Section: Anesthesia

Original Research Article

ANALGESIC ROLE OF PREGABALIN AS A PREMEDICANT IN PATIENTS UNDERGOING SUBARACHNOID BLOCK WITH CLONIDINE - A PROSPECTIVE, DOUBLE BLIND, RANDOMIZED, PLACEBO CONTROLLED STUDY

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Abstract

Background: The post operative pain management has important role in recovery of the patients. It reduces the incidence of adverse physiological and psychological effects associated with pain. Intrathecal clonidine prolongs the duration of action of local anesthetic and has potent nociceptive properties. Pregabalin has pain modifying properties on neuronal structure and receptors in pain pathways. The aim of our study is to know the efficacy of Pregabalin as a premedicant in patients undergoing subarachnoid block with Clonidine as an adjuvant in surgeries below the level of the umbilicus. **Materials and Methods:** A double blinded randomized, prospective controlled study was done on 60 ASA I and II category of patients who were randomly divided into group A (study group) received pregabalin and group B (control group) received placebo as premedication with intrathecal administration of 15 mg 0.5% Bupivacaine heavy with 1 micro gram per kg Clonidine. The sensory block, motor blockade, sedation, and pain were assessed at every 15 minutes interval intraoperatively and thereafter every thirty minutes up to first demand of analgesia by the patient. Blood pressure and heart rate were recorded every one minute in initial ten minutes and thereafter every five minutes. **Result:** There was statistically significant difference between times to achieve highest level of block and time to achieve two segmental regression, systolic blood pressure, heart rate, VAS score, modified Bromage score and somnolence score with p value less than 0.05 in between two groups. **Conclusion:** Pregabalin as a premedicant provides better pain control than placebo in patients undergoing subarachnoid block with intrathecal bupivacaine and clonidine.

INTRODUCTION

Adequacy of perioperative pain control is one of the important factor in determining safe discharge from the surgical unit and has major influence on the patient's ability to resume normal daily activity. While there have been significant advancements in options for pain assessment and therapy, effective post operative pain management remains frequent dilemma for patients and clinicians.[1]

Pain after surgery remains a significant clinical problem as it impairs recovery and may lead to chronic pain.[2] Despite recent advances in physiology of acute pain over the past decades, approximately 80% of patients undergoing surgical procedure experiences post operative pain.1 attention has been shifted over the past two decades to the understanding and treatment of movement evoked or dynamic pain. Poorly controlled movement evoked pain has been related to postoperative pulmonary,[3] cardiac,[4] and thromboembolic complications.[5] These postoperative complications can be both devastating to the patient and costly to health care system.[6,7]

Intrathecal administration of local anaesthetics with adjuvants is a commonly used regional technique for procedures below the level of umbilicus. An ideal adjuvant drug for perioperative analgesia should have analgesic properties with opioid sparing effect and should not be associated with significant adverse effects. The duration and quality of subarachnoid block is often improved with adjuvant drugs such as

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epinephrine, opioids, alpha-2 agonists, NMDA receptor blocker, and acetylcholinesterase inhibitors. Inrathecal opioids have been proved to be associated with side effects such as pruritus, nausea, vomiting, sedation, respiratory depression and urinary retention. Intrathecal administration of preservative free Clonidine as adjuvant produces dose dependent analgesia and unlike opioids does not produce unwanted side effects.[8,9] Clonidine hydrochloride is an imidazoline derivative with centrally acting alpha 2 adrenergic agonist activity.[10,11]

Anticonvulsant medications are established treatment for neuropathic pain. Pregabalin a structural analogue of gamma amino butyric acid (GABA) chemically described as 5 methyl – hexanoic acid, has been used for treatment of neuropathic pain,[12] associated with diabetic peripheral neuropathy and post herpetic neuralgia.[13] Pregabalin binds to alpha – 2 delta subunit of presynaptic voltage gated dependent calcium channels in the tissues of central nervous system. The gabapentenoid group of drugs possesses excellent pain modifying properties along with sedation and anxiolysis. These characteristics make them an attractive choice for premedicating the patients.

Pregabalin and intrathecal clonidine has been proved to have similar pain modifying effect on neuronal structure and receptors in pain pathways. We feel that Pregabalin may potentiate analgesic effects attained by administering clonidine as spinal adjuvant. The hypothesis of this study is to know the efficacy of Pregabalin as a premedicant in patients undergoing subarachnoid block with Clonidine as an adjuvant in surgeries below the level of the umbilicus.

MATERIALS AND METHODS

After institutional ethics committee and board approval 60 ASA I and II category of patients were enrolled in this randomized, double blind, prospective controlled study. Valid informed consent was taken from each patient.

This was a randomized, double blind, prospective controlled study. After routine preoperative evaluation and valid informed consent, patients were randomized into two groups by shuffle envelope method. The study group received Pregabalin as premedication while the control group received placebo.

GROUP A Patient received 150 mg oral Pregabalin 1 hour before surgery with intrathecal administration of 15 mg 0.5% heavy Bupivacaine and 1 micro gram per kg Clonidine.

GROUP B Patient received placebo as premedication with Intrathecal administration of 15 mg 0.5% heavy Bupivacaine and 1 micro gram per kg Clonidine.

After shifting patient to the operating table baseline values (HR, BP, and SpO2) were recorded. After securing intra venous access, sub arachnoid block administered to the patient in sitting posture by midline approach at L3-4 or L4-5 level using 25 G quincke spinal needle under all aseptic precautions. Once free flow of cerebro-spinal fluid was confirmed the study drug was administered. The rate of injection administration was 0.2 ml per second. Patient was made supine after administration of the drug. No tiltof table was allowed up to 15 minutes. The following variables were noted at stipulated time intervals.

Assessment Of Sensory Block

Sensory block was assessed by using 23 G IV needle or spirit-soaked cotton. It was assessed evey 15 minutes interval intraoperatively. Thereafter it was assessed every thirty minutes up to the first demand of analgesia by the patient.

Assessment of the Sedation

Sedation was assessed preoperatively. It was assessed every 15 minutes Interval intraoperatively and thereafter it was assessed every thirty minutes up to first demand of analgesia by the patient.

Assessment of the Pain

Visual analogue score was explained to the patients preoperatively and was assessed every thirty minutes postoperatively up to first demand of analgesia (VAS score >5) by the patient. VAS 0 was taken as equivalent to no pain and VAS 10 was equivalent to worst pain of the lifetime.

Assessment of the Motor Block

The intensity of motor block was also recorded simultaneously. The Bromage score of the healthy limb was recorded intra and postoperatively. Systolic blood pressure and heart rate was recorded every one minute in initial ten minutes. Thereafter it was assessed every five minutes. The duration of analgesia was recorded from the time when VAS score was zero until patient demands for additional analgesia.

Statistical Analysis

Sample size was determined based on the results of the pilot study Comparison of quantitative data between groups was done by independent sample T test, Quantitative data within the groups was compared by repeated measures of ANOVA followed by Dunnets post- hoc analysis. As the sample size was small, difference between the group were likely to be small and the differences are likely to occur at different times. A ‘p’ value of < 0.05 was taken as significant

RESULTS

Sixty patients, thirty in each group were included in the study and analyzed. The groups were compared with respect to demographic characteristics like age, height and weight. The demographic characteristics were not statistically significant between different groups. [Figure 1]

The time for first demand of rescue analgesia was 539.8 minutes in study group as compared to 435.0 minutes in placebo group. (p value - 0.0001) There was statistically significant difference between times to achieve highest level of block (p value - 0.006) and

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time to achieve two segmental regressions in between two groups. (p value - 0.005). There was no statistically significant difference in time to achieve block up to T11.

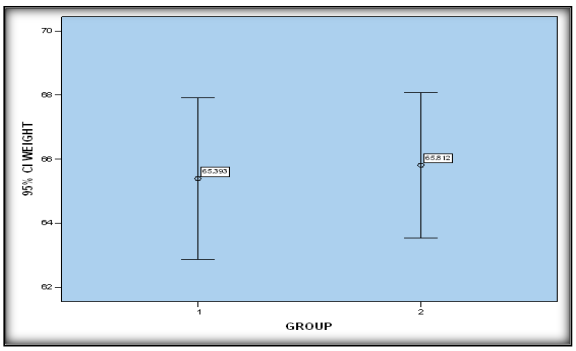

Figure 1: Comparison of weight between the groups

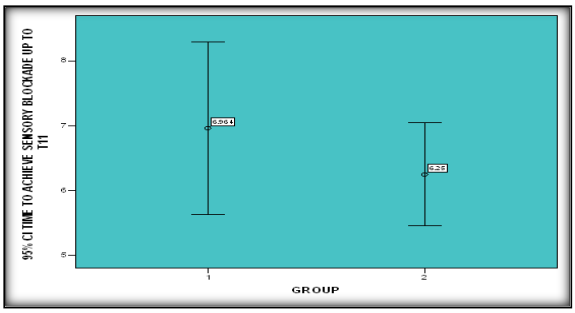

Figure 2: Comparison of time to achieve block up to T 11 between the two groups (in minutes)

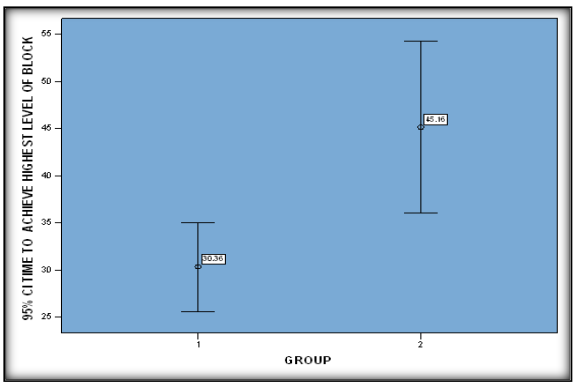

Figure 3: Comparison of time to achieve highest level of block (in minutes)

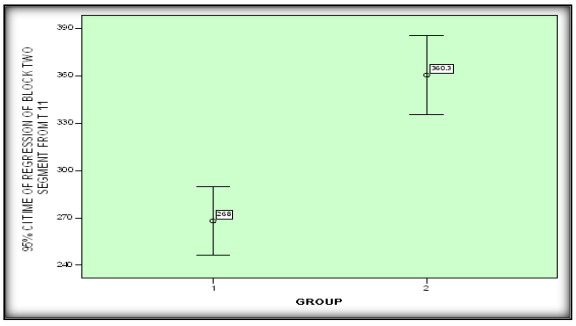

Figure 4: Comparison of two segment regression of block from T 11 between the two groups(in minutes)

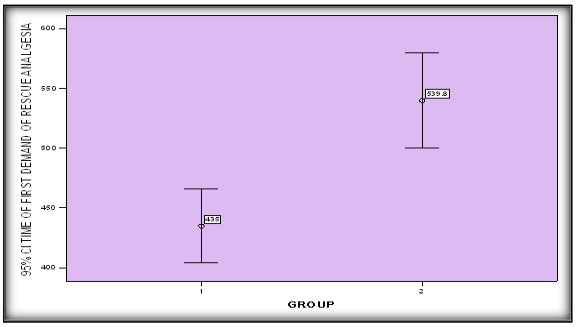

Figure 5: Comparison of time of first demand of rescue analgesia (in minutes)

There was statistically significant difference in Heart Rates between two groups intraoperatively at 1 min, 2 hr 30 min and 2 hr 45 min with p value of 0.024, 0.027 and 0.014 respectively. There was no statistically significant difference between heart rate achieved in between two groups at any point of time postoperatively. [Figure 6]

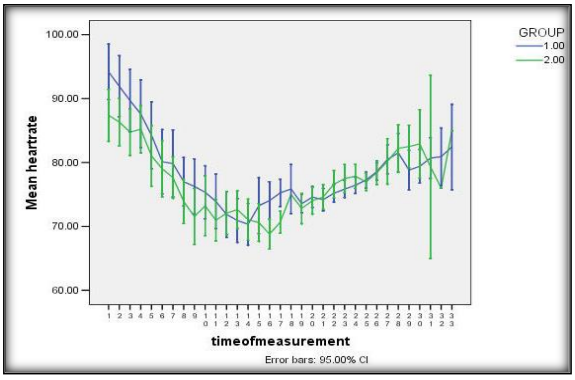

Figure 6: Comparison of mean heart rate intra and post operatively in between the two group

There was statistically significant difference in intraoperative systolic blood pressure between two groups at 2 min, 3 min, 4 min, 5 min, 10 min and 15 min with p value of 0.001, 0.001, 0.028, 0.0005, 0.006, and 0.004 respectively.

There was statistically significant difference in systolic blood pressure postoperatively between two groups at 1 hr, 1 hr 30 min, 3hr 30 min, 5 hr, 5 hr 30 min, and 6 hr with p value of 0.006, 0.005,0.019, 0.014, 0.00009 and 0.004 respectively. [Figure 7]

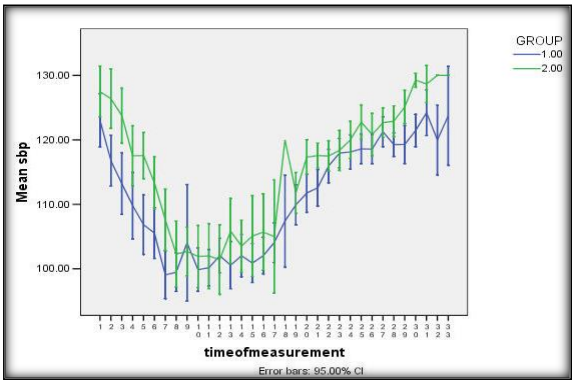

Figure 7: Comparison of SBP changes between the two groups

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There was statistically significant difference between two groups in post operative visual analogue score at 5hr 30 min, and 6 hr with p value of 0.009, 0.001 and 0.0004 [Figure 8]

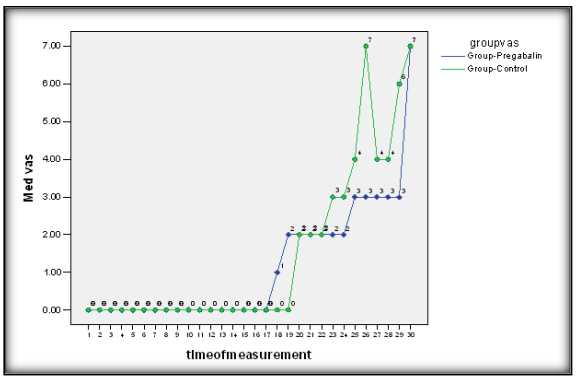

Figure 8: Comparison of VAS score between the two groups intra and postoperatively

There was statistically significant between two groups in bromage score at 5 min with p value of 0.0420. There was statistically significant between two groups in bromage score at 1hr 30 min, 2 hr, and 2 hr 30 min with p value of 0.004, 0.001 and 0.024. [Figure 9]

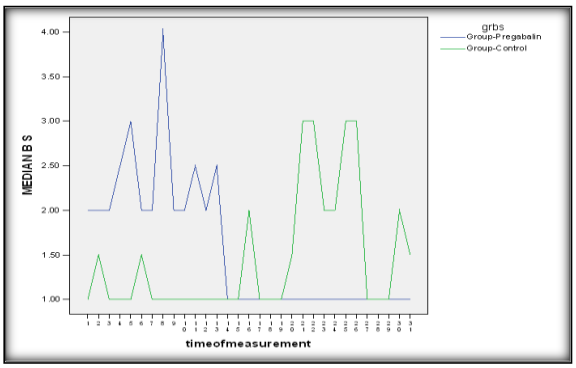

Figure 9: Comparison of Bromage score between the two groups intra and postoperatively

There was statistically significant difference in somnolence score at 45min, 1hr, 1hr 15min, 1hr 30 min, 1hr 45 min, 2hr, and 2hr 15 min with p value less than 0.05. [Figure 10]

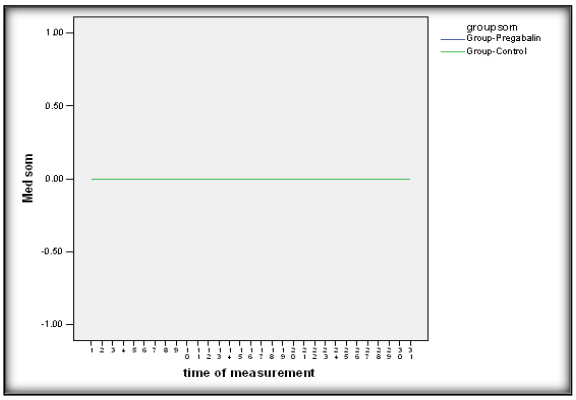

Figure 10: Comparison of Somnolence score between the two groups intra and postoperatively

DISCUSSION

This study has been undertaken to know the efficacy of Pregabalin as a premedicant in patients undergoing subarachnoid block with Clonidine as an adjuvant in surgeries below the level of the umblicus. The present study has not shown any difference in the time to achieve block up to dermatomal level T 11 in between two groups (7 min in pregabalin group and 6.3 min in placebo group). The highest mean dermatomal level of block achieved in placebo group was T 5.8 as compared to pregabalin group in which it was T 5.0 with statistically significant difference. This study has shown statistically significant higher level of block achieved in pregabalin group as compared to placebo group. The time of achieving highest level of block was 45.2 min in pregabalin group and 30.4 min in placebo group.

The present study has shown statistically significant difference of two dermatomal regression in between the two groups. Pregabalin group has taken 360 minutes as compared to 268 minutes in the placebo group for two dermatomal regression.

Hema saxena et al, has used 13.5 mg heavy bupivacaine with variable doses of clonidine as adjuvant (max dose 37.5µgm). The time to achieve sensory block up to T 10 was 2.09 min with the maximum dose of clonidine used. (37.5µgm). The maximum mean dermatomal level achieved with maximum dose of clonidine was 6.7 with two dermatomal regression time of 267 minutes in their study.

As compared to present study (placebo group) they have used lower bupivacaine dose with less dose of clonidine as spinal adjuvant. Hema saxena et al, have shown an earlier onset of sensory block up to T 10 dermatomal level as compared to our study but the highest level of block achieved was more in present study may be because of higher volume of drug used intrathecally.[14]

The total volume of drug used in their study was 3 ml as compare to our study it was 3.5 to 4 ml. The two dermatomal regression time was equivalent in both studies inspite of using higher volume and dose of local anesthetics and clonidine use in the present study. The present study has taken only orthopaedic procedures in the study as compared to study by hema saxena et al in which all below umbilicus surgeries like urological, gynaecological and orthopaedic surgeries were part of the study.

Dobrydnjov et al, has done similar study in patients coming for inguinal herniorraphy. They have used low dose Intrathecal bupivacaine with variable concentration of clonidine (max 30µgm). The highest level of mean sensory block achieved in their study were T 8 with two segment regression time of 126 min. As compared to present study (placebo group), their study has found higher level of block with more time for regression of block but the volume and the concentration of drug used in the study by

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Dobrydnjov et al was less as compared to present study.[15]

As compared to our study, Eisenach J C, et al has suggested duration of analgesia of 222 minutes with addition of inthrathecal clonidine (75 – 225 μgm). The present study has proven prolongation of analgesia 435 minutes with intrathecal 1 μ/ kg clonidine as compare to bupivacaine alone.[16]

In contrast to our study Saraswat et al, has found total analgesic time of 850.2 minutes with preoperative administration of 300 mg pregabalin in patients with below umbilical surgery. The main difference between present study with the study of Saraswat et al was that they have given higher doses of pregabalin (300 mg) but they have not used any adjuvant drug intrathecally. The mean duration of analgesic time was high with the use of single higher dose of pregabalin inspite of not using any spinal adjuvants in the study done by Saraswat et al.[17]

In contrast to our study Saraswat et al, has found total analgesic time of 850.2 minutes with preoperative administration of 300 mg pregabalin in patients with below umbilical surgery. The main difference between present study with the study of Saraswat et al was that they have given higher doses of pregabalin (300 mg) but they have not used any adjuvant drug intrathecally.

The mean duration of analgesic time was high with the use of single higher dose of pregabalin inspite of not using any spinal adjuvants in the study done by Saraswat et al.

The pregabalin group in the present study has shown earlier onset of complete motor blockade as compared to placebo group. The pregabalin group developed bromage score of one with in 5 minutes of administration of spinal anesthesia as compare to placebo group where it developed in 10 minutes.

The present study has also shown prolonged duration of motor blockade in pregabalin group as compared to placebo group. The time taken for bromage score of 6 has shown to be earlier in placebo group as compared to pregabalin group (30 minute earlier). The present study has shown 420 min of motor blockade in pregabalin group as compared to 390 min in placebo group.

Hema saxena et al, has shown onset of motor blockade with in 2.20 minutes with intrathecal clonidine of 37.5 μgm with 13.5 mg hyperbaric bupivacaine. Motor blockade lasted for 235 min with Intrathecal dose of 37.5μgm. As compared to present study this study has found earlier onset of completemotor blockade. The total duration of motor blockade was 235 minutes in their study as compared to present study where it was 390 min. The major difference between two studies were volume and dose of local anesthetics and clonidine used.

None of the previous studies has observed or assessed effect of pregabalin on motor blockade.

The present study has shown lower systolic blood pressure in pregabalin group as compared to placebo group at 2, 3, 4, and 15 minute.

The present study has not shown any significant difference in systolic blood pressure in between the two groups. The present study has shown that pregabalin as a premedicant has minimal effect on mean blood pressure and it has not caused any significant synergistic hypotensive action with intrathecal clonidine. The present study has not shown any significant drop in systolic blood pressure with the use of 1μgm/kg of clonidine in comparison to other studies where they have shown hypotensive effect of higher dose of intrathecal clonidine as adjuvant.

Sahu et al, has also not shown any significant difference in blood pressure in between pregabalin and placebo group inspite of using double dose of pregabalin (300mg) preoperatively. The main difference in their study with the present study was that they have not used inthecal clonidine as adjuvant.[18]

The present study has shown that pregabalin group has higher sedation score as compared to placebo group in intra and postoperative period as compared to placebo group. Similar effect on sedation was seen by other studies also. In the present study there was no use of perioperative anxiolytic or sedative agent. The present study has shown that the use of pregabalin as a premedicant has reduced the use of preoperative anxiolytic and intra or postoperative sedative agents. Similar results was shown by previous studies also in terms of effect of pregabalin on somnolence score.

The present study has shown no use of perioperative anxiolytic and sedative agent even in placebo group except one patient who has shown somnolence score of + 1(restless) in the placebo group. Similar effect of intrathecal clonidine on somnolence was seen with previous studies. Postoperative nausea vomiting was present in only two patients one in each group. One patient from pregabalin group required bladder catherization following urinary retention. No other side effects such as ataxia, vertigo, visual disturbances and headache were seen in the present study in the both the groups.

The limitation of current study design is that single dose of pregabalin has been used. The half life of pregabalin is 5 to 7 hrs and conclusions about the optimal dose and duration of the treatment can not be made. The results of this study suggest that post operative pain relief and quality of analgesia was better in patients who received pregabalin as a premedicant, in comparison to people who received no such medication.

In conclusion, a 150 mg dose of pregabalin as a premedicant provides better pain control than placebo, and reduces the time for first demand of rescue analgesia in patients undergoing surgeries below the level of umbilicus.

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CONCLUSION

150 mg dose of pregabalin as a premedicant provides better pain control than placebo, and reduces the time for first demand of rescue analgesia in patients undergoing surgeries below the level of umbilicus.

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