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Editorial

Using postoperative pain trajectories to define the role of regional analgesia in personalised pain medicine

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Who decides how long a regional block should last? The short answer is that the anaesthetist does. In routine clinical practice, the anaesthetist usually decides whether or not to offer a regional block and, if so, whether the block will be a single-injection (with or without adjuncts) or continuous peripheral nerve block. While in an ideal world this decision would be influenced by data, it is typically governed by several factors, not the least of which are assumptions made by the anaesthetist. The anaesthetist chooses a regional block option that may last 1, 2 or maybe 3 days depending on technique and pharmacologic agents, assuming that this duration will be sufficient, but without much data to support this assumption. Even recent initiatives that have focused on developing procedure-specific pain management protocols have lacked these data [1]. This is, in essence, putting the proverbial cart before the horse.

What if we had these data? What would we do differently? Very few studies have specifically explored the concept of pain trajectories after surgery. If we knew the typical pain trajectories and patterns of postoperative pain regression and resolution for common surgical procedures, the data could guide our approaches to regional analgesia. We need these data to put the horse back in front of the cart.

Exploring postoperative pain trajectories

Previous efficacy studies of continuous peripheral nerve block for various surgical procedures included placebo groups [2–5] which give us an opportunity to look more closely at the variability in 'normal' postoperative pain trajectories. These studies were performed primarily at a single institution under rigorous triple-blinded protocols. All study participants received an initial block with local anaesthesia but were randomly assigned to remain on local anaesthetic or change to saline continuous peripheral nerve block infusions by the morning after surgery. Using these previously published data, we have mapped the worst pain trajectories for the placebo groups from these four studies involving: total knee arthroplasty; total hip arthroplasty; mastectomy; and shoulder arthroscopy [2–5] (Fig. 1). Both studies involving total knee and hip arthroplasty measured pain daily through postoperative day six, while the mastectomy and shoulder arthroscopy studies evaluations were either on discrete days (one, four and eight) or through day three, respectively. While there are limitations to our ability to generalise the results of randomised clinical trials, viewing

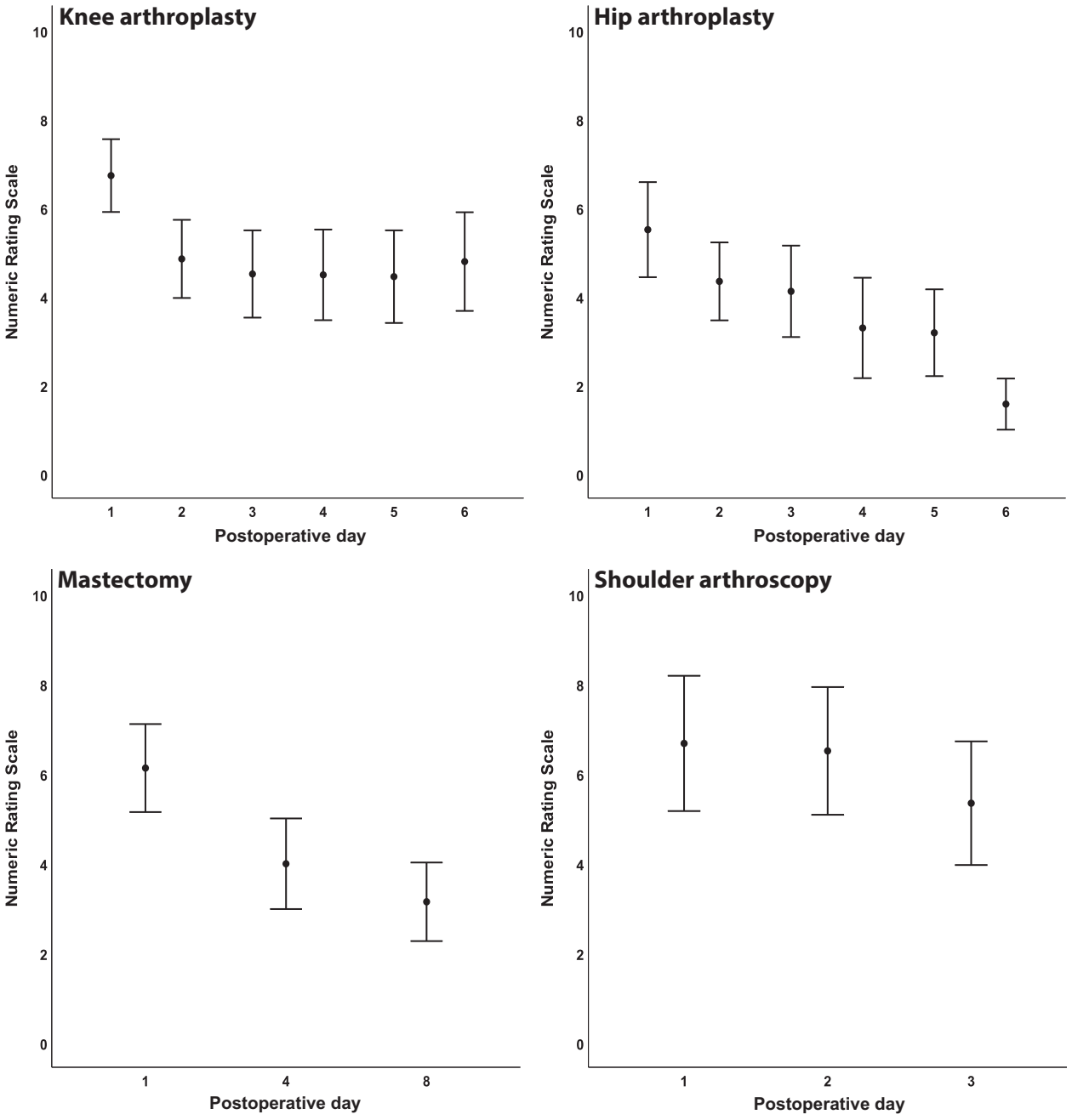

Figure 1 Mean worst pain scores for four surgical procedures: total knee arthroplasty; total hip arthroplasty; mastectomy; and shoulder arthroscopy. Error bars represent 95%CI.

these data confirms that the postoperative pain trajectory can differ greatly from one procedure to the next.

Interestingly, the pain trajectory for total knee arthroplasty (Fig. 1) essentially matches the trajectory reported by Lavand'homme et al. of knee arthroplasty patients who do not go on to develop chronic pain [6]. From Lavand'homme et al.'s study sample, we know that the average maximal pain score after total knee arthroplasty does not consistently fall below four on a numeric rating scale (NRS; 0, no pain; 10, highest pain possible) until approximately postoperative day seven [6]. It is even longer for patients who go on to develop persistent post-surgical pain. Although we cannot extrapolate these data to every surgical population, we can conclude than any single-injection regional analgesic for total knee arthroplasty in all likelihood does not last long enough. As expectations grow

for shorter lengths of stay, including outpatient total knee arthroplasty [7], the fact that nearly all of the postoperative recovery will occur at home demands an appropriate regional analgesic strategy that is matched to the anticipated trajectory of pain resolution and can be easily managed on an ambulatory basis. By applying the right duration of regional analgesia to the right surgical population, we may finally be able to move beyond immediate postoperative pain and 24-h opioid use as primary outcomes for regional anaesthesia research studies and aim to improve more meaningful outcomes such as the incidence of persistent post-surgical pain, long-term functional recovery and chronic opioid use.

We are very aware of the opioid epidemic primarily affecting North America [8] and the role of surgery in introducing patients to opioids for the first time; some of these patients will go on to become chronic opioid users [9]. We acknowledge that regional analgesia is rarely the only pain management modality for surgical patients, and postoperative pain after every surgery should be managed using a multimodal approach to minimise opioid use [10]. However, regional analgesia remains the only acute pain intervention that can specifically target the surgical site. Postoperative pain remains one of the patients' top concerns when undergoing elective surgery [11]. Poorly treated pain can limit patients' functional ability in the postoperative period [12] and early postoperative rehabilitation has been associated with improvements in longer term functional outcomes [13].

Based on our data visualisation a 3-day continuous peripheral nerve block infusion may be reasonable for total hip arthroplasty, mastectomy and outpatient shoulder arthroscopy. Through the study of postoperative pain trajectories, we can identify different patterns of pain resolution among patient groups and surgical procedures that can help us design personalised pain medicine plans specific to these procedures. Of note, none of the four surgical procedures represented in the figure seem appropriate for a traditional single-injection block.

Currently available long-acting local anaesthetics (e.g. bupivacaine, levobupivacaine and ropivacaine) generally provide analgesia of similar duration but less than 24 h [14–17].

Several different pharmacologic adjuvants have been investigated for their potential to extend single-injection peripheral nerve block duration when added to local anaesthetic solutions. These include, but are not limited to: adrenaline [18]; buprenorphine [19, 20]; alpha-2 agonists such as clonidine [21, 22] and dexmedetomidine [23–25]; and dexamethasone [26, 27]. In general, most studies of single-injection nerve blocks with adjuvants fail to demonstrate a reliable duration beyond one day postoperatively. Additionally, nearly all adjuvants have not been specifically tested and approved for nerve blocks (i.e. 'off-label' use) by national regulatory agencies like the Food and Drug Administration (FDA) in the US or the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK. Liposomal bupivacaine, an extended release formulation, has been studied for over 20 years [28] as a means to prolong nerve blockade, but has only been FDA-approved in the US for two regional anaesthetic indications: transversus abdominis plane blocks (considered a field block) and interscalene brachial plexus blocks for shoulder surgery. It has not secured approval from the MHRA or the European Medicines Agency to date.

The greatest limitation to this 'one-size-fits-all' regional analgesia in the form of long-acting single-injection blocks is that they cannot be adjusted. They cannot be decreased in the event of an insensate extremity, nor can they be extended to increase the duration of analgesia. Unfortunately, we cannot reliably predict which patients will need longer blocks in the form of continuous peripheral nerve block before surgery. When patients exhibit greater than expected pain after block resolution, it is too late.

Continuous peripheral nerve block is the only technique currently available that enables titration of local anaesthetic solutions to a peripheral nerve or fascial plane [29]. Using an electronic infusion pump with an external reservoir, the infusion duration is typically limited by the amount of local anaesthetic a patient is able to carry, and single-use elastomeric pumps with an internal reservoir for local anaesthetic rarely last beyond 3 days without replacement [29], which may not be long enough for certain surgical procedures like knee arthroplasty. Based on one systematic review and meta-analysis, patients who receive continuous peripheral nerve block: report lower maximal pain scores during infusion; experience less nausea; have decreased opioid dose requirements; sleep better; and are more satisfied with pain management for the first 2 days after surgery, when compared with single-injection blocks [30]. The differences in maximal pain scores were generally between 1-2 on an 11-point numeric rating scale: effect size −1.29 (95%CI −2.19 to −0.40) on postoperative day 0; −1.87 (95%CI −2.44 to −1.31) on postoperative day 1; and −2.03 (95%CI −2.78 to −1.29) on postoperative day 2 [30]. Unfortunately, the studies included in this meta-analysis utilised only short-term infusions, and the benefits did not persist after catheter removal [30]. These findings suggest that there is still much more work to do in terms

of determining the optimal procedure-specific continuous peripheral nerve block regimen and matching analgesia to pain trajectory. Besides continuous peripheral nerve block, few other therapies in the realm of acute pain medicine offer the potential combination of titratability and flexible duration [31]. Despite more than a decade of supportive data, adoption of continuous peripheral nerve block is still far from universal. A common obstacle to implementation of continuous peripheral nerve block reported by study participants is time pressure; additional barriers include lack of surgeon support and inadequate skills [32].

As a specialty, anaesthesia has to take the lead in defining personalised pain medicine after surgery. Future research into identifying the phenotypes and genotypes associated with greater-than-expected acute pain and persistent post-surgical pain will help design tailored peri-operative pain management plans. Observational studies of pain trajectories for all of the common surgical procedures, from populations of patients and not just randomised clinical trials with narrow inclusion/exclusion criteria, can generate much-needed data that will serve as the basis for prescribing the right regimen and duration of regional analgesic techniques. Moreover, the long-term benefits of personalised pain medicine will need to be rigorously examined. Finally, future advances in technology for continuous peripheral nerve block delivery systems, neuromodulation or new pharmacologic agents for nerve blockade may hold the key to maximising the role of regional analgesia in peri-operative pain management for every patient.

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