Pre Emptive Analgesia: A New Dimension in Pain Management

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Abstract: *Nociceptor activation is mediated by chemicals that are released in response to cellular or tissue damage, leading to an intensification of acute pain and even long-term postoperative pain, referred to as central sensitization. Chronic postsurgical pain (CPSP) seen in 10 to 50% of post surgical patients persists for 3–6 months after surgery and disrupts their quality of life. Pre-emptive analgesia (PEA) involves the introduction of an analgesic regimen before the onset of noxious stimuli, (not after surgical incision). This prevents this central sensitization and chronic neuropathic syndromes. Treatment strategies involve short and long term techniques started preoperatively and given for an increased duration in the postoperative period to decrease postoperative pain and reducing analgesic consumption in the postoperative period. Preemptive analgesia involves delivery of analgesic therapy that precedes, adequately blocks, and out-lasts the nociceptive stimuli that accompany tissue injury in order to prevent the peripheral and central sensitization that occurs in response to painful stimuli, while leaving physiological pain responses intact. This allows for a more rapid recovery and earlier discharge from hospital.*

Keywords: Pre emptive, analgesia

1. Introduction

Pain is more than a simple bodily reaction to noxious stimuli; it is an intricate and individualized experience. Post operative pain is influenced by a variety of factors like pre-existing pain (both acute and chronic), psychological influences, fear of recurring additional pain, neurovascular tissue damage from a prior operation, as well as the extent of the extent of the surgical procedures causing physical, cognitive, and emotional discomfort. Nociceptor activation is mediated by chemicals that are released in response to cellular or tissue damage, leading to an intensification of acute pain and even long-term postoperative pain, referred to as central sensitization. Chronic postsurgical pain (CPSP) generally refers to pain that persists for 3–6 months after surgery. This occurs in 10%–50% of patients after surgery and disrupts their quality of life.(1) Risk factors associated with the development of CPSP include psychosocial factors, sex, age, genetic predisposition, and level of pre-existing pain.

Pre-emptive analgesia (PEA) involves the introduction of an analgesic regimen before the onset of noxious stimuli, (***not after surgical incision***), with the goal of preventing sensitization of the nervous system to subsequent stimuli that could amplify pain. PEA prevents the development of altered processing of afferent input, which would otherwise influence postoperative pain. PEA focuses on perioperative pain control and the prevention of central sensitization and chronic neuropathic syndromes

1.1 Molecular mechanisms of central sensitization

Tissue injury results in initiation of nociceptive signals to the dorsal horn of the spinal cord by A delta fiber nociceptors and by polymodal C fiber nociceptors. The response of neurons in the dorsal horn of the spinal cord is biphasic. The initial response to a noxious stimulus is brief and correlates with the sharp, well-localized initial pain. The second phase of the response is more prolonged and correlates with the dull, diffuse pain experienced after the initial injury. This second phase is associated with a growing region of hypersensitivity around the point where the noxious stimulus was initially applied. The process through which the neurons of the dorsal horn of the spinal cord become sensitized by prior noxious stimuli is often referred to as "windup" or "central sensitization, enhancing sensitivity to noxious stimuli and increased level of pain following surgery. The activation of nociceptors is mediated by chemicals that are released in response to cellular or tissue damage. Cells release leukotrienes and potassium, platelets release serotonin, and vascular injury causes a release of bradykinin from plasma. Nociceptive signals release neurotransmitters like substance P, calcitonin gene-related peptide, and the excitatory amino acids, glutamate and aspartate. These substances amplify the responses from the dorsal horn neurons, leading to central sensitization. This phenomenon occurring post tissue injury in both neuropathic and inflammatory pain, is a cause of increased pain sensitivity described as hyperalgesia and tactile allodynia, where there is pain to light touch and persistent chronic pain. (Fig 1)
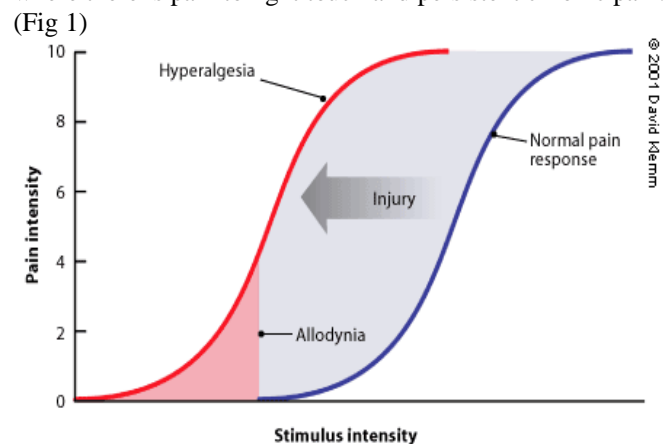

Figure 1: The normal pain response as a function of stimulus intensity is depicted by the blue curve at the right, where even strong stimuli are not experienced as pain.

However, a traumatic injury can shift the curve to the left (red) when noxious stimuli becomes more painful (hyperalgesia) and typically painless stimuli are experienced as pain (allodynia).

In addition to increased excitability, there is a reduction in inhibitory transmission from inhibitory interneurons. Treatment strategies involving modulation of central sensitization are important, both in the short and the long term. Pain hypersensitivity can occur without evidence of nerve lesions or tissue injury. Triggers in fibromyalgia or irritable bowel syndrome, where pain is driven by central amplification of peripheral inputs, is caused by central sensitization occurring autonomously. (2, 3)

1.2 History of PEA

The concept of preemptive analgesia was formulated by Crile at the beginning of the previous century on the basis of clinical observations. Crile advocated the use of regional blocks in addition to general anesthesia to prevent intraoperative nociception and the formation of painful scars caused by changes in the central nervous system during surgery. (4)

In 1986, Woolf and Wall demonstrated that the motor and sensory changes found after peripheral tissue injury were linked to peripheral activation of C afferents. In a model of central hyperexcitability produced by electrical stimulation of C-fibers and recorded in rat dorsal horn neurons, they showed that the amount of systemically administered morphine needed to prevent the development of hyperexcitability was much less than the amount needed to reverse it after the establishment of the same.(5)
Enhanced pain-related behavior was observed in circumcised boys during subsequent vaccination compared with boys who were not circumcised and boys who were circumcised after application of a local anesthetic cream.(6)

In 1993, Woolf and Chong and Wall hypothesized that an antinociceptive intervention given pre-emptively, ie, before the start of surgery, would decrease the intensity of postoperative pain, decrease hyperalgesia, and prevent central sensitization when compared with the same intervention given after the start of surgery.(7,8)

Lavand'homme et al were the first to demonstrate that postoperative systemic ketamine along with intraoperative epidural analgesia provides preventive analgesia after major gastrointestinal surgery and reduces the risk of development of chronic (persistent) postsurgical pain. (9)

Preventive analgesia was also demonstrated by Koppert et al, who showed that systemic lidocaine given perioperatively decreased postoperative pain scores and reduced overall morphine consumption in the first 72 hours after surgery. (10)
Pre emptive analgesia encompassing multimodal antinociceptive interventions, is started preoperatively and given for an increased duration including the postoperative period, was found to be more effective in terms of decreasing postoperative pain and reducing analgesic consumption in the postoperative period, reduced untoward side effects, allowed more rapid recovery and earlier discharge from hospital.

1.3 Adverse Effects of Post Operative Pain

The outcome of a surgical procedure can be affected as a result of changes arising from pain. These pain-related changes can affect insulin, cortisol, catecholamine, beta endorphin and other hormone levels. Severe pain has several adverse effects on patient outcome. Decrease in physical mobility due to pain can result in hypoventilation and predispose an individual to pneumonia. Pain induced muscle splinting can decrease blood flow to an extremity and predispose to thrombosis or embolism. Muscles can be further damaged by spasm, atrophy, and impairment of metabolism. Muscles controlling urinary bladder motility can become impaired, resulting in urinary retention. Coronary vasoconstriction from activation of the sympathetic nervous system can cause cardiovascular effects such as angina or ischemia. Furthermore, unresolved postoperative pain may give rise to sleep deprivation and psychological issues such as anxiety and depression.

1.4 Basics of Preemptive Analgesia

"Preemptive" means "preventive," not simply "before" incision. There should be proof that an intervention provides at least its direct effect. The difference in the outcome measure of an antinociceptive intervention made before and at the end of surgery is evidence of a preemptive effect. Three different definitions for preemptive analgesia have been used as the basis for clinical trials.

They are as follows:
1) Analgesic regimen starts before surgery
2) Analgesics administered prevents the establishment of central sensitization caused by incisional injury (covers only the period of surgery)
3) Analgesics administered prevents the establishment of central sensitization caused by incisional and inflammatory injuries (covers the period of surgery and the initial postoperative period).

Terms Commonly Used Relevant to Preemptive Analgesia
- *Central sensitization* —persistent post injury changes in the central nervous system that result in pain hypersensitivity
- *Central hyperexcitability* —exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage
- *Preincisional treatment* —treatment that starts before an initial surgical incision
- *Postincisional treatment* —treatment that starts immediately after the end of operation

The two fundamental requirements for adequacy of preemptive treatment are as follows:
- Verification of the effectiveness of the direct pharmacologic effect of a treatment, by measuring the degree of a difference between control and treatment groups in the initial nociceptive response (plasma β-endorphin or cortisol level) and also, by verification of the sufficiency of a neural blockade, etc.

- Extension of an antinociceptive treatment into the initial postoperative period, when generation of nociceptive stimuli by the inflammatory process may be very intensive for 12 to 48 h, depending on the type of surgery.

Intravenous doses of opioids, peripheral nerve blocks, local infiltration of the surgical site, epidural administration of opioids and local anesthetics, and multimodal combinations have all been found effective in various degrees in humans. Modulators of central sensitization, such as spinal clonidine and ketamine, can reduce the incidence of persistent postoperative pain without significantly reducing acute postsurgical pain. Pre operative systemic gabapentin, NSAID drugs and NMDA receptor antagonists have been observed to attenuate hyperalgesia after surgery, decreasing consumption of opioids, and reducings pain scores significantly. All these meta-analytic studies, demonstrate the need for perioperative and not just preoperative analgesic interventions.

The most robust analgesic effect for pre-emptive pain control was with epidural analgesia, followed by nonsteroidal anti-inflammatory drugs and local anesthetic wound infiltration. Pre-emptive opioids and systemic NMDA antagonists suppress peripheral sensitization while some treatments may reduce the intensity of chronic postsurgical pain but not that of acute postoperative pain. (Fig 2)
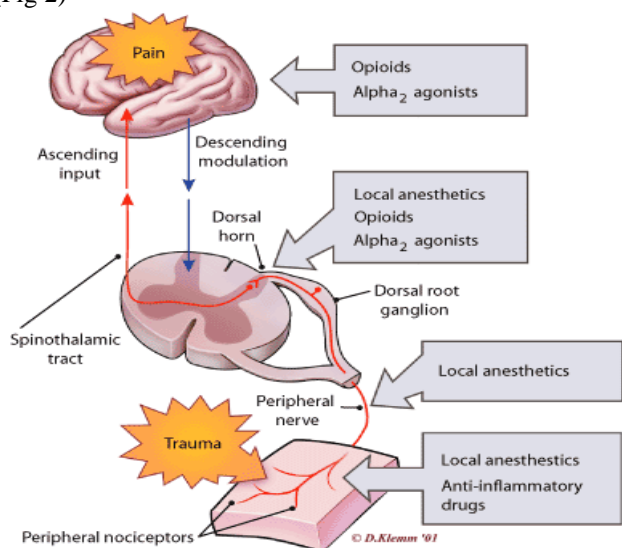

Figure 2: The pain pathway and interventions that can modulate activity at each point.

It appears that preventive analgesia involving perioperative pain control with increased duration of analgesic treatment and employing multimodal pain control techniques is more effective than sole administration of pre-emptive analgesia before the incision is made. Preventive analgesia helps to decrease hyperalgesia and peripheral and central sensitization. The duration and efficacy of a perioperative analgesic regimen is more important than the preoperative timing of an analgesic intervention alone

Local Anesthetics and Preemptive analgesia
The effectiveness of femoral nerve block with bupivacaine for knee joint (anterior cruciate ligament) reconstruction

surgery reduced the need for intramuscular opioid administration by 80%in the recovery room, and 40% in the first 24 post operative hours. Although supportive of a pre emptive effect, the nerve block is a one-time intervention, which limits the possible efficacy to the immediate postoperative period. (11)

The preemptive effects of intraoperative bupivacaine on postoperative pain in 99 children was studied. In the age group one to seven years, all were undergoing outpatient hernia repair under 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 post-operative period and at home, allowing earlier ambulation. (12) In another randomized, double-blind study in 36 patients undergoing inguinal herniorrhaphy, the addition of bupivacaine 0.25% infiltration along the line of the proposed incision significantly decreased the intensity 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. (13) A similar result was seen with ilioinguinal and iliohypogastric nerve block with bupivacaine in 45 adult patients undergoing unilateral inguinal herniorrhaphy under spinal anesthesia. The blocked 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. (14)

The effectiveness of preemptive epidural anesthesia to combined epidural plus general anesthesia and general anesthesia alone in 96 patients undergoing radical retropubic prostatectomy was studied. 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·kg–1) was followed during surgery by a continuous infusion of 0.125% bupivacaine (0.1mL·kg–1·hr–1). In the combined epidural plus general anesthesia group, 0.5% bupivacaine (0.2 mL·kg–1) was infused after induction of general anesthesia but before surgery, followed by epidural infusion of 0.125% bupivacaine (0.1 mL·kg–1·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. (15)

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.(16)

The effect of 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, com-pared 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. (17)

Opioids and preemptive 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.

The effects of pre-incisional epidural fentanyl in 30 ASA II patients undergoing elective thoracic surgery through a posterolateral thoracotomy incision was analysed 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 µg·kg–1,in 20 mL normal saline) before surgical incision, followed by epidural normal saline (20 mL) infused 15min after incision. The control group received epidural normal saline (20 mL) before surgical incision, followed by epidural fentanyl (4

µg·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 sub-therapeutic levels (less than 0.15ng·mL–1) in both groups. This low plasma opioid concentration explains the ineffectiveness of the preemptively administered fentanyl to reduce long-term central sensitization. (18)

In 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 24hr postoperatively compared with the last group. Pain sensitivity around the wound was reduced in both pre-operative 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. (19)

NSAIDs in Pre emptive 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.

The preemptive analgesic effects of diclofenac was studied in a randomized, double-blind study of 40 healthy female patients undergoing laparoscopic tubal ligation. The treatment group received intramuscular (im) diclofenac 75 mg as a 3-mL injection one to two hours before operation, and im normal saline 3mL 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. (20)
The effects of a long-acting NSAID, piroxicam (t-1/2=50 hr), given pre operatively in 60 ASA I and II patients undergoing gynecological laparoscopic surgery was analysed. 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. (21)

NMDA receptor antagonist for Preemptive analgesia

The role of NMDA receptor antagonists in the treatment of central sensitization has also prompted interest in their role in preventing central neuroplasticity.

The effects of epidural opioid(morphine) with iv NMDA receptor antagonist (ketamine) alone and in combination with placebo (epidural and iv saline) in upper abdominal surgery(gastrectomy) was studied. Although both epidural morphine and iv ketamine provided preemptive analgesia, dual receptor blockade in the combination group was significantly more effective and provided definitive pre-emptive analgesia.

Patients undergoing laparoscopic cholecystectomy were randomized into four groups of 20 patients each, who were administered the study drug intravenously 30 min before incision. Groups A, B, and C received ketamine in a dose of 1.00, 0.75 and 0.50 mg/kg, respectively, whereas group D received isotonic saline. Anesthetic and surgical techniques were standardized. Postoperatively, the degree of pain at rest, movement, and deep breathing using visual analogue scale, time of request for first analgesic, total opioid consumption, and postoperative nausea and vomiting were recorded in postanesthesia care unit for 24 h. Pain scores were highest in Group D at 0 h. Groups A, B, and C had significantly decreased postoperative pain, analgesic requirements and pain scores at 0, 0.5, 3, 4, 5, 6, and 12 h.. Group A had a significantly higher heart rate and blood pressure than groups B and C at 0 and 0.5 h along with 10% incidence of hallucinations. (22)

The effect of pre-versus post incisional epidural analgesia was investigated in a randomized, double-blind study of two groups of 30 ASA physical status patients undergoing lower urinary tract surgeries under general anaesthesia. Group A received, via a lumbar epidural catheter, ketamine 1 mgkg-1 and buprenorphine 1.5 mgkg-1, 30 minutes before surgical incision while Group B received the same drugs epidurally 30 minutes before skin closure. Visual analogue pain scores were assessed at specified times for 24 hours and tramadol 50 mg was given intravenously when pain score was > 40. The analgesic effect was assessed by the time to first analgesic requirement, total tramadol consumption in 24 hours and number of patients who needed supplemental injections. The duration of analgesia was longer (P<0.003) in Group A (23.06±12.36 h) than in Group B (15.2±9.86 h) and total tramadol consumption was less (P<0.002) in Group A than in Group B. Only one patient needed intravenous analgesic in Group A compared to six patients in Group B. In conclusion, pre incisional administration of buprenorphine and ketamine is more effective in reducing postoperative pain than when it is given postincisional. (23)

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 of preemptive analgesia 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 intra operatively.

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. 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 plasticity and postoperative pain. 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.

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 post-operative pain state, and the analgesic agents suitable for administration in each individual case. 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 post operative analgesic therapy, and act at a number of sites (peripheral, spinal and supraspinal) to produce analgesia and reduce sensitization. Ketamine and alpha-2agonists may be combined with opioid therapy to enhance analgesia and reduce central sensitization.

Clinical Pearls
- Timing of administration of pre-emptive analgesia has to be before the incision or surgery. Pre-emptive analgesia provides improved analgesia postoperatively compared with the identical analgesic treatment after incision or surgery.

- Multimodal analgesia allows for lower doses of any one medication to be used in combination, thus decreasing side effects.
- Preventive analgesia can be provided by an intervention given before or after incision and surgery, whether it is a placebo, no treatment, or analgesic treatment that reduces analgesic use or postoperative pain for a period longer than the duration of action for the intervention.
- Duration of treatment and effective analgesic regimens are the two important considerations in the administration of preventive analgesia.

2. Conclusion

Preemptive analgesia involves delivery of analgesic therapy that precedes, adequately blocks, and out-lasts the nociceptive stimuli that accompany tissue injury in order 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. Opioids, NSAIDs, local anesthetics, alpha-2agonists and NMDA receptor antagonists are considered the main agents in the preemptive analgesic arsenal. They must be administered correctly (on time, for the appropriate duration, and in the proper dosage and manner) to improve patient comfort, decrease postoperative morbidity and effect health care savings.

Without a proper pain management plan, postoperative pain has the potential to result in chronic pain, with long-term negative consequences for the patient. Prevention of this pain has been dubbed as the "holy grail of anesthesiology". Preventive analgesia is not time-constrained and involves the use of analgesic interventions and requires a commitment from the entire surgical team. Multimodal approaches that address multiple sites along the pain pathway may prove necessary to adequately prevent central sensitization in many surgical procedures. The resources to provide outstanding pain relief following surgery must be made available as it has clearly demonstrable clinical and economic benefits.

References

[1] Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. Pain 2011; 152(3) : S2–15.
[2] Yamanaka H, Noguchi K. Pathophysiology of neuropathic pain: molecular mechanisms underlying central sensitization in the dorsal horn in neuropathic pain. Brain Nerve 2012 ;64(11):1255-65.
[3] Crile GW: The kinetic theory of shock and its prevention through anoci-association. Lancet 1913; 185: 7–16
[4] Woolf CJ: Evidence for a central component of postinjury pain hypersensitivity. Nature 1983; 308: 686–8
[5] Ryan CA, Finer NN. Changing attitudes and practices regarding local analgesia for newborn circumcision. Pediatrics 1994;94:230–3
[6] Woolf, C.J. and M.S. Chong. Preemptive analgesia-treating postoperative pain by preventing the establishment of central sensitization. Anesth. Analg 1993; 77: 362-379.
[7] Cook, A.J., C.J. Woolf, P.D. Wall and S.B. McMahon. Dynamic receptive field plasticity in rat spinal cord dorsal horn following C-primary afferent inputs. Nature 1987; 325: 151-153.
[8] Lavand'homme P, De Kock M, Waterloos H. Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. Anesthesiology 2005 ;103(4):813-20.
[9] Koppert W, Weigand M, Neumann F, Sittl R et al. Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. Anesth Analg 2004 ;98(4):1050-5.
[10] Ringrose NH, Cross MJ. Femoral nerve block in kneejoint surgery. Am J Sports Med 1984; 12: 398–402.
[11] 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.
[12] Tverskoy M, Cozacov C, Ayache M, Bradley EL, Kissin I.Postoperative pain after inguinal herniorrhaphy with dif-ferent types of anesthesia. Anesth Analg 1990; 70: 29–35.
[13] 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.
[14] Shir Y, Raja SN, Frank SM. The effect of epidural versus general anesthesia on postoperative pain and anal-gesic requirements in patients undergoing radical prostatectomy. Anesthesiology 1994; 80: 49–56.
[15] Gordon SM, Dionne RA, Brahim J, Jabir F, Dubner R. Blockade of peripheral neuronal barrage reduces post-operative pain. Pain 1997; 70: 209–15.
[16] 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.
[17] Katz J, Kavanagh BP, Sandler AN, et al. Preemptive analgesia. Clinical evidence of neuroplasticity contributing to postoperative pain. Anesthesiology 1992; 77: 439–46.
[18] Richmond CE, Bromley LM, Woolf CJ. Preoperative morphine pre-empts postoperative pain. Lancet 1993;342: 73–5.
[19] Buggy DJ, Wall C, Carton EG. Preoperative or postoperative diclofenac for laparoscopic tubal ligation. Br J Anaesth 1994; 73: 766–70.
[20] O'Hanlon JJ, Muldoon T, Lowry D, McCleane G. Improved postoperative analgesia with preoperative piroxicam. Can J Anaesth 1996; 43: 102–5.
[21] 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. Anesthesiology2000; 92: 1624–30.

[22] Singh H, Kundra S, Singh RM, Grewal A, Kaul TK, Sood D. Preemptive analgesia with Ketamine for Laparoscopic cholecystectomy. J Anaesthesiol Clin Pharmacol 2013; 29(4): 478–484.

[23] Shah VR, Rawal R, Marda M. Preemptive effect of epidural buprenorphine with ketamine on post operative pain after lower urinary tract surgery. Ind J. Anaesth. 2006; 50 (4) : 271 - 274