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Review Article

PROSPECT methodology for developing procedure-specific pain management recommendations: an update

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Summary

The procedure-specific postoperative pain management (PROSPECT) working group develops evidence-based pain management recommendations. PROSPECT methodology is unique and rigorous. However, several limitations were recognised that needed to be addressed, and several new factors were identified that improved PROSPECT methodology. The aim of this article is to present updated PROSPECT methodology for development of recommendations for procedure-specific pain management, focusing on the methodological revisions we will implement. In future, included randomised clinical trials will need to be prospectively registered on a publicly accessible clinical trials database and the study design, including the primary outcome in the registration, should coincide with that in the published manuscript. Placebo-controlled studies in which the analgesic intervention of interest is solely paracetamol, non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2-specific inhibitors or opioids will not be included. Studies comparing one drug in a particular class with another in the same class will also not be included. Future projects will use the Cochrane Collaboration risk of bias tool for quality of reporting of methodology and results. A modified Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach will be used for grading of level of evidence and strength of recommendations. Finally, the updated PROSPECT methodology addresses several other limitations and implements new factors that all add rigour and transparency to developing procedure-specific pain management recommendations.

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Introduction

The procedure-specific postoperative pain management (PROSPECT) working group comprises anaesthetists and surgeons, with broad international representation, which provides evidence-based procedure-specific pain management recommendations. The PROSPECT methodology is unique in that it aims to synthesise clinical evidence while considering risks and benefits of analgesic interventions along with their relevance in current peri-operative care [1]. The aim of PROSPECT methodology is to provide a unified platform to review the evidence for procedure-specific peri-operative pain management and to provide high-quality recommendations, based on best available evidence. Examples of recent recommendations from the PROSPECT group include, among others, guidelines for the management of pain following video-assisted thoracoscopic surgery [2], total hip arthroplasty [3] and tonsillectomy [4]. These guidelines help provide clinicians and other healthcare practitioners with a framework to manage procedure-specific pain and ultimately improve patient comfort and clinical outcomes.

Our methodology is updated periodically to augment the rigour of the guideline development process by enhancing critical evaluation and synthesis of available evidence. Since the previous update [1], several limitations were recognised that needed to be addressed. These include the approach to quality assessments used to assign the level of evidence (i.e. Jadad scores; allocation concealment; statistical analyses; and 80% patient follow-up); quantitative evaluation of the effectiveness of analgesic interventions by assessing the number of studies showing a significant difference between treatment groups (i.e. use of p values reported in the study publication); and the requirement that the intervention must be proven to be beneficial in at least two randomised clinical trials (RCTs), balanced against negative studies, for it to be recommended. In addition, there was a need for refinement of the Delphi approach used to achieve consensus. Furthermore, several new factors were identified that could improve the PROSPECT methodology, such as attention to identifying flawed and fabricated research, and the use of a modified GRADE approach to assigning the level of evidence and grade the strength of recommendation. The aim of this article is to present the updated PROSPECT methodology for the development of recommendations for procedure-specific pain management. Of note, the updated PROSPECT methodology has several key aspects of guideline development that have not been modified [1].

Methods

During a face-to-face meeting, the PROSPECT working group discussed the need to update methodology and elements that required improvement. This was followed by selection of a subgroup to prepare a preliminary draft of the updated methodology. A draft manuscript was developed by the subgroup and further modified based on discussions on every element of the methodology. The final draft was presented to the working group, which was followed by discussions, and a final unanimous approval was obtained.

The updated methodology is as follows. Once the specific surgical procedure to be reviewed is identified and a subgroup selected, the protocol will be developed and registered with an appropriate registry such as PROSPERO (Fig. 1). The changes from previously published methodology aim to make the process more rigorous and increase the robustness of critical evaluation of published evidence. A comprehensive systematic search for procedure-specific literature will be performed according to the recommendations of the PRISMA statement [5]. A priori, defined inclusion/exclusion criteria will be used to

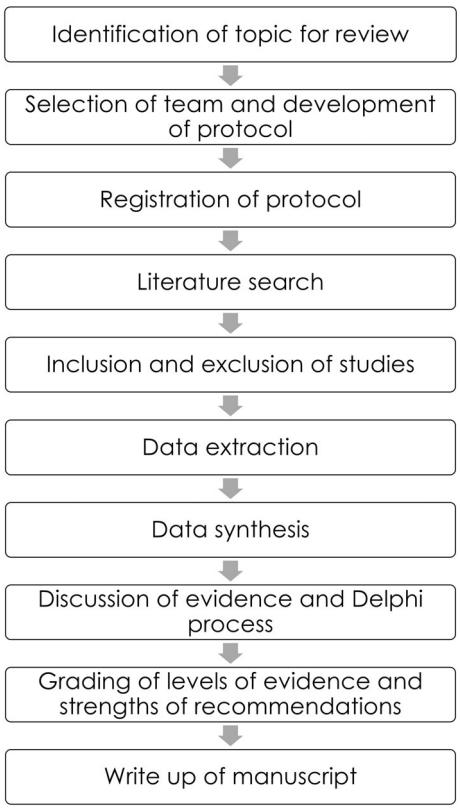

Figure 1 Flowchart summary of PROSPECT methodological processes for procedure-specific guidelines.

identify relevant RCTs (Box 1). In addition to RCTs, review articles (e.g. systematic reviews, meta-analyses and umbrella reviews) assessing analgesic interventions specific to pain management for the selected procedure will also be identified. The RCTs within these publications will be scrutinised, and those identified for inclusion will be analysed critically according to PROSPECT methodology. Studies published before the period of literature search (which is usually 10 years for a new review and from the end date of the previous review for updates) may be included if considered appropriate. Of note, the conclusions of these publications will not be used for providing recommendations, but they are deliberated in the discussion section.

Primary outcomes (i.e. pain intensity scores at rest or procedure-specific relevant movement) and secondary outcomes (i.e. 24-h, 48-h, 72-h cumulative opioid requirements) reported in included RCTs will be assessed as described previously. Studies showing benefits on movement-associated pain will be considered preferentially over those showing benefits on pain at rest. Similarly, other secondary outcome measures such as time to first request for rescue analgesia, supplementary non-opioid analgesic use and opioid-related adverse events will be evaluated when available. Clinical outcomes (e.g. type and incidence of postoperative complications; time to ambulation; hospital duration of stay), patient-reported outcome measures and treatment-related adverse effects will be noted when available.

The previous approach to assessing the quality of the study and assigning levels of evidence and grades of recommendation will be replaced with the use of the Cochrane Collaboration risk of bias 2 tool (RoB 2) for the quality of reporting of methodology and results [6]. The RoB 2 results will be published either in the manuscript or as a supplementary figure. The criteria for evaluating the strengths and limitations of the included RCTs will be used to assign the level of evidence and strength of recommendation (Box 2). The previous approach to assigning the level of evidence and grade of recommendation [1] is now replaced with the modified GRADE approach [7–9] (Box 3). This does not assign the level of evidence based on the estimate of the effect, as that may not always be possible to calculate given the heterogeneity of available evidence. Also, the modification correlates with the level of consensus achieved during the modified Delphi process. Finally, the modified Delphi process was refined, and the level of consensus was specified (i.e. near-unanimous consensus, > 90% agreement; uniform consensus, 76–90% agreement; non-uniform consensus, 50–75% agreement; and major

Box 1 Criteria for inclusion/exclusion of randomised controlled trials.

- Trials of analgesic, anaesthetic and operative interventions, published in the English language, addressing pain management related to the surgical procedure being reviewed.
- Trials should report pain scores using a linear scale (e.g. visual analogue scale or verbal or numerical rating scale). For studies that do not include the raw data values of outcomes, data will be extracted from graphs and figures using plot digitisation software.
- Trials of analgesic interventions should be included if they meet the inclusion criteria, regardless of whether basic analgesics (i.e. paracetamol and NSAIDs or COX-2-specific inhibitors) were administered.
- Trials that report data pooled from patients undergoing mixed surgical procedures from which no data tables are obtainable are excluded.
- *Placebo-controlled studies in which the analgesic intervention of interest solely is paracetamol, NSAIDs, COX-2-specific inhibitors or opioids will not be included. Studies comparing one drug in a particular class with another in the same class will also not be included.
- *Studies should be prospectively registered on a publicly accessible clinical trials database and the study design, including the primary outcome in the registration, should coincide with that in the published study. However, if there are compelling reasons, the subgroup may decide to include a study that has not been prospectively registered. In such a situation, the reasons for inclusion must be documented.

*Elements modified in this current methodological update.
NSAIDs, non-steroidal anti-inflammatory drugs; COX-2, cyclo-oxygenase-2.

Box 2 Factors considered in evaluating the strengths and limitations of included randomised controlled trials.

- Is the analgesic intervention clinically relevant to current peri-operative care?
- Are the differences in pain outcomes between the study groups clinically relevant based on minimal clinically important differences?
  - Clinically relevant differences in pain scores (≥ 10 mm/100 mm in pain scores).
  - Clinically relevant reduction in cumulative opioid use (e.g. reduced opioid-related adverse events).
- Does balance between the invasiveness of the analgesic intervention and the degree and consequences of postoperative pain allow recommendation?
  - For example, although epidural analgesia provides excellent pain relief, its use for minimally invasive surgical procedures may be inappropriate as it is invasive and provides a poor risk/benefit ratio, and similar postoperative outcomes can be achieved with combinations of non-opioid oral analgesics and local anaesthetic infiltration.
- Does the balance between efficacy and adverse effect profile of the analgesic technique allow recommendation?
  - For example, even if an analgesic technique provides excellent pain relief it may not be appropriate if it delays ambulation (e.g. femoral nerve blocks).
  - Determination of adverse effects of the analgesic intervention may not be procedure-specific; however, the risks should be adjusted for the procedure being evaluated. Case–control, cohort or observational studies can be used to determine adverse effects of analgesic interventions.
- Would the analgesic intervention further improve pain relief, reduce opioid use or improve other pain outcomes when added to a basic analgesic regimen? Alternatively, would the analgesic intervention be beneficial if a basic analgesic regimen were not administered or contraindicated? Also, would the analgesic intervention benefit challenging populations such as those at high risk of postoperative pain?
- Would the analgesic intervention potentially enhance recovery beyond the benefits on analgesia?
- *Other possible considerations
  - Overall quality of the trial (e.g. risk of bias scoring; sample size; pain at rest vs. procedure-relevant movement).
  - Although it is not appropriate to recommend an analgesic intervention based on one randomised clinical trial, neither is a specific minimum number of trials (i.e. two or more randomised controlled trials) required for providing recommendations.
  - Although not taken in isolation, the country of origin could be used to understand the context of the clinical study, to flag a need to confirm that the included studies do not come from the same institution. This information will not be included in the manuscript for publication unless there may be a potential question on interpretation of the available trials.
  - A caution is given if the recommendation is based upon several trials from the same institution(s).
  - The quality of the journal (e.g. low impact factor) in which the paper is published may be used to flag a need to check study quality.

*Elements modified in this current methodological update.

disagreement, < 50% agreement). The results of the modified Delphi approach will be used to assign the level of evidence (Box 3).

Discussion

The PROSPECT working group continues to re-evaluate the approach to guideline development with the aim of ensuring reliability and clinical validity of procedure-specific pain management guidelines. Of note, only the significant changes from the previously published methodology are discussed [1].

One of the key factors that distinguishes PROSPECT methodology is the concept of basic analgesics. Accordingly, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase-2 (COX-2)-specific inhibitors are recommended for all surgical procedures. This concept has now been extended to include other simple, safe and inexpensive drugs and

Box 3 Level of evidence and strength of recommendations.

Level of evidence	
High	High-powered randomised controlled trials or meta-analyses, and the panel has reached uniform (near-unanimous) consensus.
Moderate	Lower-level evidence but despite the absence of higher-level studies, there is uniform consensus that the recommendation is appropriate. It is assumed that these recommendations may be modified as higher-level evidence becomes available.
Low	Lower-level evidence and there is non-uniform consensus that the recommendation should be made. This suggests to the practitioner that there could be more than one approach to the intervention being examined.
Very Low	A major disagreement among the panel members. The level of evidence is not pertinent in this category because experts can disagree about the significance of high-level trials. This category informs practitioners that there is a major interpretation issue in the data and directs them to the manuscript for an explanation of the controversy.
Strength of recommendation	
Strong	Desirable effects of intervention clearly outweigh undesirable effects, or clearly do not.
Weak	Trade-offs are less certain, either because of low-quality evidence or because evidence suggests desirable and undesirable effects are closely balanced.
Conditional or no recommendation	Very low level of evidence.
Best practice statement	Level of evidence is not applicable.

techniques with well-documented procedure-specific efficacy. For example, glucocorticoids and surgeon-administered local infiltration analgesia are recommended as basic analgesics for total knee arthroplasty [10].

Another unique aspect of PROSPECT methodology is that the conclusions of systematic reviews and meta-analyses are not considered for developing recommendations because they are sometimes flawed [11, 12]. Many systematic reviews and meta-analyses lack critical evaluation of included RCTs. For example, multiple procedures with variable peri-operative pathophysiological influences are combined; the use of basic analgesic in the comparator group is not assessed; and conclusions are based on statistically significant differences in pain outcomes rather than clinically relevant differences. For example, analyses of the clinical methodology of systematic reviews and meta-analyses evaluating the role of glucocorticoids and gabapentinoids for total knee arthroplasty showed major flaws that limit interpretation and conclusions of these studies [13, 14]. Similarly, critical appraisal of systematic reviews and meta-analyses assessing regional analgesic interventions for total knee arthroplasty showed that the majority of included RCTs did not use basic analgesics [15].

Prospective registration of clinical trials has now become standard and is required by most journals. The updated methodology requires that the included studies be registered prospectively and that the study design at registration reflects the final publication. Studies in which the analgesic intervention of interest is solely paracetamol, NSAIDs, COX-2-specific inhibitors or opioids compared with placebo will not be included. In fact, it has been observed that in recent years there are only a few RCTs evaluating the analgesic efficacy of these drugs [15]. Studies comparing one drug in a particular class with another in the same class will also not be included.

Another change is the use of RoB 2 to assess the risk of bias. While this tool is adopted widely in many clinical systematic reviews and meta-analyses due to its rigorous validation, inter-individual reliability and simplicity, the information may be insufficient to properly determine whether a study is at low or high risk of bias; consequently, many trials will fall into the category of unknown risk of bias. That said, the strength of this tool stems from the assessment of seven different biases for each individual trial, allowing researchers to better balance the recommendations by giving more weight to the studies with a low risk of bias.

Our previous methodology led to recommendations being made if an intervention was shown to be beneficial in two RCTs. With this update, we have now removed this element, as we realised that such a requirement is flawed because both the RCTs may be of low quality and/or from the same institution. Therefore, a specific number of studies

will not be required to provide recommendations. Instead, we will aggregate the strengths and limitations of the included RCTs instead.

In recent years, there have been increasing concerns about research flaws and misconduct, which has led to greater attention to the country of study origin [16, 17]. Similarly, there are concerns that predatory journals lack transparency as well as editorial or reviewer diligence [18]. It is clear that these factors cannot be considered in isolation, as flawed research might originate from any country and may even be published in high-impact journals. However, this information could be used to understand the context of the clinical study and confirm that publications are analysed in greater detail [19].

The updated methodology now uses a modified GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach to define the quality of evidence and grade recommendations (Box 3). This increases the transparency in guideline development. It is emphasised that the level of recommendation would ideally match the level of evidence. Thus, a strong recommendation would be given rarely for very low level of evidence. Also, the language used to reflect the level of evidence and strength of recommendations was suggested. For example, for recommendations with high or moderate levels of evidence, the term `recommend´ should be used, while for recommendations with low or very low levels of evidence, the term `suggest´ should be used. If no recommendation is made, it could be stated that `there is insufficient evidence concerning benefits and harms to recommend´. Importantly, the reasons for not recommending analgesic interventions should be provided. For updated reviews, previously recommended interventions should be reviewed, and if there are any differences, the reasons should be discussed. Subsequently, the strengths and limitations of the study and clinical questions that need to be answered in the future will be discussed. In addition, a recommendation needs to be balanced between efficacy, adverse effects, costs and need for resources. Finally, a modified Delphi approach will be used, and the vote distribution and arguments raised will be described.

Although the updated methodology reflects significant improvements, it has some limitations. For example, although we plan to perform quantitative meta-analyses when possible, it is generally not performed due to significant heterogeneity of the included RCTs. The PROSPECT working group does not include a patient representative for the Delphi approach. Furthermore, because basic analgesics are recommended for all patients and procedures and, particularly with the addition of corticosteroids and local infiltration analgesia to paracetamol and NSAIDs or COX-2-specific inhibitors, one might argue if procedure-specific recommendations are warranted. However, regional analgesia techniques are procedure-specific and are considered a critical component of optimal multimodal analgesia techniques. Nevertheless, regional analgesia techniques are implemented occasionally in clinical practice before the publication of evidence in the literature, and this might influence the clinical relevance of the recommendations. In fact, any systematic review is limited by the evidence available for analysis.

In summary, the updated PROSPECT methodology adds rigour and transparency to the development of procedure-specific pain management recommendations. The overall process of developing recommendations includes a systematic review of literature, critical approach to study selection and evidence synthesis, appraisal and rating of evidence, and subsequent formulation and grading of the strength of recommendations. While there are no plans to apply the updated approach to previously published recommendations, this updated methodology will be used for all future projects starting in 2024.

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Appendix 1. PROSPECT Working Group

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