opioid analgesics such as paracetamol and non-steroidal anti-inflammatory drugs to attain the maximum analgesic efficacy.

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## Introduction

Local anaesthetic administration into a surgical wound (i.e. surgical site infiltration) blocks the noxious stimuli that result from surgical insult at the site of origin (i.e. blocks the peripheral receptors that play a pivotal role in the generation of pain). Reduced pain transmission at its origin should avoid peripheral and central sensitisation and limit the development of hyperalgesia, which may prevent persistent postoperative pain [1]. In addition, local anaesthetics reduce inflammatory response to surgical injury at the origin. Additionally, the systemic absorption of local anaesthetic may provide some anti-inflammatory and analgesic efficacy. Surgical site infiltration (also known as local infiltration analgesia) is easy to perform, safe and inexpensive. In addition, it avoids motor blockade, which is particularly relevant for lower limb surgery [2].

Local anaesthetics may be administered at the surgical site either as a single injection and/or as an infusion through catheters placed into the surgical wound. Further, local anaesthetic may be instilled in the cavity (e.g. intra-articular administration for joint surgery or intraperitoneal administration for abdominal surgery). Surgical site infiltration can be used as the sole anaesthetic for minor superficial surgical procedures such as hernia repair and haemorrhoidectomy surgery [3,4]. Surgical site infiltration has also been shown to improve analgesia and reduce opioid requirements in minimally invasive surgery such as laparoscopic surgery [5,6]. In recent years, it has been utilised for more extensive surgical procedures such as open abdominal surgery (e.g. colorectal surgery, abdominal hysterectomy and caesarean section surgery) and major joint arthroplasty (e.g. shoulder, hip and knee arthroplasty).

The aim of this section is to present current evidence regarding the analgesic efficacy of surgical site infiltration techniques and describe a novel approach to surgical site infiltration.

### Surgical site infiltration for abdominal surgery

The origin of pain resulting from abdominal surgery is multifactorial, including parietal pain originating from the surgical incision and visceral pain originating from the peritoneum, which is a metabolically active organ and responds to surgical insult by manifesting a local and systemic immunologic and inflammatory response [7,8]. The abdominal nerves run through the musculofascial plane, and thus, infiltration of the fascial plane is necessary [9]. Additionally, the subdermal tissue should be infiltrated to block the peripheral nerve endings. Therefore, an optimal surgical site infiltration technique for the abdominal wall would consist of the administration of local anaesthetic into the peritoneal, musculofascial, and subdermal tissue planes [10].

Surgical site infiltration performed according to the technique described above (i.e. infiltration of the peritoneal, musculofascial, and subdermal planes) has been shown to provide superior pain relief compared with bilateral transversus abdominis plane blocks in patients undergoing abdominal hysterectomy through a horizontal incision [11]. An infiltration technique for hernia surgery would involve local anaesthetic infiltration around the neck of the hernia sac (i.e. peritoneal tissue), musculofascial and subdermal layers [3]. In patients undergoing ventral hernia, in addition to the technique described above, infiltration of the local anaesthetic around the perimeter of the mesh effectively creates a field block to the entire anterior abdominal wall, which covers both the fascia closure and mesh fixation sites [12].

### Continuous wound infusion for abdominal surgery

One of the limitations of common local anaesthetics (i.e. bupivacaine and ropivacaine) is that their duration of analgesia is short, usually 12–24 h, which results in abrupt experience of pain. Several studies have reported the analgesic efficacy of surgically placed wound catheters (either preperitoneal or subfascial) in patients undergoing general surgery, gynaecological surgery, urological surgery, cardiothoracic surgery and orthopaedic surgery procedures.

A systematic review and meta-analysis of 14 randomised controlled trials (RCTs) found that continuous wound infusion of ropivacaine provides clinically meaningful reductions in opioid use and pain outcomes in a wide range of surgical procedures [13]. Another more recent systematic review and

meta-analysis showed that continuous wound infusion with preperitoneal wound catheters is an effective pain modality in abdominal surgery and can be used as an alternative for epidural analgesia [14]. Further, preperitoneal placement of wound catheters seems to be more effective than subcutaneous placement [14].

A randomised placebo-controlled trial in patients undergoing open nephrectomy compared epidural analgesia, continuous surgical site analgesia (with one catheter placed between the transversus abdominis and internal oblique muscles and the other in the subcutaneous space, and 5 mL/h of 0.2% ropivacaine infused in both catheters for 72 h), and patient-controlled analgesia (PCA) morphine [15]. Compared with the PCA control group, epidural analgesia and continuous surgical site analgesia improved postoperative analgesia and reduced postoperative morphine consumption as well as improved rehabilitation parameters and reduced the area of wound hyperalgesia and accelerated patient rehabilitation [15]. Interestingly, compared with epidural analgesia and morphine PCA, continuous surgical site analgesia was superior in the analysis of secondary outcomes with regard to reduced severity of residual pain one month after surgery and improved quality of life parameters 3 months after surgery [15].

Another recent study reported that compared with continuous preperitoneal local anaesthetic infusion, epidural analgesia provided superior pain control after colorectal surgery in the recovery room and on the day of surgery. However, the secondary endpoints of return of bowel function, length of stay and overall recovery were similar [16]. Of note, the majority of the procedures included in this study were performed using the robotic and laparoscopic approaches, in which case neither epidural analgesia nor continuous catheter techniques are necessary [2,17].

### **Intraperitoneal local anaesthetic instillation**

Instillation of local anaesthetic into the peritoneal cavity has been found to provide some pain relief after laparoscopic surgery. However, the benefits appear to be procedure specific. A systematic review reported a small effect size and large heterogeneity in laparoscopic cholecystectomy, but the efficacy in other surgical procedures was determined to be clinically significant [18]. Another systematic review in low-risk patients undergoing elective laparoscopic cholecystectomy found low-quality evidence of reduced postoperative pain [19]. The authors concluded that the clinical importance of this pain reduction is likely small [19]. Serious adverse events were rare in studies evaluating local anaesthetic intraperitoneal instillation (very low-quality evidence) [19]. Overall, the role of intraperitoneal local anaesthetic instillation in patients undergoing laparoscopic surgery remains controversial, and it is recommended only when the basic non-opioid analgesics (e.g. paracetamol and non-steroidal anti-inflammatory drugs [NSAIDs]) are contraindicated [5,6].

### **Periarticular infiltration for hip and knee arthroplasty**

With the introduction of enhanced recovery and day case surgery for hip and knee arthroplasty, neuraxial analgesia (i.e. epidural analgesia and intrathecal opioid analgesia) and peripheral nerve blocks that involve motor blockade (e.g. femoral nerve blocks and sciatic nerve blocks) are avoided because they could impair quadriceps and lower leg muscle function [20], which may delay ambulation as well as increase the potential of falls [21]. Local infiltration analgesia and periarticular infiltration analgesia (PIA) are integral components of the analgesic standard of care for patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA). The commonly used PIA technique includes systematic extensive infiltration of a low-concentration, high-volume local anaesthetic solution into the surgical site (capsule, ligaments and other soft tissues). However, there is a wide variation in the injection techniques and the solutions used (i.e. 'cocktails' – bupivacaine, ropivacaine or liposomal bupivacaine with or without one or more adjuncts).

There are several systematic reviews and meta-analysis comparing PIA with neuraxial analgesia (epidural analgesia and intrathecal morphine) and peripheral nerve blocks alone (e.g. femoral nerve block and adductor canal block) in patients undergoing THA and TKA. A systematic review of 38 RCTs

comparing PIA after primary TKA with placebo or no infiltration found that PIA reduced postoperative pain, opioid consumption, nausea and vomiting, as well as hospital length of stay [22]. Further, PIA, not intra-articular, reduced post-operative pain scores [22]. Local anaesthetic infusion through a peri-articular catheter placed extend the analgesic effects, but there are concerns of catheter-related infection [22,23]. Another systematic review of placebo-controlled randomised trials ( $n = 11$ ) in patients undergoing joint arthroplasty found that PIA reduced pain scores for 24 h and opioid consumption for 48 h [24]. A network meta-analysis concluded that there were no differences between PIA and peripheral nerve blocks with regard to analgesic efficacy or opioid consumption 24 h after THA [25]. Another systematic review found that PIA provided similar postoperative analgesic efficacy as that of a femoral nerve block after TKA [26]. However, it appears that the combination of PIA with motor-sparing nerve blocks (e.g. adductor canal block) provides the best post-operative pain relief and further reduces the opioid requirements [27,28]. Several systematic reviews and meta-analyses have assessed the benefits of PIA with liposomal bupivacaine [29–31]. However, the findings of these studies are conflicting and inconclusive.

The majority of the systematic reviews and meta-analyses have concluded that PIA is either similar or superior to other comparative analgesic techniques with regard to analgesic efficacy and/or opioid consumption as well as clinical outcomes or rates of complications. However, there is significant heterogeneity between the included studies with regard to the PIA technique and/or multimodal analgesic technique. In fact, authors of a meta-analysis concluded that low-quality evidence, small sample sizes and heterogeneity of trial designs prohibit designation of an optimal procedure-specific analgesic regimen after TKA [32,33].

### **Periarticular infiltration for shoulder surgery**

Subacromial/intra-articular local anaesthetic infiltration and catheter techniques have been studied but appear to perform only marginally better than placebo. Additionally, catheter techniques have been associated with catastrophic chondrolysis [34–36]. Thus, subacromial catheter techniques can no longer be recommended. Unlike the hip and knee arthroplasty, periarticular infiltration techniques for shoulder surgery have not been adequately studied [37]. Recently, a novel approach to periarticular infiltration technique, based on neuroanatomy, has been described for shoulder surgery [38]. Periarticular infiltration blocks the nerve supply to the synovium, capsule, articular surfaces, periosteum, ligaments, and muscles of the shoulder joint [38].

### **Basic infiltration technique**

Infiltration techniques vary from procedure to procedure, requiring knowledge of anatomy and the origin of pain from surgical procedure [39–41]. The best approach to surgical site infiltration includes meticulous, systematic and extensive surgical site local anaesthetic infiltration in various tissue planes under direct visualisation before closure of the surgical wound [41]. For example, for abdominal surgical procedures, infiltration should be performed in the peritoneal, musculofascial and subdermal tissues, while for major joint surgery, infiltration of the capsule, ligaments and other soft tissues is necessary. When direct visualisation is not possible, which is rare, the location of the needle tip may best be appreciated by the sensation of a ‘pop’ or ‘feel’ as the needle passes through the different tissue layers. Infiltration is ideally performed with a short (~2 inch) 22-gauge needle. Proper infiltration technique involves using a fanning technique (commonly referred to as a moving needle technique). Care is taken to ensure overlapping infiltration areas because of anatomic variation in nerve branching. The needle is inserted approximately 1 cm into the tissue plane (e.g. joint capsule or for abdominal surgery peritoneal, musculofascial or subdermal planes), and local anaesthetic solution is injected while slowly withdrawing the needle, which should reduce the risk of intravascular injection. Of note, when using liposomal bupivacaine, it is critical that it is injected extensively around the surgical wound because it tends to diffuse less than bupivacaine owing to its size and nature.

Typically, 1–1.5 mL of local anaesthetic solution is injected every 1–2 cm in every layer of the surgical incision. This requires the use of larger volumes of local anaesthetic solution (50–150 mL). For example, for a 10-cm abdominal incision, the total volume could be 60 mL, with 20 mL injected into the peritoneal plane, 20 mL injected in the musculofascial plane and 20 mL injected in the subdermal plane.

### **Solution for infiltration**

Local anaesthetic solutions that could be used include bupivacaine, ropivacaine, or liposomal bupivacaine. Once the maximum local anaesthetic dose has been determined typically based on patient weight (e.g. bupivacaine HCl, 150–200 mg or ropivacaine 200–400 mg or liposomal bupivacaine 266 mg), it is diluted with preservative-free normal (0.9%) saline to a total volume depending on the size of the incision. Local anaesthetic solutions are sometimes combined with additives such as epinephrine (0.5 mg), morphine (5 mg), clonidine (100 mcg), ketorolac (30 mg) and steroids (methylprednisolone 40 mg or betamethasone) presumably to improve efficacy and prolong the duration of analgesia. Liposomal bupivacaine should be combined with bupivacaine HCl in a ratio of up to but not exceeding 1 mg bupivacaine HCl to 2 mg liposomal bupivacaine, which allows for a faster onset and improved pain relief in the immediate postoperative period (i.e. post-anaesthesia care unit) [41]. Liposomal bupivacaine can be diluted to up to 0.89 mg/mL (i.e. 1:14 dilution by volume) with preservative-free normal (0.9%) sterile saline for injection. However, it must not be diluted with water or other hypotonic solutions because they cause the disruption of the DepoFoam particles. Also, liposomal bupivacaine should not be combined with lidocaine or local anaesthetics other than bupivacaine [41].

### **Local anaesthetic toxicity and other adverse effects**

Concerns with surgical site infiltration include the potential for local anaesthetic systemic toxicity [42]. The systemic absorption of local anaesthetics after local infiltration depends on the total dose and the vascularity of the surgical site (e.g. time to peak concentration is shorter for head and neck infiltration versus thigh infiltration). In addition, use of epinephrine slows the systemic absorption of bupivacaine. Overall, local anaesthetic wound infiltration generally has favourable safety profiles. In fact, several studies have reported that even with larger than recommended doses of ropivacaine (i.e. 400 mg), the maximum concentration of ropivacaine was much lower than the toxicity threshold concentration [43,44]. Similarly, the safety of liposomal bupivacaine appears to be favourable over bupivacaine [45]. Other potential concerns with surgical site infiltration include surgical site infection, delayed healing [46], chondrotoxicity [34,36], and myotoxicity. However, the clinical significance of these adverse effects is minimal [14]. In addition, local anaesthetics possess antimicrobial activity and can be considered as an adjunct to traditional antimicrobial use [47].

### **Summary**

Surgical site infiltration involves the single injection and/or infusion of a local anaesthetic near the site of surgical incision to provide targeted analgesia. Surgical site infiltration is easy to perform, safe and inexpensive. Because these techniques are performed under direct vision, they have a high success rate. Therefore, surgical site infiltration should be utilised whenever possible. However, the efficacy of surgical site infiltration for major surgical procedures has provided conflicting evidence. The reason for inconsistent results may be most often due to inadequate or improper technique (i.e. indiscriminate subcutaneous injection after closure of the wound). Attention to proper infiltration technique (i.e. infiltration into the peritoneal, musculofascial and subdermal tissue planes) is essential to attain the maximum benefits. Catheters can be placed by the surgeon directly at the site of the incision and can be left in place for days. Importantly, it is essential that surgical site infiltration is combined with other non-opioid analgesics (e.g. paracetamol and NSAIDs) to attain the maximum analgesic efficacy [48].

It is necessary to counsel patients regarding the need for non-opioid analgesics to avoid severe pain after block resolution.

### Practice points

- Surgical site infiltration involves single injection and/or infusion of a local anaesthetic near the site of surgical incision to provide targeted analgesia.
- Surgical site infiltration is easy to perform, safe and inexpensive.
- The best approach to surgical site infiltration includes meticulous, systematic and extensive surgical site local anaesthetic infiltration in various tissue planes under direct visualisation before closure of the surgical wound.
- Local anaesthetic solutions that could be used include 150–200 mg of bupivacaine HCl or 200–400 mg of ropivacaine or 266 mg of liposomal bupivacaine diluted with preservative-free normal (0.9%) saline to a total volume depending on the size of the incision.
- Bupivacaine and ropivacaine are sometimes combined with additives such as epinephrine (0.5 mg), morphine (5 mg), clonidine (100 mcg), ketorolac (30 mg) and steroids (methylprednisolone 40 mg or betamethasone). However, their benefits remain controversial.
- It is essential that surgical site infiltration is combined with other non-opioid analgesics (e.g. paracetamol and NSAIDs) to attain the maximum analgesic efficacy.

### Research agenda

- Surgical site infiltration represents a promising yet under-investigated method of post-operative pain control.
- Several areas need further investigation, including identification of the optimal combinations of local anaesthetic and analgesic adjuncts.
- In addition, the role of peripheral nerve blocks, in particular motor-sparing nerve blocks (e.g. adductor canal block for knee surgery) in combination with periarticular infiltration analgesia, needs to be evaluated further.
- Further well-designed studies are necessary to assess the analgesic efficacy of the proposed infiltration technique. Such trials should assess the effects of these techniques on relevant clinical outcomes.

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### References

- [1] Weinstein EJ, Levene JL, Cohen MS, et al. Local anaesthetics and regional anaesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children. *Cochrane Database Syst Rev* 2018;4:CD007105.
- \*[2] Joshi GP, Schug S, Kehlet H. Procedure specific pain management and outcomes strategies. *Best Prac Res Clin Anesthesiol* 2014;28:191–201.
- [3] Joshi GP, Rawal N, Kehlet H, On behalf of the PROSPECT Collaboration. Evidence-based management of postoperative pain in adults undergoing open inguinal hernia surgery. *Br J Surg* 2012;99:168–85.
- [4] Sasmour T, Barazanchi A, Hill AG, On behalf of the PROSPECT collaboration. Evidence-based management of pain after excisional haemorrhoidectomy surgery: a PROSPECT review update. *World J Surg* 2017;41:603–14.

- [5] Barazanchi A, MacFater WS, Rahiri JL, et al. Evidence-based management of pain after laparoscopic cholecystectomy: a PROSPECT review update. *Br J Anaesth* 2018;121:787–803.
- [6] Macfater H, Xia W, Srinivasa S, et al. Evidence-based management of postoperative pain in adults undergoing laparoscopic sleeve gastrectomy. *World J Surg* 2019;43:1571–80.
- \*[7] Cervero F, Laird JM. Visceral pain. *Lancet* 1999;353:2145–8.
- [8] Sammour T, Kahokehr A, Soop M, et al. Peritoneal damage: the inflammatory response and clinical implications of the neuro-immuno-humoral axis. *World J Surg* 2010;34:704–20.
- \*[9] Rozen WM, Tran TMN, Ashton MW, et al. Refining the course of the thoracolumbar nerves: a new understanding of the innervation of the anterior abdominal wall. *Clin Anat* 2008;21:325–33.
- \*[10] Joshi GP, Janis JE, Haas EM, et al. Surgical site infiltration for abdominal surgery: a novel neuroanatomical-based approach. *Plast Reconstr Surg Glob Open* 2016;4:e1181.
- [11] Gasanova I, Alexander J, Ogunnaike O, et al. Transversus abdominis plane (TAP) block versus wound infiltration for pain management after open total abdominal hysterectomy: a prospective, randomized, controlled trial. *Anesth Analg* 2015;121:1383–8.
- [12] Ramshaw B, Forman B, Moore K, et al. Real-world clinical quality improvement for complex abdominal wall reconstruction. *Surg Technol Int* 2017;30:155–64.
- [13] Raines S, Hedlund C, Franzon M, et al. Ropivacaine for continuous wound infusion for postoperative pain management: a systematic review and meta-analysis of randomized controlled trials. *Eur Surg Res* 2014;53:43–60.
- \*[14] Mungroop TH, Bond MJ, Lirk P, et al. Preperitoneal or subcutaneous wound catheters as alternative for epidural analgesia in abdominal surgery: a systematic review and meta-analysis. *Ann Surg* 2019;269:252–60.
- [15] Capdevila X, Moulard S, Plasse C, et al. Effectiveness of epidural analgesia, continuous surgical site analgesia, and patient-controlled analgesic morphine for postoperative pain management and hyperalgesia, rehabilitation, and health-related quality of life after open nephrectomy: a prospective, randomized, controlled study. *Anesth Analg* 2017;124:336–45.
- [16] Mouawad NJ, Leichte NW, Kaoutzanis C, et al. Pain control with continuous infusion preperitoneal wound catheters versus continuous epidural analgesia in colon and rectal surgery: a randomized controlled trial. *Am J Surg* 2018;215:570–6.
- [17] Kehlet H, Joshi GP. Systematic reviews and meta-analyses of randomized controlled trials on perioperative outcomes: an urgent need for critical reappraisal. *Anesth Analg* 2015;121:1104–7.
- [18] Hamill JK, Rahiri JL, Hill AG. Analgesic effect of intraperitoneal local anesthetic in surgery: an overview of systematic reviews. *J Surg Res* 2017;212:167–77.
- \*[19] Gurusamy KS, Nagendran M, Guerrini GP, et al. Intraperitoneal local anaesthetic instillation versus no intraperitoneal local anaesthetic instillation for laparoscopic cholecystectomy. *Cochrane Database Syst Rev* 2014;(3). Art. No.: CD007337.
- \*[20] Ilfeld BM. Continuous peripheral nerve blocks: an update of the published evidence and comparison with novel, alternative analgesic modalities. *Anesth Analg* 2017;124:308–35.
- [21] Ilfeld BM, Duke KB, Donohue MC. The association between lower extremity continuous peripheral nerve blocks and patient falls after knee and hip arthroplasty. *Anesth Analg* 2010;111:1552–4.
- [22] Seangleulur A, Vanasbodeekul P, Prapaitrakool S, et al. The efficacy of local infiltration analgesia in the early postoperative period after total knee arthroplasty: a systematic review and meta-analysis. *Eur J Anaesthesiol* 2016;33:816–31.
- [23] Keijsers R, van den Bekerom M, van Delft R, et al. Continuous local infiltration analgesia after TKA: a meta-analysis. *J Knee Surg* 2016;29:310–21.
- [24] Cui Y, Yang T, Zeng C, et al. Intra-articular bupivacaine after joint arthroplasty: a systematic review and meta-analysis of randomized placebo-controlled studies. *BMJ Open* 2016;6:e011325.
- \*[25] Jimenez-Almonte JH, Wyles CC, Wyles SP, et al. Is local infiltration analgesia superior to peripheral nerve blockade for pain management after THA: a network meta-analysis. *Clin Orthop Relat Res* 2016;474:495–516.
- \*[26] Albrecht E, Guyen O, Jacot-Guillarmod A, et al. The analgesic efficacy of local infiltration analgesia vs femoral nerve block after total knee arthroplasty: a systematic review and meta-analysis. *Br J Anaesth* 2016;116:597–609.
- [27] Li Y, Li A, Zhang Y. The efficacy of combined adductor canal block with local infiltration analgesia for pain control after total knee arthroplasty: a meta-analysis. *Medicine (Baltim)* 2018;97(49):e13326.
- [28] Xing Q, Dai W, Zhao D, et al. Adductor canal block with local infiltrative analgesia compared with local infiltrate analgesia for pain control after total knee arthroplasty: a meta-analysis of randomized controlled trials. *Medicine (Baltim)* 2017;96(38):e8103.
- [29] Kuang MJ, Du Y, Ma JX, et al. The efficacy of liposomal bupivacaine using periarticular injection in total knee arthroplasty: a systematic review and meta-analysis. *J Arthroplast* 2017;32:1395–402.
- [30] Hamilton TW, Athanassoglou V, Mellon S, et al. Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain. *Cochrane Database Syst Rev* 2017;2:CD011419.
- [31] Zhao B, Ma X, Zhang J, et al. The efficacy of local liposomal bupivacaine infiltration on pain and recovery after total joint arthroplasty: a systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltim)* 2019;98:e14092.
- [32] Karlens AP, Wetterslev M, Hansen SE, et al. Postoperative pain treatment after total knee arthroplasty: a systematic review. *PLoS One* 2017;12:e0173107.
- [33] Karlens AP, Mathiesen O, Dahl JB. Heterogenic control groups in randomized, controlled analgesic trials of total hip and knee arthroplasty. *Minerva Anesthesiol* 2018;84:346–62.
- [34] Piper SL, Kramer JD, Kim HT, et al. Effects of local anesthetics on articular cartilage. *Am J Sports Med* 2011;39:2245–53.
- [35] Matsen 3rd FA, Papadonikolakis A. Published evidence demonstrating the causation of glenohumeral chondrolysis by postoperative infusion of local anesthetic via a pain pump. *J Bone Jt Surg Am* 2013;95:1126–34.
- [36] Rao AJ, Johnston TR, Harris AH, et al. Inhibition of chondrocyte and synovial cell death after exposure to commonly used anesthetics: chondrocyte apoptosis after anesthetics. *Am J Sports Med* 2014;42:50–8.
- \*[37] Ramirez MA, Ramirez JM, Murthi AM. Multimodal local infiltration analgesia in total shoulder replacement. *Pain Manag* 2013;3:253–5.
- [38] Joshi GP, Hawkins RJ, Frankle MA, et al. Best practices for periarticular infiltration with liposomal bupivacaine for the management of pain after shoulder surgery: a consensus recommendation. *J Surg Orthop Adv* 2016;25:204–8.

- [39] Guild GN, Galindo RP, Marino J, et al. Periarticular regional analgesia in total knee arthroplasty: a review of the neuro-anatomy and injection technique. *Orthop Clin N Am* 2015;46:1–8.
- [40] Tran J, Peng PWH, Lam K, et al. Anatomical study of the innervation of anterior knee joint capsule: implication for image-guided intervention. *Reg Anesth Pain Med* 2018;43:407–14.
- [41] Joshi GP, Cushner FD, Barrington JW, et al. Techniques for periarticular infiltration with liposomal bupivacaine for the management of pain after hip and knee arthroplasty: a consensus recommendation. *J Surg Orthop Adv* 2015;24:27–36.
- [42] Neal JM, Bernards CM, Butterworth JF, et al. ASRA practice advisory on local anesthetic systemic toxicity. *Reg Anesth Pain Med* 2010;35:152–61.
- [43] Stringer BW, Singhania AK, Sudhakar JE, et al. Serum and wound drain ropivacaine concentrations after wound infiltration in joint arthroplasty. *J Arthroplast* 2007;22:884–92.
- [44] Knudsen K, Beckman SM, Blomberg S, et al. Central nervous and cardiovascular effects of i.v. infusion of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997;78:507–14.
- [45] Joshi GP, Patou G, Morren MD, et al. The safety of liposome bupivacaine following various routes of administration in animals. *J Pain Res* 2015;8:781–9.
- [46] Brower MC, Johnson ME. Adverse effects of local anesthetic infiltration on wound healing. *Reg Anesth Pain Med* 2003;28:233–40.
- [47] Johnson SM, Saint John BE, Dine AP. Local anesthetics as antimicrobial agents: a review. *Surg Infect (Larchmt)* 2008;9:205–13.
- [48] Joshi GP, Kehlet H. On behalf of the Prospect Working Group: guidelines for perioperative pain management: need for re-evaluation. *Br J Anaesth* 2017;119:720–2.