PREEMPTIVE ANALGESIA – REVIEW OF LITERATURE

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Abstract

The use of analgesic before noxious stimulus of a nociceptive agent is known as preemptive analgesia. There are various drugs used in preemptive analgesia- Bupivacaine, Lignocaine, Ketoprofen, Tramadol, Diclofenac Sodium, Ketamine, Morphine, Fentanyl, Meloxicam. It can be applied by different methods - Local infiltration before incision, regional blocks, intravenous narcotic agents, intravenous or intra-muscular NSAIDs, intravenous or intra-muscular Ketamine. There is some controversy about the beneficial effect of preemptive analgesia than pos-operative analgesia on human being but it has no harmful effect and it is cost effective. So we can practice preemptive analgesia and may get benefit.

Introduction

The use of analgesic before noxious stimulus of a nociceptive agent is known as preemptive analgesia. In other words it is an antinociceptive treatment that prevents establishment altered processing of afferent input, which implies postoperative pain. Surgery produces a barrage of pain signals to the spinal cord is a priming mechanism, which sensitizes the central nervous system. This is said to lead to enhanced postoperative pain. Use of analgesia before surgery prevents sensitizing neuroplastic changes within spinal cord leading to diminished postoperative analgesic requirement.[1] At the beginning of previous century, the concept of preemptive analgesia formulated by Crile[2] on the basis of clinical observations. He advocated the use of regional blocks in addition to general anesthesia to prevent intraoperative nociception. The revival of this idea was associated with a series of animal studies started by Woolf.[3] The goal of preemptive analgesia is to prevent the establishment of central sensitization which amplifies post operative pain.[4]

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Pain

Pain (L- *Poena*) is more or less localized sensation of discomfort, distress, or agony, resulting from the stimulation of specialized nerve endings. It serves as protecting mechanism as it induces the sufferer to remove or withdraw from the source. But in case of postoperative pain, there is no chance to withdraw the patient from pain source. So we can try to prevent postoperative pain as much we can. Pain involves four physiological processes: transduction, transmission, modulation and perception. It begins with peripheral nociceptors when local tissue damage, a noxious stimulus, occurs during surgery which causes the release of inflammatory substances (prostaglandins, serotonin, bradykinin and substance P). This leads to generation of electrical impulses (transduction) at the peripheral sensory nerve endings, or nociceptors. These electrical impulses are conducted by nerve fibres (A-delta and C fibres) to the spinal cord (transmission). Further relay to the higher brain centers can be modified within the spinal cord (modulation) before an individual perceives painful stimulus (perception).[1] So pain can be blocked at various levels in this complex chain by different methods. The response of the noxious stimuli can be modulated by their repeated application[5]. Their sensitivity can be further enhanced by many tissue factors and inflammatory mediators released in the course of tissue injury. The response of neurons in the dorsal horn of spinal cord of experimental elements has been found to be biphasic[6,7]. 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. The process through which neurons of the dorsal horn of the spinal cord become sensitized by prior noxious stimuli is often referred to as "windup" or "central sensitization"[8,9]. Much less is known about pain-induced sensitization of the supra-spinal components of CNS.

Effects of post-operative pain

- Humanitarian aspect: Irrespective of site and duration of operation, any suffering of pain is inhuman to every body.
- Respiratory effects: Surgery of the upper abdomen and chest reduces the vital capacity, functional residual capacity and the ability to cough and deep breathe. Any severe pain can impair the respiratory function.
- Cardiovascular effects: Sympathetic output (Tachycardia, hypertension and increasing blood catecholamines) increases due to pain, which leads to myocardial oxygen demand. So patients with pre-existing cardiac disease have a risk of myocardial ischaemia.
- Neuro-endocrine effects: Due to pain and stress response to surgery, secretion of catecholamines and catabolic hormones increase and thus increases catabolism and oxygen consumption and promotes sodium and water retention.
- Psychological effects: Severe pain may cause psychological upset of the patient.
- Economic effects: Severe pain increases hospitals stay and increase use of various drugs thus increases the cost of patients.

Role of Preemptive Analgesia

Opiates administered before the first phase and reversed with the opiate antagonist Naloxone before the expected onset of second phase were capable of preventing this last stage of pain response. Thus, preventing the initial neuronal cascade could lead to long-term benefits by eliminating the hypersensitivity produced by noxious stimuli. After administration of subcutaneous Formaline in Rats, nociceptive neuronal activity is known to follow a biphasic response in which an early nociceptive phase, responding to local anesthetic or opoid, precedes a second period of dorsal horn excitation, known as the inflammatory phase[6,7]. Local anesthetic application after phase 1 prevents phase 2 and thus the expression of c-fos. The secondary wave of neural input sustains the hyper-sensitivity state. NMDA antagonists have been reported to block the second but not the initial phase of this biphasic response.[10]

Application of an analgesic regime before the onset of the noxious stimulus to prevent the central sensitization and thus to limit the subsequent pain experience – is the concept of preemptive analgesia.

Agents for preemptive analgesia

Following agents can be used for preemptive analgesia with proved efficacy[11] –

- Local anesthetic agents
  - Bupivacaine[12,13,14]
  - Lignocaine
  - Mepivacaine[15]
- Non steroidal anti inflammatory drugs (NSAIDs)[11]
  - Ketotoprfen [16]
  - Tramadol [17]
  - Diclofenac Sodium
- Ketamine[18]
- Narcotic analgesics
  - Morphine[19]
  - Fentanyl[20]
- Others-
  - Meloxicam[21]

Above agents can be used as a single agent or can be used in combination of two or more drugs.

Methods of Preemptive Analgesia

- Local infiltration of Bupivacaine and or lignocaine before incision[12]
- Regional blocks[13]
- Intravenous Narcotic agents[19, 20]
- Intravenous or intra-muscular NSAIDs[11,16]
- Intravenous or intra-muscular Ketamine[18]

Clinical Studies

There are many clinical studies which supports the use of preemptive analgesia by different methods – local anesthetic blocked, regional blocked, NSAIDs, Ketamine injection, narcotics etc either by a single agent or in combination. A significant reduction in the post-operative analgesic requirements observed when analgesic therapy was administered before incision compared with administration of same therapy just

wound closure. A similar preemptive effect was seen when pre-incision epidural ketamine, morphine and bupivacaine were administered in combination in a randomized single blinded placebo control study[11].

Clinical evidence provided by Choe and associates[4] for efficacy of preemptive analgesia with use of epidural Morphine and ketamine in a randomized double blinded study shows significantly improved analgesia was associated with pre-incisional use compared with post-incisional use of administration of analgesics.

Study done by Akarsu et al[21], Obata et al[15] also observed better postoperative pain control in preemptive analgesia. Randomized double blinded study done by Obata and associates on pre incisional and post operative epidural blocked on thoracotomy patients. They reported a significantly reduced incidence of post operative pain at six months follow up when continuous epidural blocked was instituted before incision[15]. There are many clinical studies which reveal better postoperative pain control by the use of preemptive analgesia[12,13,16-20].

Controversy

Preemptive analgesia is an effective method of pain control in rats[6,7]. There are some controversies about the benefit of preemptive analgesia on human being, as many of the convincing results obtained from the study of rats. The most obvious reason for diverging experimental and clinical finding is that rats may differ substantially from human in pain pathophysiology and neuropharmacology[23]. On Rat sensitization is readily induced in spinal sensory pathway after conditioning stimuli, when intense activity is prevented from reaching the dorsal horn. A large effect can be seen which may not be the case in other species less prone to sensitization because of genetic differences strongly effect the development of neuronal hyperexcitability[24] and hyperagesia[25] after injury, even between various strains of Rats, comparison across species to human injury response must be suspect. Controversy arises on effectiveness of preemptive analgesia by some studies on human being.

Discussion

Though some studies have controversies but there are many clinical studies, which favors the beneficial effects of preemptive analgesia. A randomized control trial study of Ong et al[11] using opoids observed equivocal results between preemptive analgesia and post-operative analgesia but better results observed by using local anesthetic agents for preemptive analgesia. Study of Wnek et al[16] using Ketoprofen, Lee et al[18] using ketamine, Jirasiritham et al[12] using pre-incisional bupivacaine on human observed better result of preemptive analgesia. By using Visual Rating Scale (VRS) and Visual Analog Scale (VAS), on a prospective study, Machida et al observed that preemptive analgesia using continuous subcutaneous injection of morphine is a simple, safe and effective method to control postoperative pain.[19] Study of Sekar et al[17] using bupivacaine and tramadol, Ozcan et al[20] using Fentanyl-bupivacaine, O'Neal et al[13] using bupivacaine with adrenaline observed same result. A double-blinded randomized study on 80 patients had done by Monichi et al have little support on preemptive analgesia[26]. Lam and associates[27] studied on 144 patients using Linear Visual Analog Scale, comparing preemptive analgesia verses pre-closure analgesia. Their study reveals better postoperative pain control on preemptive analgesia than pre closure analgesia. Like these, there are many studies in favor of preemptive analgesia on human being.

Conclusion

The methods of application of preemptive analgesia are simple and cost effective. Though, according to some author there is doubt about the beneficial effect of preemptive analgesia on human being but there is no harmful effect. As prevention is better than cure, so if we practice preemptive analgesia it may improve the quality of management of post-operative pain.

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