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Evaluation of the pre-emptive analgesic efficacy of oral Pregabalin as epidural analgesia in elective orthopaedic lower limb surgeries

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Abstract
Background: Pre-emptive analgesia is an anti-nociceptive treatment that prevents establishment of altered processing of afferent pain input. It interferes with peripheral and central sensitization. Pregabalin has been claimed to be more effective in preventing neuropathic component of acute nociceptive pain of surgery.
Objectives: The aim of the present study is to compare the efficacy of pregabalin 300mg oral with placebo for post-operative analgesic requirement in elective lower limb orthopaedic surgeries.
Methods: 60 patients of ASA I & II undergoing elective lower limb orthopaedic surgeries were included in this trial, 30 in each group as Group A (Pregabalin), Group B (Placebo). In Group A pregabalin 300mg oral was given 90 minutes before surgery and post-operative analgesic requirements were observed. The exact protocol was followed for the Group B (Placebo) except the placebo drug was used. The pain scores through visual analogue scale, total number of epidural top- ups, required total number of rescue morphine was observed and compared between two groups. Chi-square test has been used to find the significance of categorical scale between two groups. $p<0.05$ was considered significant.
Results: The time to first epidural top up for Pregabalin group is 11.2±5.3 hours when compared to 4.67±5.3 hours for control group ($p<0.05$). The total number of top up for pregabalin group is 0.96±0.41 when compared to control group 1.7±0.7 ($p<0.05$). The total number of rescue morphine for pregabalin group is 0.47±0.6 when compared to control group 1.57 ± 0.67 ($p< 0.05$). **Conclusion:** Preoperative pre-emptive administration of oral Pregabalin 300mg effectively reducing the post-operative analgesic requirement.

Keywords: Pregabalin, pre-emptive analgesia, lower limb orthopaedic surgeries.

Introduction
Pre-emptive analgesia is defined as a treatment that is initiated before surgery in order to prevent the establishment of central sensitization evoked by the incisional and inflammatory injuries occurring during surgery.
The idea of pre-emptive analgesia is based on experimental observations demonstrating that if the afferent traffic of pain signals is prevented from reaching the central nociceptive neurons by pre injury administration of analgesics, sensitization of central neurons will not take place or it will be reduced. In contrast, a similar treatment after the injury will not be able to reverse the central sensitization once such alterations are established [1].
Pre-emptive treatment could be directed at the periphery at inputs along sensory axons and at central neurons. Different treatment regimen could be used at different levels of sensory inputs. There are various methods available for pre-emptive analgesia like non-steroidal anti-inflammatory drugs (NSAIDS), oral or parental opioid, parental NMDA antagonists, local anesthetics as neuriaxial blockade peripheral blocks and local infiltration, systemic antiepileptics (GABA analogues) [2, 3].
Pregabalin is an anticonvulsant and anti-nociceptive drug. It is close analogue of the inhibitory neurotransmitter gama amino butyric acid (GABA). Pregabalin binds with high affinity to the alpha2delta subunit containing voltage gated calcium channels. It has been effective in neuropathic pain, diabetic neuropathy, fibromyalgia and add on therapy in epilepsy.

Pregabalin was found to decrease postoperative opioid requirement and also reduce the preoperative anxiety and induce sedation without producing undesirable side effects, therefore, the present study is performed to compare the pre-emptive analgesic efficacy of pregabalin in elective lower limb orthopeadic surgeries [4, 5].

Material and Methods

This study was conducted at Saveetha Medical College and Hospital, Thandalam Kanchipuram, Tamil Nadu in accordance with the guidelines of the institutional ethical committee. Patients who were all scheduled for elective lower limb orthopedics surgery after the pre anesthetic assessment according to the inclusion criteria and exclusion criteria. This was a prospective randomized double-blind controlled study to compare two groups. 60 patients were included in this study with 30 patients in group P (pregabalin) and 30 patients in group C (Placebo). The study duration was from May 2012 to May 2014.

The patients were randomly divided into two groups of 30 patients each in double-blind manner. Computer based random numbers was generated. Each patient received an appropriate randomization number and was assigned to their group according to the number. Neither the patient nor the doctor was aware of group assignment. These 60 patients were divided into two groups. Group P received pregabalin 300mg, Group *C* received placebo.

All the patients are examined prior to study. Routine clinical examination, biochemical investigation, electrocardiogram and chest X-ray were examined thoroughly before the anaesthesia. Those patients who are qualified as per the selection criteria has given explanation regarding anesthesia procedure in their vernacular language. A written informed consent obtained in each case. Patient information was sheet given.

Patients allocated randomly based on computer generated table in double blinded fashion into two equal groups (30 in each group). Group P (Pregabalin) received a capsule of MAXGALIN 300mg, Group C (Placebo) received a tablet of alike looking multivitamin placebo of 90 minutes prior to anesthesia with sips of water. No premedication was given.

Chi-square test has been used to find the significance of study parameters on categorical scale between two groups. All analyses were two tailed and $p<0.05$ was considered significant. SPSS version 17.0 was used for data analysis.

Observation and Results

60 adult patients, belonging to ASA physical status I-II of both sex between 20-60 years of age scheduled for elective lower limb orthopaedic procedures were given combined spinal epidural. Indwelling epidural catheter for post-operative analgesia was kept. They were randomly allotted to two groups each having a total of 30 patients.

Confounding variables such as age, sex, duration of surgery, ASA status, BMI all are comparable in both the groups and there was no statistically significant difference between them. None of the patients gave any history of surgery on the same site previously.

The sex distribution in the two groups is depicted. In GROUP-P 26 are male (86.67%) and 4are female (13.33%). In GROUP-C 21 are male (70%) and females are 9 (30%). There is no statistically significance (p=0.2092) patients who are classified under ASA I in Group P is 17 patients (56.7%) and in Group C it is 20 patients (70%). ASA II in Group P is 13 patients (43.3%) and in Group C it is 10 patients (30%). There was no significance (p=0.426). Average surgery time in Group P is 105.27±7.86 minutes and in Group C was 104.87±8.02 minutes there was no significance (p=0.8460)

Time to Onset of Bromage Score 3

Table 1: Time to Onset of Bromage Score 3

Time to Onset of Bromage Score 3 in Minutes (Groups)	Group P	%	Group C	%
≤ 7 minutes	10	33.3	11	35
7.01 - 7.30 minutes	17	56.7	17	56.7
7.31 - 8 minutes	3	10	2	6.7
Total	30	100.00	30	100.00

Table 2: Time to Onset of Bromage Score 3

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	0.248a	2	0.884
Likelihood Ratio	0.249	2	0.883
Linear-by-Linear Association	0.181	1	0.671
N of Valid Cases	60		

*a - 2 cells (33.3%) have expected count less than 5. The minimum expected count is 2.50.

Statistical analysis we concluded the time to onset of Bromage score to 3 is not significant between two groups. In less than 7 minutes 10 (33%) patients Group P reached the marked level of block. In group C 11 (33%) reached to bromage score 3. In 7 to 7.30 min 17(56.7%) patients were reached in score 3 in both groups. In 7.30 to 8 minutes 3 (10%) in Group P and 2 (6.7%) in Group C reached the marked level. The sensory level at 5 minutes is statistically not significant with *p* value of 0.949 The sensory level at 10 minutes is statistically non-significant for both groups with p value of 0.988.

Discussion

Historically pain management was relatively low in medical priority. Dr. James Campbell in his 1995 Presidential Address to the American Pain Society proposed the idea of including pain as one of the vital sign[50]. The initiative was caused more interest and focus on the treatment of pain.

On January 1, 2000 U.S. Congress declared "Decade of Pain Control and Research"[51]. Now American Pain Society (APS) suggested to consider pain as a "the fifth vital sign" [5, 6].

Despite the substantially increased attention focused on pain management, acute post-operative pain is still often poorly treated. The tissue damage in surgical procedures almost invariably results in acute post-operative pain, which can range in intensity from mild to very severe.

One study [7] evaluated 250 adults who had undergone surgical procedures recently in the United States. Patients were asked about the severity of postsurgical pain, satisfaction with pain medication. Approximately 80% of patients experienced acute pain after surgery. Of these 86% had moderate to severe pain. Some patients experiencing pain after discharge too. Despite an increased focus on pain management and development of new standards many patients continue to experience intense pain after surgery. So, they have concluded further efforts are required to control the postoperative pain.

Pre-emptive analgesia prevents central and peripheral sensitization of pain stimulus and effectively reduces the post-operative pain. Various drugs and regional anaesthesia is being used pre-emptively. We studied Pregabalin as pre-emptive analgesia in lower limb orthopeadic surgeries. Pregabalin is different from its predecessor gabapentin. Amino acid substitution at third position making it more lipid soluble with better pharmacokinetic profile such as higher bioavailability, rapid absorption, and linear increase in its plasma concentration [8, 9].

The peak blood concentrations of pregabalin are attained within 1 h. The maximum rate of absorption of pregabalin is approximately 3-fold greater than that of gabapentin. Pregabalin binds to the same calcium channels as gabapentin but with high affinity makes it more potent analgesic. All these characteristics are responsible for longer pain-free interval after spinal anesthesia. Pregabalin is active in nociceptive processing associated with central sensitization [9, 10]. Evidence suggests that pregabalin can reduce enhanced pain responses by preventing sensitization at the level of the spinal cord and possibly at other sites in the nervous system [11, 12].

We studied Pregabalin as pre-emptive analgesia in lower limb orthopaedic surgeries. 60 adult patients, belonging to ASA physical status I-II of both sex between 20-60 years of age scheduled for elective lower limb orthopaedic procedures. They were randomly allotted to two groups each having a total of 30 patients. Group P was given 300 mg of Pregabalin 90 min before surgery. Group C was given placebo capsules.

Combined spinal epidural anaesthesia performed and indwelling epidural catheter kept for post-operative analgesia. Post-operative analgesic requirement measured as time to first epidural top up, number of total epidural top-up and number of rescue analgesia. Pain score were recorded and studied. Age, sex distribution, ASA status, duration of surgery, body mass index were comparable for both groups with $p > 0.05$.

Time to onset of Bromage score 3 is not significant between two groups. In less than 7 minutes 10 (33%) patients of Group P and 11 (35%) patients in Group C reached to bromage score 3. In 7 to 7.30 min 17 (56.7%) patients were reached to score 3 in both groups. In 7.30 to 8 minutes 3 (10%) in Group P and 2 (6.7%) in Group C reached the marked level (p= 0.884). The sensory level after spinal anaesthesia at 5 minutes and 10 minutes were statistically not significant with $p > 0.05$.

The mean pain score measured with visual analogue scale in 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24 hours are statistically significant for all the time. VAS score is low in pregabalin group during all the recording except in 12th hour where the pain score for pregabalin group is 3.2 ± 0.92 when compared to control group 2.1±0.89. This reduction of pain score in 12th hour in control group can be attributable to rescue doses of morphine and epidural top ups received before 12th hour in control group.

The time to first epidural top up for pregabalin group is 11.2±5.3 hours when compared to 4.67±5.3 hours for control group (p<0.001). In control group in less than 5 hours 73.33% patients required first epidural top up but in pregabalin group only 13.33% patients require epidural top up. Within 10 hours of post operative period all the patient in control group required epidural top up when compared to pregabalin group only 30% patients received first epidural top up.

The total number of top up for pregabalin group is 0.96±0.41 when compared to control group 1.7±0.7. This is statistically significant with p value of <0.001. The total number of rescue Morphine for Pregabalin group is 0.47±0.6 when compared to control group 1.57 ± 0.67(p<0.001).

The Ramsay sedation score is high for Pregabalin group in 1, 2, 4, 12, 16 and 24th hours. On 6th and 8th hour the sedation levels are high in control group when compared to Pregabalin group. Statistically 1, 2, 4, 6, 8 and 24th hours have significant difference. The sedation score of 12 and 16th hours are statistically not significant. A 200mg pregabalin was identified as sedative. Hence the pregabalin group has more sedation scales initially. Later due to morphine usage in control group the sedation score is increased in control group which results in non-significant sedation scores on 12th and 16th hour [13].

Therefore, pregabalin 300mg oral as pre-emptive analgesia is effectively reducing the pain perception with less post-operative analgesic requirements in elective lower limb orthopaedic surgeries with statistically non-significant adverse effects except increased sedation scores and dizziness.

World health organisation (WHO) expert committee on drug dependence's review report of pregabalin says it is rapidly and extensively absorbed. Plasma concentrations of pregabalin peak within 1.5 hours after administration, with oral bioavailability greater than 90% that is independent of dose and frequency of administration [14, 15]. Buvanendran *et al*. [45] concludes 2-8 hours is needed to achieve the effective CSF concentration. We administered pregabalin 1.5 hours before surgery. The effective time to administer pregabalin as pre emptive analgesia is not clearly known. We use 30mg of pregabalin as pre emptive dose. Various studies are available on various doses between 75mg to 600mg. To quantify the right dose further studies needed. The additive effect of morphine with pregabalin both in pain control and sedation levels are confounding factor in our study with regards to evaluate the sedation effect of pregabalin. The range of motion of traumatised limb is not recorded and compared. The total length of hospital stay is not studied and compared. Dizziness, vomiting, blurred vision, headache are the important side effects of pregabalin. Those all adverse effects could prolong the hospital stay. The overall satisfaction scores were not recorded.

We concluded that pregabalin 300mg given as premedication 90 minutes before surgery as pre-emptive analgesia is effectively reducing pain scores post operatively and it significantly reducing post-operative analgesic requirements in lower limb orthopaedic surgeries without any major adverse effects.

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