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Original research article

Study of Post-Operative Use of Analgesia in Stress Response and Post-Operative Pain Score

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Abstract

Background: The multimodal analgesic drugs act at all four levels of pain pathway, as it havingsynergistic effects, it is effective in preventing and treating acute pain.

Methods: This is prospective, double blind, randomized clinical trial involving 42 patients belonging to the American Society of Anaesthesiologists Class I and II scheduled to undergo elective lumbar spine surgery were allocated into two groups of 21 each. Group A (study group) received injection diclofenac sodium, paracetamol, clonidine, and skin infiltration with bupivacaine adrenaline and Group B (control group) received paracetamol and skin infiltration with saline adrenaline. Pre-emptive analgesia was practiced in both the groups. BIS guided induction was done with incremental doses of Inj propofol. Two 2 ml blood samples were drawn; one just before tracheal tube placement and another one 3.

Conclusion: Pre-emptive MMA when judiciously administered targeting all the four elements of the pain pathway reduce consumption of anaesthetic drugs and provided optimal surgical conditionsby ensuring intense analgesia with minimal adverse effects.0 min following skin incision for random serum cortisol and random blood sugar.

Keywords: Clonidine, Elective Lumbar spine surgery, Bupivacaine.

Introduction

Multimodal analgesia (MMA) is a novel direction in perioperative pain management. However the concept is not new and was pioneered by Prof Henrik Kehlet in Denmark in the early 1990s with the introduction of "Fast track surgery." The principle behind it is to administer opioid, non-opioid and adjuvant analgesics which act centrally and peripherally, targeting all the four elements of the pain pathway: 1.Transduction, 2.Transmission, 3.Modulation and 4.Perception that may have synergistic effects in preventing and treating acute pain. In the beginning of the 21th century, acute pain following surgery was treated inadequately in 50% of the patients. At the same time, the United States Congress declared the "Decade of the pain control and research" to treat acute pain effectively. Updates on acute pain from 2008 up tothe present time state that, 70% of the surgical population still suffer from moderate to severe pain, which is an abrogation of fundamental human rights. With significant progress in understanding the pathophysiology of acute pain, the Joint Commission on Accreditation of Health Care Organization has accepted pain as the "Fifth vital sign." To strike a balance between nociception and anti-nociception, search for anideal opioid analgesic is in progress, novel methods of drug delivery systems such as patient controlled intravenous and epidural

analgesia have been developed, minimally invasive surgical techniques are in practice and there is a continuous search for new multivariate indices to assess nociception e.g. the surgical pleth index. With all the above measures, the "acute pain service" has shown improvements in providing postoperative analgesia, but aggressive pain control is still lacking. Physical tissue injury releases neurotransmitters, peptides, endocannabinoids, cytokines, and hormones which operate interdependently through various neural, endocrine, and immune processes results in acute pain and hence stress response under anaesthesia. Persistent exposure of spinal neurons to these noxious stimuli can lead to postoperative pain of greater intensity and duration than expected, because of the complexity of the pain pathway and associated stress response. Conventionally, postoperative pain is treated with intraoperative or postoperative analgesics. To achieve maximum clinical benefits, analgesics have to be initiated before the surgical stimulus, a concept known as pre-emptive analgesia. It is not just the relative timing of intervention, it is also an effective proactive approach to treat pain before it is initiated to obtain maximum clinical benefit of the analgesics administered.The American Society of Anaesthesiologist Task Force, developed perioperative acute pain management practice guidelines in 2004, to assist both the practitioner and the patient. They have recommended anaesthesiologist to administer MMA to patients for effective perioperative analgesia, unless contraindicated. An annual meeting report of the American Society of The conclusion drawn by this is thatMMA technique is still a topic of discussion awaiting recommendations in clinical practice to treat acute pain.From evidence based literature it is clear that, integrating current knowledge, available efficacious analgesics and adjuvants is the need of the hour to treat pain adequately rather than developing new drugs and techniques.

Objectives

To assess the difference in serum cortisol and random blood sugar between MMA regimeand the conventional analgesic regime in patients undergoing lumbar spine surgery. To estimate propofol requirement for induction in patients with MMA regime as compared to the conventional analgesic regime to achieve bispectral.

Review of Literature

The word 'Pain' is derived from old French and Anglo-Norman peine, "paine" and from Latin poena which means punishment. But according to Greek mythology, the word is derived from 'Poine,' a Goddess of revenge who was sent to punish mortal fools who had angered the gods. Rene Descartes' pain pathway illustrated "Particles of heat" activate a spot of skin attached by a fine thread to a valve in the brain (de) where this activity opens the valve, allowing the animal spirits to flow from a cavity into the muscles causing them to flinch from the stimulus, turning the head and eyes toward the affected body part, moving the hand to protect the body. He illustrated in his Traite de l'homme (Treatise of Man), a long fibre running from the foot to the cavity in the head which is pulled by the heat and releases a fluid that makes the muscles contract. However the current concept of nociceptive pain follows the ideas of the 1960's by R. Melzack and P. Wall. Sherrington called pain the physical adjunct of an imperative protective reflex. Pain pathway is not a "hardwired" system, it allows peripheral, central, intracellular and synaptic modifications and nociceptive input to be processed from the periphery to the brain. For scientific and clinical purposes, pain is defined by the International Association for the Studyof Pain (IASP) as "an unpleasant sensory and emotional experience, associated with actual or potential tissue damage or described in terms of such damage It is defined as "the normal, predicted, physiological response to an adverse chemical, thermal, or mechanical stimulus. It is considered as "good pain" because it serves as a protective mechanism. It is described as sharp pain, electric pain or pricking pain. Mainly it is felt in the skin, arising from unmyelinated dendrites of sensory neurons located around hair follicles as

wellas deep tissue carried by Aδ pain fibers, 2-5 μm in diameter at velocities between 6 and 30 meters/second. It is felt within about 0.1 second following a painful stimulus. Sharp 'fast' pain sensations are carried in the anterolateral or neospinothalmic tract. Frequent trauma or diseases affecting peripheral nerves results in the development of chronic, often intractable 'neuropathic' pain syndrome associated with spontaneous paraesthesias, dysaesthesia and frank pain pain evoked by movement and tenderness of the partly denervated body part. It is due to activity in the C pain fibers 0.4-1.2 μm in diameter, conducting at a velocity of 0.5 to 2 meters/second. It is also known as pathological pain and is usually associated with tissue destruction. It is a dull, intense, diffuse, poorly recognised and unpleasant feeling. **Transduction:** Conversion of the stimulus from one form to another. It is an event whereby noxious thermal, chemical or mechanical stimuli are converted into an action potential. **Transmission:** Passage of nerve impulse across synapses. It occurs when the action potential is conducted through the nervous system via, the first, second, and third-order neurons, which have cell bodies located in the dorsal root ganglion, dorsal horn and thalamus, respectively. In 1965 Melzack and Wall first published the gate control therapy. It is one of the earliest proposed pain modulation mechanisms. In the initial theory, they postulated that the large fibers are "closing the gate" to nociception transmission into the higher centres. In 1982, they modified the theory to include the facilitatory and inhibitory descending mechanism.The classes of transmitter compounds integral to pain transmission are released from damaged cells, inflammatory cells (macrophages, lymphocytes and mast cells) and injured afferent neurons include the excitatory amino acids: glutamate and aspartate, the excitatory neuropeptides: substance P, neurokinin A and calcitonin gene related peptide (CGRP) and theinhibitory amino acids: glycine and GABA. These excitatory peptides alter the excitability of sensory and sympathetic nerve fibers, cause vasodilatation and extravasation of plasma proteins and act on inflammatory cells releasing chemical mediators. Surgery or trauma generates a catabolic state with increased secretion of catabolic hormones (adrenocortico trophic hormone), cortisol, ADH (antidiuretic hormone), catecholamines, angiotensin II, IL-1 (interleukin) IL-6 and TNF (tumour necrotizing factor)] and decreased secretion or action of anabolic hormones (insulin and testosterone). Nausea, vomiting and intestinal stasis; alteration in substrate metabolism; disturbance in water and electrolyte handling by the body; increased demands on the cardio vascular and respiratory systems also occur. Group of drugs having analgesic, antipyretic and anti-inflammatory properties are called non steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs in the world. Since steroids possess potent anti-inflammatory activity, to differentiate these from corticosteroids the term non-steroidal is prefixed. These are also called non-opioid or non- narcotic analgesics to differentiate them from opioids or narcotics (morphine like) which are potent analgesics. They are broadly classified into amino esters and amino amides based on the linking group. Bupivacaine belongs to the amino amide group. It is a tertiary amine attached to a substituted aromatic ring by an intermediate amide chain. The tertiary amine is a base (proton acceptor). It is a sensitive numerical rating scale having both written and verbal forms. Pictorial versions also exist. As such an assessment is clearly highly subjective, these scales are of most value when looking at change within individuals.VAS is the most commonly used scale for rating pain intensity in research.

Material and methods

This is prospective , double blind, randomized clinical trial involving 42 patients belonging to the American Society of Anaesthesiologists Class I and II scheduled to undergo elective lumbar spine surgery were allocated into two groups of 21 each. Group A (study group) received injection diclofenac sodium, paracetamol, clonidine, and skin infiltration with bupivacaine adrenaline and Group B (control group) received paracetamol and skin infiltration with saline adrenaline. Pre-emptive analgesia was practiced in both the groups. BIS guided induction was

done with incremental doses of Inj propofol. Two 2 ml blood samples were drawn; one just before tracheal tube placement and another one 3. The study was conducted at Nalanda medical college and Hospital Patna, Bihar. Study duration of two years.

Inclusion Criteria
Both sexes, BMI (Body Mass Index) 18 to 30, Age 20-65 yrs Patients undergoing lumbar spine surgery

Exclusion criteria
Pregnant women, Patients with bronchial asthma, Patients with history of drug allergy
Primary outcome measures of the study were random serum cortisol, random blood sugar and propofol requirement for induction. A power analysis ($\alpha = 0.05$, $\beta = 0.20$) indicated that at least 21 patients were required in each group. For this calculation, we used data obtained from a pilot study and assumed difference of 4.3 µg/dl in serum cortisol level between MMA group and conventional regime group to be significant with 5% level of significance and 80% power..

Clonidine: 10 ml saline with or without clonidine 0.75 µg/kg was prepared and coded. It was given over 2 min, 10 min prior to induction.

Local infiltration: 20 ml of 0.25% bupivacaine in the MMA group and 20 ml of normal saline in the conventional regime group were prepared with sterile aseptic precautions in galley pots. Two drops of Adrenaline 1:1000 were added with a 22 G needle to both the preparation. Confirming the preanaesthetic evaluation documentation, in the induction room the following monitors were connected and monitored through the surgery ECG, NIBP, SPO_2, $EtCO_2$ (end tidal carbon dioxide), BIS and TOF (train of four neuromuscular monitoring. Two intravenous lines were secured, one for fluid and another one to draw blood samples. Oxygenwas supplemented through simple O_2 mask. Once IV line was secured, midazolam 0.03 mg/kg, ondansetron 4 mg and glycopyrrolate 0.2 mg were administered intravenously to all the patients. For statistical analysis, the random serum cortisol, random blood sugar, propofol requirement forinduction, postoperative sedation score and VAS score (visual analogue scale) were assessed. Sedation was assessed by 5-point Ramsay sedation score. Pain was assessed using the pictorial versions of VAS graded from 0 (no pain) – 10 (worst imaginable pain).

Results
That there was no statistical difference in age, height, weight and BMI ofthe patients between the control and the study group.
Gender distribution

Table 1:

Gender	Control group	Study group
Male	17(81%	17(81%
Female	4(19	4(19.0
Total	21(100%	21(100%

As per the observations, the rise in serum cortisol from T_1 to T_2 was statistically significant in both, the control and the study groups (p^1 =0.001 and p^1 =0.009 respectively). Comparing therise between the two groups was not statistically significant ($p^3 = 0.887$).
Comparison of propofol requirement for induction in control group and study group.

Table 2:

propofol	Control group	Study group	p- value
Total induction dose(mg)mean+_SD	46.19+_10.71	28.57+_10.62	<0.001
Dose region mg/kg	0.71+_0.19	0.44+_0.18	<0.0012

Statistically significant at p<0.05 and 95% confidence level;

Comparison of induction dose requirement of propofol between control and study group byindependent sample t – test.
Comparison of propofol (mg/kg) requirement between control and study group by independent sample t – test.

Total dose requirement of propofol for induction (BIS 50-55) was 28.57 ± 10.62 mg in the study group where as it was 46.19 ± 10.71 mg in the control group which was significantly higher (p^1<0.001). Similarly there was a significant difference in propofol requirement per kg body weight for induction between the control and study groups (p^2<0.001).
5-point sedation Ramsays score: 1-wide awake; 2-drowsy or dozing intermittently; 3-mostly sleeping but easily awakened; 4-asleep difficulty responding to verbal commands; 5-awakened only by shaking. Statistically significant at p<0.05 and 95% confidence level; Chi-square test for comparison of sedation score.
Comparison of VAS between control group and study group.

Table 3:

VAS rating of30min	Control group	Study group	p- value
0.5	0	0	<0.001
5-44	2(9.5%)	21(100%)	
45-74	18(85.7%)	0	
70-100	1(4-8%)	0	

Statistically significant at p<0.05 and 95% confidence level; Chi-square test for comparison of VAS score.Rating: 0-0.5 - No pain, 0.5 - 4.4 - mild pain, 4.5 - 7.4 - moderate pain, and 7-10 - severe pain.

Discussion

Management of acute pain due to surgical trauma gained importance in the early 1930s followingthe detailed description of metabolic responses (stress response) to accidental injury. Stress response to surgery and anaesthesia is an established fact. To improve the quality of acute pain management, various methods like pre-emptive, preventive and multimodal analgesia have been describd. Pre-emptive analgesia is achieved by simple changes in the timing of drug administration to have profound effects on relief of postoperative pain. It prevents the establishment of central sensitization caused by incisional and inflammatory injuries. Traditionally, opioid analgesics are considered the standard approach to treat acute postoperative pain, however dose related undesirable adverse effects have given importance to the practice of multimodal intervention. The present study design was unique with the use of preventive multimodal analgesia regime to subdue stress response in patients undergoing spine surgery and
to assess postoperative pain score, adopting the fundamental principles as described in

evidence-based literature.

Acute postoperative pain is recognized to have an early inflammatory component and a later neuropathic component. To treat them, single drug therapies (opioids and NSAIDs) have limitations due to increasing incidence of side-effects with increasing doses. This has lead to the conception of the multimodal approach. It has become the standard of care to treat acute pain and opioids are taking the role of "rescue analgesic". It should target all four elements of pain processing (1 Transduction 2 Transmission 3 Modulation and 4 Perception) with drugs having different mechanisms of action, a concept clearly explained by Macres et al. Anaesthesiologists Task Force" on acute pain management, "Agency for Health Care Policy and Research," and "Joint Commission on Accreditation of Health Organization have recommended MMA as a choice to treat postoperative pain, after which it has gained popularity. Literature reviews on multimodal analgesia, including the one published in 2013 state that it is a technique for pain management wherein two or more drugs are administered. Majority of the studies in the literature who have coined the term multimodal analgesia have used only two analgesics, very few studies have administered three analgesics.In the present study, four non-opioid analgesics with opioid were used, all with different mechanisms of action, targeting all four elements of the pain pathway as follows: 1.Diclofenac sodium (transduction), 2. Bupivacaine (transduction, transmission, modulation), 3.Clonidine (modulation, perception), 4.Paracetamol (perception) and 5.Fentanyl (modulation,perception). Prior to the administration of MMA drugs, an anxiolytic dose of midazolam 0.03 mg/kg was administered i.v. to achieve stress-free hemodynamic status. Five minutes later, MMA drugs were administered in an order as per their onset of action, providing adequate time for their clinical effects. A few studies have made mention Efficacy of MMA was assessed by endocrine and metabolic responses to surgery and propofol requirement for induction to achieve a target BIS of 50-55. In the present study, random serum cortisol and RBS were assessed as biochemical markers to stress response (intubation, change of position and skin incision). One of the study objectives was to assess the difference in propofol consumption for induction between the two groups, using BIS monitoring. To assess the hypnotic component of pre- emptive MMA, we induced our patients with small titrated dose of propofol 0.3-0.35 mg/kg and 10 mg incremental doses at one minute interval to attain BIS of 50-55 and was maintained for 30 seconds. Later, anaesthetic gases were switched on and propofol consumption was documented. The total dose requirement of propofol for induction in the control group was 46.19±10.62 mg where as in the study group it was 28.57±10.62 mg guided by BIS monitoring (50-55) which wasstatistically significant ($P<0.001$). When calculated according to body weight, it was 0.7±0.19 mg/kg in the control group where as in the MMA group it was 0.44±0.18 mg/kg. In Gurses et.al study, without premedication total dose of propofol requirement for induction was 84.3±11.4 mg, whereas in Agrawal et.al study it was 109.43±20.14 mg for BIS of around 50, where as in the present study with MMA it was 28.57±10.62 mg. In a study by Parikh and Mehta, they found that the dose of propofol for induction was 1.6±0.28 mg/kg for BIS of 45-60 with diclofenac and midazolam premedication, Post extubation at 5 min, Ramsay sedation score was 3 (asleep) in 61.9% of the patients in the control group, whereas in the study group it was 33.3%. Following are the studies in agreement with the present study findings. Bashandy and Elkholy also found high median sedation score in the GA group. In their study, intraoperative fentanyl supplementation was high in the GA group but was not statistically significant. In the study by Kumar et al sedation score was found to be less in clonidine group compared to gabapentin group. This shows that sedation with clonidine iscomparatively less. It is one of the reason why clonidine was the drug of choice in MMA regime in the present study.

Conclusion

The rise in cortisol was not significantly different between the groups. This shows that as a response to tissue injury, inflammatory mediators are released irrespective of analgesics administered, but with pre-emptive analgesia as nociceptors are primed with analgesics, response to painful stimuli depends on the intensity of analgesia.The propofol requirement per kg body weight was significantly lower in the MMA group.

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