


The role of intraoperative interventions to minimise chronic postsurgical pain

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Abstract

Chronic postsurgical pain (CPSP) is the most common complication following surgery, with increasing evidence of both its prevalence and severity. While awareness of the various risk factors for this long-term condition is also increasing, effective prevention remains elusive. In this review, we describe the increasing evidence for preventive or 'protective' strategies. Controversies and conflicting human data are presented along with suggestions for improved future study.

Keywords

Pain, postoperative, pain management, acute pain, chronic pain, chest pain, pain measurement

Introduction

Chronic postsurgical pain (CPSP) is the most common complication following surgery, with increasing evidence of both its prevalence and severity.¹ While awareness of the various risk factors for this long-term condition is also increasing, effective prevention remains elusive.^{2,3}

Preventive analgesia aims to reduce sensitisation from the barrage of nociceptive afferent input to achieve neuroprotection from pathological changes in central pain pathways. The effects of this analgesia must, by definition, outlast the expected pharmacokinetic effect of the drug itself – usually described as 5.5 times the half-life ($t_{1/2} \times 5.5$).⁴

Preventive analgesia is distinct from *preemptive* analgesia, where the analgesic intervention is delivered prior to incisional injury rather than as a response to signs of nociception or to the patient description of pain. This review will argue that *preemptive* analgesics have not stood the test of prospective study.⁵

Examples of preventive analgesia

There are three main categories to consider: regional anaesthesia (RA), ketamine and gabapentinoids.

Regional anaesthesia

As described above, most of the original work was based on the *preemptive* analgesia principle and sought to establish the importance of the *timing* of RA on subsequent pain. While failing to provide evidence for this approach, the studies below shed light on the distinction of clinically meaningful – as compared to statistically significant – differences in pain studies.⁵

Randomised trials of single doses of analgesic, via the epidural route, found statistically significant difference in postoperative visual analogue scale (VAS) scores but only at certain time points, and rarely consistently throughout the entire postoperative period.⁶ One study demonstrated a reduction in VAS score of 20 mm out of a maximum score of 100.⁷ The remainder of the studies of single epidural bolus, from the late

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1990s and collated in a recent systematic review, all concluded non-significant differences.⁵

A similar pattern is seen in the literature investigating the effects of drugs administered by continuous epidural infusion. Early reports of positive studies describe VAS differences of less than 20 mm^{8,9} and in some cases as low as 8 mm.¹⁰ Later studies refute these differences, and an overall systematic review, in 2002, again concludes equivalence in terms of the timing of analgesia.⁵

Only one study describes effects of the timing of RA on subsequent CPSP. In a double-blind manner, Obata et al.⁹ randomised 70 patients to mepivacaine, either before or following thoracotomy, describing a reduction in the numbers of patients reporting postsurgical incisional pain at 3 and 6 months. While already limited by small numbers, this study also excluded 12 patients: for postoperative epidural failure (2 patients), lost to follow-up (5 patients), death before final assessment (3 patients) or recurrence of malignancy within a year (2 patients) – all arguably reasons to include and analyse data on an intention-to-treat basis. It is possible to speculate, however, that the additional blockade of hyperalgesia during the early perioperative period may have contributed to improved CPSP outcomes in this study – despite not translating into improved pain scores in the acute period.^{11–14}

Despite this paucity of data, the practice of preoperative (and not necessarily *preemptive*) insertion continues, mainly for logistical reasons. This approach allows the block to be established and tested with the patient awake, in readiness for emergence from anaesthesia at the end of surgery. There is also a school of thought that claims fewer serious technical complications owing to immediate patient feedback.

Having refuted the role of timing for the 'preemptive analgesic' regimen, it is now necessary to consider the effect of RA on preventing CPSP. Most of the evidence comes from early studies in thoracotomy and often involves comparison between paravertebral block (PVB) and thoracic epidural analgesia (TEA) with similar outcomes. This was therefore followed by enthusiasm for the use of PVB as an alternative to the neuraxial blockade by TEA, especially as epidurals may cause more complications.¹⁵ Enthusiasm for PVB as a preventive technique has been further bolstered by mechanistic evidence from intercostal nerve somatosensory-evoked potentials, demonstrating afferent blockade in the form of reduced firing.^{16,17}

Comparison between either of these techniques and opioids alone favours RA.¹⁸ Study design is, however, an issue with only a few studies and only of small numbers of patients. This is compounded, in particular, by post hoc analysis of long-term outcomes in studies designed with the intention of only assessing acute pain.¹⁹ Although these provide a useful signal for hypothesis

generation, caution is suggested, as these are not an a priori examination of the data.

An updated, recent Cochrane review reiterates this caution despite a positive conclusion in favour of PVB for breast surgery and TEA for lung surgery.²⁰ Small numbers and examination centred on these two surgical groups specifically make it difficult to generalise and extrapolate to other surgical procedures.

Ketamine

The next most commonly studied preventive agent is the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine. The putative role of the NMDA receptor in the mechanism of central sensitisation is well described in the literature.²¹

A systematic review of ketamine supports its use in the acute pain setting via the intravenous or epidural routes.²² However, this systematic review only evaluates the addition of ketamine to opioids. The CPSP literature for ketamine is furthermore limited and confused by the variability in duration and dose of ketamine used, as well as potentially due to the variable – and often underreported – efficacy of superimposed RA.

A qualitative systematic review by McCartney and colleagues in 2004⁴ described poor quality studies but found in favour of ketamine overall for preventing CPSP. Subsequent studies have demonstrated mixed results.

Suzuki and colleagues carried out a more recent confirmatory study, administering ketamine by infusion for 3 days, but at only 0.05 mg/kg/h. Despite the small dose – as compared to routine clinical doses of 0.1–0.5 mg/kg/h – they achieved a reduction in CPSP at 3 months, but not at 6 months following thoracotomy.²³

Dualé and colleagues have refuted these positive results, with a negative trial following the use of twice the dose of ketamine infusion per hour, as well as 1 mg/kg bolus administered before surgery and then repeated during the procedure.²⁴ The key limitation with this study, however, was the fact that postoperative infusion was continued for only 24 hours, and hyperalgesia would be expected to continue beyond that duration. In addition, neither of these studies reported epidural failure rates or block success, for example, in terms of levels of dermatomal block achieved.

Individual studies and systematic review provide good quality supportive, although not conclusive, evidence for the use of ketamine. Furthermore, well-conducted trials of ketamine for the prevention of CPSP are warranted.²⁵

Gabapentinoids

The gabapentinoids, comprising gabapentin and pregabalin, have received the most recent attention in the

study of preventive analgesia. Both gabapentin and pregabalin bind to the $\alpha_2\delta$ (α -2- δ) subunit of the voltage-gated calcium channel and lead to a decrease in the release of neurotransmitters such as glutamate, norepinephrine and substance P, thereby targeting the putative role of these transmitters in central sensitisation.²¹ Both agents are established in the treatment of neuropathic pain.

As with the other techniques discussed so far, there is good evidence of acute pain reduction with both gabapentin and pregabalin. Historically, most studies investigated gabapentin, but there is more recent interest in pregabalin. The gabapentin studies typically used varying doses and duration. Efficacy is seen in acute pain reduction with doses above 400 mg²⁶ or duration beyond one postoperative day.^{27,28} Likewise, pregabalin also shows efficacy, even at a single time point, as long as it is given at a high dose of 300 mg.²⁹ A systematic review and meta-regression confirm³⁰ good evidence for both these gabapentinoids in terms of analgesia, opioid-sparing properties and tolerability (with Number Needed to Harm (NNH) for sedation of 35 and dizziness of 12).

In terms of prevention of CPSP, most studies again investigated gabapentin, with only three controlled trials of pregabalin. The effects of each on CPSP is less clear due to the short duration of drug administration but particularly so for gabapentin. When the issue of adequate duration has been addressed, promising studies have provided a strong signal of efficacy.

In the small studies where gabapentin was given in addition to RA, the beneficial effects of RA were often dominant, making any extra gains from the addition of gabapentin difficult to ascertain. This phenomenon was also seen when ketamine was given in combination with RA.

As an example, a study of the effects of preoperative gabapentin as an analgesic following thyroidectomy concluded no effect in the acute setting of coexisting local anaesthetic block of the neck (superior cervical plexus block).³¹ Despite the lack of difference at 24 hours, neuropathic pain at 6 months after surgery was reduced in the gabapentin arms, suggesting either single-dose preoperative gabapentin was protective or that there may have been sufficient variation in the efficacy of cervical plexus block in 24 patients analysed per group.

In a group of 240 patients undergoing total knee replacement, Buvanendran and colleagues tested a prolonged regimen of oral pregabalin against a placebo in a randomised controlled trial. The active arm received 300 mg pregabalin before surgery, and then continued postoperatively at 150 mg twice daily for 10 days before weaning doses for a further 4 days.³² This 14-day regimen reduced the incidence of neuropathic

pain at 6 months from 5.2% to 0% (6/113–0/115 patients, $p=0.014$ but no description of confidence intervals (CIs)). They observed a significantly increased rate of sedation and confusion in the first day after surgery, which settled with continued use, and therefore led to an overall recommendation of lower doses of pregabalin, with the hope of reduced side effects, hence allowing physiotherapy and intensive rehabilitation.

These preventive findings were also confirmed in the same year by a lumbar discectomy study conducted in patients with established neuropathic pain, therefore assessing a treatment effect in addition to surgery. This study demonstrated the effect of high-dose (300 mg) pregabalin given before and 1 day following surgery on reducing persistent pain at 3 months. The pre-existing neuropathic pain is difficult to separate from CPSP, and there is an argument to be made that this is an assessment of pregabalin for treating neuropathic back pain rather than preventing CPSP. In addition, the high doses used led to visual disturbances in the active study arm.³³

Subsequently, Pesonen et al.³⁴ investigated the effect of using only half the dose of pregabalin: 150 mg before surgery followed by 75 mg twice daily and only for 5 days duration in 70 patients. The study was designed and powered to detect a reduction in acute opioid use only following cardiac surgery, which it achieved. The secondary outcomes of pain at rest and during movement at 1 and 3 months were all non-significant, except for pain on movement at 3 months. It is tempting to speculate that if the pregabalin had been given longer than 5 days or at doses higher than 75 mg twice daily, they may have found significant differences at 1 month and at rest and on movement at 1 month. However, this study was designed to show safety in the elderly population, as well as efficacy in the acute period primarily – both achieved with no difference in side effects between the two groups (despite including only patients aged above 75 years) and a reduction in oxycodone use in the active arm. With only 35 patients in each group, it is likely that this study was underpowered for its secondary outcome of CPSP on movement.

The latter study did lead to a systematic review, including all gabapentin and pregabalin preventive analgesia studies, which concluded that both agents are indeed effective overall.³⁵ In terms of pregabalin, the authors go as far as commenting that the improvement in pain outcomes (odds ratio (OR): 0.09; 95% CI: 0.02–0.79, $p=0.007$) is ‘clinically implausible’ and, especially given the small number of studies, justifies further study in different surgical groups. They do also caution against these impressive results by pointing out the potential publication bias resulting from the omission of any negative studies.³⁵

A later systematic review has refuted these findings, pointing out that study numbers remain low for gabapentinoids and the need for further, larger studies.²⁵

Discussion

How much reduction is enough?

There is an important distinction to be made between statistically significant differences in studies and clinically meaningful, relevant or important improvement for patients. This is particularly important when preventive approaches carry any risk of adverse events. There is also the consideration of the ideal primary outcome measure: reduction in VAS or number of patients with pain in each group.

Clinical trials of analgesics report outcomes in terms of the number of patients with pain at a fixed time point, functional ability of individuals, or reduction in either pain score or analgesic requirement. The reduction in pain score is considered a success if there is a reduction of 30% and impressive if above 50%.³⁶ However, patients expect even larger differences in outcomes to consider an intervention a success.³⁷

One way to overcome this is by looking for larger reductions, either in pain scores or in the number of patients remaining pain-free. Both the positive studies of preventive pregabalin, described above, found large differences in CPSP outcomes. There is a risk with powering against such large differences of a beta error (i.e. a false negative). However, this may be deemed appropriate if a positive outcome at a level below this cut off would not be considered clinically meaningful. In addition, the tougher the outcome measured, the lower the placebo effect observed.³⁷

There is also an emerging debate over the role of preventive analgesia as simply additional robust multimodal analgesia delivered well, or to provide an additional preventive effect.^{38,39} This argument is strengthened by the observed preventive effects of additional analgesics such as nitrous oxide added to a multimodal regimen.⁴⁰ The latter may be acting as an NMDA antagonist⁴¹ and may prevent the development of CPSP,⁴⁰ as well as protecting from opioid-induced hyperalgesia (OIH), for example, from the use of intraoperative remifentanyl.

The antihyperalgesic role of all the candidate agents either directly or by sparing opioid use must be considered and specifically studied. A study of epidural ketamine failed to find a difference compared to saline in preventing CPSP after limb amputation but surprisingly found a reduced prevalence of stump pain in both arms of 21% and 33% as compared to 70%–80% reported in the literature.⁴² One explanation for this is the absence of opioids throughout the postoperative

period as part of this particular protocol of local anaesthetic and ketamine only. Therefore, opioid-sparing effects may be more important than simply allowing earlier mobilisation and rehabilitation.

This mechanistic distinction between analgesic effect and antihyperalgesic effect and, in turn, OIH as opposed to incision-induced phenotypes,^{43,44} could justify the need for demonstrating changes in pathways alongside large, clinically meaningful treatment effects of prevention.^{45,46}

Complete avoidance of opioids may, of course, be as inappropriate as the complete dependence on opioids, especially in surgery where the regional blockade of an extremity is not sufficient, for example, surgery on the chest or abdomen. The judicious multimodal use of antihyperalgesic agents along with careful dosing of opioids, with the aim of providing analgesia and sparing the need for opioids, is the alternative approach, utilising the relative advantages of both in moderation.⁴⁷

Preventive analgesia – the story so far

Studies, to date, have led to contradictory results, largely attributed to the small numbers of patients included, as well as poor study design.²⁵ However, there may also be differences in the mechanisms of persistence of pain between different surgical groups, which may, in turn, be reflected in the varying efficacy of preventive analgesia.⁴⁸

Much of the confusion arises when studies are designed to test the addition of agents, such as ketamine and the gabapentinoids, to RA. The variation in block success and duration of efficacy is difficult to control and is rarely reported. This is particularly important in studies of small numbers of patients where randomisation may not account for this variability of block. This may be contributing to the conflicting conclusions. Arguably, this represents pragmatic, real-world study of the *effectiveness* of these drugs in thoracotomy, where RA is standard practice and can fail postoperatively. However, these conditions are not ideal for *efficacy* studies of additional ketamine or the gabapentinoids, when the study numbers are also small.

This is also a discussion on the power of a study, as both the regional block and the adjuvant drugs may be contributing to the prevention of CPSP. To separately study the contribution of gabapentin, it is necessary to study larger numbers. In addition, if study numbers were much larger, randomisation would remove some of the effects of this variability in block success among groups. Failing that, it is important to report in detail the quality of RA achieved throughout the postoperative period.

The limitations of animal models

Most of the evidence for neuroprotection using preventive analgesics comes from the preclinical setting. However, this has proven difficult to translate to human beings. The following features of animal models may explain the disparity:

- Pain-free, healthy subjects prior to surgery;
- No effect of polypharmacy or co-morbidities;
- Easier to control for confounders, ensuring homogeneous test populations;
- Small sample size not an issue;
- Surgical insult is typically confined to a limb extremity with segmental somatic innervation;
- Surgery is short lived;
- Differences in pain pathophysiology and neuropharmacology;
- Differences in behavioural, psychological and social contribution to pain.

Future avenues for prevention

Procedure-specific study of CPSP has the potential to help us better understand the mechanistic differences between surgical incisions and pathologies, as well as potential for variations in the efficacy of preventive strategies.⁴⁸

The important contribution of combined analgesic therapy is well established in the management of acute pain following surgery.^{49,50} Surprisingly, few studies, however, have taken this approach with chronic pain, even in established neuropathic pain, although the exceptions have stood out for their efficacy.^{51,52}

The identification of preventive measures for CPSP undoubtedly holds great promise, especially when compared to the treatment of established chronic pain. While still in its infancy, the evidence base for perioperative preventive analgesia is strengthening.^{20,25,35}

Conflict of interest

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