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PROSPECT methodology

the PROSPECT Working Group Collaborators

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Original Article

Development of evidence-based recommendations for procedure-specific pain management: PROSPECT methodology

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Summary

Effective peri-operative pain management is a prerequisite for optimal recovery after surgery. Despite published evidence-based guidelines from several professional groups, postoperative pain management remains inadequate. The procedure-specific pain management (PROSPECT) collaboration consists of anaesthetists and surgeons with broad international representation that provide healthcare professionals with practical and evidence-based recommendations formulated in a way that facilitates clinical decision-making across all stages of the peri-operative period on a procedure-specific basis. The aim of this manuscript is to provide a detailed description of the current PROSPECT methodology with the intention of providing the rigour and transparency in which procedure-specific pain management recommendations are developed. The high methodological standards of the recommendations should improve the quality of clinical practice.

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#Collaborators –see Appendix.

Introduction

Effective dynamic peri-operative pain management is a prerequisite for optimal recovery after surgery [1]. Several professional associations have published evidence-based guidelines that provide excellent information regarding available analgesic options and an overview of peri-operative pain management strategies [2, 3]. However, they have had a limited impact on the overall incidence of inadequate and inappropriate postoperative pain management [4, 5], which continues to be a major challenge. Although the reasons for the failure of these guidelines are not precisely known, it may be because they are too broad and generalised. Interestingly, a joint clinical

practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiology (ASA) suggests 'considering' almost every analgesic that was included in the analyses [2]. This included acetaminophen, non-steroidal anti-inflammatory drugs (NSAID), cyclooxygenase-2 (COX-2) specific inhibitors and analgesic adjuncts (e.g. ketamine and gabapentinoids) [2].

The possible reasons for such universal recommendations may be related to the methodology used to analyse and interpret the available evidence [6]. Conventional guidelines have predominantly reviewed single-analgesic interventions compared with placebo, although it is

well-recognised that the ideal approach to pain management is to combine analgesics (i.e. a multimodal approach). Also, because the evidence from different surgical procedures is generally pooled together, conventional guidelines do not take into consideration that different surgical procedures have variable pain characteristics, such as the nature (somatic or visceral), site, intensity and duration of pain. Additionally, different procedures have variable consequences of inadequate pain relief. For example, inadequate pain relief after open thoracic surgery may result in significant morbidity, which may not be the case with a peripheral procedure, although the severity of pain may be similar. Furthermore, generic and non-specific guidelines do not consider their applicability in modern rapidly changing peri-operative care [7], and thus are not suitable for inclusion in enhanced recovery after surgery pathways that are designed specifically for a particular surgical procedure and emphasise early mobilisation [8, 9]. Given these limitations, it is not surprising that the information from these guidelines is commonly misinterpreted, making it difficult to apply the knowledge for specific surgical procedures.

The recognition of the above-mentioned limitations of conventional guidelines led to the formation of the procedure-specific pain management (PROSPECT) initiative, which aims to provide healthcare professionals with practical and evidence-based recommendations for pain management in common, but potentially painful, operations formulated in a way that facilitates clinical decision making across all stages of the peri-operative period on a procedure-specific basis. A well-defined methodological process includes a procedure-specific systematic review of available literature as well as critical analyses of the study design of included studies for their relevance to current practice [6]. In addition, there is a focus on interventions in the context of multimodal non-opioid analgesic strategies and consideration of risks and benefits of interventions in the specific surgical setting.

The aim of this manuscript is to provide a detailed description of the current PROSPECT methodology with the intention of providing the rigour and transparency in which the procedure-specific pain management recommendations are developed.

Methods

The PROSPECT Working Group consists of anaesthetists and surgeons with broad international representation [10]. The Working Group meets face-to-face twice a year, with other communications performed via email correspondence.

During the meetings, commonly performed but painful surgical procedures are identified for review. Once the PROSPECT Working Group identifies the surgical procedure (new or update) to be reviewed, a sub-group is selected, with one lead from the Working Group. The sub-group consists of at least two members of the Working Group and co-opted external members as required (e.g. surgeons and/or anaesthetists) with specific expertise in the surgical procedure to be reviewed. In addition, specialists in literature searches and/or data analysis may also be included in the sub-group. The sub-group may also include research fellows assisting with the project. The sub-group lead is ultimately responsible for the timely completion of the project including manuscript submission for publication, if applicable, and presentation on the PROSPECT website [10].

The review process begins with a systematic search for literature specific to peri-operative pain management for the selected procedure in accordance with the preferred reporting items for systematic review and meta-analysis protocols (PRISMA) recommendations [11]. A comprehensive search of several electronic databases, including EMBASE, MEDLINE, PubMed and Cochrane Databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Abstracts or Reviews of Effects, Cochrane Database of Systematic Reviews) is performed using appropriate search strings to identify relevant studies. The time period for literature search for a new review is determined by the working group but is generally chosen to be the preceding 10 years, whereas that for updates is 3–5 years from the end-date of the previous review. The PROSPECT working group decided upon searching for relevant studies within a 10-year period because it more likely resembles current clinical practice given that rapid changes occur in peri-operative care, including surgical techniques.

Broad search terms are used for the literature review to maximise the search and reduce the risk of missing relevant publications. Search terms include words or phrases associated with specific procedures, possible interventions and pain-related outcomes. Inclusion criteria are randomised controlled clinical trials (RCT) and systematic reviews or meta-analyses of analgesic, anaesthetic or surgical interventions, published in the English language, addressing pain management relating to the surgical procedure being reviewed. In addition, included RCTs should report pain scores using a linear pain scale, such as the visual analogue scale or verbal or numerical rating scale. If multiple procedures are included in the study, authors of these studies are contacted to request data tables specifically related to the surgical procedure being reviewed. Studies

that report data pooled from patients undergoing mixed surgical procedures from which no data tables are obtainable are then excluded.

After removing duplicates, a stepwise approach is used for identifying studies for inclusion [11]. The process of study selection is undertaken with two reviewers independently screening the titles and abstracts. Included studies then undergo full-text review and irrelevant papers are excluded. At any stage, in the event of disagreement between the two reviewers, the opinion of a third reviewer is obtained. In addition, reference lists of the relevant articles are manually screened to identify additional eligible studies that may have been missed in the initial literature search. Once the studies for inclusion are finalised, the excluded studies are tabulated with reasons for exclusion in accordance with PRISMA recommendations [11]. A PRISMA flow chart is utilised to present the results of the search data, records screened, records excluded with reasons for exclusion and studies included in the qualitative analyses.

The included studies are stratified by the timing of the intervention (pre-operative, intra-operative or postoperative), and are then further categorised into the type of intervention: analgesic (systemic analgesics, analgesic adjuncts or regional analgesia techniques), anaesthetic or surgical. The studies undergo quality assessments which are used to assign the level of evidence (Table 1). Criteria employed for quality assessments include allocation concealment of treatment assignment by those involved in recruitment (A, adequate; B, unclear; C, inadequate; D, not used), quality scoring to assess randomisation using the

Jadad score (1–5) [12], assessment of blinding, reporting of the flow of patients and participant follow-up of greater or less than 80% [13].

Summary information from the included studies is extracted and tabulated using a predefined data extraction form. The extracted information includes: study design (including interventions); population characteristics; outcomes assessed; and critical evaluation. The information regarding study design includes: author name; year of publication; overall sample size; analgesic interventions evaluated; sample size in each group; treatment in the comparator group (placebo or active); population (age, sex, opioid tolerance or psychiatric comorbidities); details about surgical procedure and anaesthetic technique; and the duration of follow-up. Outcome data are extracted, including: pain scores at rest or during on activity; time-to-first request for rescue analgesia; cumulative 24-h opioid requirements; non-opioid analgesic use; opioid-related adverse events such as postoperative nausea and vomiting; analgesic intervention-related adverse events; and any other additional outcomes assessed. Critical evaluation includes relevance to current clinical practice and use of paracetamol and non-steroidal anti-inflammatory drugs or COX-2 specific inhibitors (termed as ‘basic analgesic regimen’) in the study groups.

Postoperative pain intensity scores at rest and/or pain intensity during activity (when available) are designated as primary outcome measures. A change of more than 10 mm in pain scores is considered clinically relevant [14]. Secondary outcomes include: time to first request for rescue

Table 1 Relationship between quality of the study and levels of evidence and grades of recommendation.

Study type	Study quality assessment			Level of evidence	Grade of recommendation
	Allocation concealment (A–D)	Jadad Score	Statistical analyses and patient follow-up		
Systematic review with homogeneous results	NA	NA	NA	1	A
Randomised controlled trial	A or B	1–5	Statistics reported and > 80% follow-up	1	A
Randomised controlled trial	C or D	1–5	Statistics not reported or questionable, or < 80% follow-up	2	B
Non-systematic review, cohort study, case study (e.g. adverse effect guidance)	NA	NA	NA	3	C
Clinical practice information (expert opinion), inconsistent evidence	NA	NA	NA	4	D

Allocation concealment assessment is rated as: A, adequate; B, unclear; C, inadequate; D, not used. The grade of recommendations is based on the overall level of evidence, considering the balance of clinical practice information and evidence. NA, not applicable.

analgesia; cumulative 24-h opioid requirements; other supplementary analgesic use; opioid-related adverse events; and patient-related outcome measures. The effectiveness of each intervention for each outcome is evaluated qualitatively by assessing the number of studies showing a significant difference between treatment arms ($p < 0.05$ as reported in the study publication). Meta-analyses are performed if the studies are homogenous in the analgesic technique(s) utilised, with similar outcome measures that are reported or can be estimated as mean (SD) for continuous variables and proportions for dichotomous variables.

The PROSPECT sub-group then determines if each intervention should be recommended or not recommended. To be recommended the intervention must be shown to be beneficial in at least two RCTs. Studies are not excluded from the review based on the risk of bias scoring. Additionally, to ensure clinical relevance, the relevance to current peri-operative practice is assessed. Likewise, we assess if the intervention would improve postoperative pain relief and/or outcomes when added to the 'basic analgesic regimen' or would be beneficial if this regimen is not possible or is contra-indicated. Furthermore, the balance between the invasiveness of the analgesic technique and the consequences of postoperative pain, as well as a balance between the analgesic efficacy and the adverse event profile of the analgesic technique is also considered. In addition, relevant patient characteristics (e.g. opioid tolerance and psychiatric comorbidities) may be included to ensure not only procedure-specific but also patient-specific aspects of pain management. Of note, efficacy data from 'similar' procedures are not used for recommendations. Adverse effects of analgesic interventions are identified through an extensive literature search, which is not procedure-specific; however, risks are adjusted for the procedure being evaluated. Case-control studies and cohort studies or observational studies can be used to determine adverse effects of analgesic interventions.

Finally, a draft table or algorithm of the recommendations of analgesic, anaesthetic or surgical interventions is prepared with each recommendation assigned a grade based on the overall level of evidence and balance of clinical practice information and evidence (Table 1).

The proposed recommendations are then sent to all members of the Working Group along with data extraction files, included studies and excluded studies with reasons for exclusion, level of evidence of the included studies and reasons for recommending or not recommending

interventions. Members of the Working Group also have access to the publications of included studies so that they can review the evidence for themselves. Five questions are then asked of the Working Group about each recommendation:

- 1 Is the recommended intervention clinically relevant?
- 2 Does it add to the 'basic analgesic' technique?
- 3 Does the balance between efficacy and adverse effects allow recommendation?
- 4 Does the balance between invasiveness of the analgesic intervention and degree of pain after surgery allow recommendation?
- 5 Are the reasons for not recommending an analgesic intervention appropriate?

A modified Delphi approach is utilised, which includes several rounds of individual comments followed by round-table discussions [15, 16]. Each Working Group member provides comments to the sub-group leader via email. These comments are collated for presentation during the face-to-face meeting when one of the sub-group members presents evidence and the reasons for recommendations. This is followed by a discussion among the members and a consensus is developed, but any disagreements are recorded as a matter of good practice.

The group also develops clinical questions that need to be answered in the future for each procedure. After the face-to-face meeting, the sub-group prepares a final document, which includes edits based on the discussions during the face-to-face meeting. The final document with the consensus agreements is circulated to the Working Group for review and approval. No major changes are incorporated during this final review stage. Finally, the sub-group prepares a manuscript for publication in a peer-reviewed journal, if appropriate. Subsequently, a web copy is prepared with the help of a medical writer. Of note, the PROSPECT website also includes the overall recommendations in several languages.

Discussion

The strength of the PROSPECT methodology is that it goes beyond making recommendations based on conventional systematic review and meta-analysis. Often, evidence from a high-quality RCT may not be appropriate for recommendation due to a lack of clinical applicability, inappropriate study design such as the lack of inclusion of simple non-opioid analgesics as part of baseline analgesic technique, or concerns of adverse effects. The PROSPECT recommendations are provided in the context of a contemporary and pragmatic clinical setting. Enhanced recovery programmes, which are rapidly becoming

standard of care, emphasise early mobilisation, and thus any analgesic strategy must consider a rational multimodal analgesic technique that facilitates ambulation. For example, a network meta-analysis assessing the analgesic efficacy of peripheral nerve blocks for patients undergoing total knee arthroplasty concluded that a combination of sciatic and femoral nerve blocks is the best analgesic approach because they reduce pain scores [17]. This conclusion overlooks the fact that these blocks cause quadriceps weakness and can delay ambulation.

The opioid-sparing effects of paracetamol and NSAIDs or COX-2 inhibitors are well described for all surgical procedures [18–23]. The PROSPECT group assesses if the addition of an analgesic intervention would further improve pain relief when combined with simple, effective, non-opioid analgesics (i.e. paracetamol and NSAIDs or COX-2 specific inhibitors). For example, adding intravenous lidocaine infusions or transversus abdominis plane blocks to patients undergoing laparoscopic surgery may not have significant benefits over and above the analgesic regimen of paracetamol with an NSAID or COX-2 specific inhibitor and port site local anaesthetic infiltration [7].

One of the clinical considerations when recommending an analgesic intervention is the balance between the invasiveness of the analgesic technique and the degree of postoperative pain. For example, although epidural analgesia or intrathecal morphine may provide excellent pain relief, their use for minimally invasive surgical procedures may be inappropriate due to the invasiveness of the interventions, a poor risk/benefit ratio and the fact that similar postoperative outcomes can be achieved with combinations of non-opioid oral analgesics and local anaesthetic infiltration [7].

PROSPECT recommendations weigh the efficacy of analgesic interventions and potential risks. The relevance of adverse effects of different analgesics may depend on the type of surgical procedure. For example, the risk of bleeding associated with NSAIDs may be more relevant for operations with greater potential for bleeding complications than in others. Similarly, although opioid use should be reduced for all surgical procedures, the consequences of opioid-related adverse effects may vary between surgical procedures.

The validity of any guideline is dependent on the composition of the guideline panel, the identification and synthesis of the evidence and the applied method of guideline construction [24]. It is critical that the selection of panellists is based upon their expertise in the area of interest. In addition, safeguards must be in place to eliminate bias and potential conflicts of the panellists. The

entire process of developing guidelines should be transparent to the intended guideline users [25]. The PROSPECT Working Group and the approach to developing and presenting guidelines fulfil the above-mentioned requirements.

Procedure-specific recommendations for several surgical procedures have been completed by the PROSPECT collaboration and are accessible on the website [10] and published in the peer-reviewed literature. The currently available procedures are subject to formal review and updating, within a prescribed time-frame, usually every 3–5 years, so that they remain valid and clinically relevant. During this period, a literature review is performed every year for all surgical procedures and appropriate studies will be added to a separate section on the website.

Despite the rigour of the PROSPECT methodology, there are some limitations. The strength of the systematic review is based on the quality of published studies. Most RCTs assess a single-analgesic intervention with a placebo group commonly receiving opioid monotherapy and opioids as a rescue. Also, there is a lack of evidence on analgesic interventions in the setting of some specific surgical procedures as well as lack of accurate dosing and duration data, which makes providing precise recommendations challenging. Another limitation is that there may be interventions, doses or routes of administration in published studies that are no longer appropriate in current practice. Alternatively, some analgesic techniques may be introduced into current clinical practice without being subjected to a rigorous comparative study. Moreover, published literature may lag behind clinical practice, thus decreasing the clinical relevance of the review. Most studies of analgesic interventions do not assess their effects on clinically-relevant outcomes, such as movement-related pain scores or surgery-related physical function [26]. Similarly, when determining the benefits of an analgesic intervention, pain scores and/or opioid requirements should not be considered in isolation of clinically-relevant outcome measures. For example, in patients undergoing abdominal surgery, assessment of analgesic intervention on functional outcomes such as bowel function and consequences on length of hospital stay is critical. Furthermore, there is a lack of high-quality procedure- and patient-specific evidence with sufficient information on the efficacy and safety of simple basic analgesia integrated into a fully implemented evidence-based enhanced recovery programme [8].

We continue to identify significant gaps in clinically-relevant research on peri-operative pain management.

There is an urgent need for procedure-specific RCTs, with fewer variables such that pain-related confounders are controlled for while peri-operative care is based on the most updated evidence. In addition, well-designed, highly standardised prospective cohort studies, designed to minimise bias and confounding factors, may address relevant clinical questions. There is a further need for assessing the incorporation of procedure-specific pain interventions in clinical pathways on improving compliance with protocols as well as improving peri-operative outcomes.

In summary, judgments about the best evidence for analgesic interventions and peri-operative pain management recommendations can be complex. Current guidelines for peri-operative pain management are limited by their inability to be applied in a procedure-specific pathway. The PROSPECT initiative aims to overcome the limitations of conventional guidelines and provide healthcare professionals with evidence-based, procedure-specific, clinically-relevant information for the use of analgesic interventions. These guidelines offer rapid access to practical advice on pain management and provide clinicians with supporting arguments for and against the use of analgesic interventions for surgical procedures. The ultimate aim is to encourage practitioners to incorporate the recommendations that are relevant to their practice into procedure-specific clinical pathways, which should improve overall postoperative outcomes.

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Appendix

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