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Guidelines for perioperative pain management: need for re-evaluation

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Optimal perioperative pain management facilitates postoperative ambulation and rehabilitation, and is considered a prerequisite to enhancing recovery after surgery.^{1 2} Despite well-documented benefits, postoperative pain continues to be inadequately treated.^{3–5} Although the reasons for the lack of appropriate pain management are not precisely known, conflicting and confusing evidence as well as lack of clear guidance could be contributing factors.

The recently published clinical practice guidelines from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, the American Society of Anesthesiologists' Committee on Regional Anesthesia⁴ and the Australian–New Zealand College of Anaesthetists⁵ provide some excellent guidance with respect to preoperative assessment and patient education. However, the recommendations with regards to pharmacological therapy for pain are too broad and difficult to apply in day-to-day clinical practice.¹ The American guidelines suggest 'considering' almost every available analgesic [e.g. paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)] and analgesic adjuncts (e.g. ketamine and gabapentinoids).⁴ However, the analgesic efficacy for a given analgesic depends on the type of surgical procedure.⁶

It is recommended that multimodal analgesic techniques should be offered, but there is no guidance with respect to appropriate combinations of analgesics for specific procedures.^{4 5} Therefore, it is not surprising that a recent analysis of data from 315 hospitals in the USA found that there was a wide variation in analgesic combinations in the 800 000 patients undergoing the four most common major surgical procedures.⁷ In fact, use of regional anaesthetic techniques, which are considered the basis of an optimal analgesic technique,¹ was low. Further, opioid administration was the primary analgesic, despite their significant limitations.⁸

Because many randomized controlled trials (RCTs) assessing analgesic interventions are underpowered, data from several RCTs are frequently combined to perform meta-analyses. However, the conclusions of such meta-analyses have been questioned.^{9 10} Although there has been an emphasis on performing trial sequential analysis and assessing heterogeneity between RCTs,^{11 12} investigators often focus on 'bias' between RCTs without considering many other clinically relevant factors that could influence decision making.¹³ The aggregation of RCTs usually does not take into account the nature, location and severity of surgical injury, as studies from several surgical procedures are often grouped together when performing a meta-analysis. Also, many RCTs are placebo controlled with the control group receiving only opioids as rescue. This might be appropriate for assessing a new analgesic intervention,¹⁴ but once the efficacy of an analgesic intervention has been established, it is necessary to assess its role as a component of the currently considered 'optimal' or 'best practice' multimodal analgesic technique. In other words, it is necessary to assess if addition of an analgesic intervention would further improve pain control or allow replacement of another analgesic intervention to improve cost effectiveness and/or safety. Also, they do not take into consideration that many analgesic interventions might not have relevance in the rapidly changing clinical practice.¹

In recent years, traditional <mark>meta-analyses</mark> have been <mark>replaced</mark> by network meta-analyses, and are considered to be the best approach for evaluating available evidence and providing guidelines for evidence-based decision making.15-17 Network metaanalyses assess the relative treatment effects through direct and indirect comparisons of available evidence. This approach allows comparisons between competing interventions that have not been directly compared head-to-head. Thus, a network meta-analysis provides not only the relative treatment effect for pairwise comparisons, but also a ranking of treatments. Although network meta-analyses are considered to be an improvement over the traditional meta-analyses, they too suffer from some of the same limitations of traditional meta-analyses. This is illustrated from the conclusions of a recent network meta-analysis assessing postoperative analgesic interventions that evaluated pain management modalities for total knee arthroplasty surgery from a total of 170 RCTs comparing 17 treatment modalities.¹⁸ The authors concluded that multiple nerve blocks are preferable to single nerve blocks, periarticular infiltration and epidural analgesia. Furthermore, they recommended that a combination of femoral nerve block and sciatic nerve block is the optimal approach. It is clear that the results of this study are not currently clinically applicable, because the recommended best approach has been questioned because of concerns of safety and delayed time to safe ambulation. Also, it did not compare other relevant non-opioid multimodal interventions. Thus, this network meta-analysis might be an interesting methodological exercise, but misleading to the clinician.

Another network meta-analysis assessed 135 RCTs assessing 14 non-opioid analgesics.¹⁹ The authors concluded that a combination of paracetamol and NSAIDs or nefopam had superior opioid-sparing effects compared with non-opioid analgesics alone. Furthermore, if used alone NSAIDs, cyclooxygenase (COX)-2-specific inhibitors and α -2 agonists provided the best analgesic efficacy, whereas tramadol and paracetamol alone had the least analgesic efficacy. Here again, the authors combined studies from different surgical procedures and in most studies the comparator groups received only opioids as rescue and failed to consider combination of other non-opioid techniques or other outcomes.

Given the aforementioned limitations of traditional approaches to assessing evidence (i.e. use of meta-analyses and network meta-analyses), it is necessary to modify the process by which recommendations are formulated. The methodological process for critical analysis of evidence and development of recommendations for procedure-specific analgesic interventions starts with performing a systematic review based on the protocol of the Cochrane Collaboration. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines are used to perform the literature search and assess quality and level of evidence of included studies. Importantly, the process of inclusion/exclusion of RCTs is critical and should be clearly defined. For studies to be grouped together they should have uniformity in analgesic technique(s) utilized. However, a critical interpretation of 'bias' in the available RCTs can lead to only a few 'low-risk bias' studies¹³ and limit the possibility for a proper procedure-specific analysis. Thus, there is an urgent need for procedure-specific RCTs with fewer variables such that pain-related confounders are controlled while perioperative care is based upon the most updated evidence. In addition, welldesigned, highly standardized prospective cohort studies, designed to minimize bias and confounding factors, could address a relevant clinical question.

In addition to considering the quality of available procedurespecific evidence, it is necessary to assess **current** clinical **relevance** and **safety** (e.g. adverse effects and impact on rehabilitation) of the analgesic techniques assessed in included studies. Thus, it is necessary to determine if the analgesic intervention would further improve postoperative pain relief and/or outcome when added to current 'best practice' analgesic regimens. For **ex**ample, adding **i.v** lidocaine infusion or transversus abdominis plane blocks to patients undergoing laparoscopic cholecystectomy might not be beneficial over the analgesic regimen of paracetamol + NSAIDs or COX-2-specific inhibitors + port site infiltration.^{1 9} Such a change in approach is necessary to gain evidence for improvements in multimodal pain management, and not to investigate alternative single treatment approaches.

Analyses of the balance between invasiveness of the analgesic technique and the consequences of postoperative pain, as well as a balance between analgesic efficacy and adverse event profile of the intervention should be used to develop recommendations to ensure patient safety.²⁰ In addition, different relevant patient characteristics (e.g. opioid tolerance, psychiatric ailments) can be included to ensure not only procedure-specific but also patient-specific aspects of pain management.

In summary, judgments about 'best' evidence for analgesic interventions and perioperative pain management recommendations are complex. Current guidelines for perioperative pain management are limited by their inability to be applied in a procedure-specific pathway. The current approach to traditional meta-analyses and network meta-analyses of RCTs of pain interventions is not optimal and can lead to inadequate or inappropriate conclusions and clinical guidance. Optimal recommendations for perioperative pain management should be based on a critical appraisal of evidence, focus on specific procedures and be interpreted against the backdrop of contemporary patterns of clinical practice. Therefore, in addition to experts in literature searches and/or data analysis, it is necessary to include specific expertise in the surgical procedure reviewed.

Clinicians must be responsible for critical analysis of the design as well as relevance to current perioperative care in order to determine if RCTs identified in systematic reviews should be used in clinical decision making. The **PROSPECT** (PROcedure-SPEcific Postoperative Pain ManagemenT) Working Group, which consists of an international collaboration of anaesthesiologists and surgeons, is in the process of optimizing pain management recommendations based upon the aforementioned considerations. The PROSPECT initiative aims to provide healthcare professionals with practical procedure-specific pain management recommendations formulated in a way that facilitates clinical decision making across all stages of the perioperative period in a procedure-specific manner. The web-based (postoppain.org) recommendations are subject to formal review and updating within a prescribed time (usually every 3-5 yrs), so that they remain valid and clinically relevant. Finally, the main problem relates to the lack of high-quality procedure- and patient-specific data with sufficient information on efficacy vs safety of simple basic analgesia approaches integrated into fully implemented evidence-based enhanced recovery programmes. Hopefully, clinical pain researchers will fulfil these requirements in future trials in order to optimize perioperative pain management recommendations.

Authors' contributions

All authors have made substantial contribution to conception and design of the editorial, drafting the article and revising it critically, final approval of the version to be published and agree to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interest

G. P. J. has received honoraria from Pacira, Baxter, Merck and Mallinckrodt pharmaceuticals.

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Appendix

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