Timing of treatment and preemptive analgesia

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The management of acute postoperative pain has been dominated by an outdated conceptualization of pain.[1] Pain is viewed as the endproduct of a passive transmission system that faithfully transmits a peripheral signal to the spinal cord and on up to a pain center in the brain. This view has led to an approach to managing postoperative pain that does not provide adequate control of pain, in part because it focuses on treating the patient only after the pain is well entrenched. Patients are transported to the recovery room after surgery, often in agonizing pain, where they then receive incremental doses of opioids in an effort to reduce already established pain. However, basic science and clinical data show that brief, noxious inputs or frank injury due to C-fiber activation (e.g. cutting tissue, nerve, and bone) induce long-lasting changes in central neural function that persist after the offending stimulus has been removed or the injury has healed.[2] The recognition that the processes involved in pain perception involve a dynamic interplay between peripheral and central mechanisms is inconsistent with the simplistic notion that pain results from transmission of impulses along a straight through pathway from the site of injury to the brain.

The practice of treating pain only after it has been established is slowly being supplanted by a preventive approach that aims to block transmission of noxious inputs before, during, and after surgery. The idea behind this approach is not simply that it reduces nociception and stress during surgery – although these are obviously worthwhile goals. The hypothesis is that the transmission of noxious afferent input from the periphery (e.g. arising from preoperative pain, incision, noxious intraoperative events, and postoperative inflammation and ectopia) to the spinal cord induces a prolonged state of central neu-ral sensitization or hyperexcitability that amplifies subsequent input from the wound and leads to heightened postoperative pain. By interrupting the transmission of noxious perioperative inputs to the spinal cord at various points in time throughout the perioperative period, a preventive approach can significantly reduce the induction of central sensitization, resulting in reduced pain intensity and lower analgesic requirements.

The goal of this chapter is to critically review the literature that examines the effect of the timing of administration of a variety of analgesic and anesthetic agents on postoperative pain and analgesic consumption. The first section provides a brief review of the history and recent progress in preemptive analgesia, followed by a description of the targets of a preemptive analgesic approach, and the definitions of preemptive and preventive analgesia used in the present review. Experimental designs are outlined that distinguish preemptive and preventive analgesia. The second section describes the criteria used for including studies in the present review and the experimental designs and treatment combinations that have been used in clinical studies that alter the timing of administration of analgesic agents. In the third section, the outcomes of the identified studies are reviewed according to the target agent(s) administered, the timing of administration relative to incision, route and dose of administration, and use of additional analgesic agents in the perioperative period. Outcomes are described in terms of the presence or absence or a preemptive or preventive effect. The final section concludes with recommendations for future research. Throughout the chapter, an attempt is made to highlight the enormous variability present in many aspects of the clinical studies.

DEFINITIONS AND TERMINOLOGY

History and recent progress in preemptive analgesia

The possibility that pain after surgery might be amplified by the noxious events induced by surgical incision was initially put forward by Crile[3] and more recently by Wall,[4] who coined the term "preemptive preoperative analgesia." Wall suggested that administration of opioids and/or local anesthetics before surgery might reduce the central (spinal) neural effects of the C-fiber-induced injury barrage associated with incision and thereby reduce postoperative pain intensity.

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.[5,6] Moreover, it appears that systemic opioids may not provide a sufficiently dense blockade of spinal nociceptive neurons to prevent central sensitization.[7] The clinical significance of these findings for patients that receive general anesthesia during surgery is that, while they are unconscious, the processes leading 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.

Notably absent from this first definition of preemptive analgesia was the imperative to compare a preoperative intervention with a postoperative intervention.[8] This requirement, adopted shortly thereafter, imposed a constraint that limited the demonstration of preemptive analgesia to a narrow set of experimental designs with little potential for clinically significant effects. The almost exclusive focus on this narrow definition of preemptive 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-controlled condition) because they did not conform to what had become the accepted definition of preemptive analgesia.

Since its introduction into the pain and anesthesia literatures, the concept of preemptive 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 triggered central sensitization has been expanded to include the sensitizing effects of preoperative noxious inputs and pain, other noxious intraoperative stimuli, as well as postoperative inflammatory mediators and ectopic neural activity.

Targets of preemptive and preventive analgesia

From a conceptual point of view, the perioperative period can be divided into three fairly distinct phases: preoperative, intraoperative, and postoperative (Fig. 7.1). The roles of specific factors within these three phases (as well as the interaction between factors) contribute to the development of acute postoperative pain. These factors include: (1) preoperative noxious inputs and pain, (2) noxious intraoperative inputs arising from the cutting of skin, muscle, nerve and bone, wound retraction, etc., and (3) postoperative noxious inputs, including those arising 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 contribution of these three factors to acute postoperative pain is dependent on the surgical procedure, extent and nature of tissue damage, duration of surgery, timing of treatments relative to incision, pharmacological activity of the agent(s) used preoperatively, presence or absence of additional analgesia intraoperatively, nature of postoperative analgesia, and a host of other variables. Minimizing the negative impact 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 7.1 depicts the eight possible treatment combinations of administering or not administering analgesics across the three perioperative phases (preoperative, intraoperative, and postoperative). The preoperative period encompasses interventions that begin days before surgery up to those administered just minutes before skin incision. The intraoperative period includes interventions started immediately after incision up to those initiated just prior to 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 in the pre- and postoperative periods (e.g. from days to minutes), but even within the intraoperative period there is considerable potential for differences among studies as to when a postincisional intervention is administered (e.g. from minutes to hours). The eight treatment combinations give rise to 28 different two-group designs.

Defining preemptive and preventive analgesia

There has been substantial debate over the appropriate definition of preemptive analgesia.[8-18] This has led to a variety of different terms and considerable confusion over what constitutes a preemptive analgesic effect.

Perioperative period

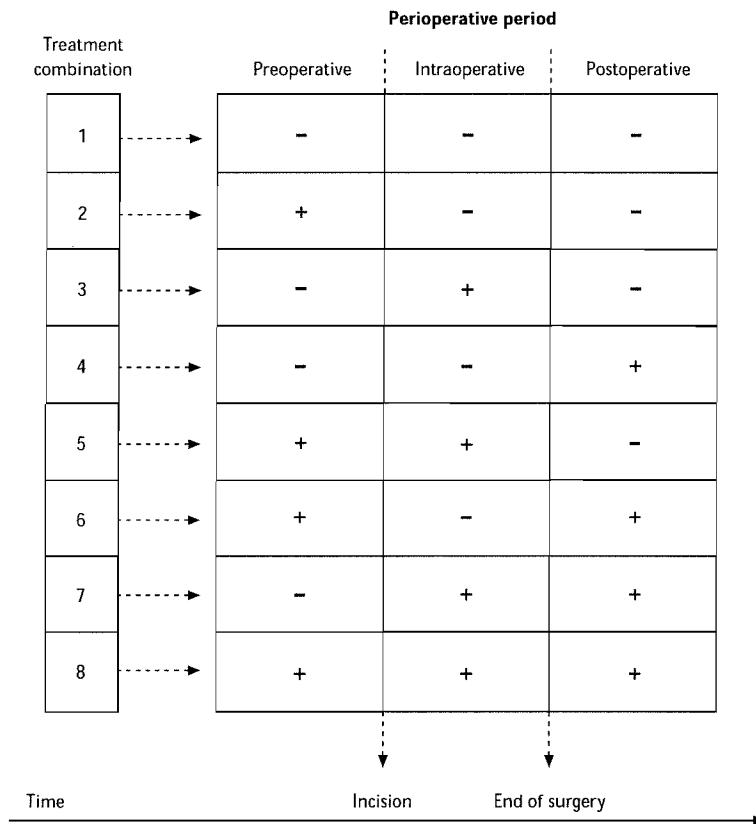| Treatment combination	Preoperative	Intraoperative	Postoperative
1	−	−	−
2	+	−	−
3	−	+	−
4	−	−	+
5	+	+	−
6	+	−	+
7	−	+	+
8	+	+	+

Time   Incision   End of surgery

Figure 7.1 *Schematic representation showing the presence (+) or absence (−) of analgesic or local anesthetic administration during the three perioperative phases of surgery (preoperative, intraoperative, and postoperative). The administration or nonadministration of analgesics during the three perioperative phases yields eight different treatment combinations.*

For historical purposes, and to avoid further confusion, I will use the term *preemptive analgesia* to refer to evidence (i.e. reduced pain and/or analgesic consumption) that preoperative treatment is more effective than the identical treatment administered after incision or surgery (e.g. treatment combinations 2;3 or 2;4 in Fig. 7.1). According to this definition, the only difference between the groups is the timing of administration of the pharmacological agent relative to incision.[8,14] As it turns out, the requirement that the groups be treated identically with the exception of timing is rarely achieved because it necessitates treating the two groups differently with respect to other potentially important anesthetic factors that may unwittingly influence the outcome of the study. Given identical analgesia, it may not be desirable or even safe to ensure that the groups are treated similarly with respect to other anesthetic agents.

As previously noted, this definition of preemptive analgesia is too restrictive and narrow.[13,14,19] Demonstrating that presurgical treatment with analgesics, but not a placebo, lessens pain and decreases postoperative analgesic requirements at a time when the agents are no longer clinically active[7,20] suggests that some aspect of postoperative pain can be prevented [although the mechanism(s) for this effect and the time frame within which the effect occurs remain obscure]. Thus, I will use the term *pre-*

ventive analgesia to refer to results from designs that do not incorporate a postincision or postsurgical intervention (e.g. treatment combination 1;2 or 1;8 in Fig. 7.1), or, if they do, the pre- and post-treatments are not administered in an identical manner (e.g. differences in dose or route). A preventive analgesic effect is demonstrated when postoperative pain and/or analgesic consumption is reduced relative to another treatment, a placebo treatment, or no treatment *as long as the effect is observed at a point in time that exceeds the expected 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-controlled condition is evidence of a preventive analgesic effect; such a design, however, does not provide information about the factors underlying 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;3 in Fig. 7.1) or even after surgery (e.g. treatment combination 1;4 in Fig. 7.1). For example, a preventive effect would be demonstrated if postoperative administration of a local anesthetic but not a placebo (in the context of an unchecked injury barrage from incision and other intraoperative events) resulted in reduced

postoperative pain and analgesic consumption after the effects of the local anesthetic wore off.[21,22,84] Thus, the aim of preemptive and preventive analgesia is to prevent or minimize central sensitization brought about by noxious preoperative, intraoperative, and postoperative stimuli.

SEARCH STRATEGIES AND CRITERIA FOR INCLUDING STUDIES

A PubMed® database search was conducted from December 1987 to January 2001 using the following keywords and limiting the search strategy to English language publications using human subjects: pre-emptive or preemptive analgesia, preempts, pre-operative, preoperative, post-operative, postoperative, pre-incision, preincision, post-incision, postincision, 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 empirical studies for review in the present chapter:

1 Randomized.
2 Double-blind assessments of pain and analgesic use.
3 Report of pain using a reliable and valid measure.
4 Report of analgesic consumption.
5 For studies that assess the effect of timing according to the preventive definition 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. This criterion was included to ensure that the observed effects are not simply analgesic effects.
6 The final criterion was the absence of design flaws, methodological problems, or confounds that render interpretation of the results ambiguous.

Table 7.1 contains the studies that were excluded from review and shows which one or more of the six inclusion criteria were not met.

The results of the PubMed® search and subsequent review of identified articles resulted in 148 clinical studies that met the above inclusion criteria. Table 7.2 shows the various experimental designs and the frequency with which they were used across the 148 studies and specifically for the different classes of analgesic and anesthetic agents. For each design, the table also shows whether the effect being evaluated is preemptive or preventive as defined above. The enormous variability in timing of treatment is evident from the fact that 29 different designs have been implemented. Table 7.3 summarizes the outcomes of the studies reviewed below according to the target agent administered. Positive studies are those that report a significant preemptive 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 the control condition. Also listed is the frequency of studies reporting effects opposite to that predicted.

LITERATURE REVIEW

Timing of administration of local anesthetics

Table A7.1 describes the 59 studies that were found to have examined the timing of administration of local anesthetic agents relative to incision. A variety of surgical procedures has been studied, including third molar extraction,[74**,75,76**,77] tonsillectomy,[78**-80,81,82**,83] thyroid surgery,[84**,85**] cholecystectomy,[86-88] laparoscopic surgery,[89**-91,92,93**,94**] inguinal hernia repair,[21**,22**,95,96**,97**,98,99**-101,102**,103] appendectomy,[107-109] circumcision,[104] hypospadias repair,[106**] major abdominal–gynecological surgery,[110-113,114**,115**] cesarean section,[116**-119] lower abdominal surgery,[120**] laparotomy,[121] lumbar diskectomy,[122**] arthroscopic knee surgery,[123] posterolateral thoracotomy,[124**] hemorrhoidectomy,[125,126] breast biopsy,[127] strabismus surgery,[128] and hand and forearm surgery.[129]

The most frequent designs compared preoperative administration of a local anesthetic with a placebo or another active agent (i.e. evaluation of preventive effects). The next most commonly used designs compared preoperative administration of a local anesthetic with the same agent administered intraoperatively, postoperatively, or both preoperatively and postoperatively (Tables 7.2 and 7.3). Local anesthetics were administered by cutaneous, subcutaneous, and fascial infiltration, wound infiltration, topical spray, nerve blocks, and by the epidural and spinal routes.

Across these various factors, there is a significant difference in outcome between studies that evaluate preemptive compared with preventive effects of local anesthetics (Table 7.3). Specifically, there is a greater proportion of positive preventive analgesic effects than would be expected by chance alone. Seventy percent (16/23) of the preemptive effects evaluated using local anesthetics do not show a superiority of pre- versus postincisional/surgical administration, whereas 30% do. On the other hand, 65% of the comparisons examining preventive analgesia show significant preventive effects (beyond the duration of action of agents used). Taken together, these data support the idea that, for the majority of studies, blocking noxious intraoperative factors interferes to the same degree with the development of central sensitization as does blocking posteroperative factors (i.e. these factors contribute equally to central sensitization), indicating that there is a benefit to the postoperative blockade. What we do not know is the extent to which these factors contribute independently (i.e. additively) to

Table 7.1 *Studies excluded from review in the present chapter for failing to meet one or more criteria[a]*

Reference	Year	Criterion not met	Reference	Year	Criterion not met
Local anesthetics			54	1998	DB
23	1983	P	55	1998	DF
24	1984	R, DB, P	56	1998	R
25	1990	P	57	1999	DA
26	1990	P, DF	58	2001	DB
27	1991	DF			
28	1991	R, DB	Opioids		
29	1991	A	59	1991	DA
30	1992	P	60	1991	DA
31	1994	R, DB	61	1992	DA
32	1995	DF	62	1992	R, DB
33	1996	DF	63	1999	DA
34	1996	A, DA	64	2000	A, DA
35	1996	P			
36	1996	DB, P, DF	*N*-Methyl-D-aspartate antagonists		
37	1998	R	65	1999	P
38	1998	DA			
39	1998	A	Local anesthetics and opioids		
40	1999	A	66	1988	DB
41	2000	DB	67	1992	R
			68	1993	P, DA
Nonsteroidal anti-inflammatory drugs			69	1998	P, A
42	1986	DA			
43	1987	DA	Multimodal analgesia		
44	1987	DF	70	1994	R, DB
45	1988	DA	71	1996	A
46	1990	DA	72	1999	R, DB
47	1991	DA	73	2000	DB
48	1991	DA, DF			
49	1994	DF			
50	1994	DA			
51	1996	DF			
52	1996	DA, DF			
53	1997	R			

a. R, *randomized*; DB, *double-blind* assessments; P, report of *pain* using a reliable and valid measure; A, report of *analgesic consumption*; DA, for studies that assess the effect of timing using the definition of preventive analgesia outlined in the chapter, measures of pain, and analgesic consumption reported at a point in time that exceeds the *duration of action* of the target agent; DF, absence of *design flaw*, methodological problem, or confound that renders interpretation of the results ambiguous.

central sensitization This can only be ascertained by incorporating appropriate control conditions (e.g. treatment combinations 1 and/or 8) into the classical two-group model of preemptive analgesia.

Tonsillectomy

Seven studies examined the efficacy of preoperative topical anesthesia or a local anesthetic infiltration in reducing pain and analgesic consumption after tonsillectomy.[78-83,130] Three studies[81-83] evaluated both preemptive and preventive analgesic effects; the remaining studies evaluated only preventive effects. Overall, significant preventive analgesic effects were found by five of the seven studies.[78**-80,82**,130**] Significant preemptive analgesic effects were not observed, suggesting that preoperative and postoperative blockade are equally effective in minimizing postoperative central sensitization. This conclusion seems defensible given that all but two studies[81,83] showed significant preventive effects when the preoperative local anesthetic infiltration was compared with preoperative saline or a no treatment control condition. The two studies that failed to find preventive effects may be explained by use of either a topical lidocaine (lignocaine) spray along with two nonsteroidal anti-inflammatory drugs (NSAIDs)[81] or too small a dose of bupivacaine (2 ml 0.25%).[83]

In general, the magnitude and duration of the preventive effects are impressive and clinically significant, especially considering that patients received only a single preoperative infiltration. Pain, either at rest or at rest and after swallowing, was found to be significantly less intense than the control group for up to 8–10 days after tonsillectomy.[78**,79**,80,**130**]

Laparoscopic surgery

Six studies examined the effects of timing of intraperitoneal local anesthetic spray or infiltration by preventive analgesia,[89**,90**,92,94**] or both preventive and preemptive analgesia,[91**,93**] for laparoscopic surgery, including cholecystectomy, tubal ligation, and diagnostic gyneco-

Table 7.2 *Variety and frequency of experimental designs used to evaluate the timing of administration of different classes of analgesic agents relative to incision*

Design number	Preemptive and/ or preventive	Treatment combination (Fig. 7.1)	Local anesthetics	Opioids	NSAIDs	NMDA antagonists	LAs and opioids	Multimodal	Total number of studies
1	PV	1;2	14	3	4	10	1	2	34
2	PE and PV	1;2;3	6	–	2	4	1	–	13
3	PE and PV	1;2;3;5	1	–	–	–	–	–	1
4	PE and PV	1;2;3;6	–	–	1	–	–	–	1
5	PE and PV	1;2;4	3	–	1	–	–	–	4
6	PE and PV	1;2;7;8	–	1	–	–	–	–	1
7	PV	1;3	7	1	–	–	–	–	8
8	PV	1;3;5	1	–	–	–	–	–	1
9	PV	1;4	3	–	–	–	–	–	3
10	PV	1;5	2	4	–	2	–	–	8
11	PV	1;8	1	–	–	–	–	–	1
12	PV	2	1	–	2	–	1	–	4
13	PE	2;3	7	10	–	4	2	1	24
14	PE	2;4	7	–	2	–	1	–	10
15	PE and PV	2;4;6	1	–	1	–	–	–	2
16	PE or PV	2;5	1	1	1	–	1	–	4
17	PE	2;6	1	–	4	–	–	–	5
18	PE	2;7	–	–	1	–	–	–	1
19	PV	3;5	–	–	–	1	–	1	2
20	PV	4	–	1	–	–	–	–	1
21	PV	4;5	–	–	–	–	1	–	1
22	PV	4;6	1	–	1	–	–	–	2
23	PE and PV	4;6;7	–	–	–	–	1	–	1
24	PE or PV	4;8	2	–	–	–	6	1	9
25	PV	5	–	–	–	1	–	–	1
26	PV	5;8	–	–	–	–	1	–	1
27	PE and PV	6;8	–	–	–	1	–	–	1
28	PE or PV	7;8	–	–	–	1	2	–	3
29	PV	8	–	–	–	–	1	–	1
	Total		59	21	20	24	19	5	148

Each design (column 1) is defined in terms of specific treatment combinations (column 3) depicted in Fig. 7.1. Each design is also described as evaluating preemptive and/or preventive effects.
PE, preemptive; PV, preventive; NSAIDs, nonsteroidal anti-inflammatory drugs; NMDA, *N*-methyl-D-aspartate; LAs, local anesthetics.

Table 7.3 *Summary of studies according to target agent administered*

Agent(s)	Number of studies	Preemptive effects		Preventive effects		Opposite effects	Total no. effects
		Positive	Negative	Positive	Negative		
Local anesthetics[a]	59	7 (10.1)	16 (23.2)	26 (37.7)	14 (20.3)	6 (8.7)	69 (100)
Opioids	21	4 (16.7)	5 (20.8)	9 (37.5)	3 (12.5)	3 (12.5)	24 (100)
NSAIDs	20	1 (4.2)	10 (41.7)	3 (12.5)	8 (33.3)	2 (8.3)	24 (100)
NMDA antagonists	24	4 (12.9)	6 (19.4)	15 (48.4)	5 (16.1)	1 (3.2)	31 (100)
LAs and opioids	19	3 (14.3)	4 (19.0)	7 (33.3)	6 (28.6)	1 (4.8)	21 (100)
Multimodal	5	1 (14.3)	0 (0)	2 (28.6)	3 (42.9)	1 (14.3)	7 (100)
Total[b]	148	20 (11.4)	41 (23.3)	62 (35.2)	39 (22.2)	14 (7.9)	176 (100)

Table shows the total number of studies, and number (%) with positive and negative preemptive and preventive effects. Also shown is the number (%) of studies reporting effects opposite to those predicted and the total number of effects (positive, negative, and opposite). The total number of effects exceeds the number of studies because some studies were designed to evaluate both preemptive and preventive effects. See text for definition of preemptive and preventive effects.

NSAIDs, nonsteroidal anti-inflammatory drugs; NMDA, N-methyl-D-aspartate; LAs, local anesthetics.

a. $P = 0.01$ for the number of positive preventive effects by Fisher's exact test.
b. $P = 0.0001$ for the number of positive preventive effects by chi-squared test.

logical procedures. Only one study did not coadminister systemic opioids during surgery.[92] All but one[92] of these studies showed a significant reduction in pain and/or morphine consumption that long outlasted the duration of analgesia of the preoperatively administered local anesthetic agent (i.e. from 24 h to 48 h after surgery).[89**-91,93**,94**] Preoperative plus postoperative local anesthesia was significantly more efficacious in reducing postoperative pain than preoperative,[91**] postoperative[90**,91**] or no administration,[90**,91**] supporting recent suggestions that prolonged blockade may maximize the preventive effects of local anesthesia.[13,19]

Inguinal hernia repair

Twelve studies evaluated timing of local anesthetic blockade with lidocaine or bupivacaine for inguinal hernia repair using a field block,[98,100] aerosol spray,[21**] infiltration,[96**,99**] ilioinguinal nerve block,[22**] spinal/caudal anesthesia,[96**,103,105] or a combination of two or more techniques[95**,97,101,102**] (two studies[103,105] also included patients undergoing other surgical procedures including circumcision and orchiopexy).

Timing of administration varied considerably, with some studies evaluating preemptive analgesia in the narrowest sense,[98,99**,101,103,105] others evaluating preventive preoperative effects using various treatment combinations,[95,96**,97**,102**] and still others evaluating preventive postoperative effects.[21**,22**]

Only one of the five studies evaluating preemptive analgesia was significant; however, the effect was small and limited to lower opioid consumption in favor of the pretreated group 6 h after surgery only.[99**] Of the five studies to evaluate preoperative preventive effects, three showed remarkably large and prolonged reductions in pain and analgesic consumption in favor of the pretreated groups between 2 days[97**] and 10 days[96**,102**] after surgery. The largest effects were found in a recent study that provided thorough blockade before, during, and after

surgery; pain while walking about was significantly lower up to day 5 after surgery, and by day 10 only 10% of the pretreated patients reported pain compared with approximately 50% of the control group.[102**]

The two studies[21**,22**] that examined preventive postoperative effects compared local anesthetic blockade of postoperative noxious inputs with a placebo and a no treatment control condition (i.e. treatment combination 1;3 in Fig. 7.1) in the context of an unchecked injury barrage from incision and subsequent intraoperative events. Both studies found a preventive effect 24 h after surgery; pain at rest,[21**,22**] after movement,[21**] and in response to pressure applied at the wound[21**] were significantly lower in the group administered the local anesthetic blockade after surgery than in the placebo or untreated groups. Also, significantly lower doses of postoperative analgesics were found in the treated groups. These results suggest that postoperative noxious inputs from the wound contribute to central sensitization (increased pain, hyperalgesia) independent of the central sensitizing effects of incision and subsequent noxious intraoperative events. The results also support the argument that "negative" studies of preemptive analgesia (e.g. treatment combination 2;3 in Fig. 7.1) may be due to the relative efficacy of postoperative blockade and not the inefficacy of preoperative blockade. They also point to the importance of implementing appropriate control conditions in studies of preemptive analgesia (e.g. treatment combination 1 and/or 8 in Fig. 7.1) to allow for an unambiguous interpretation of the results.[13]

Taken together, these studies suggest that, for inguinal hernia repair, the contribution of postoperative noxious inputs to central sensitization (and hence postoperative pain and opioid consumption) is greater than that of noxious inputs arising from incision. This is supported by the absence of any large preemptive effects and the presence of significant preventive effects, most notable among these are the preventive postoperative effects.

Cesarean section and abdominal gynecological surgery

All four of the studies that evaluated the preventive effects of a preoperative ilioinguinal nerve block using bupivacaine for women undergoing cesarean section (C-section) found significant effects between 24 and 48 h after surgery.[116**-119] Six studies were found in which a preemptive or preventive approach was evaluated in women undergoing major abdominal gynecological surgery.[110-115] The timing relative to incision, routes of administration, and use of additional analgesics varied considerably. Only two of the six studies found evidence for a preventive effect.[114**,115**] There were no preemptive effects.

Summary

Of the 69 effects that were tested (in the 59 trials), approximately 48% were significant. A greater proportion of preventive (38%) than preemptive (10%) effects (Table 7.3) were found to be significant, consistent with the expectation that a postincisional or postsurgical intervention should attenuate, to some extent, the course of postoperative central sensitization. Local anesthetic infiltration before tonsillectomy or inguinal hernia repair appears to produce clinically significant reductions in pain and analgesic consumption that long outlast the duration of action of the local anesthetics; in the case of tonsillectomy, the effects are particularly prolonged.

Timing of administration of opioid analgesics

Table A7.2 shows the 21 studies that were found to have examined the effects of altering the timing of administration of a variety of opioids, including alfentanil, fentanyl, morphine, meperidine (pethidine), sufentanil, tramadol, and the morphine metabolite morphine 6-glucuronide (M6G). The studies are almost evenly divided between designs comparing preoperative administration with a placebo or an active agent (i.e. evaluation of preventive effects) and those evaluating preoperative administration against the same agent administered intraoperatively, postoperatively, or both preoperatively and postoperatively (i.e. preemptive effects; see Tables 7.2 and 7.3).

The effects of opioids have been studied on a variety of surgical procedures that differ widely in duration, extent, and nature of damage to tissue, bone, and nerve. These include abdominal hysterectomy,[7**,132**,133,136,137**-139,141,143**,145] back surgery,[142,144**] major abdominal surgery,[134**] neurosurgical procedures,[149**] orthopedic surgery,[140,147**,148**] postepisiotomy pain,[135**] third molar extraction,[150] thoracotomy,[131**] and a variety of other surgical procedures.[146**]

Routes of administration include oral, intramuscular, intravenous, epidural, and intrathecal. Intravenous opioids have been administered as a single bolus dose,[131**,] 132**,136,137**,138,141-143**,145,148**,149** repeated bolus doses,[7**,133] or as a bolus dose followed by a continuous infusion.[7,149**] With two exceptions,[146**,147**] all studies using epidural opioids have administered a single bolus dose.

Time of administration before skin incision is not specified in all studies. For the intravenous (i.v.) route, most studies indicate administration is at induction of the general anesthesia or between 10 and 30 min before skin incision. Opioids administered by the epidural route have been given between 30 and 60 min before induction of the general anesthetic. The timing of treatment before surgery ranges between 30 min and 2 h presurgery for the intramuscular (i.m.) route and 1 h before surgery for the intrathecal route.

There is considerable variability in the timing of the second intervention for studies evaluating preemptive effects. The second intervention was administered intraoperatively as early as at the start of skin incision[145] or 1 min after incision.[136] Not surprisingly, neither study demonstrated a preemptive effect. The absence of differences between the groups in postoperative morphine consumption and pain at 24 h may be confirmation, in the clinical setting, of basic science findings that high-intensity noxious stimulation of C-fiber afferents located in skin is considerably less effective in inducing prolonged central facilitation than stimulation of afferents located in deep tissue.[151] Since the opioid was administered at skin incision[145] or 1 min after incision[136] in the postincisional group, it is unlikely that damage had been done to deeper tissues which contain the C-fiber afferents responsible for inducing long-lasting central neural hyperexcitability.

The absence of significant preemptive effects raises the issue of the time-course of postincisional central sensitization and whether the neural hyperexcitability can be prevented by an early postincisional treatment. Electrophysiological studies in rats have shown that second-phase formalin responses of dorsal horn nociceptive neurons are inhibited to the same degree when a μ opioid agonist is administered intrathecally before or shortly (i.e. 9 min) after formalin injury.[152] However, preinjury administration is significantly more effective at inhibiting second-phase responses than late (i.e. 30 min) postinjury administration. One implication of these findings for clinical studies is that administration of μ opioid agonists may be equally effective before and after incision until a windup-like state has developed, but, once established, higher doses may be required post surgery to provide the same degree of postoperative pain relief. It is likely that central sensitization had not fully developed by the time of the second intervention,[136,145] suggesting that the preemptive analgesic potential of the opioid was missed by virtue of too early a postincisional intervention.

The remaining studies administered the second intervention between 10 min[133] and 15 min[131**,143**] after incision, later during the procedure,[141] at the time of closure[132**,146**,147**] or at the end or surgery.[144**,150] Two

studies administered three interventions, the third occurring intraoperatively[138] or 10 h after surgery.[140]

Significant preventive effects were observed in eight studies,[7**,134**,135**,137**,146**-149] significant preemptive effects in three studies,[131**,143**,144**] and both preemptive and preventive effects in one study[132**] for a total of 13 (54%) significant effects (Table 7.3). Overall, the magnitude of the significant effects ranges from small[7**,131**,132**,137**,143**,149**] to moderate, with maximum mean intergroup differences in visual analog scale (VAS) pain scores (100-mm scale) at rest between 10 mm and 20 mm at 24 h[144**] to 48 h[134**,137**,146**,147**] after surgery. In two studies,[146**,147**] differences in VAS pain scores of approximately 15 mm in favor of the pretreated group were accompanied by a mean difference of between 3 and 4 mg epidural morphine, increasing the overall magnitude of the preventive effects.

Two recent lines of basic research are relevant to the efforts to prevent central sensitization by the preoperative administration of opioids. First, there is a growing body of evidence suggesting that opioid administration may lead to the development of acute opioid tolerance[153,154] and opioid-induced facilitation of nociceptive processing,[155-157] thereby increasing the requirements for postoperative analgesia and enhancing postoperative pain. The effects of opioid agonist-induced hyperalgesia are operating at cross-purposes to the analgesic effects, thereby reducing the overall magnitude of the preventive and preemptive effects of these agents.

Second, basic science[158] and clinical[159] studies indicate that coadministration of opioid agonists and low-dose opioid antagonists (e.g. naloxone, naltrexone) actually enhance opioid analgesia, in part by reducing acute opioid tolerance.[160] In two recent clinical studies, Aida et al.[146**,147**] administered epidural morphine or saline before surgery followed by i.v. naloxone (0.008 mg/kg) after skin closure in order to "erase the aftereffects of the morphine." Both studies reported significant preventive effects [reduced pain and lower epidural patient-controlled analgesia (PCA) requirements] that extended up to 48 h after surgery. These intriguing data raise the possibility that the relatively large preventive effects observed in these studies[146**,147**] may be due to the combined actions of morphine and naloxone in preventing acute tolerance.

In summary, of the 24 effects tested in the 21 studies reviewed, approximately 38% and 21% showed significant preventive and preemptive effects respectively. Thus, a total 59% of the effects tested showed that pain and/or analgesic consumption were reduced by altering the timing of administration of opioid analgesics relative to incision or after the analgesic effect of the opioid had worn off. The lower pain intensity and opioid-sparing effect were observed in large part between 24 and 48 h after administration of the target opioid used to prevent or preempt pain.

Two-group studies that did not find significant differences in pain and analgesic consumption between pre- and postincision groups are difficult to interpret because of the absence of an appropriate control group (e.g. treatment combination 1 in Fig. 7.1). The negative results may point to the relative efficacy of postincisional or postoperative blockade and not the inefficacy of preoperative blockade. Other explanations for the negative findings include the possibility that preoperative administration of opioid analgesics contributes to establishing acute opioid tolerance and opioid-induced hyperalgesia. Taken together, the findings that coadministration of low-dose NMDA antagonists (see section on Timing of administration of NMDA receptor antagonists) and low-dose opioid antagonists reduce or reverse the development of acute opioid tolerance and opioid-induced hyperalgesia[155] raise the possibility of increasing the magnitude of the preventive and preemptive analgesic effects of opioids in the clinical setting.

Timing of administration of NMDA receptor antagonists

A variety of agents that have an antagonistic action at the NMDA receptor are clinically available, including amantadine, dextromethorphan, ketamine, ketobemidone, memantine, and methadone. At the present time, preventive or preemptive analgesic effects have been investigated using ketamine or dextromethorphan but not the other NMDA antagonists. Although ketamine hydrochloride[161] and dextromethorphan[162] act on a variety of receptor systems, their NMDA channel-blocking properties quickly became the focus of intense research once this receptor-ion channel complex was discovered to play a critical role in the induction and maintenance of central sensitization and pathological pain.[163,164] The major mechanism proposed to underlie the reduced opioid consumption and pain in studies of preemptive analgesic effect is the prevention (or reversal) of NMDA-mediated sensitization of spinal cord dorsal horn neurons.[19,165] The NMDA channel blockers dextromethorphan and ketamine are of particular interest, therefore, in testing the hypothesis that their administration before surgery reduces pain and analgesic consumption compared with saline administration or their administration after incision.

Table A7.3 shows the 24 studies that were found to have used ketamine (n = 14) or dextromethorphan (n = 10). The most frequent designs have compared preoperative administration of dextromethorphan or ketamine with a placebo or an active agent (i.e. evaluation of preventive effects). The next most commonly used designs compare preoperative administration of dextromethorphan or ketamine with the same agent administered intraoperatively, postoperatively, or both preoperatively and postoperatively (Table 7.2).

Ketamine

The timing of ketamine administration relative to incision has been studied on a variety of surgical procedures including abdominal hysterectomy,[20**,172,173**,177] abdominal surgery,[169**,171] arthroscopy,[178**] cesarean section,[168**] cholecystectomy,[166**] gastrectomy,[167**,176**] laparoscopic cholecystectomy,[175] mastectomy,[174] and total knee replacement.[170**] There is usually no rationale given for the patient population studied in spite of the fact that important differences clearly exist among the various surgical procedures that may have a bearing on the outcome of the results [e.g. duration of procedure relative to that of the target agent, extent (deep vs. superficial) and nature (nerve, muscle, viscera) of tissue damage and inflammation].

Ketamine has been administered via the intravenous[20**,166**,168**,169**,172,174,175,177,178**] and epidural[167**,170**,171,173**,176**] routes. Intravenous ketamine has been administered as a single bolus dose,[166**,168**,174,175,177,178**] repeated bolus doses,[172] or as a bolus dose followed by a continuous infusion[20**,169**] for the duration of the surgical procedure. Intravenous bolus doses of ketamine have ranged from 0.15 mg/kg up to 2.0 mg/kg, with the majority between 0.4 mg/kg and 1.0 mg/kg i.v.

There is somewhat less variability in the dose of ketamine administered by the epidural route. The five studies of epidural ketamine administered a single bolus dose of 30 mg[173**] or 60 mg,[167**,171] repeated bolus doses between 10 and 20 mg,[170**] or a bolus dose of 1.0 mg/kg followed by a continuous infusion of 0.5 mg/kg/h until closure.[176**]

The surgical procedures were performed under general anesthesia in all but one of the studies, the exception being a positive study of patients undergoing total knee replacement with a combination of epidural lidocaine, morphine, and ketamine.[170**]

Certain studies have combined ketamine with other agents, including acetaminophen (paracetamol),[175] morphine[167**] or morphine and lidocaine,[170] making it difficult to separate the effect of ketamine from that of the other agents on postoperative pain and analgesic consumption. In seven studies, an opioid[166**,168**,173**,174,177,178**] or an opioid plus an NSAID[175] (preceded by preoperative local anesthetic infiltration) were administered as premedication or at induction of the general anesthesia.

Of the five studies that administered ketamine without opioids, three showed a preventive effect up to 2 days after surgery[20**,169**,176**] and two showed no effect of preoperative ketamine, but these latter studies did not include an appropriate control condition (i.e. treatment combination 1 in Fig. 7.1). Thus, ketamine appears to produce a preventive effect when administered alone. The coadministration of ketamine with an opioid appears to produce greater effects than that of morphine alone or ketamine alone, as illustrated by Aida et al.,[176**] who found that epidural morphine plus i.v. ketamine produced a preventive effect at 24 h and 48 h after surgery when compared with epidural morphine plus i.v. saline or epidural saline plus i.v. ketamine. The magnitude of the effect of epidural morphine appeared to equal that of i.v. ketamine alone.

The exact time of administration before skin incision is not specified in all studies, but it appears to be 3–10 min for the i.v. route and 20–30 min for the epidural route. Timing of preoperative administration is often specified relative to induction rather than incision. There is understandably more variability in the time of administration postincision for studies evaluating preemptive effects or for studies in which the groups are not given the same dose of ketamine during the first and second intervention. The exact time after incision is not always specified; instead, it is equally common to report administration relative to a fixed surgical event (e.g. removal of specimen, wound closure). Because of this and interstudy differences in the duration of the various surgical procedures, an accurate estimate of the interval between the first and second intervention cannot be calculated. However, the timing of the second intervention occurred between 20 and 30 min postincision,[170**,172,173**] at closure,[169**,171,174,175,177,178**] or at end of surgery.[176**] Some studies administered more than two interventions.[170,175]

Significant preventive effects were observed in seven studies,[20**,166**,168**,169**,173**,176**,178**] significant preemptive effects in one study,[167**] and both preemptive and preventive effects in one study.[170**] The significant effects were primarily observed as an analgesia- or opioid-sparing effect with the treated groups receiving or self-administering significantly lower doses of postoperative analgesia than the untreated or placebo-treated groups. In two studies, the preemptive[170**] or preventive[170**,176**] effects involved both reduced pain intensity and reduced opioid requirements, and in one study the effect was a reduction in postoperative hyperalgesia.[20**] The majority of the significant effects were observed between 24 h and 48 h after surgery.

Dextromethorphan

Surgical procedures include laparotomy,[188] tonsillectomy,[179**,181] lower[180**] or upper[186**] abdominal surgery, hysterectomy,[184] laparoscopic cholecystectomy,[183**,187**] mastectomy,[182**] and hemorrhoidectomy.[185**] Of the 10 studies, one[180**] examined preemptive effects, eight[179**,181,182**,184**-188] examined preventive effects, and one study examined both preemptive and preventive effects.[183**] Dextromethorphan has been administered by the oral,[179,181,184**,187,188] i.m.,[182**,183**,185**,186**] and i.v.[180**] routes. Oral and i.m. preparations have been administered in a single dose ranging from 10 mg to 150 mg. Intravenous dextromethorphan was administered in one study as a slow infusion of 5 mg/kg over a 30-min interval starting 30 min before induction of the general anesthetic.[180**] Time of administration for the oral route has been at least 60 min before the start of surgery. Time of administration for the i.m. route uniformly has been 30 min before incision. Time of postin-

cisional administration of dextromethorphan was after removal of the specimen[183]** and at skin closure.[180]** General anesthesia was administered for all but one procedure, the exception being hemorrhoidectomy performed under lidocaine infiltration.[185]** Intravenous morphine,[188] i.v. fentanyl,[180]**,[182]**,[183]** i.v. morphine and p.r. acetaminophen,[181] and i.v. fentanyl and i.v. lidocaine[186]** were administered either as a premedication or during surgery as a supplement to the general anesthetic. Only two studies did not administer an analgesic agent as premedication or during surgery.[179]**,[185]

The outcomes of the studies examining the timing of administration of dextromethorphan are similar to those of ketamine. Significant preventive effects were observed in six studies,[65]**,[179]**,[182]**,[185-187]** significant preemptive effects in one study[180]** and both preemptive and preventive effects in one study.[183]** Effects were observed at least 24 h after administration of dextromethorphan and, with three exceptions,[65],[180]**,[182]** consisted of a reduction both in analgesics administered and in pain at rest and/or after movement. One study reported significantly lower pain intensity and analgesic consumption for 7 days after bilateral tonsillectomy following a single dose of 45 mg dextromethorphan.[179]**

Design considerations: importance of control conditions

As noted above, negative results of two-group studies pose a problem in interpretation because of the absence of an appropriate control group (e.g. treatment combination 1 or 8 in Fig. 7.1). This problem is illustrated in two recent studies of epidural ketamine.[171],[173]** Using a two-group design (treatment combination 2;3 in Fig. 7.1), preincisional epidural ketamine (60 mg) was compared with postincisional epidural ketamine (60 mg) without finding the anticipated reduction in postoperative pain and analgesic consumption in favor of the preincisional group; preincisional ketamine was no better than postincisional ketamine in preempting postoperative pain.[171] Since there is no good rationale for a postincisional treatment in the clinical setting (i.e. one would not administer epidural ketamine near the end of surgery without also having used the epidural route preoperatively), the impression that negative studies such as this one give is that neither preincisional nor postincisional treatment is clinically useful.

However, as previously argued, preincisional and postincisional noxious stimuli make separate contributions to central sensitization.[13] It is conceivable that in the study by Kucuk et al.[171] pre- and postincisional noxious stimuli contributed equally to postoperative pain intensity so that administration of ketamine reduced (the respective pre- and postincisional contributions to central sensitization and) postoperative pain when given before or after incision. This possibility raises the question of how the pre- and postincisional groups would have fared had they been compared with a group that did not receive ketamine at all.

This question was addressed by Abdel-Ghaffar et al.,[173]** who used the treatment combination 1;2;3 in Fig. 7.1. Cumulative postoperative morphine consumption 24 h after surgery was reduced by approximately 40% among patients given epidural ketamine (30 mg) before or after incision when compared with a control group that received epidural saline before and after incision (i.e. no ketamine). Consistent with the results of Kucuk et al.,[171] preincisional ketamine was no better than postincisional ketamine in preempting postoperative pain. Importantly, a clinically significant opioid-sparing effect was found in both the preincisional and postincisional groups when compared with the placebo-controlled group, pointing to the importance of a proper control condition.

Summary

Taken together, the results of the studies that have examined the timing of administration of ketamine or dextromethorphan have proved most successful in terms of the total percentage of studies showing significant preventive or preemptive effects. As shown in Table 7.3, approximately 61% of studies have reported that administration of ketamine or dextromethorphan before surgery (compared with after surgery or a placebo-controlled condition) results in significantly lower pain intensity and/or reduced analgesic requirements after the duration of action of the NMDA antagonists has worn off.

The preponderance of positive studies of preemptive ketamine and dextromethorphan may be due not only to the ability of these agents to block the neural processes underlying central sensitization[161] but also, in a related vein, to their ability to attenuate the development of acute opioid tolerance[153,154] and reverse opioid-induced facilitation of nociceptive processing.[156,157] As reviewed above, opioids were administered (as premedication, during surgery, or as part of the preemptive intervention) in all but six of the studies. Preoperative administration of ketamine or dextromethorphan may have prevented acute opioid tolerance, opioid-facilitated activation of NMDA processes, and opioid-induced hyperalgesia relative to the control group, leading to a reduction in postoperative opioid requirements and postoperative pain intensity in the preoperatively treated groups.

Timing of administration of nonsteroidal anti-inflammatory drugs

The analgesic effects of NSAIDs have been attributed to their peripheral anti-inflammatory actions in inhibiting the synthesis of prostaglandins through the inactivation of cyclo-oxygenase.[189] This effect is an indirect one in that prostaglandins themselves do not produce pain but sensitize receptors at the site of injury to a variety of neurochemicals (e.g. bradykinin, serotonin, substance P, calcitonin gene-related peptide). Thus, at least insofar as their peripheral effects are concerned, NSAIDs are more

accurately antihyperalgesic than analgesic in action. Observations that the anti-inflammatory and analgesic effects of NSAIDs could be dissociated raised the possibility of a central site of action for these agents.[189] The spinal effects of NSAIDs are not as well documented, but include the possibility of a nonanti-inflammatory analgesic action brought about by the inhibition of cyclo-oxygenase in the spinal cord and a consequent reduction in spinal NMDA-mediated events.[189,190]

When administered prior to injury, opioid agonists and local anesthetics prevent central sensitization by attenuating nociceptive processing and blocking nerve conduction respectively. In contrast, NSAIDs may prevent central sensitization by attenuating the inflammatory response, thereby reducing peripheral sensitization and its effects on spinal nociceptive processing. In addition to this indirect peripheral effect, the direct central actions of NSAIDs may also contribute to reducing central sensitization by preventing spinal prostanoid synthesis, thus reducing pre- and postsynaptic release of neurotransmitter (e.g. neuropeptides and excitatory amino acids) from primary afferent terminals and spinal interneurons. The net effect of both actions would be to prevent or attenuate development of a hyperexcitable state in spinal cord dorsal horn neurons. In terms of the patient's experience of pain after surgery, this would translate into less intense pain and a reduced requirement for postoperative analgesics.

Table A7.4 shows the 20 studies that were found to have examined the preemptive or preventive effects of an NSAID alone or in combination with a local anesthetic. Studies of patients undergoing oral surgery such as third molar extraction[191,193,194**,195,196,198,204] or pulpectomy[192**] were among the earliest to be conducted. More recently, other procedures have been studied, including abdominal hysterectomy,[203,205,209] orthopedic surgery,[200**,201**,202,206,207,210] and laparoscopy.[197] Routes of administration include oral, rectal, i.m., and i.v. A variety of NSAIDs has been used, including the propionic acids, acetic acids, oxicams, and acetaminophen, these differing in the extent of their anti-inflammatory activity, analgesic effects, antipyretic actions, and pharmacokinetics.

Of the 20 studies conducted to date, seven evaluated preventive effects, nine evaluated preemptive effects, and four both preventive and preemptive effects (Table 7.2). Overall, significant effects (i.e. preemptive or preventive) were found in 4 out of the 20 studies (20%): there was one preemptive analgesic effect[201**] and three preventive effects.[192**,194**,200**]

Not only is the proportion of positive studies small, but the magnitude of the effects, when present, is modest at best. The only study[201**] to report a preemptive effect found that cumulative i.v. PCA morphine consumption was lower in the presurgery than in the postsurgery group up to 6 h after surgery but not later. This effect amounted to a mean morphine-sparing effect of approximately 1 mg/h over the first 6 h after surgery. Preventive

effects[192**,194**,200**] were observed at, or up to, 24 h after surgery and consisted of small differences in pain and/or opioid consumption in favor of the pretreated group.

In general, the ability to demonstrate preventive or preemptive analgesic effects using NSAIDs (vs. opioids or local anesthetics) is made more difficult by the fact that these agents do not block nociceptive processing or nerve conduction. As a consequence, clinical studies are inevitably confounded by the coadministration of systemic opioids and/or a local anesthetic infiltration to all patients in order to provide sufficient analgesia or anesthesia during the surgical procedure. This would have the unintended effect of reducing pain in the control group, thus minimizing the intergroup differences in pain and analgesic consumption.

The coadministration of these agents before, during, and after surgery makes it difficult to assess, in a clinical setting, the degree to which NSAIDs, per se, contribute to preventive or preemptive analgesic effects. Nevertheless, it appears that from a clinical perspective NSAID treatment does not produce meaningful preemptive or preventive analgesic effects on pain or analgesic consumption over and above those of the analgesic and anesthetic agents routinely administered during the perioperative period.

Timing of administration of local anesthetics and opioid analgesics in combination

Table A7.5 contains a description of the 19 studies that examined the effects of timing of administration of a local anesthetic and an opioid. As shown in Table 7.2, designs assessing preventive analgesia[212,213,216–219,221–224] are considerably more frequent than preemptive analgesia.[211,214,225,226,228] Two studies examined both preventive and preemptive effects.[215,220]

Effects of timing have been evaluated on a variety of surgical procedures, including abdominal hysterectomy,[226] amputation,[221] antireflux repair,[227] arthroscopic knee surgery,[220**] cesarean section,[212**] colonic surgery,[211] hernia repair,[225**] lower back surgery,[222**] posterolateral thoracotomy,[217] radical prostatectomy,[216**,224] third molar extraction,[219] tonsillectomy,[215] total knee arthroplasty,[214] and upper abdominal surgery.[213**,218,223,228**]

All but two of the studies[215,219] used the epidural or spinal route, either alone or in combination with a second route (e.g. intra-articular,[220**] infiltration[212**]).

Among the studies evaluating preemptive analgesia, seven administered a postoperative continuous epidural infusion of a local anesthetic and an opioid to both the preoperative and postsurgical groups. The continuous infusion was maintained postoperatively for 2 days[217] to 3 days[211,213**,214,218,221,227] after surgery. Not surprisingly, six of the seven showed no effect, and only one[213**] reported a very small difference in analgesic consumption in favor of the preoperative group.

These studies do not permit an unbiased test of the preemptive analgesia hypothesis because continuous postoperative epidural infusion would be expected to attenuate the development of central sensitization in both groups and minimize any group differences due to the timing of administration. Studies that examine the timing of treatment must allow patients to demonstrate their level of pain either directly, through verbal report (e.g. VAS pain scores), or indirectly, through their consumption of postoperative analgesics. However, if the postoperative analgesic regimen is fixed (i.e. not titrated to patient need, as with a continuous epidural infusion) and effective (pain levels are low), it may not be possible to detect whether the afferent barrage produced by the surgical trauma had a prolonged central effect.

Overall, seven studies (33%) showed a significant preventive effect[212**,213**,216**,220**,222**,224**] and three (14%) showed a significant preemptive effect[220***,225**,228**] (Table 7.3). The effects vary in magnitude from minor reductions in postoperative analgesic consumption[213**] to clinically significant reductions in pain and/or analgesic consumption lasting for 4–5 days after surgery.[224**,228**] In one notable study, the incidence of pain 9 weeks after surgery was significantly lower among patients who had received preoperative epidural fentanyl or bupivacaine than among a saline control group.[224**]

Timing of administration of multimodal analgesia

The rationale for a preoperative multimodal approach to postoperative pain management is to capitalize on the combined actions of a variety of classes of analgesic and anesthetic agents at different receptor sites in reducing peripheral and central sensitization.[229]

Five studies evaluated the effects of timing of administration of a combination of a local anesthetic, opioid, and an NSAID[230,231**,232**,233,234**] (Table A7.6). Surgical procedures include lateral thoracotomy,[230,231**,234**] abdominal surgery,[232**] and third molar extraction.[233] Not only are the study designs quite varied, with only one evaluating the effects of the same interventions before and after surgery (i.e. preemptive analgesia),[234**] but routes of administration for a given class of agent also differ, as do the durations of action of agents within and between classes.

In general, the magnitude of the significant effects are surprisingly small given the combined use of three agents. For example, in the study by Rockemann et al.,[232**] the PCA morphine-sparing effect of a combined preoperative regimen of thoracic epidural mepivicaine and morphine, i.v. metamizole, and i.m. diclofenac did not appear to exceed that observed by Katz et al.,[131**] who compared preincisional with postincisional lumbar epidural fentanyl. The possible exception is the study by Doyle and Bowler,[234**] who found that preoperative but not postop-

erative administration of i.v. morphine, i.m. diclofenac, and intercostal nerve blocks with bupivacaine resulted in significantly reduced pain on movement of about 20 mm on a VAS from 12 h to 48 h after posterolateral thoracotomy. Interestingly, this study was similar in patient population, agents used, and route of administration (of two of the agents) to the study by Kavanagh et al.,[230] but opposite in effect. In that study, the placebo-treated group self-administered significantly less PCA morphine at 48 h than the group treated with preoperative intercostal bupivacaine nerve blocks, i.m. morphine and perphenazine, and p.r. indomethacin.

RECOMMENDATIONS FOR FUTURE RESEARCH

Relationship between preexisting pain and timing of analgesic administration

Recent evidence suggests that, in the presence of presurgical pain, preoperative administration of analgesics does not lead to the anticipated lessening of postoperative pain or analgesic consumption, perhaps because central sensitization has already been established. Postoperative pain and analgesic consumption were significantly reduced by pre- and intraoperative epidural morphine but not saline for patients who did not report presurgical pain.[147**] However, among patients with presurgical pain, pre- and intraoperative epidural morphine was no more effective than saline. It is not clear whether the absence of a difference in phantom limb pain or stump pain after amputation between groups treated with preoperative and intraoperative epidural morphine and bupivacaine versus saline[221] also relates to the presence of preamputation pain and the possibility that central sensitization had already been established before the preoperative treatment. Future studies should report presence (and duration) or absence of presurgical pain.

Offsetting the competing effects of preventive opioid analgesia and opioid-induced tolerance/hyperalgesia

As noted above, recent basic scientific evidence points to the possibility that, under certain circumstances, preoperative administration of opioid analgesics may contribute to the establishment of acute opioid tolerance[153] and opioid-induced hyperalgesia.[157,235] The mechanisms underlying the reduced pain and opioid consumption brought about by preemptive opioid analgesia, and the increased pain and opioid consumption underlying acute opioid tolerance and opioid-induced hyperalgesia, concern competing processes involving the NMDA receptor–ion channel complex. These findings have important implications for the conduct of clinical studies evaluating

the preeemptive and preventive effects of opioid analgesics since the main outcome measures (pain and opioid consumption) will be directly affected by the mechanisms underlying these competing neural processes. The net effect of this competition is to attenuate (or even reverse) the desired preemptive and preventive effects. Coadministration of opioids and low-dose NMDA antagonists or low-dose opioid antagonists has been found to interfere with the development of acute opioid tolerance[154,236] and opioid-induced hyperalgesia.[155] A mechanism-based approach to postoperative pain management involving coadministration of these agents would be expected to facilitate the preventive and preemptive analgesic effects of opioids in patients undergoing major surgery.

Recommendations to improve the quality of studies

Design considerations

The importance of including a standard treatment control group in studies that aim to evaluate the effects of the timing of administration of drugs relative to incision was illustrated by example in the section on NMDA antagonists, but the problem is not limited to this class of agents (e.g. see Molliex et al.[82]). Two-group studies that do find significant differences in postoperative pain or analgesic consumption between pre- and postincision groups are inherently flawed because of the absence of an appropriate control group (e.g. treatment combination 1 and/or 8 in Fig. 7.1). The negative results may point to the relative efficacy of postincisional or postoperative blockade and not the inefficacy of preoperative blockade.

The preponderance of positive preventive studies over positive preemptive studies (Table 7.3) is understandable when one considers that both preincisional and postincisional or postsurgical noxious inputs contribute to postoperative central sensitization. The degree to which noxious inputs contribute during each of these phases is probably dependent on a host of factors. The continued use of incomplete designs that consist of preincisional and postincisional or postsurgical conditions (e.g. treatment combination 2;3 or 2;4 in Fig. 7.1) without a true placebo condition (e.g. treatment combination 1 in Fig. 7.1) or a complete blockade condition (e.g. treatment combination 8 in Fig. 7.1) will hinder progress in our understanding of preemptive analgesia. This is because negative results leave us with no idea of the significance of the preoperative or postoperative intervention relative to a group that receives no treatment or total blockade.

Adhering to the narrow definition of preemptive analgesia currently accepted by many in the field will perpetuate problems of interpretation and will not lead to the evolution and progress that is needed to move us beyond the current state of confusion. Inclusion of appropriate control conditions is essential if we are to advance our knowledge about the factors that contribute to acute postoperative pain.

Measures of pain

The most appropriate pain measurement instruments are patient-rated pain scales that have demonstrated reliability and validity (e.g. VAS, numeric rating scale, McGill Pain Questionnaire).[237] Measurement of pain with the patient in a resting position is reported by almost all studies. However, the measurement of hyperalgesia is important. The simplest and most clinically significant test of mechanical hyperalgesia is to have the patient perform a standardized movement after surgery (e.g. sitting up from a lying position, inspirational spirometry) and rate the intensity of the pain that ensues. More sophisticated measures of primary and secondary mechanical hyperalgesia include pressure algometry applied either on or near the wound dressing[20,87,238] or on the side of the body contralateral to the incision,[230] measurement of thresholds to electrical stimulation,[142,172] temperature,[187] and use of von Frey filaments at a distance from the wound to determine the extent of secondary mechanical hyperalgesia.[132,137,187,239] Baseline (preoperative) measures are important as is testing at a control site (e.g. a noninjured body part) to rule out a generalized effect due to factors such as anxiety, anticipatory pain, or a response bias.

Measures of analgesic consumption

The degree of pain that a patient experiences in the postoperative setting is in part a function of postoperative analgesic consumption. Use of patient-controlled analgesia (either i.v. or epidural) as a modality for postoperative pain management has dominated the literature on preemptive and preventive analgesia. This is largely because PCA is now the gold standard for postoperative pain management at most institutions worldwide. Analgesic consumption is usually the primary outcome measure because patients self-administer the agent to achieve a relatively constant pain level. However, from the point of view of demonstrating preemptive or preventive analgesia, analgesic consumption is not the most ideal measure because the main hypothesis deals with pain and hyperalgesia. Allowing pain to fluctuate by holding constant the level of postoperative analgesics administered would be a more direct test of the hypothesis,[20,96] but this is not always feasible or ethical given the evolving standards of pain management practice.

Cumulative analgesic consumption at the end of the study is a common measure, but report of a single value may not provide information that is specific enough to pinpoint the nature of the effect (analgesic or prevention of central sensitization) or exactly when it occurs. The latter point may not be relevant if a postincision control group is employed. It may be especially relevant in studies that evaluate the preventive effect of a preoperative intervention (i.e. when comparing it with a placebo) since it is likely that the largest difference in PCA consumption between treated and untreated groups will

occur at the time of peak effect of the target agent used preventively. Report of a single value of cumulative analgesic consumption at the end of the study may be misleading depending on the pattern of consumption over time. For example, if a difference in analgesic consumption occurs within the first few hours after surgery (but not thereafter), when the effects of the analgesics used preventively are still active, then this is an analgesic effect. Likewise, report of a single value for cumulative analgesic consumption at the end of the study may result in failure to detect the presence of group differences at earlier time points. Unless cumulative analgesic consumption is reported at multiple times across the study period, an analgesic effect may be misinterpreted as a preemptive or preventive effect or either effect may be missed. Another approach that circumvents this problem is to calculate analgesic consumption within intervals bounded by the times when pain is assessed.[7,120,131,178] This method has the advantage of specifying an interval within which an opioid-sparing effect has occurred.

Time from end of surgery to first request for analgesics has been used as an indication of analgesic efficacy.[54,65,67,87,98,126,144,150,168,173,182,185,186,205,206,225] This is a valid measure of the duration of analgesia providing (1) the timing of administration of pre- and intraoperative analgesia is the same for all treatment groups and (2) pain scores do not differ at the time of first request for analgesia. However, the time interval between end of surgery and first analgesic request is not meaningful when the main intervention that distinguishes groups is the timing of administration of a target analgesic agent relative to incision.[240] Since the study groups are designed to differ with respect to the timing of administration of a target agent, nonsignificant intergroup difference[138,141] in the time from end of surgery to the time of first request for analgesics is difficult to interpret. A more meaningful measure would be time from administration of the target agent to the first request for analgesia. But even this measure is not recommended because it can be influenced by analgesic and anesthetic agents administered during surgery, some of which may differ between the groups directly as a function of the target agent used preemptively or preventively.

Finally, some studies report the number of patients requiring rescue analgesics[22,74,84,85,94,99,102,106,115,167,179,183,200,220] or the number of supplemental doses of analgesics administered.[99,115,179,220] These measures lack the sensitivity of cumulative analgesic consumption or analgesics administered within specified intervals. It should be noted that no study included for review in this chapter used these latter methods as the sole measure of analgesic efficacy.

SUMMARY AND CONCLUSIONS

Overall, across the classes of agents reviewed, the proportion of significant preventive effects is greater than the proportion of significant preemptive effects (Table 7.3). Sixty-two percent of the preventive effects reported showed significant benefits associated with analgesic or local anesthetic administration that extended beyond the clinical duration of action of these agents. These results suggest that central sensitization can be minimized by a preventive approach aimed at blocking noxious stimuli during the preoperative, intraoperative, and/or postoperative periods.

The proportion of significant preemptive effects also appears to be greater than that expected by chance alone. Although only 20 (33%) of the 61 preemptive effects that were reviewed found preoperative administration of analgesics or local anesthetics to result in significantly lower pain and/or analgesic consumption than administration of the same agent(s) after incision or surgery, this percentage is considerably greater than the conventional type I error rate of 5% that would be expected if pre- and postoperative interventions did not differ in their efficacy. The finding that the proportion of significant preventive effects is greater than the proportion of preemptive effects is consistent with the suggestion that for most preemptive studies postincisional or postoperative administration is as efficacious as preincisional administration. The enormous variability between studies is one factor that likely contributes to the equivocal results when studies of preemptive analgesia are considered.

Nevertheless, even though the majority of studies show that there is little additional benefit to preoperative administration of analgesic agents over postoperative administration, there is a clear advantage to adding local anesthetic blockade to general anesthesia under certain conditions. For example, local anesthetic administration before tonsillectomy or inguinal hernia repair appears to produce clinically significant reductions in postoperative pain that long outlast the duration of local anesthetic blockade.

Timing of administration of opioids, with or without local anesthetics, is less conclusive, possibly because of the competing processes associated with acute opioid tolerance and opioid-induced hyperalgesia. There appears to be little evidence that the timing of administration of NSAIDs produces preemptive or preventive effects. Given the small number of studies of multimodal analgesia and the relatively large variability in the routes of administration, agents, timing, and patient populations, there are insufficient data to generate a reliable conclusion on the efficacy of the timing of administration of local anesthetics, opioids, and NSAIDs. Administration of the NMDA antagonists ketamine or dextromethorphan before surgery resulted in significantly lower pain intensity and/or reduced analgesic requirements in approximately 61% of the effects tested.

The distinction between preventive and preemptive analgesia is an important one from the clinical perspective. Demonstration of preventive analgesia allows for a more stringent test of the extent to which postopera-

tive central sensitization is dampened than does a finding of preemptive analgesia. This is because preventive analgesia requires pain and/or analgesic consumption to be reduced at a point in time after the duration of action of the analgesic agent used preventively. Otherwise, the effects are analgesic. The results reviewed above indicate that preventive effects are more frequent than preemptive effects, and in general they are of greater magnitude. It is ironic then that some of the most clinically important findings of preventive analgesia have been eclipsed by a decade or more of controversy over the clinical benefits of preemptive analgesia.

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APPENDIX

The appendix tables are on the following pages.

Table A7.1 *Studies examining the timing of local anesthetic administration relative to incision*

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/post-incision drug	Route and dose	Timing of preincision intervention	Timing of postincision intervention	Systemic analgesics[a]	Nature and time after surgery of preventive or preemptive analgesic effect
74 (1989)	Third molar extraction (n = 70)	1;2	GA plus: G1: BUP/NA G2: PRI/NA G3: Ø/NA	Infiltration G1: 8 ml 0.5% BUP G2: 8 ml 3% PRI	After induction, before incision	NA	No	Preventive effect – yes on postoperation day 1 Pain: G1 = G2 < 3 Analgesics: G1 = G2 < G3
75 (1997)	Third molar extraction (n = 38)	2;3	GA plus: S1: Ø/BUP S2: BUP/Ø	Nerve block 2 ml 0.5% BUP per nerve	Before incision (≥ 10 min after nerve block)	After removal of tooth	No	Preemptive effect – no
76 (1997)	Third molar extraction (n = 48)	1;2	GA plus: G1: BUP + EPI/NA G2: SAL + EPI/NA	Intraoral injection 56 mg 0.5% BUP + 1:200,000 EPI	At least 5 min before induction	NA	NS	Preventive effect – yes at 48 h postoperation Pain: G1 < G2 Analgesics: G1 < G2
77 (1998)	Third molar extraction (n = 32)	2;3	GA plus: S1: Ø/BUP S2: BUP/Ø	Nerve block 2 ml 0.5% BUP per nerve	After induction (≥ 10 min after nerve block), before incision	After removal of tooth	TEN i.v. 20 mg ALF i.v. 2 mg	Preemptive effect – no
78 (1989)	Tonsillectomy (n = 38)	1;2	G1: GA only/NA G2: LID + EPI/NA	Topical spray 30–40 mg LID Infiltration of peritonsillar tissues 20–30 ml of 5 mg/ml LID + 5 μg/ml EPI	Immediately before operation	NA	G1: FEN i.v. dose NS	Preventive effect – yes on days 5 and 8 postoperation Pain: G2 < G1 No; ready for work/ school: G2 > G1
79 (1991)	Tonsillectomy (n = 14)	1;2	GA plus: G1: BUP + EPI/NA G2: SAL/NA	Infiltration of peritonsillar tissues 3–5 ml 0.25% BUP + 1:200,000 EPI	5 min before incision	NA	No	Preventive effect – yes up to day 10 postoperation Pain at rest: G1 < G2 Pain on swallowing: G1 < G2
80 (1993)	Tonsillectomy and/or adenoidectomy (n = 22)	1;2	GA plus: G1: BUP + EPI/NA G2: SAL + EPI/NA	Infiltration of peritonsillar tissues 0.25% BUP + 1:200,000 EPI dose NS	5 min before incision	NA	NS	Preventive effect – yes up to day 10 postoperation Pain at rest: G1 < G2 Pain on swallowing: G1 < G2 Time to swallow: G1 < G2

81 (1995)	Tonsillectomy (n = 75)	1;2;3	GA plus: G1: LID/Ø G2: Ø/LID G3: Ø/Ø	Topical spray of tonsillar areas 4 mg/kg 10% LID aerosol spray	3 min before incision	After removal of tonsils	KET i.m. 1 mg/kg DIC p.r. 2 mg/kg	Preemptive effect – no Preventive effect – no
130 (1996)	Tonsillectomy (n = 19)	1;2	GA plus: G1: BUP/NA G2: SAL/NA	Infiltration of tonsils and peritonsillar muscles 15 ml 0.25% BUP	7 min before surgery	NA	ACE p.r. 1,500 mg FEN i.v. 250 µg	Preventive effect – yes at days 4, 6, 7, and 9 postoperation Pain: G1 < G2
82 (1996)	Tonsillectomy (n = 68)	1;2;4	GA plus: G1: BUP + EPI/Ø G2: SAL + EPI/Ø G3: Ø/BUP + EPI	Infiltration of peritonsillar tissues 6–9 ml 0.25% BUP + 1:200,000 EPI	After induction, 5 min before surgery	After surgery, before awakened from GA	FEN i.v. 3 µg/kg	Preemptive effect – no Preventive effect – yes at 17 h postoperation Pain: G1 = G3 < G2
83 (2000)	Tonsillectomy (n = 30)	1;2;4	GA plus: G1: SAL/Ø G2: BUP/Ø G3: Ø/BUP	Peritonsillar infiltration 2 ml 0.25% BUP	5 min before tonsillar excision	After completion of the procedure	MOR i.m. 0.07 mg/kg	Preemptive effect – no Preventive effect – no Pain: G1 > G2 at 4 h postoperation
84 (1994)	Thyroidectomy (n = 40)	1;4	GA plus: G1: NA/BUP G2: NA/Ø	Infiltration of surgical edges of wound 10 ml 0.5% BUP	NA	At end of surgery	FEN i.v. G1: 3.72 µg/kg G2: 3.81 µg/kg	Preventive effect – yes at 24 h postoperation Pain: G1 < G2 Analgesics: G1 < G2
85 (1999)	Thyroid surgery (n = 62)	1;2;3	GA plus: G1: LID/Ø G2: Ø/LID G3: SAL/Ø	Infiltration of skin 10 ml 1% LID	5 min prior to surgery	Prior to skin closure	FEN i.v. ≥ 2 µg/kg	Preemptive effect – yes Preventive effect – yes Both at 24 h postoperation Pain: G1 < G2 < G3 Analgesics: G1 = G2 < G3
86 (1991)	Cholecystectomy (n = 80)	1;3	GA plus: G1: NA/BUP G2: NA/BUP G3: NA/SAL G4: NA/SAL	G1 and G3: infiltration into peritoneal, fascial, and subcutaneous layers 40 ml 0.25% BUP G2 and G4: topical into wound 40 ml 0.25% BUP	NA	At time of closure	FEN or MPE dose NS	Preventive effect – no
87 (1994)	Cholecystectomy (n = 69)	1;2	GA plus: G1: ROP/NA G2: ROP/NA G3: SAL/NA	Infiltration of cutis, subcutis, and fascia G1: 70 ml 0.25% ROP G2: 70 ml 0.125% ROP	15 min before incision	NA	MPE i.m. 75–100 mg FEN i.v. dose NS	Preventive effect – no, but at 74 h postoperation analgesics: G1 < G3 (P = 0.051)
88 (1995)	Cholecystectomy (n = 30)	4;8	GA plus: G1: BUP/BUP G2: SAL/BUP	Interpleural block Bolus 20 ml 0.5% BUP followed by infusion of 7 ml/h 0.25% BUP	Bolus 20–25 min before incision followed by infusion for 24 h in G1	G2: bolus in recovery room followed by infusion for 24 h	ALF i.v. G1: 13.6 µg/kg G2: 39.2 µg/kg	Preemptive effect – no

Table A7.1 *Continued*

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/post-incision drug	Route and dose	Timing of preincision intervention	Timing of postincision intervention	Systemic analgesics[a]	Nature and time after surgery of preventive or preemptive analgesic effect
89 (1991)	Laparoscopy (n = 80)	1;2	GA plus: G1: Ø/NA G2: SAL/NA G3: LID + EPI/NA G4: BUP + EPI/NA	Intraperitoneal infiltration G3: 80 ml 0.5% LID + 1:320,000 EPI G4: 80 ml 0.125% BUP + 1:800,000 EPI	After creation of pneumoperitoneum	NA	ALF i.v. 15 µg/kg	Preventive effect – yes up to 48 h postoperation Pain: G3 = G4 < G1 = G2
90 (1994)	Laparoscopic cholecystomy (n = 42)	1;3;5	GA plus: G1: SAL/SAL G2: SAL/BUP + EPI G3: BUP + EPI/ BUP + EPI	Peritoneal topical spray 20 ml 0.5% BUP + 1:200,000 EPI	After creation of pneumoperitoneum, 10 min before surgery	At end of operation	FEN i.v. 5 µg/kg	Preventive effect – yes at 24 h postoperation Pain: G3 < G2 < G1 Analgesics: G3 < G2 < G1
91 (1996)	Laparoscopic cholecystomy (n = 120)	1;2;3;5	GA plus: G1: SAL/SAL G2: SAL/BUP + EPI G3: BUP + EPI/ BUP + EPI G4: BUP + EPI/SAL	Peritoneal topical spray 20 ml 0.5% BUP + 1:200,000 EPI	After creation of pneumoperitoneum, 10 min before surgery	At end of operation	FEN i.v. 0.15 mg/kg	Preemptive effect – yes at 24 h postoperation Pain: G4 < G2 Analgesics: G4 < G2 Preventive effect – yes at 24 h postoperation Pain: G3 = G4 < G2 < G1 Analgesics: G3 = G4 < G2 < G1
92 (1997)	Laparoscopic cholecystomy (n = 80)	1;5	GA plus: G1: BUP/BUP G2: SAL/SAL	Intraperitoneal infiltration 15 ml 0.5% BUP	After creation of pneumoperitoneum	At end of operation	No	Preventive effect – no Pain: G1 < G2 up to 8 h postoperation Analgesics: G1 < G2 up to 4 h postoperation
93 (1998)	Diagnostic laparoscopy or laparoscopic tubal ligation (n = 57)	1;2;3	G1: BUP/SAL G2: SAL/BUP G3: SAL/SAL	Infiltration of skin and fascia 10 ml 0.5% BUP	5 min prior to incision for trocar placement	Immediately before closure	FEN i.v. 2 µg/kg	Preemptive effect – yes Preventive effect – yes Both at 24 h postoperation: MPQ: G1 < G2 = G3 TFA: G1 > G2 = G3
94 (2000)	Laparoscopic gynecological surgery (n = 28)	1;2	GA plus: G1: BUP/NA G2: SAL/NA	Infiltration into cutaneous, subcutaneous, and subfascial tissues 20 ml 0.25% BUP	15 min before incision	NA	MPE i.m. 50 mg	Preventive effect – yes Pain: G1 < G2 at 10 h postoperation Analgesics: G1 < G2 at 24 h postoperation

95 (1982)	Inguinal hernia repair (n = 117)	1;2	GA plus: G1: LID/NA G2: Ø/NA	Infiltration of operative field and IINB 50 ml 0.5–1% LID	Immediately before operation	NA	FEN i.v. NS	Preventive effect – opposite Analgesics: G1 > G2
21 (1988)	Inguinal hernia repair (n = 30)	1;3	GA plus: G1: NA/LID G2: NA/PLA G3: NA/Ø	Aerosol spray of cutaneous and subcutaneous surface or wound 200 mg LID	NA	Before closure	NS	Preventive effect – yes at 24 h postoperation Pain: G1 < G2 = G3 Pain on movement: G1 < G2 = G3 Pain to pressure: G1 < G2 = G3 Analgesia: G1 < G2 = G3
22 (1989)	Inguinal hernia repair (n = 60)	1;3	GA plus: G1: NA/BUP G2: NA/Ø	IINB 10 ml 0.5% BUP	NA	Before closing the external oblique aponeurosis	PAP MPE dose NS	Preventive effect – yes at 24 h postoperation Pain: G1 < G2 Analgesics: G1 < G2 at 12 h
96 (1990)	Inguinal herniorrhaphy (n = 36)	1;2	G1: GA only/NA G2: GA + BUP/NA G3: BUP/NA	G2: Infiltration 40 ml 0.25% BUP G3: spinal 12.5 mg 0.5% BUP	G2: 5 min before incision G3: NS	NA	No	Preventive effect – yes up to day 10 postoperation Pain at rest: G2 = G3 < G1 Pain on movement: G2 < G3 < G1 Pain to pressure: G2 < G3 < G1
97 (1990)	Inguinal herniorrhaphy (n = 45)	2	Spinal LID plus: G1: BUP/NA G2: Ø/NA	Spinal LID 5% G1: 72 mg G2: 74 mg IINB 10 ml 0.5% BUP	Spinal NS Nerve block NS	NA	No	Preventive effect – yes up to 48 h postoperation Pain: G1 < G2 Analgesics: G1 < G2
98 (1992)	Herniorrhaphy (n = 32)	2;4	GA plus: G1: LID + EPI/Ø G2: Ø/LID + EPI	Inguinal field block 55 ml 1% LID + EPI	15 min before operation	After closure but before awake	ALF i.v. 10 µg/kg and ~ 0.5 µg/kg/min	Preemptive effect – no
99 (1992)	Inguinal herniotomy (n = 37)	2;3	GA plus: G1: LID/Ø G2: Ø/LID	Infiltration of surgical area 40 ml 1% LID	5 min before incision	Immediately before skin closure	No	Preemptive effect – yes at 6 h postoperation Analgesics: G1 < G2
100 (1992)	Inguinal herniorrhaphy (n = 50)	2;3	GA plus: G1: BUP/Ø G2: Ø/BUP	Inguinal field block with BUP G1: 40 ml 0.25% G2: 10 ml 0.5%	After induction, before incision	Before closure of wound layers	FEN i.v. 1 µg/kg	Preventive effect – no

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/post-incision drug	Route and dose	Timing of preincision intervention	Timing of postincision intervention	Systemic analgesics[a]	Nature and time after surgery of preventive or preemptive analgesic effect
101 (1996)	Inguinal hernioplasty (n = 54)	2;4	GA plus: G1: BUP/SAL G2: SAL/BUP	Infiltration subcutaneously plus IINB 2.5 mg/ml, 1 mg/kg BUP	Before start of surgery	After surgery but before end of anesthesia	No	Preemptive effect – no
102 (2000)[b]	Inguinal hernia repair (n = 70)	1;8	GA plus: G1: BUP/BUP/BUP/BUP G2: SAL/SAL/SAL/SAL	Infiltration of proposed incision site and field block of iliohypogastric and ilioinguinal nerves 1 ml/kg BUP 0.25% intraoperative infiltration 0.8 ml/kg BUP subcutaneous wound infiltration 0.2 ml/kg BUP subcutaneous wound infiltration 1 ml/kg BUP	1.5 h before skin incision	Intraoperative/ after wound closure/6 h after preoperative field block	NS	Preventive effect – yes % pain on walking: G1 < G2 up to day 10 postoperation Analgesics: G1 < G2 up to day 2 postoperation
103 (1990)	Hernia repair, orchiopexy, hydrocelectomy (n = 40)	2;4	GA plus: G1: BUP/Ø G2: Ø/BUP	Caudal block 0.5 ml/kg 0.25%	After induction before surgery	After completion of surgery before emergence	NS	Preemptive effect – no
104 (1994)	Circumcision (n = 25)	2;4	GA plus: G1: LID/Ø G2: Ø/LID	Caudal block 0.5 ml/kg 1%	30 min before surgery	Immediately after surgery	No	Preemptive effect – no
105 (1997)	Herniorraphy, orchiopexy, circumcision (n = 51)	2;4	GA plus: G1: BUP + EPI/Ø G2: Ø/BUP + EPI	Caudal 0.6 ml/kg 0.25% + 1:200,000	After induction, before incision	After surgery, prior to emergence	No	Preemptive effect – no
106 (1997)	Hypospadias repair (n = 98)	2;4;6	GA plus: G1: BUP/Ø G2: Ø/BUP G3: BUP/BUP	Penile block G1, G2: 0.5 ml/kg 0.5% BUP G3: 0.25 ml/kg 0.5% BUP	Immediately before incision	Immediately after surgery before emerging from GA	No	Preemptive effect – no Preventive effect – yes up to 24 h postoperation Pain: G3 < G2 Analgesics: G3 < G2
107 (1994)	Appendectomy (n = 90)	1;2;3	GA plus: G1: LID + EPI/Ø G2: Ø/LID + EPI G3: Ø/Ø	Infiltration of skin and subcutaneous tissue 15 ml 1.5% + 1:200,000	3 min before incision	At wound closure	FEN i.v. G1: 118 μg G2: 141 μg G3: 116 μg	Preemptive effect – no Preventive effect – no

108 (1997)	Appendectomy (n = 60)	1;5	GA plus: G1: LID + BUP/ LID + BUP G2: SAL/SAL G3: Ø/Ø	Infiltration of skin and subcutaneous tissues 1% LID + 0.5% BUP 10 ml	Immediately before incision	At wound closure	NS	Preventive effect – no
109 (1997)	Appendectomy (n = 43)	1;2	GA plus: G1: LID + BUP/NA G2: SAL/NA	Infiltration dose NS	After induction, before incision	NA	FEN "minimal doses"	Preventive effect – no but on days 3–5 postoperation Analgesia: G1 < G2 (P = 0.07, two-tailed)
110 (1992)	Gynecological laparotomy (n = 24)	1;3	GA plus: G1: NA/LID G2: NA/Ø	Aerosol spray of subcutaneous tissue 200 mg LID	NA	After closure of fascia	FEN i.v. 0.1 mg	Preventive effect – no
111 (1993)	Abdominal hysterectomy (n = 36)	2;3	GA plus: G1: BUP + EPI/Ø G2: Ø/BUP + EPI	Lumbar epidural 15 ml 0.5% BUP + 1:200,000 EPI	15 min before start of surgery	15 min before waking at end of operation	MOR i.m. 7.5–10 mg	Preemptive effect – no
112 (1995)	Abdominal hysterectomy (n = 56)	1;2;3	GA plus: G1: Ø/Ø G2: BUP + EPI/Ø G3: Ø/BUP + EPI	Infiltration of incision 40 ml 0.5% BUP + 5 µg/ml EPI	15 min before incision	At end of surgery before skin suture	SUF i.v. G1: 92 µg G2: 94 µg G3: 96 µg	Preemptive effect – no Preventive effect – no
113 (1996)	Total abdominal hysterectomy (n = 38)	2;4	GA plus: G1: BUP/Ø G2: Ø/BUP	Spinal 3 ml 0.5% BUP	Before induction	At end of operation, prior to extubation	MOR i.m. 0.15 mg/kg	Preemptive effect – opposite at 12 h postoperation i.v. PCA: G1 > G2
114 (1996)	Hysterectomy or myomectomy (n = 60)	1;2	G1: BUP/NA G2: GA only/NA	Spinal 3 ml 0.5% BUP	After loss of sensation to pinprick at T8, before incision	NA	No	Preventive effect – yes up to 24 h postoperation Pain at rest: G1 < G2 Pain on cough: G1 < G2 i.v. PCA: G1 < G2
115 (1996)	Hysterectomy (n = 50)	1;2	GA + plus: G1: BUP/NA G2: SAL/NA	Infiltration of surgical area 40 ml 0.25% BUP	5 min before incision	NA	PIR p.r. 40 mg FEN i.v. 0.3 mg BPR i.m. 0.3 mg	Preventive effect – yes up to day 3 postoperation Analgesics: G1 < G2
116 (1988)	Cesarean section (n = 26)	1;3	GA plus: G1: NA/BUP G2: NA/SAL	Bilateral IINB 10 ml 0.5% BUP	NA	At end of surgery before reversal	FEN i.v. 100 µg	Preventive effect – yes up to 24 h postoperation Pain: G1 < G2 Analgesics: G1 < G2

Table A7.1 *Continued*

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/post- incision drug	Route and dose	Timing of preincision intervention	Timing of postincision intervention	Systemic analgesics[a]	Nature and time after surgery of preventive or preemptive analgesic effect
117 (1991)	Cesarean section (*n* = 28)	1;3	GA plus: G1: NA/BUP G2: NA/SAL	Infiltration of subcutaneous tissues 0.4 ml/kg 0.5% BUP	NA	After closure of peritoneum	MOR i.v. 5–10 mg	Preventive effect – yes at 24 h postoperation i.v. PCA: G1 < G2
118 (1994)	Cesarean section (*n* = 62)	1;2;3	GA plus: G1: BUP/Ø G2: Ø/BUP G3: Ø/Ø	G1: bilateral IINB 10 ml 0.5% on each side G2: wound infiltration 20 ml 0.5% BUP	Before surgery	NS	FEN i.v. 100 μg	Preventive effect – yes Pain: G1 < G3 up to 24 h postoperation Analgesics: G1 < G2 at 20 h postoperation
119 (1996)	Cesarean section (*n* = 46)	2;5	Preoperative spinal BUP plus: G1: BUP + EPI/Ø G2: Ø/BUP + EPI G3: Ø/Ø	Spinal 15 ml plus: IINB 10 ml 0.5% BUP + 1:200,000 EPI	IINB after spinal but before incision	Immediately after C-section	NS	Preemptive effect – yes at 24–48 h postoperation Pain at rest: G1 < G2 Pain on movement: G1 < G2 Preventive effect – opposite at 24–48 h postoperation Pain at rest: G2 > G3 = G1 Pain on movement: G2 > G3 = G1
120 (1994)	Lower abdominal surgery (*n* = 42)	2;3	GA plus: G1: BUP/SAL G2: SAL/BUP	Lumbar epidural 15 ml 0.5% BUP	35 min before incision	30 min after incision	No	Preemptive effect – yes MPQ: G1 < G2 at 24 h and 72 h postoperation i.v. PCA: G1 < G2 up to 48 h
121 (1997)	Laparotomy (*n* = 200)	2;3	GA plus: G1: BUP/Ø G2: Ø/BUP	Infiltration of midline incision 40 ml 0.25% BUP	5 min before incision	Immediately before skin closure	FEN i.v. NS	Preemptive effect – opposite at 24 h postoperation Pain: G1 > G2
122 (1993)	Lumbar diskectomy (*n* = 60)	1;3	GA plus: G1: NA/BUP G2: NA/Ø	Infiltration of wound and subcutaneous tissues 20 ml 0.5% BUP	NA	Immediately before wound closure	MOR i.v. 0.1 mg/ kg	Preventive effect – yes at 24 h postoperation Incidence of severe pain: G1 < G2 i.v. PCA: G1 < G2

123 (1999)[c]	Arthroscopic knee surgery (n = 44)	4;6	GA plus: G1: ROP/ROP/ROP G2: SAL/ROP/SAL	Femoral three-in-one nerve block 40 ml 0.2% ROP Intra-articular instillation 30 ml 0.2% ROP Peri-incisional infiltration 20 ml 0.2% ROP	Three-in-one block before surgical incision	Intra-articular and peri-incisional ROP at end of surgery	FEN i.v. 1.5 µg/kg	Preventive effect – no
124 (1999)	Posterolateral thoracotomy (n = 70)	4;8	GA plus: G1: MEP/MEP G2: Ø/MEP	Thoracic epidural MEP 4 ml 1.5% bolus followed by 4 ml/h infusion	Bolus 20 min before incision followed by 72-h infusion	Bolus at completion of operation followed by 72-h infusion	NS	Preemptive effect – yes up to 3 days and at 6 months postoperation Pain: G1 < G2
125 (1990)	Hemorrhoidectomy (n = 40)	1;4	GA plus: G1: NA/BUP + EPI G2: NA/EPI	Perianal infiltration 1.5 mg/kg 0.5% BUP + 1:200,000 EPI	NA	Postoperative	No	Preventive effect – no
126 (1993)	Hemorrhoidectomy (n = 30)	1;4	GA plus: G1: EPI/BUP G2: EPI/SAL	Infiltration 1:200,000 EPI 20 ml 0.5% BUP	Before excision	After excision	NS	Preventive effect – opposite Pain: G1 > G2 up to 2 days postoperation
127 (2000)	Breast biopsy (n = 74)	2;6	GA plus: G1: TEN + BUP/Ø G2: TEN/BUP	Infiltration 10 ml 0.5% BUP i.v. 20 mg TEN	TEN at induction, BUP 5 min before incision	After skin closure, while still anesthetized	ALF i.v. 5 µg/kg	Preemptive effect – no
128 (1998)	Strabismus surgery (n = 30)	1;2;4	GA plus: G1: Ø/Ø G2: BUP/Ø G3: Ø/BUP	G2: retrobulbar block 2 ml 0.5% BUP G3: subconjunctival injection 0.25 ml 0.5% BUP	10 min before surgery	At conclusion of surgery	NS	Preventive effect – no
129 (2000)	Hand and forearm surgery (n = 55)	2;4	GA plus: G1: BUP/Ø G2: Ø/BUP	Axillary block 2 mg/kg 0.25% BUP	20 min before incision	After surgery (15 min before the end of GA)	No	Preemptive effect – opposite at 24 h postoperation Cumulative pain: G1 > G2 Analgesics: G1 > G2

a. Administered to all patients as premedication or during surgery.

b. This study has four interventions, the second occurring intraoperatively, the third at the end of surgery, and the fourth 6 h after preoperative field block.

c. This study has three interventions, the second and third occurring at the end of surgery.

ACE, acetaminophen (paracetamol); ALF, alfentanil; BPR, buprenorphine; BUP, bupivacaine; DIC diclofenac; i.v. PCA, intravenous patient-controlled analgesia; EPI, epinephrine (adrenaline); FEN, fentanyl; GA, general anesthesia; IINB, ilioinguinal and iliohypogastric nerve block; i.m., intramuscular; i.v., intravenous; KET, ketamine; KTO, ketorolac; LID, lidocaine (lignocaine); MEP, mepivacaine; MPE, meperidine (pethidine); MPQ, McGill Pain Questionnaire; MOR, morphine; NA, not applicable; NS, not stated; PAP, papaveretum; PIR, piroxicam; p.r., per rectum; PRI, prilocaine; ROP, ropivacaine; S1 and S2, first and second sides of body in studies using patients as their own controls (i.e. within-subject design); SAL, saline; SUF, sufentanil; TEN, tenoxicam; Ø, nothing administered.

Table A7.2 *Studies examining the effects of timing of opioid administration relative to incision*

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/ postincision drug	Route and dose	Timing of preincision intervention	Timing of postincision intervention	Systemic opioid[a]	Nature and time after surgery of preventive or preemptive analgesic effect
131 (1992)	Posterolateral thoracotomy (n = 30)	2;3	GA plus: G1: FEN/SAL G2: SAL/FEN	Lumbar epidural 4 µg/kg FEN	30 min before incision	15 min after incision	No	Preemptive effect – yes Pain: G1 < G2 at 6 h postoperation i.v. PCA: G1 < G2 between 12 h and 24 h postoperation
132 (1993)	Abdominal hysterectomy (n = 60)	2;3	GA plus: G1: MOR/Ø G2: MOR/Ø G3: Ø/MOR	G1: i.m. 10 mg MOR G2: i.v. 10 mg MOR G3: i.v. 10 mg MOR	G1: 1 h preoperation G2: at induction	Closure of peritoneum	No	Preemptive effect – yes at 24 h postoperation i.v. PCA: G2 < G3 Preventive effect – yes at 24 h postoperation Relative pain thresholds: G3 > G1 = G2 Preemptive effect – opposite at 48 h postoperation Pain on movement: G2 > G3
133 (1994)	Abdominal hysterectomy (n = 60)	2;3	GA plus: G1: ALF/MOR G2: Ø/ALF + MOR	i.v. G1: 7.5 µg/kg ALF per bolus G2: 15 µg/kg ALF 0.2 mg/kg MOR	One bolus at induction and one bolus 90 s before incision	10 min after incision	No	Preventive effect – no
134 (1994)	Major abdominal surgery (n = 20)	1;2	GA plus: G1: MOR/NA G2: Ø/NA	Lumbar epidural 5 mg MOR	Before induction	NA	FEN i.v. G1: 465 µg G2: 983 µg	Preventive effect – yes up to 72 h postoperation Pain: G1 < G2 i.v. PCA: G1 < G2
135 (1994)	Postepisiotomy pain (n = 90)	4	G1: MOR/SAL + SAL G2: SAL/MOR + ACE	Lumbar epidural 2 mg MOR	After episiotomy repair	Onset of episiotomy pain	No	Preventive effect – yes Pain: G1 < G2
136 (1994)	Abdominal hysterectomy (n = 40)	2;3	GA plus: G1: ALF/SAL + MOR G2: SAL/ALF + MOR	i.v. 40 µg/kg ALF 0.1 mg/kg MOR	At induction 10 min before incision	1 min after incision	No	Preventive effect – opposite at 24 h postoperation Pain at rest: G1 > G2
137 (1995)	Abdominal hysterectomy (n = 49)	2;5	GA plus: G1: MOR/MOR G2: MOR/Ø	i.v. G1: 10 mg/dose MOR G2: 20 mg MOR	At induction	Closure of peritoneum	No	Preventive effect – yes at 48 h postoperation Pain on movement: G2 < G1

138 (1995)[b]	Abdominal hysterectomy (n = 85)	2;3	GA plus: G1: FEN/SAL/SAL G2: SAL/FEN/SAL G3: SAL/SAL/FEN G4: SUF/SAL/SAL G5: SAL/SUF/SAL	i.v. G1–G3: 10 µg/kg FEN G4–G5: 1 µg/kg SUF	5 min before induction	After incision of peritoneum/after removal of uterus	No	Preemptive effect – no
139 (1996)	Abdominal hysterectomy (n = 51)	1;2	GA plus: G1: MOR/PLA G2: PLA/MOR G3: PLA/PLA	p.o. 30 mg/dose MOR	q 12 h for 42 h before surgery	2 h before surgery	FEN i.v. 1 µg/kg	Preventive effect – no
140 (1996)[c]	Total knee arthroplasty (n = 41)	1;2;7;8	Spinal BUP plus: G1: MOR/MOR + MOR G2: SAL/MOR + MOR G3: MOR/SAL + SAL G4: SAL/SAL/SAL	Spinal 3 ml 0.5% BUP first intervention i.m. 0.14 mg/kg MOR second intervention epidural 4 mg MOR third intervention 3 mg MOR	1 h before operation	Immediately after the operation/10 h after the operation	NA	Preemptive effect – no Preventive effect – opposite at 16 h postoperation Pain: G3 > G4
7 (1996)	Abdominal hysterectomy (n = 45)	1;5	GA plus: G1: Ø/NA G2: ALF/NA G3: ALF/NA	i.v. G2: 30 µg/kg followed by 10–20 µg/kg ALF G3: 100 µg/kg followed by 1–2 µg/kg/min ALF	Bolus at induction followed by hourly boluses in G2 and intraoperative infusion in G3	NA	No	Preventive effect – yes up to 12 h postoperation IAA: G3 < G1 = G2
141 (1996)	Abdominal hysterectomy (n = 39)	2;3	GA plus: G1: SUF/SAL G2: SAL/SUF	i.v. 1 µg/kg SUF	5 min before induction	Ligation of round ligaments	No	Preemptive effect – no
142 (1996)	Back surgery (n = 30)	1;2	GA plus: G1: FEN/NA G2: SAL/NA	i.v. 3 µg/kg FEN	5 min before induction	NA	No	Preventive effect – no but sensory thresholds: G1 > G2
150 (1997)	Third molar extraction (n = 40)	2;3	GA plus: G1: MPE/SAL G2: SAL/MPE	i.m. 50 mg MPE	1–2 h before surgery	Immediately after surgery	FEN i.v. 1.5 µg/kg	Preemptive effect – no
143 (1997)	Abdominal hysterectomy (n = 38)	2;3	GA plus: G1: ALF/Ø G2: Ø/ALF	i.v. 70 µg/kg ALF	15 min before incision	15 min after incision	No	Preemptive effect – yes from 48 h to 72 h postoperation i.v. PCA: G1 < G2

Table A7.2 *Continued*

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/ postincision drug	Route and dose	Timing of preincision intervention	Timing of postincision intervention	Systemic opioid[a]	Nature and time after surgery of preventive or preemptive analgesic effect
144 (1997)	Lumbar laminectomy ($n = 30$)	2;3	GA plus: G1: MOR/SAL G2: SAL/MOR	Lumbar epidural 3 mg MOR	60 min before surgery	End of surgery	MOR i.v. 0.1 mg/kg	Preemptive effect – yes up to 24 h post operation Pain: G1 < G2 Analgesics: G1 < G2 TFA: G1 > G2
145 (1998)	Abdominal hysterectomy ($n = 60$)	2;3	GA plus: G1: MOR/SAL G2: SAL/MOR	i.v. 0.3 mg/kg MOR	At induction, 30 min before incision	At start of skin incision	No	Preemptive effect – no
146 (1999)	Limb surgery, radical mastectomy, gastrectomy, hysterectomy, appendectomy ($n = 268$)	1;5	GA plus: G1: MOR/NAL G2: SAL/SAL	Epidural bolus of 0.06 mg/ kg MOR followed by 0.02 mg/kg/h MOR infusion i.v. 0.008 mg/kg NAL	Bolus 40 min before incision followed by intraoperative infusion until end of surgery	After skin closure	NS	Preventive effect – yes up to 48 h post operation for limb surgery and mastectomy Pain: G1 < G2 E-PCA: G1 < G2
147 (2000)	Orthopedic surgery: removal ($n = 59$); fracture ($n = 56$); arthritis ($n = 58$)	1;5	GA plus: Removal surgery G1: MOR/NAL G2: SAL/SAL Fracture surgery G3: MOR/NAL G4: SAL/SAL Arthritis surgery G5: MOR/NAL G6: SAL/SAL	Cervical or lumbar epidural bolus of 0.06 mg/ kg MOR followed by 0.02 mg/kg/h MOR infusion i.v. 0.008 mg/kg NAL	Bolus 40 min before incision followed by intraoperative infusion until end of surgery	After skin closure	NS	Preventive effect – yes up to 48 h post operation only among the group of patients without preoperative pain (i.e. removal surgery) Pain at rest: G1 < G2 Pain on movement: G1 < G2 at 12 h post operation E-PCA: G1 < G2
148 (2000)	Open knee surgery ($n = 37$)	1;3	GA plus: G1: NA/MOR G2: NA/M6G G3: NA/SAL	i.v. G1: 0.15 mg/kg MOR G2: 0.1 mg/kg M6G	NA	At beginning of wound closure	ALF i.v. 20–30 μg/ kg	Preventive effect – yes up to 24 h post operation i.v. PCA: G1 < G2, G1 < G3, G2 = G3

| 149 (2000) | Major neurosurgical procedures ($n = 42$) | 1;5 | GA plus:
G1: TRA/NA
G2: TRA/NA
G3: FEN/NA | i.v.
G1: 1 mg/kg bolus TRA
G2: 0.5 mg/kg bolus followed by 150 µg/kg/h continuous infusion TRA
G3: 2 µg/kg/h continuous infusion FEN | Bolus beginning at induction and for G2 and G3 continuous infusion throughout the operation | NA | No | Preventive effect – yes at 4 h and 8 h post operation
Pain: G3 = G2 < G1 |

a. Opioid, other than the target intervention, administered to all patients as a premedication or during surgery.

b. This study has three interventions, the third occurring after removal of the uterus.

c. This study has three interventions, the third occurring 10 h after the operation

ALF, alfentanil; BUP, bupivacaine; E-PCA, epidural patient-controlled analgesia; FEN, fentanyl; IAA, integrated analgesic assessment; i.v., intravenous; i.m., intramuscular; M6G, morphine-6-glucuronide; MOR, morphine; NAL, naloxone; ACE, acetaminophen (paracetamol); MPE, meperidine (pethidine); PLA, placebo; p.o., per os; NA, not applicable; NS, not stated; SAL, saline; SUF, sufentanil; TRA, tramadol; TFA, time to first analgesic request; Ø, nothing administered.

Table A7.3 *Studies examining the effects of timing of administration of the NMDA receptor antagonists ketamine or dextromethorphan relative to incision*

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/ postincision drug	Route and dose	Timing of preincision intervention	Timing of postincision intervention	Systemic analgesics[a]	Nature and time after surgery of preventive or preemptive analgesic effect
Ketamine								
166 (1993)	Cholecystectomy (n = 22)	1;2	GA plus: G1: KET/NA G2: SAL/NA	i.v. 0.5 mg/kg KET	5 min before incision	NA	FEN i.v. 2 µg/kg	Preventive effect – yes at 24 h post operation Analgesics: G1 < G2
20 (1994)	Transabdominal hysterectomy (n = 27)	1;5	GA plus: G1: KET/NA G2: FEN/NA G3: Ø/NA	i.v. G1: 2 mg/kg KET bolus followed by 20 µg/kg/min infusion G2: 5 µg/kg FEN bolus followed by 0.02 µg/kg/min infusion	Bolus at induction followed by infusion until end of surgery	NA	No	Preventive effect – yes up to 48 h post operation Hyperalgesia: G1 = G2 < G3
167 (1997)	Radical subtotal gastrectomy (n = 60)	2;3	GA plus: G1: MOR + KET/SAL G2: SAL/MOR + KET	Thoracic epidural 2 mg MOR 60 mg KET	Before induction	After removal of specimen	No	Preemptive effect – yes at 48 h post operation Analgesics: G1 < G2
168 (1997)	Cesarean section (n = 40)	1;2	GA plus: G1: KET/NA G2: THI/NA	i.v. 1 mg/kg KET	Induction	NA	MOR i.v. 0.15 mg/kg	Preventive effect – yes up to 24 h post operation i.v. PCA: G1 < G2
169 (1997)	Abdominal surgery (n = 40)	3;5	GA plus: G1: KET/Ø G2: Ø/KET	i.v. G1: 0.5 mg/kg KET bolus followed by 10 µg/kg/min infusion G2: 0.5 mg/kg KET bolus	Bolus at induction followed by infusion until closure	After wound closure	No	Preventive effect – yes up to day 2 post operation i.v. PCA: G1 < G2
170 (1997)[b]	Total knee replacement (n = 45)	7;8	G1: LID + MOR + KET/ LID/LID + MOR + KET G2: LID/ LID + MOR + KET/ LID + MOR + KET G3: GA + SAL/MOR + KET/ LID + MOR + KET	Lumbar epidural First intervention 15 ml 2% LID 1.5 mg MOR 20 mg KET Second intervention 10 ml 2% LID 1.5 mg MOR 20 mg KET Third intervention 10 ml 0.32% LID 1 mg MOR 10 mg KET	30 min before incision	30 min after incision/at end of surgery and q 12 h	No	Preemptive effect – yes at 72 h post operation Pain: G1 < G2 Incident pain: G1 < G2 i.v. PCA: G1 < G2 Preventive effect – yes up to 72 h post operation Pain: G1 < G3 Incident pain: G1 < G3 i.v. PCA: G1 < G2 < G3

171 (1998)	Upper abdominal surgery (n = 98)	2;3	GA plus: G1: KET/NA G2: NA/KET	Thoracic epidural 60 mg KET	20 min before induction	Closure of parietal peritoneum	No	Preemptive effect – no
172 (1998)	Abdominal hysterectomy (n = 45)	5	GA plus: G1: FEN/FEN G2: KET/KET G3: MAG/MAG	i.v. G1: 1.5 µg/kg FEN and 0.75 µg/kg q 30 min G2: 0.5 mg/kg KET and 0.25 mg/kg q 30 min G3: 20 mg/kg MAG and 10 mg/kg q 30 min	3 min before induction, 5 min before incision	25 min after incision and q 30 min until 45 min before end of surgery	No	Preventive effect – no but on day 5 post operation Pain: G1 = G3 < G2 (P = 0.054)
173 (1998)	Total abdominal hysterectomy (n = 61)	1;2;3	GA plus: G1: KET/SAL G2: SAL/KET G3: SAL/SAL	Lumbar epidural 30 mg KET	Before induction, incision	20 min after incision	ALF i.v. G1: 5.1 mg G2: 2.5 mg G3: 4.0 mg	Preemptive effect – no Preventive effect – yes up to 24 h post operation E-PCA: G1 < G2 = G3
174 (1999)	Total mastectomy (n = 128)	2;3	GA plus: G1: KET/SAL G2: SAL/KET	i.v. 0.15 mg/kg KET	5 min before incision	At skin closure	SUF i.v. G1: 19.9 µg G2: 20.4 µg	Preemptive effect – no
175 (1999)ᶜ	Laparoscopic cholecystectomy (n = 60)	6;8	Preoperative BUP infiltration of incision lines plus GA plus: G1: (R)-KET/SAL/ACE G2: SAL/(R)-KET/ACE G3: SAL/SAL/ACE	Infiltration BUP dose NS i.v. 1.0 mg/kg (R)-KET p.r. 1,000 mg ACE	i.v. KET 3–10 min before incision	i.v. KET at skin closure/ACE on arrival in recovery room	KTO i.v. 30 mg FEN i.v. 1.5–2.0 µg/kg ALF 0.5–1.0 mg	Preemptive effect – no Preventive effect – no
176 (2000)	Gastrectomy (n = 121)	1;5	GA plus: G1: MOR (epidural) + SAL (i.v.)/NAL (i.v.) G2: SAL (epidural) + KET (i.v.)/SAL (i.v.) G3: MOR (epidural) + KET (i.v.)/ NAL (i.v.) G4: SAL (epidural) + SAL (i.v.)/SAL (i.v.)	Thoracic epidural 0.06 mg/kg MOR bolus followed by 0.02 mg/kg/h infusion i.v. First intervention 1.0 mg/kg KET bolus followed by 0.5 mg/kg/h infusion Second intervention 0.008 mg/kg NAL bolus	Epidural 40 min prior to skin incision followed by infusion until skin closure i.v. 10 min prior to skin incision followed by infusion until skin closure	Immediately after surgery	No	Preventive effect – yes Movement pain: G2 < G4 at 12 h post operation Rest pain: G3 < G1 = G2 < G4 at 24 h and 48 h post operation E-PCA: G3 < G1 = G2 < G4 at 24 h and 48 h post operation

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/ postincision drug	Route and dose	Timing of preincision intervention	Timing of postincision intervention	Systemic analgesics[a]	Nature and time after surgery of preventive or preemptive analge- sic effect
177 (2000)	Abdominal hysterectomy (n = 99)	1;2;3	GA plus: G1: SAL/SAL G2: KET/SAL G3: SAL/KET	i.v. 0.4 mg/kg KET	5 min before skin incision	At end of skin closure	ALF i.v. 15 µg/ kg	Preemptive effect – no Preventive effect – opposite at 60 min Post operation pain: G3 < G1 = G2
178 (2000)	Arthroscopic anterior cruciate ligament repair (n = 45)	1;2;3	GA plus: G1: KET/SAL G2: SAL/KET G3: SAL/SAL	i.v. 0.15 mg/kg KET	10 min after induction before tourniquet inflation	After skin closure	SUF i.v. 0.5–0.6 µg/kg	Preemptive effect – no Preventive effect – yes at 24 h and 48 h post operation i.v. PCA: G1 = G2 < G3
Dextromethorphan								
188 (1998)	Laparotomy (n = 37)	1;2	GA plus: G1: DEX/NA G2: PLA/NA	p.o. 60 mg/dose DEX	Night before and 1 h before surgery	NA	MOR i.v. G1: 13 mg G2: 17 mg	Preventive effect – no
179 (1998)	Bilateral tonsillectomy (n = 36)	1;2	GA plus: G1: DEX/NA G2: DEX/NA G3: PLA/NA	p.o. G1: 30 mg DEX G2: 45 mg DEX	60 min before arrival in OR	NA	No	Preventive effect – yes up to day 7 post operation Pain at rest: G2 < G3 Pain on swallowing: G2 < G1 = G3 Analgesics: G1 = G2 < G3
180 (1999)	Lower abdominal surgery (n = 60)	2;3	GA plus: G1: DEX/SAL G2: SAL/DEX	i.v. 5 mg/kg DEX	30 min before induction over 30 min	During skin closure	FEN i.v. 3 µg/kg	Preemptive effect – yes up to day 2 post operation i.v. PCA: G1 < G2
181 (1999)	Adenotonsillectomy (n = 60)	1;2	GA plus: G1: DEX/NA G2: DEX/NA G3: PLA/NA	p.o. G1: 0.5 mg/kg DEX G2: 1.0 mg/kg DEX	60 min before start of surgery	NA	MOR i.v. 0.075 mg/kg ACE p.r. 25–35 mg/kg	Preventive effect – no
182 (1999)	Modified radical mastectomy (n = 60)	1;2	GA plus: G1: DEX + CPM/NA G2: CPM/NA	i.m. 40 mg DEX 20 mg CPM	30 min before incision	NA	FEN i.v. 2 µg/kg	Preventive effect – yes at 48 h post operation Analgesics: G1 < G2

183 (1999)	Laparoscopic cholecystectomy (*n* = 90)	1;2;3	GA plus: G1: DEX + CPM/Ø G2: Ø/DEX + CPM G3: CPM/Ø	i.m. G1 and G2: 40 mg DEX + 20 mg CPM G3: 20 mg CPM	30 min before incision	Removal of gall bladder	FEN i.v. 2 μg/kg	Preemptive effect − yes Preventive effect − yes Both at 48 h post operation Pain: G1 < G2 = G3 Analgesics: G1 < G2 = G3
184 (2000)	Total abdominal hysterectomy (*n* = 50)	1;2	GA plus: G1: DEX/NA G2: PLA/NA	p.o. 150 mg DEX	1 h before surgery	NA	FEN i.v. 0.4 mg	Preventive effect − no i.v. PCA: G1 < G2 from 0 to 4 h post operation
185 (2000)	Hemorrhoidectomy (*n* = 60)	1;2	G1: LID + EPI + CPM/NA G2: LID + EPI + DEX + CPM/NA	Infiltration 10 ml 2% LID + 0.4 mg EPI in 30 ml SAL i.m. 40 mg DEX 20 mg CPM	Infiltration NS i.m. injection 30 min before skin incision	NA	No	Preventive effect − yes at 48 h post operation Worst pain: G2 < G1 Analgesics: G2 < G1
186 (2000)	Upper abdominal surgery (*n* = 60)	1;2	GA plus: G1: CPM/NA G2: DEX + CPM/NA G3: DEX + CPM/NA G4: DEX + CPM/NA	i.m. G2: 10 mg G3: 20 mg G4: 40 mg	30 min before intramuscular incision	NA	FEN i.v. 2 μg/kg LID i.v. 1.5 mg/kg	Preventive effect − yes up to 3 days post operation Cough pain: G4 < G1, G2, G3 i.v. PCA: G4 < G1
187 (2001)	Laparoscopic cholecystectomy or inguinal hernioplasty (*n* = 30)	1;2	GA plus: G1: DEX/NA G2: PLA/NA	p.o. G1: 90 mg	90 min before the operation	NA	FEN i.v. 2.5 μg/kg	Preventive effect − yes at 24 h post operation Pain: G1 < G2 Analgesics: G1 < G2

a. Administered to all patients as a premedication or during surgery.
b. This study has more than three interventions, the third occurring at the end of surgery and q 12 h thereafter.
c. This study has three interventions, the third occurring on arrival in the recovery room.
ACE, acetaminophen (paracetamol); ALF, alfentanil; BUP, bupivacaine; CPM, chlorpheniramine maleate; DEX, dextromethorphan; E-PCA, epidural patient-controlled analgesia; EPI, epinephrine (adrenaline); FEN, fentanyl; GA, general anesthesia; i.m., intramuscular; i.v., intravenous; KET, ketamine; KTO, ketorolac; LID, lidocaine (lignocaine); MAG, magnesium; MOR, morphine; NA, not applicable; NS, not stated; NAL, naloxone; OR, operating room; PLA, placebo; p.o., per os; p.r., per rectum; SAL, saline; SUF, sufentanil; THI, thiopentone; Ø, nothing administered.

Table A7.4 *Studies examining the effects of timing of NSAIDs relative to incision*

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/ postincision drug	Routes and doses	Timing of preincision intervention	Timing of postincision intervention	Systemic opioid[a]	Nature and time after surgery of preventive or preemptive analgesic effect
191 (1983)	Third molar extraction (n = 50)	2;6	Preoperative LID + EPI infiltration plus: S1: ACE/PLA S2: PLA/ACE	Infiltration 1.8 ml LID + 12.5 µg/ml EPI p.o. 1,000 mg ACE	p.o. medications before surgery (time NS)	After surgery (time NS)	NS	Preemptive effect – no
192 (1987)	Pulpectomy (n = 120)	1;2;3;6	Preoperative LID + EPI infiltration plus: G1: FLU/FLU G2: FLU/PLA G3: PLA/FLU G4: PLA/PLA	Infiltration 2% LID + 1:100,000 EPI p.o. 100 mg FLU/dose	p.o. medications 30 min before surgery, 15 min before infiltration	3 h after first dose of FLU or PLA	No	Preemptive effect – no Preventive effect – yes at 24 h post operation Pain: G1 = G3 < G4
193 (1989)	Third molar extraction (n = 20)	2;6	Preoperative infiltration ± i.v. sedation plus: S1: DIF/PLA S2: PLA/DIF	Infiltration agent and dose NS p.o. 1,000 mg DIF	p.o. medications 30 min before surgery	30 min after surgery	No	Preemptive effect – no
194 (1990)	Third molar extraction (n = 160)	1;2	GA plus: G1: DIC/NA G2: DIC/NA G3: FEN/NA G4: SAL/NA	iv in 18 ml G1: 1 mg/kg DIC G3: 1 µg/kg FEN i.m. in 3 ml G2: 1 mg/kg DIC G4: SAL	Immediately after induction, before surgery	NA	NS	Preventive effect – yes on day 1 post operation Pain: G1 < G3, G1 < G4 Analgesics: G1 < G3, G1 < G4
195 (1990)	Third molar extraction (n = 36)	2;6	Preoperative infiltration ± i.v. sedation plus: S1: NAP/PLA S2: PLA/NAP	Infiltration 2% LID + 1:100,000 EPI p.o. 550 mg NAP	p.o. medications 30 min before surgery	30 min after completion of surgery	No	Preemptive effect – no
196 (1990)	Third molar extraction (n = 44)	2	Preoperative infiltration plus: S1: FEB/NA S2: PLA/NA	Infiltration 2% LID + 1:80,000 EPI p.o. 450 mg FEB	p.o. medications 2 h before surgery	NA	No	Preventive effect – no

197 (1992)	Laparoscopic sterilization (n = 56)	1;2	GA plus: G1: IND/NA G2: PLA/NA	p.r. 200 mg IND	2 h before surgery	NA	FEN i.v. 1.5 µg/kg	Preventive effect – no
198 (1992)	Third molar extraction (n = 150)	2	Preoperative infiltration plus: G1: DIC + PLA/NA G2: DIC + PLA/NA G3: PLA + PLA/NA	Infiltration 20 mg/ml LID + 12.5 µg/ml EPI p.o. G1: 150 mg DIC i.m. G2: 150 mg DIC	20 min before operation	NA	No	Preventive effect – no
199 (1993)	Thoracotomy (n = 50)	4;6	GA plus: G1: IND/IND + PAP G2: Ø/IND + PAP	p.r. 200 mg IND first dose and 100 mg thereafter i.v. infusion PAP dose NS	IND night before surgery and b.i.d. thereafter	IND after completion of surgery and b.i.d. thereafter PAP infusion started after surgery for 48 h	MOR 10–20 mg	Preemptive effect – no
200 (1994)	Minor orthopedic surgery (n = 180)	1;2;4	GA plus: G1: NAP/PLA G2: PLA/NAP G3: PLA/PLA	Route NS 1,100 mg NAP	1 h before surgery	Immediately after surgery	No	Preemptive effect – no Preventive effect – yes at 24 h post operation Pain: NS Analgesics: G1 = G2 < G3
201 (1995)	Total hip replacement (n = 60)	1;2;3	GA plus: G1: KTO/SAL G2: SAL/KTO G3: SAL/SAL	i.v. 60 mg KTO	After arrival in OR before induction	At skin closure	FEN i.v. G1: 225 µg G2: 242 µg G3: 218 µg	Preemptive effect – yes up to 6 h post operation i.v. PCA: G1 < G2 Preventive effect – no
202 (1995)	Knee arthroscopy (n = 60)	2;5	GA plus: G1: PIR/BUP G2: PIR/Ø	i.m. 20 mg PIR infiltration of incisions + intra-articular injection 20 ml 0.25% BUP	After induction, before surgery	At end of procedure, before application of dressing	ALF i.v. 10 µg/kg	Preventive effect – no
203 (1995)	Abdominal hysterectomy (n = 90)	1;2;3	GA plus: G1: KTO/SAL G2: SAL/KTO G3: SAL/SAL	i.v. infusion 10 mg KTO in 50 ml 0.9% SAL	Between induction and skin incision	Between skin closure and recovery ward	ALF i.v. 30 µg/kg followed by 40 µg/kg/h intraoperatively	Preemptive effect – no Preventive effect – no

Table A7.4 *Continued*

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/ postincision drug	Routes and doses	Timing of preincision intervention	Timing of postincision intervention	Systemic opioid[a]	Nature and time after surgery of preventive or preemptive analgesic effect
204 (1996)	Third molar extraction (*n* = 21)	2;6	Preoperative LID + EPI infiltration plus: S1: DIC/PLA S2: PLA/DIC	Infiltration 2% + 1:100,000 p.o. 100 mg DIC	p.o. medications 1 h before surgery	p.o. medications at the end of the operation	NS	Preemptive effect – no
205 (1996)[b]	Abdominal hysterectomy (*n* = 40)	2;7	GA plus: G1: BUP + DIC/Ø/Ø G2: Ø/BUP/DIC	Thoracic epidural 20 ml 0.5% BUP p.r. 100 mg DIC	30 min before incision	30 min after incision/ immediately after surgery	No	Preemptive effect – opposite up to 12 h post operation i.v. PCA: G1 > G2
206 (1996)	Minor orthopedic procedures (*n* = 60)	2;4	GA plus: G1: KTO/PLA G2: PLA/KTO	i.v. 30 mg	30 min before surgery	On arrival in PACU	No	Preemptive effect – no
207 (1999)	Knee arthroscopy (*n* = 100)	1;2	GA plus: G1: PRO/NA G2: TEN/NA G3: PRO + TEN/NA G4: PLA/NA	i.v. 30 mg/kg PRO 0.5 mg/kg TEN	1 h before GA	NA	ALF i.v. 10 µg/kg	Preventive effect – no
208 (2000)	Laparoscopic gynecological procedures (*n* = 51)	2;4	GA plus: G1: KTO/SAL G2: SAL/KTO	i.v. 30 mg KTO	In OR before surgery	At completion of surgery	FEN i.v. 1–2 µg/kg	Preemptive effect – opposite up to 24 h post operation Pain: G1 > G2
209 (2000)	Total abdominal surgery (*n* = 45)	1;2	GA plus: G1: TEN/NA G2: TEN/NA G3: SAL/NA	i.v. G1: 20 mg G2: 40 mg	10 min before induction of GA	NA	FEN i.v. 5 µg/kg	Preventive effect – no
210 (2001)	Knee arthroscopy (*n* = 121)	2;4;6	GA plus: G1: DIC/PLA G2: PLA/DIC G3: DIC/DIC	p.o. G1: 50 mg G2: 50 mg G3: 25 mg/25 mg	1 h preoperation	30 min post operation	No	Preemptive effect – no

a. Administered to all patients as a premedication or during surgery.
b. This study has three interventions, the third occurring immediately after surgery.
ALF, alfentanil; BUP, bupivacaine; DIC, diclofenac; DIF, diflunisal; E-PCA, epidural patient-controlled analgesia; EPI, epinephrine (adrenaline); FEB, fenbufen; FEN, fentanyl; FLU, flubiprofen; GA, general anesthesia; i.m., intramuscular; IND, indomethacin; i.v., intravenous; KTO, ketorolac; LID, lidocaine (lignocaine); MOR, morphine; NA, not applicable; NAP, naproxen sodium; NS, not stated; OR, operating room; PACU, postanesthetic care unit; PAP, papaveretum; ACE, acetaminophen (paracetamol); PIR, piroxicam; PLA, placebo; p.o., per os; p.r., per rectum; PRO, propacetamol; SAL, saline; S1 and S2, first and second sides of body in studies using patients as their own controls; Ø, nothing administered.

Table A7.5 *Studies examining the effects of timing of administration of a combination of a local anesthetic and opioid as the target treatments*

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/ postincision drug	Route and dose	Timing of preincision intervention	Timing of postincision intervention	Systemic opioid[a]	Nature and time after surgery of preventive or pre-emptive analgesic effect
211 (1992)	Colonic surgery (n = 32)	4;8	GA plus: G1: BUP + MOR/ BUP + MOR G2: Ø/BUP + MOR	Thoracic epidural bolus dose 7 ml 7.5 mg/ml BUP + 2 mg MOR First infusion 4 ml/h 7.5 mg/ml BUP + 0.05 mg/ml MOR Second infusion 4 ml/h 2.5 mg/ml BUP + 0.05 mg/ml MOR	G1: bolus 40 min before incision followed by first infusion for 2 h followed by second infusion for 72 h	G2: bolus at wound closure followed by first infusion for 2 h followed by second infusion for 72 h	FEN i.v. 0.1–0.2 mg	Preemptive effect – no
212 (1993)	Cesarean section (n = 28)	5;8	S1: BUP + SUF/BUP S2: BUP + SUF/SAL	Lumbar epidural infusion of 0.1% BUP + 5 μg/ml SUF at 10–12 ml/h followed by bolus of 0.25% BUP wound infiltration 1 ml/cm 0.25% BUP	Before section	Infiltration of wound edge at time of closure	No	Preventive effect – yes at 24 h Pain: G1 < G2
213 (1994)	Upper abdominal surgery (n = 49)	8	GA plus: G1: (BUP + MOR) + BUP/ (BUP + MOR) G2: (BUP + MOR) + Ø/ (BUP + MOR)	Thoracic epidural bolus 9 ml 0.5% BUP + 2 mg MOR followed by infusion of 4 ml/h 0.25% BUP + 0.2 mg/h MOR infiltration of skin, subcutis, and subfascial area 40 ml 0.25% BUP	Epidural before induction; infiltration after induction, before surgery	Epidural infusion started 30 min after initial bolus and continued for 72 h post operation	ALF i.v. 1 mg	Preventive effect – yes at 24 and 48 h Analgesics: G1 < G2

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/ postincision drug	Route and dose	Timing of preincision intervention	Timing of postincision intervention	Systemic opioid[a]	Nature and time after surgery of preventive or pre-emptive analgesic effect
214 (1994)	Total knee arthroplasty (n = 32)	4;8	GA plus: G1: BUP + MOR/ BUP + MOR G2: Ø/BUP + MOR	Lumbar epidural bolus dose 16 ml 7.5 mg/ml BUP + 2 mg MOR First infusion 4 ml/h 1.25 mg/ml BUP + 0.05 mg/ml MOR Second infusion 4 ml/h 0.625 mg/ml BUP + 0.05 mg/ml MOR	G1: bolus 30 min before incision followed by first infusion for 24 h followed by second infusion for 24 h	G2: bolus at wound closure followed by first infusion for 24 h followed by second infusion for 24 h	FEN i.v. 0.3 mg	Preemptive effect – no
215 (1994)[b]	Tonsillectomy (n = 35)	4;6;7	GA plus: G1: BUP/Ø/FEN G2: Ø/BUP/FEN G3: SAL/Ø/FEN	Infiltration of tonsillar tissues 4 ml 0.25% BUP i.v. 1 µg/kg FEN	After induction, 5 min before incision	BUP after removal of tonsils in G2/ FEN at end of the operation	No	Preemptive effect – no Preventive effect – no
216 (1994)	Radical prostatectomy (n = 96)	4;8	G1: BUP (no GA)/FEN G2: GA + BUP/FEN G3: GA only/FEN	Lumbar epidural BUP G1: bolus of 0.25 ml/ kg 0.5% followed by 0.1 ml/kg/h 0.125% infusion G2: bolus of 0.2 ml/ kg 0.5% followed by 0.1 ml/kg/h 0.125% infusion FEN 100 µg	G1: before incision G2: bolus after induction (≥ 20 min before incision) followed by infusion until skin closure	During skin closure	G2: FEN i.v. 1–2 µg/kg G3: MOR i.v. 0.2 mg/kg	Preventive effect – yes Pain: G1 < G3 on day 1 post operation E-PCA: G1 < G2 = G3 on days 2 and 3 post operation
217 (1996)[c]	Posterolateral thoracotomy (n = 45)	7;8	GA plus: G1: BUP + EPI/SAL/FEN/ BUP + EPI + FEN G2: SAL/BUP + EPI/FEN/ BUP + EPI + FEN G3: SAL/SAL/FEN/ BUP + EPI + FEN	Thoracic epidural 8 ml 0.5% BUP + 1: 200,000 EPI 50 µg FEN 2 ml/h 0.125% BUP + 1:400,000 EPI + 6 µg/ml FEN	30 min before incision	15 min after incision/at end of operation/infusion started in recovery room for 48 h	ALF i.v. bolus + infusion G1: 12.5 mg G2: 10 mg G3: 10.8 mg	Preventive effect – no

Ref (year)	Surgery		Treatment groups	Intervention	Pre-op	Intra/post-op	Other	Result
218 (1996)[d]	Upper abdominal surgery (n = 40)	7;8	GA plus: G1: BUR + MEP/MEP/Ø/BUR + MEP G2: Ø/MEP/BUR + MEP/BUR + MEP	Thoracic epidural First/third intervention bolus of 0.1 mg BUR + 5 ml 1.5% MEP Second intervention 1.5% MEP intermittent boluses Fourth intervention 1.7 mg/h infusion of 40 ml 1.5% MEP + 0.3 mg BUR	BUR + MEP bolus after induction, 15 min before incision	MEP boluses during surgery/BUR + MEP bolus after the end of surgery/continuous infusion of MEP + BUR started after extubation and maintained for 3 days	No	Preventive effect – no
219 (1996)	Third molar extraction (n = 36)	2	GA plus: S1: LID + EPI + MOR/NA S2: SAL + MOR/NA	Inferior alveolar nerve block and infiltration 2 ml 2% BUP + 1:200,000 EPI i.v. 0.15 mg/kg MOR	5 min before surgery	NA	No	Preventive effect – no
220 (1997)	Arthroscopic knee surgery (n = 80)	2;5	Spinal with BUP plus: G1: Ø/MOR G2: MOR/Ø G3: Ø/MOR G4: MOR/Ø G5: Ø/BUP G6: Ø/MOR + BUP G7: Ø/NaCl	Spinal 0.7–1.0 ml 1% BUP intra-articular G1 and G2: 2 mg MOR G3 and G4: 5 mg MOR G5: 20 ml 0.25% BUP G6: 2 mg MOR + 20 ml 0.25% BUP	Spinal before surgery 10 min before intra-articular lavage and surgery	10 min before release of thigh tourniquet	No	Preventive effect – yes up to 24 h post operation Pain: G1 = G2 = G3 = G4 < G7
220 (1997)	Arthroscopy-assisted anterior cruciate ligament reconstruction (n = 60)	1;2;3	GA plus: G1: Ø/MOR G2: Ø/MOR G3: MOR/Ø G4: Ø/BUP G5: Ø/MOR + BUP G6: Ø/NaCl	Intra-articular (20 ml) G1: 2 mg MOR G2 and G3: 5 mg MOR G4: 0.25% BUP G5: 2 mg MOR + 0.25% BUP	10 min before intra-articular lavage and surgery	10 min before release of thigh tourniquet	FEN i.v. 2 μg/kg	Preemptive effect – yes at 24 h post operation Analgesics: G2 < G3 Preventive effect – yes at 24 h post operation Pain: G3 < G6 Analgesics: G2 < G6, G3 < G6

Table A7.5 *Continued*

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/ postincision drug	Route and dose	Timing of preincision intervention	Timing of postincision intervention	Systemic opioid[a]	Nature and time after surgery of preventive or pre-emptive analgesic effect
221 (1997)	Lower limb amputation ($n = 60$)	4;8	GA plus: G1: MOR + BUP/ MOR + BUP G2: SAL/MOR + BUP	Lumbar epidural bolus dose 2 mg MOR + 5–10 ml 0.5% BUP First infusion 0.16–0.28 mg/h MOR + 4–7 ml 0.25% BUP Second infusion 3–7 ml/h 0.25% BUP + bolus doses of 2–8 mg MOR 2–4 times/day	Bolus 18 h before operation followed by first infusion until end of anesthesia	Second infusion started after surgery and maintained for 2–3 days	FEN i.v. 25–100 µg boluses	Preventive effect – no
222 (1997)	Bilateral lumbar laminotomy ($n = 60$); lumbar fusion ($n = 60$)	1;2	GA plus: G1: BUR + BUP/NA G2: Ø/NA	Caudal epidural 0.1 mg BPR + 20 ml 0.25% BUP	After induction, 10 min before incision	NA	NS	Preventive effect – yes up to day 5 post operation Pain: G1 < G2 in laminectomy patients with a decrease in blood pressure after caudal injection
223 (1997)	Upper abdominal surgery ($n = 110$)	4;5	GA plus: G1: BUP + SUF/Ø G2: Ø/BUP + SUF	Thoracic epidural G1: 0.2 ml/kg 0.25% BUP + 1 µg/kg SUF followed by 0.1 ml/ kg SUF 100 µg in BUP 0.25% 50 ml q 60 min intraoperatively G2: 0.2 ml/kg 0.25% BUP + 1 µg/kg SUF	Bolus 65 min before incision followed by intraoperative boluses q 60 min	In recovery room (316 min after incision)	No	Preventive effect – opposite on days 1, 4 and 5 post operation E-PCA: G1 > G2

224 (1998)	Radical retropubic prostatectomy (n = 100)	4;8	GA plus: G1: Ø/MOR + LID G2: FEN/MOR + LID G3: BUP + EPI/MOR + LID	Lumbar epidural G2: FEN 20 ml 4 µg/kg followed by 13 ml 0.75 µg/kg FEN q 2 h G3: 20 ml 0.5% BUP + 1:200,000 EPI followed by ≥ 13 ml BUP + EPI q 2 h G1-G3: 5 mg MOR + 8 ml 2% LID	Bolus prior to induction followed by boluses q 2 h until fascial closure	Bolus at beginning of fascial closure	FEN i.v. G1: 39 µg G2: 75 µg G3: 43 µg	Preventive effect – yes up to day 4 post operation Pain at rest: G3 < G1 E-PCA: G3 < G1 Incidence pain-free: G2 = G3 > G1 at 9.5 weeks post operation
225 (1998)	Hernia repair (n = 60)	2;3	GA plus: G1: BUP + MOR/Ø G2: Ø/BUP + MOR	Caudal 0.66 ml/kg 0.25% BUP + 0.02 mg/kg MOR	After induction, 15 min before surgery	After surgery	No	Preemptive effect – yes Pain: G1 < G2 up to 8 h post operation Analgesics: G1 < G2 at 24 h post operation TFA: G1 > G2
226 (1998)	Abdominal hysterectomy (n = 50)	2;3	GA plus: G1: SAL/BUP + FEN G2: BUP + FEN/SAL	Lumbar epidural 15 ml 0.5% BUP + 50 µg FEN	After induction	15 min before skin closure	No	Preemptive effect – no
227 (2000)	Nissin antireflux repair (n = 26)	4;8	GA plus: G1: MEP + MOR/ BUP + MOR G2: Ø/BUP + MOR	Thoracic epidural G1: 7–13 ml 20 mg/ml 2% MEP + 4 mg MOR followed by continuous infusion of 6–10 ml/h 2% MEP/continuous infusion of 4 ml/h 2.5 mg/ml 0.25% BUP + 0.125 mg/ml MOR G2: continuous infusion of 4 ml/h 2.5 mg/ml 0.25% BUP + 0.125 mg/ml MOR	Bolus 30–45 min before incision followed by continuous infusion until after skin closure	After skin closure continuous infusion for 3 days	FEN i.v. at induction 100–300 µg FEN i.v. during surgery G1: 325 µg G2: 568 µg	Preventive effect – no

Table A7.5 *Continued*

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/ postincision drug	Route and dose	Timing of preincision intervention	Timing of postincision intervention	Systemic opioid[a]	Nature and time after surgery of preventive or pre-emptive analgesic effect
228 (2000)	Upper abdominal or thoracic surgery (n = 80)	2;4	GA plus: G1: MOR/SAL G2: MOR + BUP/SAL G3: SAL/MOR G4: SAL/MOR + BUP	Lumbar epidural G1/G3: 10 ml 50 µg/ kg MOR G2/G4: 10 ml 50 µg/ kg MOR + 10 mg 0.1% BUP	20 min before induction	At end of surgical procedure	MOR i.v. 0.1 mg/kg	Preemptive effect – yes up to 5 days postoperation EPI analgesia: G2 < G4, G2 < G1, G1 = G3

a. Administered to all patients as a premedication or during surgery.
b. This study has three interventions, the third occurring at the end of the operation.
c. This study has four interventions, the third occurring at the end of the operation and the fourth in the recovery room.
d. This study has four interventions, the third occurring after the end of surgery and the fourth after extubation.
ALF, alfentanil; BUP, bupivacaine; BUR, buprenorphine; E-PCA, epidural patient-controlled analgesia; EPI, epinephrine (adrenaline); FEN, fentanyl; GA, general anesthesia; i.v., intravenous; LID, lidocaine (lignocaine); MEP, mepivacaine; MOR, morphine; NA, not applicable; NS, not stated; S1 and S2, first and second sides in studies using patients as their own controls; SAL, saline; SUF, sufentanil; TFA, time to first analgesic request; Ø, nothing administered.

Table A7.6 *Studies examining the timing of administration of local anesthetics, opioids, and NSAIDs as the target treatments*

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/ postincision drug	Routes and doses	Timing of preincision intervention	Timing of postincision intervention	Systemic opioid[a]	Nature and time after surgery of preventive or preemptive analgesic effect
230 (1994)	Posterolateral thoracotomy (n = 30)	1;2	GA plus: G1: MOR + PER + IND + BUP + EPI/NA G2: MID + PLA + SAL/NA	i.m. G1: 0.15 mg/kg MOR + 0.3 mg/kg PER G2: 0.5 mg/kg MID p.r. G1: 100 mg IND G2: PLA intercostal blocks G1: 15 ml 0.5% BUP + 1:200,000 EPI G2: 15 ml SAL	i.m. and p.r. medications 60 min before surgery; intercostal blocks after induction	NA	FEN i.v. 1 µg/kg	Preventive effect – opposite at 24 h post operation i.v. PCA: G1 > G2
231 (1994)	Thoracotomy (n = 56)	4;8	GA plus: G1: DIC + MOR + BUP/ DIC + MOR + BUP G2: DIC + MOR/ DIC + MOR + BUP G3: MOR + BUP/ DIC + MOR + BUP G4: MOR/DIC + MOR + BUP G5: DIC + BUP/ DIC + MOR + BUP G6: DIC/DIC + MOR + BUP G7: BUP/DIC + MOR + BUP G8: Ø/DIC + MOR + BUP	Paravertebral blockade 10 ml 0.5% BUP p.r. 100 mg DIC i.m. 10 mg MOR ICNB 0.1 ml/kg/h 0.5% BUP postoperation	1 h before surgery	After surgery DIC q 12 h MOR NS ICNB for 48 h	FEN i.v. 3 µg/kg	Preventive effect – yes on day 1 post operation Pain: G1 + G3 + G5 + G7 < G2 + G4 + G6 + G8

Reference (year)	Procedure (number of patients)	Treatment combination (Fig. 7.1)	Group: preincision drug/ postincision drug	Routes and doses	Timing of preincision intervention	Timing of postincision intervention	Systemic opioid[a]	Nature and time after surgery of preventive or preemptive analgesic effect
232 (1996)	Abdominal surgery (*n* = 142)	3;5	GA plus: G1: MEP + MOR + MET + DIC/Ø G2: Ø/ MEP + MOR + MET + DIC G3: Ø/Ø	Thoracic epidural G1: 0.2 ml/kg 1% MEP and 75 µg/kg MOR followed by 0.1 ml/kg 1% MEP q 60 min G2: 0.2 ml/kg 1% MEP and 75 µg/kg MOR i.v. 1,000 mg MET i.m. 75 mg DIC	85 min before skin incision followed by epidural bolus doses intraoperatively q 60 min	~ 60 min before end of surgery (221 min after start of surgery)	FEN i.v. 2 µg/kg	Preventive effect – yes on days 1–2 post operation E-PCA: G1 = G2 < G3; days 3–4 postoperation E-PCA: G1 < G2 < G3
233 (1996)	Third molar extraction (*n* = 40)	1;2	GA plus: G1: PLA + TEN + LID + EPI/ NA G2: DIC + TEN + LID + EPI/ NA G3: MTH + TEN + LID + EPI/ NA	p.o. G1: PLA G2: 100 mg DIC G3: 10 mg MTH i.v. 20 mg TEN infiltration 8–10 ml 2% LID + 1: 100,000 EPI	p.o. medications 60–90 min before surgery i.v. TEN soon after induction, before surgery infiltration after induction, 5 min before surgery	NA	ALF i.v. 10 µg/kg	Preventive effect – no
234 (1998)	Posterolateral thoracotomy (*n* = 30)	2;3	GA plus: G1: MOR + DIC + BUP/PLA G2: PLA/MOR + DIC + BUP	i.v. 10 mg MOR i.m. 75 mg DIC intercostal blocks 40 ml 0.5% BUP	≥ 20 min before start of surgery	At end of surgery, 20 min before end of anesthesia	No	Preemptive effect – yes from 12–48 h post operation Pain on movement: G1 < G2

a. Administered to all patients as a premedication or during surgery.

ALF, alfentanil; BUP, bupivacaine; DIC, diclofenac; E-PCA, epidural patient-controlled analgesia; FEN, fentanyl; GA, general anesthesia; i.m., intramuscular; IND, indomethacin; ICNB, intercostal nerve block; i.v., intravenous; LID, lidocaine (lignocaine); MEP, mepivacaine; MET, metamizole; MTH, methadone; MID, midazolam; MOR, morphine; NA, not applicable; NS, not stated; p.o., per os; PER, perphenazine; PLA, placebo; p.r., per rectum; SAL, saline; TEN, tenoxicam; Ø, nothing administered.