

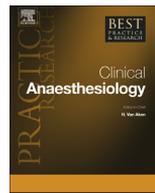


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Procedure-specific pain management and outcome strategies



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Optimal dynamic pain relief is a prerequisite for optimizing post-operative recovery and reducing morbidity and convalescence. Procedure-specific pain management initiative aims to overcome the limitations of conventional guidelines and provide health-care professionals with practical recommendations formulated in a way that facilitates clinical decision making across all the stages of the perioperative period. The procedure-specific evidence is supplemented with data from other similar surgical procedures and clinical practices to balance benefits and risks of each analgesic technique. There is emphasis on the use of multimodal analgesia and preventive analgesia aimed at reducing central sensitization. Importantly, the benefits of dynamic pain relief may only be realized if other aspects of perioperative care such as the use of minimally invasive surgery, approaches to reduce stress responses, optimizing fluid therapy and optimizing post-operative nursing care with early mobilization and oral feeding are utilized.

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Introduction

Multimodal, multidisciplinary fast-track surgery, also known as accelerated post-operative rehabilitation or enhanced recovery after surgery (ERAS) pathways, has been shown to reduce perioperative morbidity and enhance functional recovery after surgery and, thus, shorten the duration of hospital stay [1–4]. Optimal dynamic pain relief is considered a prerequisite for the success of fast-track surgery programs [5]. Also, inadequately treated pain may have long-term consequences with regard to the development of chronic pain, which can be a significant economic burden for health systems and societies [6,7].

Although the benefits of optimal pain management are well recognized, the treatment of post-operative pain continues to be a major challenge. Several studies conducted worldwide have reported that a large proportion of patients suffer from moderate-to-severe pain after surgery [8,9]. A recent large observational trial reported that patients undergoing surgical procedures that have the reputation of being less painful received inadequate pain relief. By contrast, patients undergoing highly painful surgical procedures received more aggressive analgesic therapy [9]. The reasons for suboptimal pain management, despite the considerable progress in analgesic pharmacology and techniques of administration, may be related to inadequate or improper application of available analgesic therapies, probably due to the significant amount of new and conflicting information that is increasingly available.

Conventional approaches that guide pain management

Several evidence-based pain management guidelines are available that offer general advice for optimal pain management [10,11]. These guidelines provide excellent information regarding the overall concepts of optimal pain management as well as the benefits and limitations of available analgesics and analgesic techniques. However, they do not seem to have made any impact on the overall incidence of inadequate post-operative pain management. The failure of these guidelines may be that they are generalized for all surgical procedures and, therefore, may confuse a practitioner who intends to use them for specific surgical procedures.

Another approach that can guide daily practice is the use of number-needed-to-treat (NNT, number of patients that need to be treated with an analgesic to achieve at least 50% pain relief in one patient, compared with placebo) league tables as a guide to measuring efficacy of various analgesics [12]. These NNT league tables allow easy comparisons between drugs. However, there are several limitations of using NNT tables to guide pain therapy. The NNT concept does not take into consideration gradual effects of an analgesic as it sets a cut-off at 50% pain relief compared with placebo. Because the therapeutic objectives may vary based upon patient population and surgical procedures, an analgesic providing 30% pain relief may be considered clinically relevant. However, this may be deemed to be ineffective based on NNT league tables. Furthermore, the clinical significance of a 50% reduction in pain scores may vary based upon the degree of pain at the time of measurement. For example, a reduction from a pain score of 8/10–4/10 would be clinically significant; however, a reduction from a pain score of 4/10–2/10 may not be clinically significant [13,14].

Another important limitation of the guidelines [10,11] and the NNT league tables is that they are derived from multiple surgical procedures with varying pain characteristics (e.g., type (somatic vs. visceral), location, intensity and duration). Because different surgical procedures may result in different types, intensities and locations of pain, the efficacy of an analgesic may vary depending upon the type of surgical procedure (e.g., differing efficacy of paracetamol in different pain models).

Also, the efficacy of combinations of analgesics (i.e., the multimodal analgesia approach) varies significantly between surgical procedures. For example, the combination of paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) can provide significant pain relief after mild or moderately invasive surgical procedures, but their benefits may be smaller in patients undergoing more extensive surgical procedures receiving epidural analgesia.

It is well recognized that the intensity of pain may not always correlate with the consequential effects on post-operative outcome. For example, the severity of pain after dental surgery may be similar to that after thoracotomy; however, inadequate pain relief after thoracotomy may result in significant

morbidity including pulmonary dysfunction, which is not the case with the dental procedure. Therefore, the risk–benefit ratio and thus the choice of analgesic technique may vary based upon the type of the surgical procedure. Similarly, the consequences of pain after an open procedure are different from that after an endoscopic procedure (e.g., laparotomy vs. laparoscopy or thoracotomy vs. thoracoscopy). Thus, epidural analgesia may be preferable for pain management after thoracotomy or “open” major abdominal surgery but it may not be appropriate for its routine use after a thoracoscopic or laparoscopic surgery because of less influence of pain on pulmonary or bowel function. A systematic review of randomized trials in patients undergoing laparoscopic colonic surgery revealed that pain scores in patients receiving multimodal analgesia were within an acceptable range (i.e., <4/10), suggesting that epidural analgesia may not be necessary for laparoscopic procedures [15].

Of note, the relevance of adverse effects of different analgesics may depend on the type of surgical procedure. For example, the risk of bleeding that is associated with NSAIDs may be more relevant for operations with greater potential for bleeding complications (e.g., tonsillectomy, plastic surgery and major joint replacement) than in others (e.g., cholecystectomy and herniorrhaphy). Similarly, the consequences of opioid-related adverse effects may vary between surgical procedures, although opioid use should be reduced for all surgical procedures. Also, some analgesic modalities (e.g., intraperitoneal or intra-articular treatments and peripheral nerve blocks) are specific for certain surgical procedures, thus emphasizing the problems with general guidelines.

The procedure-specific pain management (PROSPECT) initiative

Recognition of the above-mentioned limitations of general pain management guidelines and NNT league tables led to the concept of procedure-specific pain management recommendations. The PROSPECT (PROcedure-SPECific Postoperative Pain Management) Working Group is made up of an international panel of anaesthesiologists and surgeons (Appendix 1). The PROSPECT initiative aims to provide health-care professionals with practical procedure-specific pain management recommendations formulated in a way that facilitates clinical decision making across all the stages of the perioperative period. The development of recommendations is based on a rigorously defined methodological process, which includes systematic reviews of the literature (using the protocol of the Cochrane Collaboration to evaluate randomized controlled trials of analgesic, anaesthetic and surgical interventions affecting post-operative pain) in the specific type of surgery [16]. The procedure-specific evidence is supplemented with data from other similar surgical procedures (i.e., transferable evidence) and current clinical practices to balance benefits and risks of each analgesic technique (Table 1). These recommendations allow for a balance between the invasiveness of the analgesic technique and the consequences of post-operative pain. The overall PROSPECT recommendations are presented in the form of a flow diagram (Figs. 1 and 2).

Table 1

Relationship between quality and source of evidence, levels of evidence (LoE) and grades of recommendation (GoR). From PROSPECT website – www.postoppain.org.

Study type	Study quality assessments			LoE	Grade of recommendation*	
	Statistical Analyses and Patient Follow-up Assessment	Allocation Concealment (A–D)	Jadad score		Specific procedure	Transferable evidence
Systematic review with homogeneous results	NA	NA	NA	1	A	B
Randomized controlled trial	Statistics reported and >80% follow-up	And A B	1–5 3–5	1	A	B
Randomized controlled trial	Statistics not reported or questionable, or <80% follow-up	Or/or B Or/and C And/and D	1–2 1–5 1–5	2	B	C
Non-systematic review, cohort	NA			3	C	
Clinical practice or expert opinion				4	D	

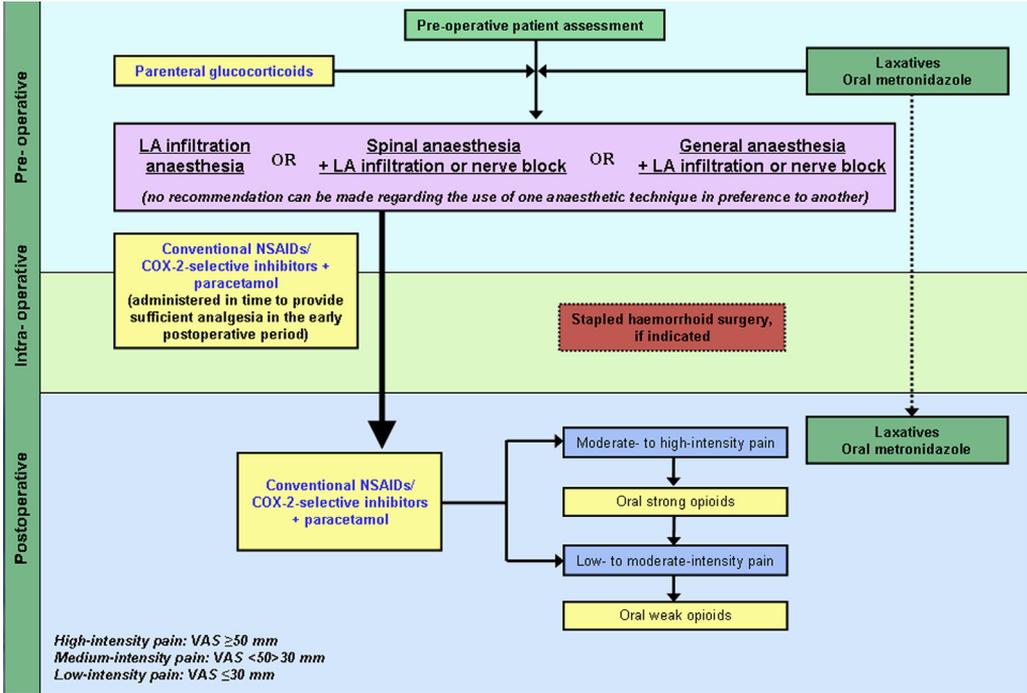


Fig. 1. Overall PROSPECT recommendations for pain management after haemorrhoid surgery. Modified from PROSPECT website – www.postoppain.org. LA = local anaesthetic, NSAID = non-steroidal anti-inflammatory drug, COX-2 = cyclooxygenase-2, VAS = visual analogue score.

Intraoperative interventions in time to secure analgesia in immediate postoperative period	
<ul style="list-style-type: none"> • Single dose of dexamethasone 4-8 mg • Intravenous cyclo-oxygenase (COX)-2 specific inhibitor or conventional non-steroidal anti-inflammatory drug (NSAID) and intravenous paracetamol (acetaminophen) • Wound infiltration with long-acting local anaesthetic at the end of surgery • Intravenous lidocaine bolus followed by continuous infusion 	
Postoperative Period	
High-intensity pain (VAS ≥ 50 mm)	<ul style="list-style-type: none"> • COX-2 specific inhibitor or NSAID + paracetamol + intravenous patient-controlled analgesia opioid • Intravenous lidocaine infusion, if above therapy is ineffective
Moderate-intensity pain (VAS > 30 < 50 mm) or Low-intensity pain (VAS ≤ 30 mm)	<ul style="list-style-type: none"> • COX-2 or NSAID + paracetamol ± weak opioid
Multi-modal rehabilitation protocols	

Fig. 2. Overall PROSPECT recommendations for pain management after colonic resection. Modified from PROSPECT website – www.postoppain.org. VAS = visual analogue score.

These web-based guidelines offer rapid access to detailed information that allows the readers to provide supporting arguments for and against the use of various interventions and make their own decisions based on their practice. 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 vs. their post-operative administration across different types of surgery. The ultimate aim is to encourage practitioners to incorporate these recommendations into their practice by developing procedure-specific clinical pathways for pain management that are relevant to their practice.

A recent observational trial showed significant improvement in pain management after the implementation of procedure-specific multimodal analgesic protocols as a part of a “quality management system”. Such observations strengthen the importance of and need for evidence-based procedure-specific pain management guidelines [17].

PROSPECT recommendations

The PROSPECT group has systematically reviewed pain and other outcomes following analgesic, anaesthetic and surgical interventions for several surgical procedures including laparoscopic cholecystectomy, total hip arthroplasty, total knee arthroplasty, abdominal hysterectomy, non-cosmetic breast surgery, thoracotomy, haemorrhoid surgery, herniorrhaphy, colonic resection and radical prostatectomy [15,18–23]. In addition to the procedures already available on the website (www.postoppain.org), reviews of pain management for other surgical procedures are either under current evaluation or are scheduled to be started within a short timescale. The currently available procedures are subject to formal review and updating so that the recommendations remain valid and clinically relevant for the future.

Limitations of PROSPECT recommendations

Despite the rigour of the systematic review and consensus processes, the PROSPECT initiative has some limitations. The strength of a systematic review depends entirely on the quality of the published studies. In addition, there may be descriptions of interventions, doses or routes of administration in published studies that are no longer appropriate in current practice or alternatively some pain management techniques may be introduced into current clinical practice without being subjected to a rigorous comparative study, thus decreasing the clinical relevance of the review. Therefore, the PROSPECT group has had to depend upon transferable evidence and best clinical practices to provide recommendations.

The concept of multimodal analgesia

It is obvious from the above text that PROSPECT recommends ‘multimodal’ analgesia for all procedures assessed thus far. The recommendations for use of multimodal analgesia date back to the 1990s, when it was realized that single analgesic modalities such as the sole administration of opioids do not control post-operative pain, in particular movement-related pain, with acceptable adverse effects [24]. This led to the development of the concept of ‘multimodal’ or ‘balanced’ analgesia [25]. This concept suggests that combining analgesics with different mechanisms or sites of action should lead to improved analgesia, reduced opioid requirements and/or reduced adverse effects. It is based on assumed synergistic effects of combinations of systemically and locally administered analgesic drugs. There are several analgesic combinations for which such an effect has been shown in meta-analyses such as combinations of paracetamol with NSAIDs [26] and paracetamol with opioids [27]. Other proven combinations include non-selective NSAIDs and selective cyclooxygenase (COX)-2 inhibitors with opioids [27] and alpha-2-delta modulators (i.e., gabapentin and pregabalin) with opioids [28,29]. The *N*-methyl-*D*-aspartate (NMDA), antagonists ketamine [30] and magnesium [31] as well as the alpha-2 agonists clonidine and dexmedetomidine [32] in combination with opioids are also supported by meta-analyses. Perioperative use of intravenous lidocaine infusion [33] and corticosteroids, namely dexamethasone [34], has also been shown to be useful adjuncts to opioid analgesia.

Although the concept of multimodal analgesia is well accepted, there are several concerns with the published meta-analyses discussed above. These meta-analyses have included data from studies with different surgical procedures rather than conducting procedure-specific analyses. In addition, these analyses have focused on the combination of only two analgesics, of which one was an opioid, which does not reflect a common clinical practice of using three or more analgesic combinations including opioids. Only limited data are available evaluating three or more analgesic combinations, for example, the combination of COX-2 inhibitor and gabapentin along with opioids improve pain relief after abdominal hysterectomy [35]. However, for the same surgical procedure, the addition of pregabalin and dexamethasone to paracetamol and opioid had no beneficial effects [36], while after tonsillectomy both combinations were superior to paracetamol plus opioid [37]. Combining dexamethasone and pregabalin after lumbar spinal surgery is also superior to the single components [38]. Overall, several recently published studies show the superiority of a multimodal approach using a combination of multiple analgesics compared with simple opioid analgesia. However, identification of the useful components is impossible due to methodological limitations. Examples here are studies assessing multimodal analgesic techniques for lumbar decompression surgery [39] and total knee replacement [40].

With regard to local and regional analgesic techniques as a component of multimodal analgesia approach, it is intuitively obvious that their use as well as their efficacy and risk–benefit ratio is procedure specific. For example, wound infiltration of local anaesthetics is effective after caesarean section [41], but has only questionable benefit after lumbar spine surgery [42]. Similarly, the use of local infiltration analgesia is supported after total knee replacement, but not after total hip replacement [43]. Also, there are increasing data to suggest that the benefits of systemic analgesics as a component of multimodal analgesia are procedure specific. Pregabalin and gabapentin are a useful component of multimodal analgesia for lumbar spine surgery [44], but not for arthroscopic knee ligament repair [45] and cosmetic surgery [46].

Overall, there is good evidence-based support for the concept of multimodal analgesia; but data are lacking on the procedure specificity of this approach and on the relevance of combinations of multiple analgesics in this setting. In addition, it is not clear if the currently available tools are appropriate for the assessment of the value of multimodal analgesia regimens [47]. Future studies should enable individualization of multimodal approaches with respect to the type of surgery, specific adverse effects of analgesics and the risks factors for specific patients.

The concept of preventive analgesia

The last 25 years have seen an extensive debate on the issue of ‘prevention of post-operative pain’, initiated by a paper by Wall with the same title in 1988 [48]. This led initially to the classical definition of ‘pre-emptive’ analgesia, that is, analgesic therapy initiated prior to surgical insult in contrast to the same treatment after surgery [49]. This rather simplistic concept has been challenged by the findings of trials assessing it, which showed inconsistent and clinically insignificant benefits [50]. A careful analysis of the underlying concepts revealed that providing analgesia pre-, intra- and post-operatively permits eight different treatment combinations, which might yield different outcomes [49], leading to the suggestion that the term ‘pre-emptive’ analgesia should be abandoned [50–52].

As a consequence, a new concept of ‘preventive analgesia’ was coined, which is commonly defined as preventing central sensitization [50–52] and operationally assessed as the analgesic effect of a medication outlasting its clinical duration of action by 5.5 half-lives [48]. The effects of such an approach, if proven, could translate into improved analgesia in the post-operative period and/or into prevention of persistent post-surgical pain [53].

Preventive analgesic effects of regional anaesthetic techniques have been reported in meta-analyses, which suggest extended post-operative analgesia [54] as well as reduced incidence of persistent post-surgical pain [55]. However, it is not yet clear if these benefits are, at least in part, due to the systemic effects of local anaesthetics similar to those observed with intravenous administration of lidocaine [54]. Also, it is possible that the observed benefits of local/regional anaesthesia techniques are due to opioid sparing, as opioids enhance central sensitization [53]. Similar effects of preventive analgesia have been shown with alpha-2-delta modulators, which not only improve post-operative

analgesia as discussed above, but also reduce the incidence of persistent post-surgical pain [56]. A meta-analysis gives limited support to the preventive effect of perioperative ketamine [57]. Interestingly, a randomized controlled trial shows preventive effects of intraoperative nitrous oxide use leading to improved post-operative analgesia [58] and reduced incidence of persistent post-surgical pain [59].

As there continues to be concerns about the methodology of many of the trials included in these meta-analyses and as a recent meta-analysis with a different methodology contradicts some of these results [57], it may be too early for definitive conclusions [50]. Nevertheless, the reports of 'preventive' analgesia are more promising than those of the obsolete concept of 'pre-emptive' analgesia. They have also more clinical relevance in view of their potential to reduce the underestimated problem of persistent post-surgical pain. Furthermore, they integrate nicely into the concept of multimodal analgesia discussed above.

Integration of procedure-specific pain relief with fast-track recovery programs

As mentioned above, the increased implementation of standardized procedure-specific post-operative pain treatment protocols is a prerequisite for optimizing post-operative recovery and reducing morbidity and convalescence [1–4]. The concept of "fast-track" surgery or "enhanced recovery programs" is based upon a multimodal implementation of evidence-based perioperative care components. The concept has been demonstrated to enhance recovery and reduce morbidity as well as costs across many surgical procedures. However, in addition to optimal post-operative pain management, several other aspects need to be controlled to gain the full benefits of the provided dynamic analgesia, such as minimal invasive surgery, regional anaesthetic techniques to reduce stress responses, optimizing fluid therapy and optimizing post-operative nursing care with early mobilization and oral feeding [60,61].

Although much evidence is available, a continuous flow of regional or national surveys show that implementation is lacking behind the existing evidence [60,62]. In order to enhance the use of the fast-track methodology, there is a critical need for collaboration between various health-care providers involved in perioperative patient care (e.g., anaesthesiologists, surgeons, nurses and physiotherapists). In this process, the availability of procedure-specific perioperative analgesic treatment strategies is crucial. Hopefully, further development of more effective components of multimodal opioid-sparing analgesia will facilitate this process.

Summary

The importance of effective pain control in improving outcome from surgery is well recognized. With increasing complexity of surgical procedures being performed in patients with challenging co-morbid conditions as well as increasing choice of confusing analgesic regimens, there is a need for sound and easily available advice on which to base decisions about optimal post-operative pain management.

The PROSPECT initiative aims to overcome the limitations of conventional guidelines and provide health-care professionals with evidence-based, procedure-specific information for the use of analgesic interventions. To produce clinically relevant recommendations, transferable evidence from other appropriate surgical procedures as well as currently accepted clinical practice are taken into consideration. The proposed recommendations weigh the analgesic efficacy and potential risks and provide optimal analgesia with minimal adverse events. These web-based guidelines offer rapid access to practical advice on pain management. This approach offers a foundation for the development of clinical decision-making process, which may be incorporated in a clinical pathway in an effort to improve the overall outcome.

There is a further need for assessing the role of incorporating procedure-specific pain therapies in clinical pathways for improving compliance with protocols and thus improving perioperative outcome and reducing hospital stay as well as achieving early return to activities of daily living.

Practice points

- Post-operative recovery and mobilization are influenced by effective pain control.
- The goal of pain therapy should be to minimize pain, not only at rest but also during activity. However, the ultimate aim should be to improve perioperative outcome and ambulation rather than achieve a specific pain score.
- There is good evidence supporting the concept of multimodal analgesia; but this evidence is often not procedure specific and mainly limited to combinations of only two analgesics, one of which is an opioid.
- The concept of preventive analgesia defined as techniques preventing central sensitization has currently only limited support in the literature but shows significant promise.
- Incorporation of procedure-specific pain management recommendations such as those proposed by PROSPECT into clinical pathways improves pain relief and post-operative outcome. When using these recommendations, clinicians must still consider the clinical circumstances, local regulations and local prescribing information in each case.
- In addition to optimal post-operative pain management, several other aspects need to be controlled to gain the full benefits of the provided dynamic analgesia, such as minimal invasive surgery, regional anaesthetic techniques to reduce stress responses, optimizing fluid therapy and optimizing post-operative nursing care with early mobilization and oral feeding.

Research agenda

- Systematic reviews conducted by the PROSPECT collaboration have revealed several areas for future research where current literature is insufficient or conflicting. Most of the studies are underpowered and have a significant variability in the methodological quality. Therefore, several questions about the relative benefits—risks of the various approaches in improving post-operative pain management remain unanswered, until further large, well-designed trials have been performed.
- Future research should focus on well-defined analgesic and adverse effect outcomes after well-defined types of surgery. Because the pain models and efficacies of analgesics may vary between procedures, studies need to assess procedure-specific dynamic pain outcomes and perform well-defined assessment of opioid-related adverse effects.
- There is a need to identify optimal analgesic combinations and optimal route of analgesic administration to optimize current concepts of multimodal analgesia.
- The impact of preventive analgesia on long-term outcomes including return to activities of daily living and incidence of chronic pain needs further evaluation.
- There is a need for comparing the intensity of pain and analgesic approaches after surgical procedures with similar pathophysiology of pain, which would allow determination of transferable evidence.
- Finally, future trials should include multimodal rehabilitation protocols (i.e., fast-track or enhanced recovery programs) as an integral part of the study design. This will permit to differentiate the effects of the analgesic interventions on perioperative outcome from those of the enhanced recovery programs, which are becoming the standard of care.

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Appendix 1. Prospect Collaboration.

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