Current status of pre-emptive analgesia

Joel Katz[a,b,c,d] and Colin J.L. McCartney[a,b,d]

Purpose of review

The controversy over pre-emptive analgesia continues unabated, with studies both supporting and refuting its efficacy. The timing of an analgesic intervention and presence of a placebo control may have significant impact on the interpretation of results and may have led to the premature conclusion that pre-emptive analgesia is of limited clinical utility. A review of the recent literature using strict definitions of pre-emptive and preventive analgesia is required in order to clarify the broader issue of the benefits of perioperative analgesia.

Recent findings

A total of 27 studies, published from April 2001 to April 2002, were found to evaluate pre-emptive ($n = 12$) or preventive analgesia ($n = 15$). Evidence for a benefit of preventive analgesia was strong, with 60% of studies finding reduced pain or analgesic consumption beyond the clinical duration of action of the analgesic intervention. Evidence for a benefit of pre-emptive analgesia was equivocal, with 41.7% of studies demonstrating that preincisional treatment reduces pain or analgesic consumption to a greater extent than does postincisional treatment.

Summary

Studies that used a preventive design had a greater likelihood of finding a beneficial effect. The application of preventive perioperative analgesia (not necessarily preincisional) is associated with a significant reduction in pain beyond the clinical duration of action of the analgesic agent, in particular for the *N*-methyl-D-aspartate antagonists. The classical definition of pre-emptive analgesia should be abandoned in favor of preventive analgesia. This will broaden the scope of inquiry from a narrow focus on preincisional versus postincisional interventions to one that aims to minimize postoperative pain and analgesic requirements by reducing peripheral and central sensitization arising from noxious preoperative, intraoperative and postoperative inputs.

Keywords

pre-emptive analgesia, pre-empts, preoperative, postoperative, preincision, postincision, timing

[a]Department of Anesthesia and Pain Management, University Health Network and [b]Mount Sinai Hospital, [c]Department of Public Health Sciences and [d]Department of Anaesthesia, University of Toronto, Toronto, Ontario, Canada

Correspondence to Joel Katz, PhD, Department of Anesthesia and Pain Management, Toronto General Hospital, 200 Elizabeth Street, EN 3-440, Toronto, Ontario, M5G 2C4, Canada
Tel: +1 416 340 3777; fax: +1 416 340 3698; e-mail: jkatz@uhnres.utoronto.ca

Abbreviations

NMDA	*N*-methyl-D-aspartate
NSAID	nonsteroidal anti-inflammatory drug
VAS	visual analog scale

Introduction

The possibility that pain after surgery might be amplified by the noxious events induced by surgical incision was initially put forward by Crile [1] and more recently by Wall [2], who coined the term 'pre-emptive preoperative analgesia'. Wall suggested that administration of opioids or local anesthetics before surgery might reduce the central (spinal) neural effects of the C-fiber induced injury barrage associated with incision, and thereby would reduce the intensity of postoperative pain.

Since then it has been documented that, although general anesthesia may attenuate the transmission of noxious afferent information from the periphery to the spinal cord and brain, it does not block it [3,4]. Moreover, systemic opioids may not provide a sufficiently dense blockade of spinal nociceptive neurons to prevent central sensitization [5]. The clinical significance of these findings for patients who receive general anesthesia during surgery is that while they are unconscious the processes that lead to sensitization of dorsal horn neurons are unaffected by the general anesthesia or routine doses of opioids. This sets the stage for increased postsurgical pain and an increased requirement for analgesics.

The first definition of pre-emptive analgesia [2] did not include the imperative to compare a preoperative intervention with a postoperative intervention. This requirement, adopted shortly thereafter [6], imposed a constraint that limited the demonstration of pre-emptive analgesia to a narrow set of experimental designs with little potential for clinically significant effects. The almost exclusive focus on this narrow definition of pre-emptive analgesia had the unintended effect of diverting attention away from certain clinically significant findings (e.g. from studies that compared a preoperative intervention with a placebo-control condition) because they did not conform to what had become the accepted definition of pre-emptive analgesia.

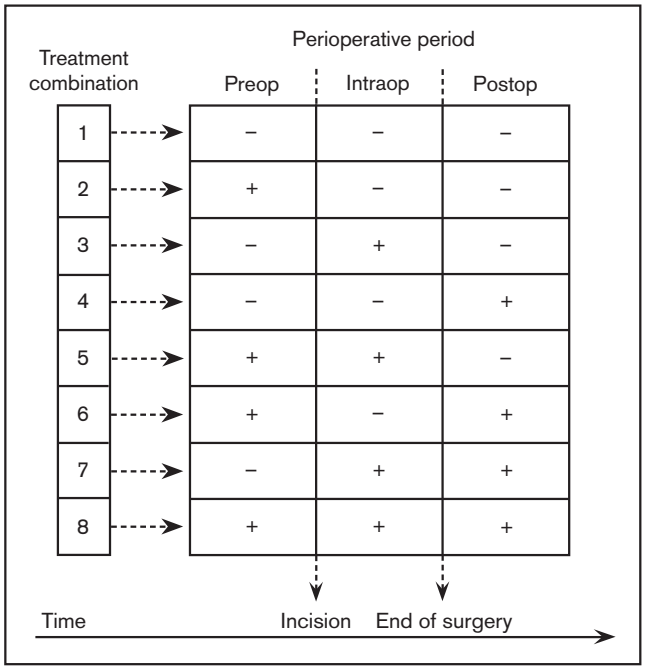
Since its introduction into the pain and anesthesia literatures, the concept of pre-emptive analgesia has evolved, based in part on confirmatory and contradictory evidence from clinical studies, new developments in basic science, and critical thought. This evolution has led to progress in our understanding of the mechanisms that contribute to acute postoperative pain. The suggestion that surgical incision triggers central sensitization has been expanded to include the sensitizing effects of

preoperative noxious inputs and pain, other noxious intraoperative stimuli, and postoperative inflammatory mediators and ectopic neural activity.

Targets of pre-emptive and preventive analgesia

The perioperative period can be divided into three distinct phases (Fig. 1): preoperative, intraoperative, and postoperative. Specific factors within these three phases contribute to the development of acute postoperative pain. These factors include the following: preoperative noxious inputs and pain; noxious intraoperative inputs that arise from the cutting of skin, muscle, nerve, and bone; and postoperative noxious inputs, including those that arise from the inflammatory response and ectopic neural activity in the case of postsurgical nerve injury. Each of these factors can contribute to both peripheral and central sensitization, and each is a legitimate target for a preventive approach. The relative contributions of the three factors to acute postoperative pain are dependent on the surgical procedure, extent and nature of tissue damage, duration of surgery, timing of treatments relative to incision, pharmacologic activity of the agent(s) used preventively, presence or absence of additional analgesia intraoperatively, nature of postoperative analgesia, and a host of other variables. Minimizing the negative impacts of as many of these factors in the three phases will increase the likelihood of preventing the induction and maintenance of peripheral and central sensitization. Preventing sensitization will reduce pain and analgesic requirements.

Figure 1. The various treatment combinations used to evaluate pre-emptive and preventive analgesia



The figure depicts the presence (+) or absence (−) of analgesic or local anesthetic administration during the three perioperative phases of surgery [preoperative (Preop), intraoperative (Intraop), and postoperative (Postop)]. The administration or nonadministration of analgesics during the three perioperative phases yields eight different treatment combinations and 36 possible two-group designs.

Figure 1 depicts the eight possible treatment combinations of administering or not administering analgesics across the three perioperative phases. The preoperative period encompasses interventions that begin days before surgery and up to those administered just minutes before skin incision. The intraoperative period includes interventions started immediately after incision to those initiated just before the end of surgery (i.e. skin closure). The postoperative period includes interventions started immediately after the end of surgery and may extend for days thereafter. Variability in the timing of administration of analgesic agents is greatest during the preoperative and postoperative periods (e.g. from days to minutes), but even within the intraoperative period there is considerable potential for differences among studies regarding when a postincisional intervention is instituted (e.g. from minutes to hours).

Definitions of pre-emptive and preventive interventions

For historical purposes, the term 'pre-emptive analgesia' is used in the present review to refer to evidence (i.e. reduced pain or analgesic consumption, or both) that preoperative treatment is more effective than the identical treatment administered after incision or surgery (e.g. treatment combination 2 versus 3, or 2 versus 4 in Fig. 1). According to this definition, the only difference between the groups is the timing of administration of the pharmacologic agent relative to incision [6,7]. As noted above, this definition is too restrictive and narrow [8,9]. A demonstration that presurgical treatment with analgesics, but not with a placebo, lessens pain and decreases postoperative analgesic requirements at a time when the agents are no longer clinically active (e.g. see the reports of Giannoni *et al.* [10••] and Reuben *et al.* [11••]) suggests that some aspect of postoperative pain can be prevented. However, the mechanism(s) for this effect and the time frame within which the effect occurs remain obscure.

The term 'preventive analgesia' [12] is used in the present review to refer to results from studies with designs that do not incorporate a postincision or postsurgical intervention (e.g. treatment combination 1 versus 2, or 1 versus 8 in Fig. 1), or if they do the preoperative and postoperative treatments are not administered in an identical manner (e.g. differences in dose, route, etc.). A preventive analgesic effect is demonstrated when postoperative pain or analgesic

consumption is reduced relative to another treatment, to a placebo treatment, or to no treatment, as long as the effect is observed at a point in time that exceeds the clinical duration of action of the target agent. Thus, in the absence of a post-treatment condition, the finding that pain or analgesic consumption is reduced relative to an untreated or placebo control condition is evidence of a preventive analgesic effect. However, such a design does not provide information regarding the factors that underlie the effect or the time frame within which the effect occurred.

Demonstration of a preventive effect does not require that an intervention be initiated before surgery; the timing of treatment may be during the procedure (e.g. treatment combination 1 versus 3 in Fig. 1) or even after surgery (e.g. treatment combination 1 versus 4 in Fig. 1). For example, a preventive effect is present if postoperative administration of a target analgesic agent but not a placebo results in reduced postoperative pain or analgesic consumption after the effects of the target agent have worn off (e.g. see the reports of Nguyen *et al.* [13•] and Reuben *et al.* [11••]).

Methodology

We conducted a PubMed database search, using the following keywords and limiting the search strategy to English language reports published from April 2001 to April 2002: pre-emptive or preemptive analgesia, preempts, pre-operative, preoperative, post-operative, postoperative, pre-incision, preincision, post-incision, postincision, and timing. The reference sections of the relevant articles were reviewed and additional articles were obtained if they evaluated the question of timing of analgesic administration.

The following criteria were used to select studies for review: randomized protocol; double-blind assessment of pain and analgesic use; report of pain using a reliable and valid measure; report of analgesic consumption; and, for studies that assessed the effect of timing according to the definition of preventive analgesia outlined above, measures of pain and analgesic consumption reported at a point in time that exceeds the duration of action of the target agent whose effect on postoperative pain is being examined. The latter criterion was included to ensure that the observed effects were not simply analgesic effects. The final criterion was the absence of methodologic problems that render the results ambiguous, and thus make interpretation difficult. Table 1 [14–30] lists the studies that were excluded from this review and shows which one or more of the six inclusion criteria were not met.

The PubMed search and subsequent review of identified articles yielded 27 studies that met the inclusion criteria. Table 2 [10••,11••,13•,31,40,41•,43••,44–54] shows the various experimental designs and the frequency with which they were used across the 27 studies. Tables 3 and 4 summarize the study outcomes according to the target agent administered and are divided into pre-emptive and preventive analgesia, respectively. Positive studies are those that reported a significant pre-emptive or preventive effect (i.e. reduced pain or analgesic consumption, or both). Negative studies are those for which the timing of treatment had an effect that was not significantly different from that in the control condition.

Table 1. Studies excluded from the present review for failing to meet one or more of the inclusion criteria

Reference	Year	Criterion not met
Local anesthetics		
[14]	2001	DB, DA
[15]	2001	DB, DA
[16]	2001	MP
[17]	2002	A
NSAIDs		
[18]	2001	DA
[19]	2002	P
[20]	2002	DB
Opioids		
[21]	2001	DA
NMDA antagonists		
[22]	2001	P
[23]	2001	MP
[24]	2001	P
[25]	2001	P
Tricyclic antidepressants		
[26]	2001	DA, MP
Local anesthetics and opioids		
[27]	2001	DB
[28]	2002	DB
[29]	2001	DA
Local anesthetics and NSAIDs		
[30]	2001	DB

The inclusion criteria are as follows: randomized (R); double-blind assessments (DB); report of pain using a reliable and valid measure (P); report of analgesic consumption (A); for studies that assess the effect of timing using the definition of preventive analgesia outlined in the text, measures of pain and analgesic consumption reported at a point in time that exceed the duration of action (DA) of the target agent; and absence of methodological problem (MP) or design flaw that render the results ambiguous, and thus make interpretation difficult. NMDA, *N*-methyl-D-aspartate; NSAID, nonsteroidal anti-inflammatory drug.

Pre-emptive analgesia

The literature search isolated 12 studies [35,38,43••,46–49,52–54] that examined pre-emptive analgesia, as defined above (Table 3). Five (41.7%) of those studies [36,43••,48,52,53] demonstrated positive pre-emptive analgesic effects, whereas seven (58.3%) [35,37,38,46,47,49,54] were negative.

The five positive studies included two that used nonsteroidal anti-inflammatory drugs (NSAIDs) [43••,53], one that used dextromethorphan [36], one

Table 2. Variety and frequency of experimental designs used to evaluate the timing of administration of different classes of analgesic agents relative to incision

Design number	Pre-emptive or preventive	Treatment combinations in Fig. 1	Total number of studies	References
1	PV	1, 2	3	[31–33]
2	PV	1, 2, 2	2	[10,34]
3	PE	1, 2, 3	2	[35,36]
4	PV	1, 3	1	[13•]
5	PV	1, 3, 3	1	[11••]
6	PE	1, 4, 6	2	[37,38]
7	PV	1, 5	1	[39]
8	PV	2, 2	4	[40,41•,42,44]
	PE	2, 2	1	[43••]
9	PV	2, 2, 2	1	[45]
10	PE	2, 2, 4	1	[46]
11	PE	2, 3	2	[47,48]
12	PE	2, 4	1	[49]
13	PV	3, 5	2	[50,51]
14	PE	5, 5	1	[52]
15	PE	7, 8	2	[53,54]
		Total	27	

Each design (column 1) is defined in terms of specific treatment combinations (column 3) shown in Fig. 1. Each design is also described as evaluating pre-emptive (PE) or preventive (PV) effects.

Table 3. Studies that evaluated pre-emptive effects

Agent(s)	Total number of studies	Pre-emptive effects [*n* (%)]	
		Positive	Negative
Local anesthetics	1	0 (0%)	1 (100%)
Opioids	3	0 (0%)	3 (100%)
NSAIDs	4	2 (50%)	2 (50%)
NMDA antagonists	1	1 (100%)	0 (0%)
Local anesthetics and opioids	2	1 (50%)	1 (50%)
Multimodal	1	1 (100%)	0 (0%)
Total	12	5 (41.7%)	7 (58.3%)

Shown is a summary of studies according to target agent administered, indicating the total number of studies and the numbers of studies with positive and negative pre-emptive effects. NMDA, *N*-methyl-D-aspartate; NSAID, nonsteroidal anti-inflammatory drug.

Table 4. Studies that evaluated preventive effects

Agent(s)	Total number of studies	Preventive effects [*n* (%)]	
		Positive	Negative
Local anesthetics	5	1 (20%)	4 (80%)
Opioids	1	1 (100%)	0 (0%)
NSAIDs	1	1 (100%)	0 (0%)
NMDA antagonists	6	4 (66.7%)	2 (33.3%)
Clonidine	2	2 (100%)	0 (0%)
Total	15	9 (60%)	6 (40%)

Shown is a summary of studies according to target agent administered, indicating the total number of studies and the numbers of studies with positive and negative preventive effects. NMDA, *N*-methyl-D-aspartate; NSAID, nonsteroidal anti-inflammatory drug.

that used a local anesthetic and an opioid [52], and one that used a multimodal regimen [47]. Particularly noteworthy is the study reported by Norman *et al.* [42••], who used a clever design to isolate the peripheral and central actions of intravenous ketorolac 30 mg when given before or after the inflation of a tourniquet for ankle surgery. The treatment group therefore had the benefit of both preincisional peripheral and central cyclo-oxygenase inhibition. Visual analog scale (VAS) pain scores were significantly lower in the treatment group up to 6 h after surgery. The positive results may point to the importance of peripheral cyclo-oxygenase inhibition as a mechanism for the observed pre-emptive effect, supporting the suggestion that NSAIDs may pre-empt different components of postoperative pain (e.g. peripheral and central sensitization) by more than one mechanism [55]. In a three-group study of patients undergoing elective upper abdominal surgery, Helmy and Bali [36] examined the use of intramuscular dextromethorphan 120 mg or saline given 30 min before skin incision or 30 min before the end of surgery as compared with a placebo control group of patients who received saline before and after surgery. A positive pre-emptive analgesic effect was demonstrated, with mean VAS scores at 6 h after surgery significantly lower in the preincisional group (13 mm) than in the postincisional (31 mm) and placebo (37 mm) groups. In addition, 24 h after surgery, cumulative meperidine consumption (via patient-controlled analgesia) in the preincisional group was reduced by 64% and 75% as compared with the postsurgical and placebo control groups, respectively.

Of the seven negative pre-emptive studies, four [46,47,49,54] did not include an appropriate control group that would have allowed for the evaluation of preventive analgesic effects. In addition, the two negative pre-emptive studies that evaluated both pre-emptive and preventive effects [35,37] actually found a significant reduction in cumulative analgesic intake between the preincisional and saline-treated control groups. However, because only a single value for cumulative intake was reported, it is not possible to determine whether the opioid-sparing effect occurred within (analgesic effect) or after (preventive effect) the period when the target agent was still active.

Preventive analgesia

The literature search isolated 15 studies that examined preventive analgesia (Table 4) [10••,11••,13•,31–34,39,40,41•,42,44,45,50,51]. Nine (60%) of those studies [10••,11••,13•,34,41••,42,44,45,50] found positive preventive analgesic effects and six (40%) [31–33,39,40,51] did not.

The nine positive studies included four that used *N*-methyl-D-aspartate (NMDA) antagonists [34,42,45,50], two that used clonidine [10••,41•] and three single studies that used a local anesthetic [13•], an opioid [11••]

and an NSAID [44]. A fascinating study by Reuben *et al.* [11••] demonstrated a significant reduction in pain 24 h after postincisional administration of 5 mg morphine injected intramuscularly or infiltrated directly into the exposed cancellous bone and bone marrow cavity [56] in patients undergoing iliac bone harvest. The incidence of pain 1 year later was significantly lower in the iliac infiltration group (5%) than in the intramuscular injection group (37%).

Of the six preventive studies that examined the use of NMDA antagonists, four found positive preventive effects [34,42,45,50]. Himmelseher *et al.* [42] gave a single, preincisional bolus dose of epidural ropivacaine and S(+)-ketamine, or ropivacaine and saline to patients undergoing total knee arthroplasty. Patients who received S(+)-ketamine had significantly lower pain scores at rest and on movement at both 24 and 48 h after surgery. In addition, cumulative consumption of ropivacaine (via patient-controlled epidural analgesia) was reduced significantly by approximately 40% in the ketamine group. Consistent with the conclusions of a recent review [57], NMDA antagonists have higher rates of success in producing preventive analgesia than do other agents. This may reflect their role in reducing central sensitization by their actions at the NMDA receptor–ion channel complex [58] or by reducing acute opioid tolerance [59].

The two studies that examined the role of clonidine demonstrated positive preventive analgesic effects [10••,41•]. Giannoni *et al.* [10••] administered a peritonsillar injection of ropivacaine and clonidine 1.5 mg/kg, ropivacaine alone, or saline before tonsillectomy. Patients in the ropivacaine and clonidine group used significantly fewer analgesics than did the saline control group between postoperative days 3 and 5. In addition, VAS scores were significantly lower in the ropivacaine and clonidine group on days 3 and 5. Yanagidate *et al.* [41•] gave oral clonidine 4 μg/kg or placebo as premedication to patients undergoing elective cesarean delivery, using a combined spinal/epidural technique. A significant reduction in cumulative morphine consumption (via patient-controlled analgesia) was found in the clonidine group as compared with the placebo group. The opioid-sparing effect was delayed and only became apparent 24 h after surgery. The promising results using clonidine warrant further study of the preventive effects of α_2 agonists alone and in combination with other analgesic agents.

Of the six negative preventive studies, five evaluated the role of local anesthetic agents [31–33,39,40] and one used ketamine [51]. Surprisingly, half of those studies demonstrated little [39] or no analgesic [32,51] effect of the treatment intervention, and therefore would have been unlikely to demonstrate a preventive analgesic effect.

Conclusion

The definition of preventive analgesia used in the present review broadens the scope of inquiry from a narrow focus on pre-emptive analgesia [60] to one that aims to minimize postoperative pain and analgesic requirements by reducing peripheral and central sensitization arising from noxious preoperative, intraoperative and postoperative inputs. Under certain circumstances, blocking or reducing transmission of noxious postoperative inputs (in the context of an unchecked injury barrage during surgery) leads to a significant reduction in pain long after the effects of the agent have worn off. Remarkably, in one study [11••] postincisional infiltration of morphine into the bone appeared to be associated with reduced pain incidence one year after surgery.

Sixty percent of the 27 studies examining the efficacy of preventive analgesia reported between April 2001 and April 2002, were found to produce a beneficial effect either by reduction in analgesic consumption, pain scores, or both. We believe this figure to be an underestimate of the true percentage of positive studies for two reasons. First, two studies that examined both pre-emptive and preventive analgesia [35,37] demonstrated a significant reduction in cumulative analgesic use over a time period that extended beyond the duration of action of the target intervention, and this might have represented a preventive analgesic effect. However, because it was not possible to determine from the data presented whether the difference in analgesic consumption occurred within or beyond the duration of analgesic action of the target drug, these significant effects were not included in the tally of preventive analgesic effects. Second, 50% of the negative preventive studies demonstrated little or no analgesic benefit of the target intervention, and therefore could not be expected subsequently to produce a preventive analgesic effect.

Inclusion of appropriate control groups when evaluating the effects of the timing of administration of analgesics relative to incision is essential if continued progress is to be made. Two-group studies (of pre-emptive analgesia) that do not find significant differences in postoperative pain or analgesic consumption between preincision and postincision groups are inherently flawed because of the absence of an appropriate control group (e.g. treatment combination 1 versus 8 in Fig. 1). The negative results from the studies of pre-emptive analgesia may point to the relative efficacy of postincisional or postoperative blockade (e.g. see the reports of Reuben *et al.* [11••] and Nguyen *et al.* [13•]) and not the inefficacy of preoperative blockade. Further research is needed to define the conditions under which blockade of perioperative

noxious inputs prevents central sensitization and interferes with the development of acute postoperative pain and the progression to chronicity.

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