PROSPECT: evidence-based, procedure-specific postoperative pain management

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Existing general guidelines for perioperative pain management do not consider procedure-specific differences in analgesic efficacy or applicability of a given analgesic technique. For the clinician, an evidence-based, procedure-specific guideline for perioperative pain management is therefore desirable. This chapter reviews the methodology and results of PROSPECT: a public web site (www.postoppain.org) which provides information and recommendations for evidence-based procedure-specific postoperative pain management.

Key words: postoperative pain; evidence-based medicine; clinical decision support systems.

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Inadequately controlled postoperative pain remains a widespread problem despite the development of specialized acute pain teams over the past 20 years or so. Two large surveys in the United States show that 77–83% of patients suffer postoperative pain in the 2-week period following surgery.\textsuperscript{1,2} A major review\textsuperscript{3} and systematic review\textsuperscript{4} similarly confirm the practical difficulties of providing effective postoperative pain management to large populations of surgical patients. Published guidelines for managing acute pain exist at a local level in many hospitals, but may be influenced by local factors such as the available surgical and anaesthetic experience and skills (particularly applicable for regional techniques), ward routines, and cultural and social preferences. National and international guidelines are also available\textsuperscript{5–7}, but in the main these offer rather general advice for pain management and can be difficult to relate to specific surgical procedures.

**WHY POSTOPERATIVE PAIN MANAGEMENT SHOULD BE PROCEDURE-SPECIFIC**

In their daily practice, clinicians may seek advice on principles for postoperative pain management in general guidelines for acute pain management\textsuperscript{5} or in major textbooks. Another approach to helping clinicians in choosing analgesics for postoperative analgesia has been the continuously updated Oxford League Tables.\textsuperscript{6} These tables show, in a simplified manner, the overall efficacy of an analgesic agent expressed as NNT values, i.e., the number of patients needed to be treated to achieve one patient with a pain response of at least 50% compared with placebo. At the same time, such tables are beginning to appear with a focus on side-effects (NNH, number needed to harm). Although these tables are immediately attractive and easy to use, the data used to construct them are predominantly from studies in dental procedures or other relatively minor or poorly defined surgical procedures. The view has therefore arisen that such information needs to be procedure-specific, since the analgesic efficacy of drugs varies between different types of surgery: e.g. the analgesic efficacy of paracetamol is twofold less in orthopaedic procedures compared with dental procedures.\textsuperscript{8} In addition, the difference in analgesic efficacy between non-steroidal anti-inflammatory agents (NSAIDs) and paracetamol has been demonstrated to depend on the magnitude of surgery.\textsuperscript{9} Finally, a 50% decrease in pain may have a different clinical relevance depending on whether pain decreases from 40 to 20 or from 80 to 40 on a hundred-point visual analogue scale. Thus, recommendations based on the league tables may not be useful in all types of surgery, despite the attractive simplicity of the data presentation.

Optimal dynamic pain relief, allowing early function, is a prerequisite for accelerated postoperative rehabilitation (fast-track surgery)\textsuperscript{10}, and therefore the clinician needs procedure-specific information in order to optimize the choice of analgesia. Further supporting a need for procedure-specific information is the fact that the intensity of pain and the consequential effects on organ functions may be procedure-related. Although in general the intensity of pain corresponds to magnitude of surgical injury, this may not always be so. For example, dental pain from a rather small injury may be relatively more painful compared with the pain from a larger tissue injury such as a thoracotomy. Also, the consequences of the injury and pain are entirely different between these procedures: whereas a thoracotomy may result in pulmonary dysfunction and morbidity, this is not the case with the dental operation despite significant pain. Therefore, the clinician with responsibility for analgesia may find it worthwhile to consider more invasive analgesic techniques in those operations where a reduction of stress and pain may be of most benefit in preventing organ dysfunction and thereby improving...
outcome. For instance, the use of continuous epidural analgesia with local anaesthetics for major abdominal and thoracic surgery, in addition to providing good analgesia, improves pulmonary function and reduces ileus and catabolism compared with systemic analgesia. 10 Thus, the choice of analgesic should depend on the type of surgical procedure.

Another argument for procedure-specific analgesia is that the importance of side-effects from different analgesics may depend on the procedure. For example, the well-established inhibition of platelet aggregation and, therefore, risk of bleeding that is associated with NSAIDs 11 will be more relevant in those operations where there is greater potential for bleeding complications (e.g. tonsillectomy 12,13, plastic surgery, major joint replacement) than in others (e.g. cholecystectomy, herniorrhaphy, etc). In this way, analgesics with no effects on platelet function are preferable in operations where bleeding may have significant consequences.

In recent years there has been a focus on the opioid-sparing effects of non-opioid analgesics 14, and significant clinical benefits have been achieved in reducing the incidence of some opioid-associated side-effects (nausea, vomiting and sedation). 14,15 Since opioid-related side-effects may be more frequent in some procedures than in others (for example, nausea and vomiting may occur most commonly in head, neck, ear, and gynaecological surgeries), it may be expected that reduction of opioid use and related side-effects will be of greater benefit in these procedures, which again argues for a procedure-specific approach to analgesia. However, it must be admitted that so far there is no firm evidence for a procedure-dependent reduction of opioid-related side-effects with the use of non-opioid analgesics.

Finally, the fact that some analgesic modalities — such as intraperitoneal or intra-articular treatments, and peripheral nerve blocks — can only be applied to certain surgical procedures will also argue for a procedure-specific approach, in contrast to analgesics such as paracetamol, NSAIDs, ketamine, and gabapentin, which in principle may be used in all types of surgery provided that the analgesic effect is satisfactory and that there are no contra-indications.

From the preceding information, it appears that there may be potential shortcomings of using general analgesic guidelines or league tables when choosing an analgesic for a given surgical procedure. On the other hand, there are strong arguments for the availability of procedure-specific analgesic guidelines that are based upon the available evidence from randomized controlled trials (RCTs) in each particular surgical procedure.

PROSPECT: A UNIQUE INITIATIVE

The PROSPECT initiative provides a novel web-based clinical decision support programme 16 developed to overcome the limitations of the generalized guidelines. The PROSPECT Working Group conducts systematic reviews of the literature related to acute postoperative pain in specific surgical procedures. The Working Group is made up of an international panel of both surgeons and anaesthesiologists (Table 1), supported by a team of medical writers. The objective is to report the findings of a qualitative and quantitative systematic review of RCTs comparing the efficacy of analgesic methods and agents for postoperative pain management in adult patients undergoing a particular surgery. This review also includes randomized studies assessing the effects of anaesthetic and surgical techniques on postoperative pain. The systematic review provides the basis for comprehensive recommendations — derived by consensus of the PROSPECT Working Group — for the clinical practice of pain management in a particular surgical
procedure. Where there is lack of evidence for a particular intervention in the surgical procedure in question, supplementary ‘transferable’ evidence may be used, i.e. data from RCTs or systematic reviews in comparable surgical procedures in the same anatomical area (for example, abdominal or limb surgery). The evidence is further supplemented by information about the balance of benefits or risks of each analgesic technique in the context of current clinical practice, considering such factors as adverse effects, ethical constraints, validity of efficacy assessments, practicality of analgesic techniques and patient groups.

The PROSPECT methodology

The PROSPECT methodology is summarized in Figure 1. For each PROSPECT review of procedure-specific postoperative pain management, a systematic review of the scientific literature is conducted according to the guidelines provided by the Cochrane Collaboration. The PROSPECT Working Group defines search terms, study inclusion criteria, and study outcomes to be assessed. Searching MEDLINE and EmBASE

Table 1. The PROSPECT Working Group.

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Location</th>
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<tr>
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Figure 1. Formulation of PROSPECT recommendations.
identifies relevant RCTs of postoperative analgesia for the particular surgical procedure. Only RCTs of perioperative interventions compared with placebo or other interventions — in which all patients or a definable subgroup underwent the specific surgical procedure — are included. The results of pain assessments using a visual analogue scale (VAS) or verbal or numerical rating scales (VRS or NRS) are also required for inclusion of a study. Preoperative, intraoperative and postoperative pain management regimens are included. Excluded studies, and the reasons for exclusion, are recorded.

In 2006 the PROSPECT methodology was refined to take greater account of the quality of the RCTs in each review (Neugebauer et al, 2006, submitted for publication). Each study that is selected for the systematic review is assessed for methodological quality, and assigned a level of evidence accordingly.

Summary information for each study is recorded in tables. This information includes, if available in the published study, the interventions compared and the size of patient groups, the analgesia given to all patients, the qualitative outcomes for pain scores, for supplementary analgesic use, for time to first supplementary analgesic requirement, other qualitative pain outcomes (e.g. McGill questionnaire scores) and postoperative nausea and vomiting (PONV) or other recovery outcomes.

Studies are stratified according to mode of analgesic delivery (local, systemic, neuraxial) and type of agent. The value of pre-emptive analgesia is examined by grouping studies that contain arms with pre- and postoperative administration of the same agent or technique.

Quantitative evaluation of analgesic efficacy uses meta-analyses of the weighted (by study size and SD) mean differences in pain scores or other outcomes using Review Manager software, which has been developed for Cochrane Collaboration systematic reviews. When meta-analyses cannot be performed (e.g. when the study does not report data as means and SD), the consistency of efficacy and the homogeneity of the data are further examined with scatter plots, correlational analyses or other techniques.

When there is limited procedure-specific evidence on the analgesic technique, the PROSPECT Working Group may agree to include additional evidence, transferable from other procedures in the same anatomical area or from other systematic reviews, as well as pertinent information from clinical practice.

The process for the formulation of recommendations is based on established methods for achieving group consensus to minimize potential bias towards the views of any one member of the PROSPECT Working Group. Firstly, two or three members of the PROSPECT Working Group, together with a team of medical writers, draft procedure-specific recommendations for each perioperative intervention, based on the evidence from the systematic review, the transferable evidence, and clinical practice. Secondly, each member of the whole PROSPECT Working Group provides comments on the review and draft recommendations using the Delphi method. Comments are forwarded only to a moderator and not to the whole group, and individual comments are then collated for discussion at a round-table meeting of the PROSPECT Working Group, where the recommendations are debated until a consensus is achieved.

The recommendations concerning the use of each intervention are graded A–D according to the type and quality of the source material and its level of evidence. Recommendations based on high-quality and consistent (level of evidence 1) procedure-specific evidence are graded A, while those based on limited or poor-quality, procedure-specific evidence or on high-quality transferable evidence are graded B. Where information from lower-quality transferable evidence (which may include data on adverse effects, for example), or from clinical practice (expert opinion), determines the recommendations, they are graded C or D, respectively.
The PROSPECT evidence and recommendations are presented on an easily accessible web site and are organized in a tree structure with folders labelled to direct the reader to preoperative, intraoperative and postoperative interventions. Each of these folders contains details of analgesic, anaesthetic and surgical interventions where evidence is available. Colour-coded symbols help to identify procedure-specific evidence, transferable evidence, current clinical practice information and PROSPECT recommendations. Each piece of evidence is presented as an argument for or against an analgesic, anaesthetic or surgical technique. On the PROSPECT web site, hyperlinks to full abstracts and meta-analyses complete the background information. In contrast, other existing procedure-specific guidelines for postoperative pain management provide insufficient information about the evidence from the literature reviews used to formulate them. This limits the reader in assessing the relevance of these guidelines to their own clinical practice. On the PROSPECT web site, levels of evidence and grades of recommendation are provided, allowing the reader to evaluate the strength and validity of the recommendations. Several examples of recommendations (Table 2) illustrate the PROSPECT procedure-specific approach to postoperative pain

<table>
<thead>
<tr>
<th>Table 2. Examples of PROSPECT recommendations.</th>
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<tr>
<td>The use of epidural analgesia in abdominal hysterectomy and open colonic resection surgery</td>
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<tr>
<td>(A) Open colonic resection:</td>
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<tr>
<td>• Continuous thoracic epidural for anaesthesia and analgesia is recommended for routine use in colonic resection based on its benefits in reducing postoperative pain, systemic opioid use and bowel recovery time (grade A)</td>
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<tr>
<td>• A combination of epidural local anaesthetic and strong opioid is recommended for analgesia, in preference to either agent alone, based on evidence of their combined efficacy in reducing postoperative pain and systemic opioid use compared with local anaesthetic alone (grade A). However, the addition of high doses of opioid to epidural local anaesthetic results in an increase in the time to first bowel movement (grade A)</td>
</tr>
<tr>
<td>• Patients unable to receive an epidural should receive postoperative systemic analgesia (grade D)</td>
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<tr>
<td>(B) Abdominal hysterectomy:</td>
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<tr>
<td>• Intraoperative administration of single-dose epidural analgesia, in addition to anaesthesia, is not recommended for the treatment of postoperative pain based on evidence of limited duration of effect in reducing postoperative pain and a lack of benefit in reducing supplementary analgesic consumption (grade A)</td>
</tr>
<tr>
<td>• Continuous postoperative epidural infusion is not recommended for routine use in hysterectomy patients because its analgesic benefits compared with systemic analgesia are short-lasting and are of marginal clinical significance (grade A). Therefore, the risks of epidural technique outweigh the analgesic benefits in low-risk patients (grade D)</td>
</tr>
<tr>
<td>• Continuous postoperative epidural analgesia with local anaesthetic plus strong opioid is recommended in high-risk patients (e.g. those at risk of organ dysfunction and some patients undergoing extensive surgery for malignancy) — and in these patients it is recommended that the epidural is also used for anaesthesia — because the benefits of epidural technique, e.g. reduction in inhaled anaesthetics and systemic opioids as well as reduced paralytic ileus and improved pulmonary function (grade A and B), outweigh the risks in these patients (grade D)</td>
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<tr>
<td>• Despite the analgesic benefits of epidural clonidine, it is not recommended to control postoperative pain following abdominal hysterectomy because of the incidence of hypotension (grade A), sedation and bradycardia (grade D)</td>
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The use of local anaesthetic in herniorrphoy, abdominal hysterectomy and laparoscopic cholecystectomy

(A) Herniorrphoy:
- Local anaesthetic injection techniques (inguinal nerve block/field block/infiltration), administered preoperatively or intraoperatively or both, are recommended (grade A) because they reduce early postoperative pain and supplementary analgesic use compared with placebo. The effect of preoperative administration is comparable to post-incisional administration
- There are insufficient data to recommend (grade D) one injection technique (inguinal nerve block/field block/infiltration) or combination in preference to another
- Local anaesthetic instillation administered at closure cannot be recommended at this time despite evidence for its analgesic efficacy, because of limited data (grade D)
- Long-acting local anaesthetics are recommended in preference to short-acting local anaesthetics (grade D)
- Addition of epinephrine to local anaesthetic solution is not recommended because of lack of additional or prolonged analgesic effect from limited procedure-specific data (grade A)
- Postoperative continuous wound infusion with local anaesthetic cannot be recommended at this time, despite evidence for its analgesic efficacy, because of limited data (grade D)
- Postoperative single/repeat dose of local anaesthetic by catheter in the wound is not recommended because of lack of analgesic effect (grade A)
- Subfascial infiltration with local anaesthetic cannot be recommended in preference to subcutaneous infiltration at this time because of limited data (grade D)

(B) Abdominal hysterectomy:
- Intraoperative wound infiltration is recommended based on specific evidence that it reduces pain following hysterectomy at 8 h (grade A). Although this outcome did not reach clinical significance, this method of analgesia is convenient and has a favourable safety profile
- Intraperitoneal analgesia is not recommended based on its lack of benefit in reducing pain scores and supplementary analgesic consumption following abdominal hysterectomy (grade A)
- Postoperative wound infiltration administered by PCA may have a benefit in controlling postoperative pain, but there is not currently enough evidence to recommend it.

(C) Laparoscopic cholecystectomy:
- Incisional local anaesthetic infiltration is recommended at the end of surgery (grade A). Combined incisional/intraperitoneal local anaesthetic is recommended (grade C) provided dose is monitored to prevent toxicity
- Despite analgesic effects (grade C), interpleural local anaesthetics are not recommended due to the invasive nature of the technique
- Intraperitoneal local anaesthetics are recommended, although the effects are of limited duration (grade A)

management. These examples clearly show that similar analgesic techniques or similar drugs are not always associated with an equivalent balance between efficacy and risk in the different operations.

Finally, for each procedure reviewed, the overall recommendations are summarized in a table or algorithm that helps the end-user in understanding the strategy for postoperative pain management after that particular surgery. As an example, the algorithm for postoperative pain management for thoracotomy is shown in Figure 2.

Despite the rigour of the systematic review and consensus processes, there still are limitations in the PROSPECT initiative. The systematic reviews include only published articles, in English, and it is possible that some studies are not identified because they are not recorded in the Embase or MEDLINE databases. In addition, the systematic
reviews rely heavily on qualitative analyses because the outcome data suitable for meta-analyses are often limited in the published studies.

PROSPECT is not a substitute for the published generalized guidelines and does not impose standards for postoperative analgesic treatment. PROSPECT is an instrument to support rational clinical decision-making in postoperative pain management. The primary advantage of the PROSPECT initiative is that the recommendations take into consideration the particular characteristics of the different operative procedures reviewed. PROSPECT allows the end-user to assess the reliability of the evidence and to make informed clinical decisions for postoperative pain management on a procedure-specific basis, since the supporting evidence for each recommendation is provided on the web site. When using these recommendations, clinicians must still consider the clinical circumstances, local regulations and local prescribing information in each case before making their final judgement. Recent publications illustrated the impact on clinical practice of the PROSPECT recommendations for procedures such as total hip arthroplasty and laparoscopic cholecystectomy.20,21

Aside from providing clinicians with a recommended strategy for optimal procedure-specific pain management, the PROSPECT systematic reviews and the evidence behind each recommendation will help interested clinicians to investigate whether different analgesic techniques are comparable for the management of pain in a particular surgery. The information will also help clinicians in exploring the efficacy of analgesic interventions across different surgical procedures. For instance, one could look up the benefits of the preoperative administration of systemic analgesics versus their postoperative administration across different types of surgery.

SUMMARY

The importance of effective pain control in minimizing the deleterious effects of the surgically induced stress response and improving outcome from surgery is now well recognized.10,14 With the increasing complexity of surgery and anaesthesia, the often challenging co-morbidities of the patient population, and a bewildering choice of drug regimens and delivery systems for postoperative analgesia, the practising anaesthesiologist requires sound and easily available advice on which to base decisions about postoperative pain management. Web-based guidelines such as PROSPECT16 and the Department of Veterans Affairs in the USA19 offer rapid access to practical advice on pain management.

To produce clinically relevant, evidence-based recommendations for postoperative pain management, PROSPECT assesses not only the procedure-specific evidence but also transferable evidence from other appropriate surgical procedures, and takes account of currently accepted clinical practice, within the limits of a rigorously defined methodological process.

PROSPECT offers a number of alternative, evidence-based recommendations for each surgical procedure, which inform and support the clinical decision-making process at a number of stages in the management of postoperative pain. In addition to the six procedures already available on the website (laparoscopic cholecystectomy, total hip arthroplasty, abdominal hysterectomy, open colonic resection, herniorrhaphy and thoracotomy), reviews of pain management for other major surgical procedures are either under current evaluation or are scheduled to be started within a short time-scale. These include total knee arthroplasty and extensive breast surgery. The currently available procedures are all subject to formal review and updating within
a prescribed time-frame, so that PROSPECT web-based recommendations remain valid and clinically relevant for the future.

### CONFLICT OF INTEREST STATEMENTS

**Frederic Camu** has functioned on advisory boards and received research grants from different pharmaceutical companies (Janssen-Cilag, Novartis, Roche, Pfizer, Glaxo—Smith Kline, AstraZeneca, Fulcrum, Boots, Merck Sharpe Dohme). **Barrie Fischer** has acted as advisor to a number of pharmaceutical and medical equipment companies (Pfizer, AstraZeneca, B Braun). **Roseanne Wilkinson** is employed by Choice Medical Communications, who receive funding from Pfizer to support PROSPECT. **Henrik Kehlet** has acted on advisory boards in Pfizer and Glaxo—Smith Kline.

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Figure 2. Overall PROSPECT recommendations for postoperative pain management following thoracotomy.
Practice points

- web-based PROSPECT recommendations (www.postoppain.org) are designed to be used within the workplace wherever the anaesthesiologist has access to the internet
- the recommendations offer clinical decision support from the preoperative period onwards; they are useful when assessing patients prior to surgery and assist both the surgical and anaesthetic aspects of care when planning the optimal postoperative pain management programme
- although aimed primarily at clinicians, some of the information is useful as educational material for the patients; well-informed patients have a more realistic expectation of their own role in postoperative pain management, and this can contribute to lower pain scores and increased patient satisfaction

Research agenda

- although there are strong arguments for procedure-specific analgesic recommendations, such as those provided by the PROSPECT collaboration, the reviews conducted in several procedures to date have unfortunately shown a severe need for more research due to relatively little procedure-specific information, small-sized studies, and use of different doses and formulations etc
- future research should focus on well-defined analgesic and side-effect outcomes, and well-defined types of surgery; additionally, studies need to assess procedure-specific dynamic pain outcomes and perform well-defined assessment of opioid-related side-effects
- future research should focus on multi-modal analgesic techniques in order to enhance analgesia and reduce side-effects. Most procedure-specific studies are based on single-analgesic interventions instead of a more rational multi-modal approach. Hopefully, such studies will be able to achieve more effective dynamic pain relief, which is a prerequisite for optimal recovery

ACKNOWLEDGEMENTS

The authors would particularly like to acknowledge the PROSPECT Working Group (Table 1) for their contributions to this unique collaboration to review the evidence and formulate recommendations for procedure-specific pain management.

PROSPECT is supported by an educational grant from Pfizer Inc., New York, NY, USA. This paper makes no specific recommendations about the use of any medical products, drugs or equipment manufactured by Pfizer Inc. or by any of its subsidiaries.

REFERENCES


