Regional Anesthesia and Pain

Preemptive analgesia II: recent advances and current trends

[L'analgésie préventive II : progrès récents et nouvelle orientation]

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Purpose: This two-part review summarizes the current knowledge of physiological mechanisms, pharmacological modalities and controversial issues surrounding preemptive analgesia.

Source: Articles from 1966 to present were obtained from the MEDLINE databases. Search terms included analgesia, preemptive; neurotransmitters; pain, postoperative; hyperalgesia; sensitization, central nervous system; pathways, nociception; anesthetic techniques; analgesics, agents.

Principal findings: In Part I of this review article, techniques and agents that attenuate or prevent central and peripheral sensitization were reviewed. In Part II, the conditions required for effective preemptive techniques are evaluated. Specifically, preemptive analgesia may be defined as an antinociceptive treatment that prevents establishment of altered central processing of afferent input from sites of injury. The most important conditions for establishment of effective preemptive analgesia are the establishment of an effective level of antinociception before injury, and the continuation of this effective analgesic level well into the post-injury period to prevent central sensitization during the inflammatory phase. Although single-agent therapy may attenuate the central nociceptive processing, multimodal therapy is more effective, and may be associated with fewer side effects compared with the high-dose, single-agent therapy.

Conclusion: The variable patient characteristics and timing of preemptive analgesia in relation to surgical noxious input require individualization of the technique(s) chosen. Multi-modal analgesic techniques appear more effective.

Objectif : *La présente revue, en deux parties, résume les connaissances actuelles sur les mécanismes physiologiques et les modalités pharmacologiques de l'analgésie préventive ainsi que sur les questions controversées qui l'entourent.*

Source : *Des articles, de 1966 à aujourd'hui, obtenus à partir des bases de données MEDLINE. Les termes de la recherche comprennent : analgesia, preemptive ; neurotransmitters ; pain, postoperative ; hyperalgesia ; sensitization, central nervous system ; pathways, nociception ; anesthetic techniques ; analgesics, agents.*

Constatations principales : *Dans la Partie I de cet exposé de synthèse, les techniques et les médicaments qui atténuent ou préviennent la sensibilisation centrale et périphérique ont été réexaminés. Dans la Partie II, les conditions nécessaires à l'efficacité des techniques préventives sont évaluées. Plus précisément, on peut définir l'analgésie préventive comme un traitement antinociceptif qui prévient la transmission centrale altérée du stimulus afférent provenant des sites de lésion. Les conditions les plus importantes de son efficacité sont l'établissement d'un niveau suffisant d'antinociception avant la lésion et l'entretien de ce niveau d'analgésie efficace après la lésion afin d'empêcher la sensibilisation centrale pendant la phase inflammatoire. Même si le traitement avec un médicament unique peut diminuer la sensibilisation nociceptive centrale, le traitement multimodal est plus efficace et peut comporter moins d'effets secondaires comparativement à la forte dose d'un médicament unique.*

Conclusion : *La diversité des patients et le moment choisi pour administrer l'analgésie préventive en relation avec le stimulus chirurgical nocif exigent une individualisation des techniques choisies. Des techniques analgésiques multimodales semblent plus efficaces.*

THE definitions of preemptive analgesia have recently been reviewed by Kissin.[1] Preemptive analgesia is defined as an antinociceptive treatment that prevents establishment of altered central processing of afferent input from injuries.

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Earlier definitions that have been used in various clinical trials had limitations. Preemptive analgesia has been defined as: (1) antinociceptive treatment starting before surgery; or (2) antinociceptive treatment that prevents central sensitization.

It is important to consider the definition used in a clinical trial for determining the effectiveness of preemptive analgesia. There are at least two essential requirements in the new definition. The first is that establishment of an effective level of analgesia is paramount. The presence of an inadequate antinociceptive preoperative intervention should not be regarded as preemptive analgesia. Therefore, "preemptive" does not simply mean "before incision." An insufficient block established prior to incision cannot be regarded as preemptive treatment.

The second requirement present in the current definition provides the key concept that inflammatory mediators should be kept inhibited, or nociceptive input blocked, well into the postoperative period, and cover the period of tissue injury associated with postoperative inflammation. Central sensitization may not be prevented if the treatment is terminated during the inflammatory phase. Clinical trials that do not include the concept of blocking nociceptive input secondary to inflammatory mediators may not show a clinically significant benefit. In these trials, the onset of postincisional pain is simply delayed, while central sensitization occurs later and is not prevented effectively.

Compared to physiological pain, pathological pain results from extensive and intense tissue injury, which may result in central sensitization. This lowers the threshold for perception of pain with future injuries. Similar central activation leading to perception of pain may occur in response to less noxious stimuli (hyperalgesia) or even non-noxious stimuli (allodynia).

Preemptive analgesic interventions

Preemptive analgesic modalities have been used as single entities and in combination. Regional and opioid analgesia has been studied extensively and compared to non-steroidal anti-inflammatory drugs (NSAIDs) and N-methyl-D-aspartate (NMDA) receptor antagonist induced analgesia. While a large amount of the experimental work on preemptive analgesia suggests that it has a major role in reducing postoperative pain, clinical studies have been less conclusive. Differences in the interpretation of terminology by authors contribute to the confusing results.[1]

Recently, many authors have reviewed the literature assessing various modalities of treatment.[2–6] Most authors concluded that there were no major differences, and the benefits of pre-incisional treatment were either small, or if statistically significant, without significant clinical implications. Although most of the work has been done on regional anesthesia, the benefits achieved with neuraxial opioids and NMDA receptor antagonists appear to have more promise. The long-term benefits of prolonged epidural analgesia on convalescence time have been reported previously.[7] There are, however, other studies that used preemptive regional anesthesia but showed no important differences on convalescence parameters.[8] With the limited data available on convalescence time, it is difficult to draw any meaningful conclusions on the benefits of preemptive regional anesthesia in terms of health care savings. We present a brief review of some important studies within each class and discuss their limitations in the context of the recent definition. The effectiveness of regional anesthesia (Table I), pretreatment with opioids (Table II), pre- *vs* postoperative administration of NSAIDs (Table III) are also summarized.

Regional anesthesia

Studies involving regional anesthesia have, overall, been supportive of the effectiveness of preemptive analgesic techniques. Studies that have included key aspects of the current definition have been more conclusive. We review recent studies that have used regional anesthesia as a primary anesthetic technique.

Ringrose *et al.*[9] assessed the effectiveness of femoral nerve block with bupivacaine for knee joint (anterior cruciate) reconstruction surgery. This technique reduced the need for *im* opioid administration by 80% in the recovery room, and 40% in the first 24 postoperative hours. Although supportive of a preemptive effect, the nerve block is a one-time intervention, which limits the possible efficacy to the immediate postoperative period.

Langer *et al.*[10] studied the preemptive effects of intraoperative bupivacaine on postoperative pain in 99 children aged one to seven years undergoing outpatient hernia repair with general anesthesia. Ilioinguinal and iliohypogastric nerve blocks with bupivacaine or saline were performed in a randomized, double-blinded fashion. The treatment group (bupivacaine) had lower analgesic requirements in the immediate postoperative period and at home, allowing earlier ambulation. This study, although supportive of a preemptive effect, did not prevent the afferent input during the inflammatory phase that follows the immediate (24-hr) postoperative period.

Tverskoy *et al.*[11] performed a randomized, double-blind study in 36 patients undergoing inguinal herniorrhaphy with three types of anesthesia: general (thiopentone-nitrous oxide-halothane); general with

TABLE I The effect of pre-incisional *vs* postincisional regional anesthesia on postoperative pain

Study	*Type of analgesia in preemptive group*	*Type of surgery*	*Postop pain scores (preemptive group)*	*Opioid requirements (preemptive group)*	*Duration of follow-up (hr)*	*Supportive/not supportive of preemptive effect*
Ringrose *et al.**[9]	nerve block 0.5% bupivacaine	knee joint surgery	N/A		24	supportive
Langer *et al.*[10]	nerve block 0.5% bupivacaine	inguinal herniorrhaphy	N/A		48	supportive
Tverskoy *et al.*[37]	1. local infiltration 0.5% bupivacaine with general anesthesia 2. spinal 0.5% bupivacaine	inguinal herniorrhaphy			10 days	supportive
Bugedo *et al.*[12]	nerve block 0.5% under spinal anesthesia	inguinal herniorrhaphy			48	supportive
Ejlersen *et al.*[13]	local infiltration 1% lidocaine	inguinal herniorrhaphy	NS		6	supportive
Dierking *et al.**[14]	local infiltration & nerve block 0.5% & 1% lidocaine	inguinal herniorrhaphy	NS	NS	24	not supportive
Pryle *et al.**[15]	epidural anesthesia 0.5% bupivacaine	abdominal hysterectomy & myomectomy	NS	NS	24	not supportive
Aguilar *et al.**[16]	epidural anesthesia	thoracotomy	NS	NS	48	not supportive
Shir *et al.*[17]	1. epidural anesthesia 0.25 mL·kg^{-1} of 0.5% bupivacaine + 0.1 mL·kg^{-1}·hr^{-1} of 0.125% bupivacaine	radical retropubic prostatectomy	1.	1.	5 days	supportive
	2. epidural with general 0.2 mL·kg^{-1} of 0.5% bupivacaine + 0.1 mL·kg^{-1}·hr^{-1} of 0.125% bupivacaine		2.	2.		
Ding *et al.*[18]	nerve block bupivacaine 0.25%	inguinal herniorrhaphy			24	supportive
Dakin *et al.**[19]	spinal anesthesia	abdominal hysterectomy	—	NS	24	not supportive
Pasqualucci *et al.**[20]	intraperitoneal topical 0.5% bupivacaine	laparoscopic cholecystectomy			24 24	supportive supportive
Johansson *et al.*[21]	local infiltration 1. ropivacaine 0.5% 2. ropivacaine 0.25%	inguinal herniorrhaphy			7 days	supportive
Gordon *et al.*[22]	local infiltration 0.5% bupivacaine	3rd molar tooth extraction	NS		48	supportive
Gottchalk *et al.**[23]	epidural 1. bupivacaine	retropubic prostatectomy	1.	1.	9.5 weeks	supportive
	2. fentanyl		2.	2.		

*=opiod used as a premedicant or at induction of anesthesia; NS=non-significant change; =significant decrease; N/A=data not reported.

TABLE II Influence of timing of opioid administration on postoperative pain

Study	*Type of analgesia in control group*	*Type of analgesia in preemptive group*	*Type of surgery*	*Postop pain scores (preemptive group)*	*Opioid requirements (preemptive group)*	*Duration of follow-up (hr)*	*Supportive/not supportive of preemptive effect*
Katz *et al.*[24]	fentanyl 4 $\mu g \cdot kg^{-1}$ epidurally 15 min post-incision	fentanyl 4 $\mu g \cdot kg^{-1}$ epidurally pre-incision	thoracotomy	NS		12–24	supportive
Richmond *et al.*[25]	morphine 10 mg *iv* at peritoneal closure	morphine 10 mg *iv* at induction	abdominal hysterectomy			24	supportive
Mansfield *et al.**[26]	alfentanil 15 $\mu g \cdot kg^{-1}$ *iv* 10 min after incision	alfentanil 7.5 $\mu g \cdot kg^{-1}$ *iv* on induction, 7.5 $\mu g \cdot kg^{-1}$ *iv* 90 sec before incision	abdominal hysterectomy	NS	NS	24	not supportive
Moiniche *et al.*[8]	general anesthesia with *im* opioids	epidural bupivacaine with morphine	hip and knee arthroplasty			4 days	supportive
Wilson *et al.**[27]	alfentanil *iv* (40 $\mu g \cdot kg^{-1}$) at incision	alfentanil *iv* (40 $\mu g \cdot kg^{-1}$) at induction	abdominal hysterectomy		NS	24	not supportive

*=both groups in this study received opioid supplementation intraoperatively; NS=non significant change; =significant decrease; =significant increase.

TABLE III The effect of timing of NSAID administration on postoperative analgesia

Study	*Control group*	*Preemptive analgesic group*	*Type of surgery*	*Postop pain scores (preemptive group)*	*Opioid requirements (preemptive group)*	*Supportive/not supportive of preemptive effect*
Sisk *et al.*[28]	naproxen sodium 550 mg *po* 30 min postop	naproxen sodium 550 mg *po* 30 min pre-op	dental surgery	N/A	N/A	not supportive
Murphy *et al.*[29]	indomethacin 100 mg bid commencing after surgery	indomethacin 200 mg *pr* night before surgery & 100 mg bid thereafter	thoracotomy	NS	NS	not supportive
Buggy *et al.**[30]	diclofenac 75 mg 75 mg *im* immediately postop	diclofenac *im* 1–2 hr pre-op	laparoscopic tubal ligation	NS	NS	not supportive
O'Hanlon *et al.*[31]	piroxicam 20 mg *po* at induction or 1 hr postop	piroxicam 20 mg *po* 2 hr pre-op	laparoscopic gynecologic surgery	in the recovery room, NS at other times		supportive

NS=non-significant change; =significant decrease; *po*=oral; *im*=intramuscular; *pr*=per rectum; bid=twice daily; N/A=data not reported.

TABLE IV Formulating a preemptive analgesic plan

1. Type of surgery
- surgical site
- potential intensity of noxious stimuli (related to degree of tissue injury, nerve transection, surgical site, etc.)
- potential duration of nociceptive impulses (related to site, extent of surgery, wound healing, patient's personality and pain threshold, etc.)

2. Patient characteristics
- personality and pain threshold (shown to influence degree of pain perception)
- pathology necessitating surgery
- co-existing diseases
- postoperative plan - e.g., intensive care unit *vs* regular ward admission, tracheal intubation *vs* extubation, overnight stay *vs* ambulatory surgery, etc.

3. Pharmacologic options
- dependent upon which agents can be safely administered to the patient (e.g., avoidance of NSAIDs in patients with hemorrhagic tendency)
- institutional and nursing protocols (e.g., in many institutions, ward nursing staff may not be in-serviced with regard to postoperative care of patients who received intrathecal narcotics)
- Which route of administration is best suited to the individual cases - *po*, *iv*, *im*, *pr*, epidural, intrathecal, nerve block
- The methods of drug delivery: continuous infusion, intermittent bolus, or patient controlled analgesia (PCA) via *iv*, epidural or intrathecal route
- The dosage of the individual agents is selected based on patient characteristics, the site and nature of surgery and the intensity of postoperative monitoring

4. *Assessment*
- The effectiveness of the selected drug and its dosage must be reviewed and modified to optimize treatment. One must ensure that sufficient analgesia is being provided by incorporating patient feedback
- The intensity of the nociceptive impulses may vary with time of day and with the level of activity. Unless the analgesic level changes appropriately, the patient may experience pain

the addition of bupivacaine 0.25% infiltration along the line of the proposed incision; and spinal (0.5% bupivacaine) anesthesia. Constant incisional pain, movement associated pain, and pain upon pressure applied to the surgical wound was assessed 24 hr, 48 hr, and ten days after surgery. The addition of local anesthetic significantly decreased the intensity of all types of postoperative pain. This effect was particularly evident with constant incisional pain that disappeared almost completely 24 hr after surgery. Pain secondary to pressure was significantly less in the general plus local group even ten days after the surgery. Spinal anesthesia was less effective than local infiltration presumably because of its shorter duration of action.

Bugedo *et al.*[12] studied prospectively the preemptive effects of ilioinguinal and iliohypogastric nerve block with bupivacaine in 45 adult patients undergoing unilateral inguinal herniorrhaphy under spinal anesthesia. The block group (receiving spinal anesthesia supplemented with nerve block) had less pain at three, six, 24 and 48 hr after surgery compared with the control (spinal anesthesia alone) group. A spinal anesthetic alone is therefore a less effective preemptive technique.

Ejlersen *et al.*[13] conducted a randomized, double-blind trial to compare the efficacy of pre-incisional and postincisional wound infiltration with 1% lidocaine on postoperative pain in 37 patients undergoing inguinal herniotomy. The demand for additional postoperative analgesics was higher, and occurred earlier, in those patients who received postincisional lidocaine infiltration compared to those who received pre-incisional lidocaine. Although the study is supportive of a preemptive effect, the treatment was not continued well into the postoperative period, thus limiting the efficacy of the intervention.

Dierking *et al.*[14] performed a randomized double-blind study using an identical inguinal field block, performed either before or immediately after inguinal herniorrhaphy in 32 healthy patients. The treatment group received the inguinal field block with lidocaine after induction of general anesthesia and 15 min before incision. The control group received the field block immediately after the operation. No significant differences were observed between the groups. Since the infiltration was performed after induction of gen-

TABLE V Perioperative therapy to optimize postoperative analgesia

1. Transduction
- NSAIDs prior to induction of anesthesia
- Intra-articular opioid administration
- ? Topical NSAIDs, opioids

2. Transmission
- Peripheral local anesthetic infiltration, nerve or plexus block; epidural or intrathecal local anesthetic blockade prior to surgical incision
- continuation of blockade of afferent nociceptive input until healing

3. Spinal modulation
- Ketamine at induction of anesthesia and postoperatively
- Opioids - intrathecal or epidural prior to surgical incision and postoperatively
- ? Role of systemic opioids
- $Alpha_2$ agonists preoperatively

4. Perception
- Opioid premedication *po/im/iv*
- *iv* opioids perioperatively
- Postoperative PCA opioids
- $Alpha_2$ agonists as premedication or at induction of anesthesia

eral anesthesia, the conclusions of this study are limited: first, the adequacy of treatment (infiltration) was not established prior to incision; and second, the analgesic/anesthetic treatment was time-limited and not extended into the postoperative period.

Pryle *et al.*[15] performed a double-blind study in 36 patients who received a general anesthetic for abdominal hysterectomy or myomectomy. Patients received either 15 mL of 0.5% bupivacaine with epinephrine by lumbar epidural injection 15 min before surgery, or the same epidural dose injected at the end of surgery, but before emergence from the general anesthetic. The study did not find any significant differences in opioid requirements in the first 24 hr. According to the current definition of preemptive analgesia, this technique would not fulfill the criteria of a preemptive intervention.

Aguilar *et al.*[16] studied the efficacy of epidurally administered bupivacaine in 45 patients undergoing thoracotomy. The preemptive treatment group received 8 mL of 0.5% bupivacaine with epinephrine 30 min before incision, and 8 mL of saline 15 min after incision. The second treatment group received saline before incision and local anesthetic after incision; the third group (control) received saline before and after incision at the same intervals. Postoperative epidural analgesic requirements were assessed until 43 hr postoperatively, and follow-up assessment for postthoracotomy pain was done at three months. No significant differences were observed between the three groups, rendering the study non-supportive. Although the intervention was studied for 43 hr postoperatively, the preemptive intervention allowed a "window" period for central sensitization to occur before the analgesic treatment was resumed.

Shir *et al.*[17] compared the effectiveness of preemptive epidural anesthesia to combined epidural plus general anesthesia and general anesthesia alone in 96 patients undergoing radical retropubic prostatectomy. Patients were randomized to the three groups and a lumbar epidural catheter was inserted and tested in all patients. In the epidural only group, an initial dose of 0.5% bupivacaine (0.25 $mL \cdot kg^{-1}$) was followed during surgery by a continuous infusion of 0.125% bupivacaine (0.1 $mL \cdot kg^{-1} \cdot hr^{-1}$). In the combined epidural plus general anesthesia group, 0.5% bupivacaine (0.2 $mL \cdot kg^{-1}$) was infused after induction of general anesthesia but before surgery, followed by epidural infusion of 0.125% bupivacaine (0.1 $mL \cdot kg^{-1} \cdot hr^{-1}$). In the general anesthesia only group, anesthesia was maintained with morphine, isoflurane, and nitrous oxide. Postoperatively, patient controlled epidural analgesia with bupivacaine and fentanyl was provided to all patients. The neuraxial blockade and surgical anesthesia achieved by epidural local anesthetics was associated with decreased postoperative analgesic demands compared to the combined epidural and general anesthesia and general anesthesia only groups. The authors concluded that an efficient intraoperative blockade of noxious afferent signals to the central nervous system (CNS) is fundamental in reducing postoperative pain.

Ding *et al.*[18] performed a double-blind randomized study using an ilioinguinal and hypogastric nerve

block with bupivacaine 0.25% (treatment) or normal saline (control) in 30 patients undergoing inguinal herniorrhaphy with infiltration. The study supported the intervention, but did not show any differences in time to ambulation between the two groups. The difference likely is due to the lack of analgesia provided to cover the postoperative inflammatory pain.

Dakin *et al.*[19] studied the effects of preoperative spinal anesthesia with bupivacaine in 38 patients undergoing total abdominal hysterectomy and general anesthesia. One group (pre-induction spinal) received a spinal block (T3–S5) prior to induction of general anesthesia, while the other patient group received the block after surgery but prior to tracheal extubation. Patient controlled analgesia using morphine was administered postoperatively to both groups during the first 24 hr. The study did not demonstrate any difference in morphine consumption between the groups within the first 24 postoperative hours. Morphine consumption was actually increased in the first 12 hr in the pre-induction spinal group. Since the spinal block is likely to have completely receded in this patient group within the first 12 hr, the one-time intervention (spinal anesthetic) delivered after surgery in the second group probably delayed the afferent input from the surgical wound, and initially decreased the morphine requirements.

Pasqualucci *et al.*[20] studied 120 patients undergoing laparoscopic cholecystectomy under general anesthesia with topical peritoneal local anesthetic (0.5% bupivacaine with epinephrine) or saline (control) given immediately after the creation of pneumoperitoneum and at the end of the operation. Metabolic endocrine responses (blood glucose and cortisol concentrations) three hours after surgery were significantly less in groups receiving bupivacaine before surgery. The study is supportive of preemptive analgesia, but lack of objective evidence of the presence of adequate analgesia before surgery, and early termination of the study limit the possible efficacy.

Johansson *et al.*[21] assessed the effects of preemptive local infiltration with ropivacaine for hernia repair in a randomized, double-blinded, placebo-controlled trial in 131 male patients. Three groups received 0.5% ropivacaine 40 mL (200 mg), 0.25% ropivacaine 40 mL (100 mg) or saline 40 mL. Outcome measures were supportive of an early preemptive effect (within 24 hr), but did not show any difference between the groups at seven days, probably because the single intervention only delayed but not prevented the noxious afferent input.

Gordon *et al.*[22] evaluated the effects of blockade of sensory input with bupivacaine for reducing postoperative pain beyond the local anesthetic duration of action. In a double-blind, placebo-controlled study, 48 patients underwent two to four third molar tooth extractions under general anesthesia, randomly receiving either 0.5% bupivacaine or saline intraoral injections without administration of systemic opioids. In addition to 24 and 48 hr postoperative pain and analgesic intake assessments, plasma beta-endorphin levels were measured at baseline, intraoperatively and at one-hour intervals postoperatively as an index of CNS response to nociceptor input. Plasma beta-endorphin levels increased significantly from baseline to the end of surgery in the saline group compared to the bupivacaine group, indicating effective blockade of nociceptor input into the CNS by the local anesthetic. Pain intensity was not significantly different between the groups at 24 hr; however, pain and self-administered oral analgesic intake was lower at 48 hr in the bupivacaine group. The results suggest that blockade of nociceptive input by administration of a long acting local anesthetic decreases the development of central hyperexcitability, resulting in less pain and analgesic intake. Since molar tooth extraction does not usually require an incision, a mild postoperative inflammatory component is expected. The study is therefore supportive evidence for preemptive analgesia by blocking peripheral afferent neuronal barrage from the tissue injury and also reducing CNS hyperexcitability.

Gottchalk *et al.*[23] studied preemptive epidural analgesia on postoperative pain in radical retropubic prostatectomy in a randomized double-blind trial in 100 generally healthy patients. Patients received epidural bupivacaine, epidural fentanyl, or no epidural drug prior to induction of anesthesia and throughout the entire operation, followed by aggressive postoperative epidural analgesia for all patients. The epidural fentanyl or bupivacaine groups experienced 33% less pain during hospitalization compared to the control group. Pain scores in the treatment groups were also significantly lower at 9.5 weeks, but were not significantly different at 3.5 or 5.5 weeks. At 9.5 weeks, 86% of patients receiving preemptive analgesia were pain-free, compared with 47% of the patients in the control group. The authors concluded that even in the presence of aggressive postoperative pain management, preemptive epidural analgesia significantly decreased postoperative pain during hospitalization and long after discharge.

Opioid analgesia

Studies using preemptive opioid analgesic techniques have been fewer compared to regional anesthesia. This is probably due to the difficulty of obtaining objective evidence of establishment of adequate analgesic levels prior

to commencement of surgery. Overall, the evidence for opioid efficacy is positive, despite this limitation.

Katz *et al.*[24] prospectively studied the effects of preincisional epidural fentanyl in 30 ASA II patients undergoing elective thoracic surgery through a posterolateral thoracotomy incision in a randomized, double-blind manner. Epidural catheters were placed via the L2–L3 or L3–L4 interspaces preoperatively, and placement was confirmed with lidocaine. The treatment group received epidural fentanyl (4 $\mu g \cdot kg^{-1}$, in 20 mL normal saline) before surgical incision, followed by epidural normal saline (20 mL) infused 15 min after incision. The control group received epidural normal saline (20 mL) before surgical incision, followed by epidural fentanyl (4 $\mu g \cdot kg^{-1}$, in 20 mL normal saline) infused 15 min after incision. No additional analgesics were given before or during the operation, which was performed under a general anesthetic. Postoperative analgesia consisted of patient controlled *iv* morphine. Pain scores were significantly lower in the treatment group at six hours after surgery, by which time plasma fentanyl concentrations had decreased to subtherapeutic levels (less than 0.15 $ng \cdot mL^{-1}$) in both groups. This low plasma opioid concentration explains the ineffectiveness of the preemptively administered fentanyl to reduce long-term central sensitization.

Richmond *et al.*[25] performed a randomized, double-blind study comparing the effects of parenteral morphine given before or after total abdominal hysterectomy in 60 patients. Morphine 10 mg was given either intramuscularly one hour preoperatively, intravenously at induction of anesthesia, or intravenously at closure of the peritoneum. Morphine consumption was significantly reduced in the second group for 24 hr postoperatively compared with the last group. Pain sensitivity around the wound was reduced in both preoperative treatment groups compared with the last group. The authors concluded that preemptive analgesia with *iv* morphine prevented the establishment of central sensitization during surgery, and reduced the postoperative pain, analgesic requirements, and secondary hyperalgesia.

Mansfield *et al.*[26] studied the preemptive effects of alfentanil in 60 patients undergoing total abdominal hysterectomy with or without bilateral salpingo-oophorectomy. The treatment group of 30 patients received alfentanil 7.5 $\mu g \cdot kg^{-1}$ on induction of general anesthesia, followed by alfentanil 7.5 $\mu g \cdot kg^{-1}$ 90 sec before surgical incision. The control group of 30 patients received alfentanil 15 $\mu g \cdot kg^{-1}$, ten minutes after abdominal incision. In addition, ten minutes after surgical incision both groups received morphine 0.2 $mg \cdot kg^{-1}$, given over a ten-minute period. The pain scores 24 hr after surgery were higher in the treatment group, with a slightly higher consumption of morphine. The study does not support preemptive analgesic efficacy with alfentanil. One could postulate that the limited duration of analgesia offered by alfentanil did not block all afferent nociceptive input and the analgesic efficacy was not maintained in the postoperative inflammatory phase.

Moiniche *et al.*[8] studied 42 patients undergoing total knee or hip arthroplasty, randomized to receive either continuous epidural bupivacaine/morphine for 48 hr postoperatively plus oral piroxicam, or general anesthesia followed by a conventional *im* opioid and acetaminophen regimen. Patients treated with epidural analgesia had significantly lower pain scores during mobilization than patients receiving conventional treatment. After cessation of therapy, the treatment (epidural) group required less morphine compared to the control group over the ensuing four days.

Wilson *et al.*[27] studied 40 patients undergoing total abdominal hysterectomy who were randomly allocated to receive intravenously either 40 $\mu g \cdot kg^{-1}$ of alfentanil on induction of general anesthesia, or 40 $\mu g \cdot kg^{-1}$ of alfentanil after skin incision. Intraoperative and postoperative morphine consumption for the first 24 hr postoperatively was recorded. There were no differences between the two groups in morphine consumption, but the treatment group had significantly higher pain scores at rest. Although the study was not supportive of a preemptive effect, it had the inherent limitations of a single intervention of short duration (24 hr), using a short-acting agent that allowed a "window" period for central sensitization.

NSAIDs analgesia

Preemptive analgesic therapy with NSAIDs has been aimed at maintaining and extending the analgesic intervention into the postoperative inflammatory phase. Like opioids, the limitation of NSAID therapy relates to the difficulty in establishing objective, effective analgesic levels prior to surgical trauma. Sisk *et al.*[28] designed a within-subject, crossover experimental design, in which they compared the efficacy of naproxen sodium, 550 mg, administered either 30 min preoperatively, or 30 min postoperatively to 36 patients undergoing removal of impacted third molar teeth. Pain intensity was assessed postoperatively for eight hours. Treatment with naproxen sodium, 550 mg, 30 min following completion of surgery was just as effective as pre-surgical administration in controlling postoperative pain. Although the study does not support the efficacy of preemptive analgesia, its design

might be criticized based on the lack of establishment of an effective pre-procedural analgesic state.

Murphy *et al.*[29] compared the preemptive analgesic effects of indomethacin with the analgesic effects of postoperative indomethacin administration in patients who underwent elective thoracic surgery. In addition to indomethacin, all patients received *iv* opioids titrated to their individual analgesic requirements. The authors found no significant differences between the two groups in the quality of pain relief or in the cumulative opioid requirement. The study is not supportive of a preemptive effect of NSAIDs, but a one-time intervention, which does not prevent the initial afferent nociceptive input, is not likely to affect central sensitization. Discontinuation of anti-inflammatory therapy in the postoperative period simply delays the onset of nociception during the subsequent inflammatory phase.

Buggy *et al.*[30] compared the preemptive analgesic effects of diclofenac in a randomized, double-blind study of 40 healthy female patients undergoing laparoscopic tubal ligation. The treatment group received *im* diclofenac 75 mg as a 3-mL injection one to two hours before operation, and *im* normal saline 3 mL immediately after surgery. The control group patients received *im* normal saline 3 mL before operation and *im* diclofenac 75 mg immediately after surgery. The treatment group had lower pain scores at 30 min, one, three and six hours and had a longer latent period until they requested the first dose of morphine. Although supportive for preemptive analgesia, the study limits its efficacy to the inflammatory component of the concept.

O'Hanlon *et al.*[31] studied the effects of a long-acting NSAID, piroxicam (t-1/2=50 hr), given preoperatively in 60 ASA I and II patients undergoing gynecological laparoscopic surgery. Patients received either oral piroxicam (20 mg) or a placebo two hours preoperatively, immediately before induction of anesthesia or one hour postoperatively in a randomized, double-blind manner. Postoperative pain scores were lower on admission to the recovery room in patients given piroxicam preoperatively than in the other two treatment groups. However, pain scores did not differ at any other times. Time to first analgesic request was also greater in the preoperative treatment group than in the other two groups.

NMDA receptor antagonist analgesia

The role of NMDA receptor antagonists in the treatment of central sensitization has also prompted interest in their role in preventing central neuroplasticity. However, limited data are available to define their preemptive properties in large studies.

Tverskoy *et al.*[32] studied the efficacy of ketamine in reducing postoperative pain and wound hyperalgesia beyond its pharmacologic duration of action. In a double-blind, randomized study, 27 patients undergoing elective hysterectomy were divided into three groups. In the fentanyl group, general anesthesia was induced with fentanyl 5 $\mu g \cdot kg^{-1}$ plus thiopentone 3 $mg \cdot kg^{-1}$, and maintained with isoflurane and fentanyl 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In the ketamine group, general anesthesia was induced with ketamine 2 $mg \cdot kg^{-1}$ in combination with thiopentone 3 $mg \cdot kg^{-1}$ and maintained with isoflurane plus ketamine 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In the control group, anesthesia was induced with thiopentone 5 $mg \cdot kg^{-1}$ and maintained with isoflurane only. Patients in all three groups received identical postoperative pain treatment. The surgical wound hyperalgesia measured at 48 hr with an algometer showed lower pain thresholds in the control group and similar thresholds in the fentanyl and ketamine groups.

Recently, Aida *et al.*[33] compared epidural opioid (morphine) with *iv* NMDA receptor antagonist (ketamine) alone and in combination with placebo (epidural and *iv* saline) in upper abdominal surgery (gastrectomy). Although both epidural morphine and *iv* ketamine provided preemptive analgesia, dual receptor blockade in the combination group was significantly more effective and provided definitive preemptive analgesia.

Strategies for success

The emphasis should not be solely on the timing of treatment initiation, but on the pathophysiologic phenomenon it is intended to prevent altered sensory processing. The underlying principle is that the therapeutic intervention be made prior to the onset of pain, rather than as a reaction to it. The preemptive treatment should provide analgesia throughout the period of noxious stimulation that induces the altered sensory processing (central hyperexcitability). Inflammatory reactions to tissue damaged during surgery (secondary phase of injury) may provide a source of sensory signaling postoperatively, and can induce central sensitization, even if it were initially prevented from occurring intraoperatively. To be maximally effective, some preventive treatment (possibly in steadily decreasing doses) should be administered until the peripheral triggers, which could potentially reinitiate central sensitization, have subsided as a result of normal wound healing. Thus, prolonged prevention of peripheral and central sensitization may decrease the incidence of chronic pain syndrome such as phantom limb pain.[34] In the presence of a complex regional pain syndrome, a plexus infusion with local anesthetic 24–72 hr before the surgical procedure is employed to decrease central plas-

ticity and postoperative pain.[35] The antinociceptive treatment should completely block the noxious signals to the CNS, or else central sensitization may occur in response to those nociceptive impulses, which break through the analgesic barrier. Furthermore, total blockade of nociceptive afferent fibres may not be produced by conventional analgesic doses or methods. The aim of treatment is to minimize patient discomfort, while leaving physiologic nociceptive mechanisms intact so that they continue to function as an early warning system.[36] An analgesic plan must include consideration of the best route of delivering analgesia (oral, *iv*, epidural, intrathecal or infiltration), the potential intensity of the noxious stimuli, the temporal relationship of nociceptive impulses to the timing and duration of surgery, the duration of the postoperative pain state, and the analgesic agents suitable for administration in each individual case (Table IV). Different treatment regimes can be used at different times relative to surgery to maximize the prevention of pain in response to different levels of sensory input.

The best approach is probably to administer a number of analgesic agents and techniques in combination, each of which decreases nociception by working on a different limb of the pain pathway and at different sites. Such an approach will allow synergism between the different medications while decreasing the risk of toxicity by limiting the dose of each of the individual agents. Peripheral nociceptor sensitization can be attenuated by NSAIDs and local anesthetic blockade. Opioids are frequently the cornerstone of postoperative analgesic therapy, and act at a number of sites (peripheral, spinal and supraspinal) to produce analgesia and reduce sensitization. Ketamine and alpha-$_2$ agonists may be combined with opioid therapy to enhance analgesia and reduce central sensitization. A treatment regimen designed to maximize postoperative analgesia is outlined in Table V. The exact clinical role of other agents is, for the most part, still under investigation, but may provide better understanding of pain mechanisms and improved perioperative care of the surgical patient.

Conclusion

Preemptive analgesia is not a new concept, but dates to the early twentieth century. It involves delivery of analgesic therapy that precedes, adequately blocks, and outlasts the nociceptive stimuli that accompany tissue injury. The aim is to prevent the peripheral and central sensitization that occurs in response to painful stimuli, while leaving physiological pain responses intact. Such an effect reduces primary and secondary hyperalgesia, allodynia and the receptive field changes of dorsal horn cells. While opioids, NSAIDs, local anesthetics, alpha-$_2$ agonists and NMDA receptor antagonists are considered the main agents in the preemptive analgesic arsenal, a variety of other potentially beneficial agents are under investigation. Until further data are complete, the presently available analgesics administered correctly (on time, for the appropriate duration, and in the proper dosage and manner) can improve patient comfort, decrease postoperative morbidity and have the potential to effect health care savings.

References

1 *Kissin I.* Preemptive analgesia. Anesthesiology 2000; 93: 1138–43.

2 *Grass JA* Preemptive analgesia. *In*: Grass JA (Ed.). Problems in Anesthesia, vol. 10. Philadelphia: Lippincott-Raven, 1998: 107–21.

3 *Kehlet H.* Controlling acute pain-role of pre-emptive analgesia, peripheral treatment, and balanced analgesia, and effects on outcome. *In*: Max M (Ed.). Pain 1999 - An Updated Review. Seattle: IASP Press, 1999: 459–62.

4 *Schmid RL, Sandler AN, Katz J.* Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain 1999; 82: 111–25.

5 *Niv D, Lang E, Devor M.* The effect of preemptive analgesia on subacute postoperative pain (Editorial). Minerva Anestesiol 1999; 65: 127–40; discussion 140–1.

6 *Pasqualucci A* Experimental and clinical studies about the preemptive analgesia with local anesthetics. Possible reasons of the failure. Minerva Anestesiol 1998; 64: 445–57.

7 *Williams-Russo P, Sharrock NE, Haas SB, et al.* Randomized trial of epidural versus general anesthesia. Outcomes after primary total knee replacement. Clin Orthop 1996; 331: 199–208.

8 *Møiniche S, Hjortsø N-C, Hansen BL, et al.* The effect of balanced analgesia on early convalescence after major orthopaedic surgery. Acta Anaesthesiol Scand 1994; 38: 328–35.

9 *Ringrose NH, Cross MJ.* Femoral nerve block in knee joint surgery. Am J Sports Med 1984; 12: 398–402.

10 *Langer JC, Shandling B, Rosenberg M.* Intraoperative bupivacaine during outpatient hernia repair in children: a randomized double blind trial. J Pediatr Surg 1987; 22: 267–70.

11 *Tverskoy M, Cozacov C, Ayache M, Bradley EL, Kissin I.* Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. Anesth Analg 1990; 70: 29–35.

12 *Bugedo GJ, Cãrcamo CR, Mertens RA, Dagnino JA, Munoz HR* Preoperative percutaneous ilioinguinal and iliohypogastric nerve block with 0.5% bupivacaine for

post-herniorrhaphy pain management in adults. Reg Anesth 1990; 15: 130–3.
13 *Ejlersen E, Andersen HB, Eliasen K, Mogensen T.* A comparison between preincisional and postincisional lidocaine infiltration and postoperative pain. Anesth Analg 1992; 74: 495–8.
14 *Dierking GW, Dahl JB, Kanstrup J, Dahl A, Kehlet H.* Effect of pre- vs postoperative inguinal field block on postoperative pain after herniorrhaphy. Br J Anaesth 1992; 68: 344–8.
15 *Pryle BJ, Vanner RG, Enriquez N, Reynolds F.* Can pre-emptive lumbar epidural blockade reduce postoperative pain following lower abdominal surgery? Anaesthesia 1993; 48: 120–3.
16 *Aguilar JL, Cubells C, Rincon R, Preciado MJ, Valldeperas I, Vidal F.* Pre-emptive analgesia following epidural 0.5% bupivacaine. In thoracotomy. Reg Anesth 1994; 19: 72.
17 *Shir Y, Raja SN, Frank SM.* The effect of epidural versus general anesthesia on postoperative pain and analgesic requirements in patients undergoing radical prostatectomy. Anesthesiology 1994; 80: 49–56.
18 *Ding Y, White PF.* Post-herniorrhaphy pain in outpatients after pre-incision ilioinguinal- hypogastric nerve block during monitored anaesthesia care. Can J Anaesth 1995; 42: 12–5.
19 *Dakin MJ, Osinubi OYO, Carli F.* Preoperative spinal bupivacaine does not reduce postoperative morphine requirement in women undergoing total abdominal hysterectomy. Reg Anesth 1996; 21: 99–102.
20 *Pasqualucci A, De Angelis V, Contardo R, et al.* Preemptive analgesia: intraperitoneal local anesthetic in laparoscopic cholecystectomy. A randomized, double-blind, placebo-controlled study. Anesthesiology 1996; 85: 11–20.
21 *Johansson B, Hallerbäck B, Stubberod A, et al.* Preoperative local infiltration with ropivacaine for postoperative pain relief after inguinal hernia repair. A randomised controlled trial. Eur J Surg 1997; 163: 371–8.
22 *Gordon SM, Dionne RA, Brahim J, Jabir F, Dubner R* Blockade of peripheral neuronal barrage reduces postoperative pain. Pain 1997; 70: 209–15.
23 *Gottschalk A, Smith DS, Jobes DR, et al.* Preemptive epidural analgesia and recovery from radical prostatectomy. A randomized controlled trial. JAMA 1998; 279: 1076–82.
24 *Katz J, Kavanagh BP, Sandler AN, et al.* Preemptive analgesia. Clinical evidence of neuroplasticity contributing to postoperative pain. Anesthesiology 1992; 77: 439–46.
25 *Richmond CE, Bromley LM, Woolf CJ.* Preoperative morphine pre-empts postoperative pain. Lancet 1993; 342: 73–5.
26 *Mansfield M, Meikle R, Miller C* A trial of pre-emptive analgesia. Influence of timing of peroperative alfentanil on postoperative pain and analgesic requirements. Anaesthesia 1994; 49: 1091–3.
27 *Wilson RJT, Leith S, Jackson IJB, Hunter D* Pre-emptive analgesia from intravenous administration of opioids. No effect with alfentanil. Anaesthesia 1994; 49: 591–3.
28 *Sisk AL, Grover BJ.* A comparison of preoperative and postoperative naproxen sodium for suppression of postoperative pain. J Oral Maxillofac Surg 1990; 48: 674–8.
29 *Murphy DF, Medley C* Preoperative indomethacin for pain relief after thoracotomy: comparison with postoperative indomethacin. Br J Anaesth 1993; 70: 298–300.
30 *Buggy DJ, Wall C, Carton EG* Preoperative or postoperative diclofenac for laparoscopic tubal ligation. Br J Anaesth 1994; 73: 766–70.
31 *O'Hanlon JJ, Muldoon T, Lowry D, McCleane G* Improved postoperative analgesia with preoperative piroxicam. Can J Anaesth 1996; 43: 102–5.
32 *Tverskoy M, Oz Y, Isakson A, Finger J, Bradley EL Jr, Kissin I.* Preemptive effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia. Anesth Analg 1994; 78: 205–9.
33 *Aida S, Yamakura T, Baba H, Taga K, Fukuda S, Shimoji K.* Preemptive analgesia by intravenous low-dose ketamine and epidural morphine in gastrectomy. A randomized double-blind study. Anesthesiology 2000; 92: 1624–30.
34 *Bach S, Noreng MF, Tjéllden NU.* Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. Pain 1988; 33: 297–301.
35 *Saberski LR, Calkins JM.* Reflex sympathetic dystrophy (complex peripheral pain syndrome). *In*: Roizen MF, Fleisher LA (Eds.). Essence of Anesthesia Practice. Philadelphia: W.B. Saunders, 1997: 271.
36 *Woolf CJ, Chong M-S.* Preemptive analgesia – treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993; 77: 362–79.