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EFFECT OF PRE-OPERATIVE ORAL CLONIDINE VERSUS PREGABALIN ON POST-OPERATIVE ANALGESIA AFTER SUB-ARACHNOID REGIONAL ANAESTHESIA: A COMPARATIVE RANDOMISED DOUBLE BLIND CONTROLLED STUDY.

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ABSTRACT **Background:** Pain is a distressing feeling often caused by intense or damaging stimuli to tissue. Almost all the surgical procedures induce acute pain. Delaying the onset of post-operative pain by using various adjuvants during sub-arachnoid block and hence decreasing post-operative analgesic requirement are being used. The aim of our study was to evaluate the duration of analgesia with oral pregabalin and oral clonidine after sub-arachnoid block and number of times rescue analgesia used during the first 24 hours after surgery. **Patients and Methods:** This prospective, randomised study registered in Clinical Trials Registry of India (CTRI/2019/04/018641). We included 90 patients for the study in three groups of 30 each. Group A: received 150µg of oral clonidine, Group B: received 300 mg of oral pregabalin, Group C (placebo): received oral calcium tablet one hour prior to spinal anaesthesia. **Results:** Comparing the intensity of post-operative pain through VAS score, p Value between oral clonidine and oral calcium group <0.05. p value between Pregabalin and oral calcium group <0.05. p value between the VAS score of pregabalin and clonidine group: 0 h p = 0.0013, 6th h; p = 0.0001, 1st h ; p=0.0001, 12th h; p=0.0001, 2nd h; p=0.507, 24th h, p=0.0001, 4th h; p=0.0824. Beyond 6th of observation the VAS scores were lower in the Pregabalin group. **Conclusion:** Oral pregabalin in the dose of 300 mg prolonged the duration of spinal analgesia and provided better post-operative analgesia, less analgesic requirement and less sedation than oral clonidine in the dose of 150 µg in patients receiving spinal anaesthesia.

KEYWORDS : Clonidine, Pregabalin, Spinal Anaesthesia

INTRODUCTION

Pain is a distressing feeling often caused by intense or damaging stimuli to tissue. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[1] Almost all the surgical procedures induce acute pain. In order to return back soon to normal physiological function and to prevent development of chronic pain adequate pain relief must be done.

Opioids, Non-steroidal Anti-inflammatory Drugs (NSAIDS), regional techniques have remained the traditional modes of pain relief for long and continues to be the same. These techniques have complications of their own. When given at high doses opioids may lead to increased incidence of complications like respiratory depression, sedation, vomiting, constipation, pruritus, immune dysfunction and urinary retention. [2] Regional techniques require additional intervention and expertise along with potential adverse effects and drug toxicity. Hence the search for an ideal analgesic, for post-operative pain control, with minimal adverse effects and with anxiolytic properties.

Delaying the onset of post-operative pain by using various adjuvants during sub-arachnoid block and hence decreasing post-operative analgesic requirement are being used. [3-5] Pregabalin is an γ-amino butyric acid analog that binds to the α2-δ subunit of presynaptic voltage-gated calcium channels. Pregabalin has been shown to be effective in neuropathic pain, incisional and inflammatory injury. [6] Depolarisation-induced calcium influx at nerve terminal is reduced and reduction of several excitatory neurotransmitters. Pre-operative oral pregabalin administration has been reported to reduce acute postoperative pain and prolong the duration of anaesthesia produced by single-injection peripheral nerve blockade. [7]

Clonidine is a selective partial alpha2 receptor agonist, which has sedative and anti-nociceptive properties. Oral clonidine administration results in dose-dependent analgesia, sedation, and hemodynamic depression. The aim of our study was to evaluate the duration of analgesia with oral pregabalin and oral clonidine after sub-arachnoid block and number of times rescue analgesia used during the first 24 hours after surgery. We also studied the adverse effects of the study drugs like hypotension and bradycardia.

MATERIALS AND METHODS

This study was conducted after obtaining the ethical approval from the Institutional Ethical Committee (IEC/861/ACAD dated 25.07.2017) for a period of two years (January 2018 to December 2019). The trial was registered, prior to first patient enrolment, with Clinical Trial Registry–India [ctri.nic.in] vide registration number CTRI/2019/04/018641, Principal Investigator: Navin Kumar, Date of registration: 16-04-2019. The study was conducted at Indira Gandhi Institute of Medical Sciences, Patna India. Written informed consent was obtained from all the patients before enrolling them for the study. A total of ninety patients in the age group 18 to 60 years of American Society of Anaesthesiologists (ASA) - physical status I and II undergoing elective below umbilical surgery were selected for the study. Power analysis based on standard deviation data from previously published reports a group size of 30 was determined. [8] Patients with known contraindication to spinal anaesthesia and sensitivity to clonidine, pregabalin or bupivacaine and patients on concomitant analgesics or sedative medications were excluded from the study. Preoperative clinical evaluation was done for all patients and the relevant laboratory investigations were obtained for each one of them. The selected patients were randomly allocated in to three groups of each based on a computer generated randomization table with thirty patients in each group. Each group was given the study drug orally 1 h before the procedure in the following manner: Group A: received 150µg of oral clonidine, Group B: received 300 mg of oral pregabalin, Group C (placebo): received oral calcium tablet.

METHOD OF STUDY

In the operating room all the multi parameter monitoring including Heart Rate (HR), Non-Invasive Blood Pressure (NIBP), Oxygen Saturation (SpO2), and Temperature (T) probe were attached to the patient. A baseline HR, BP and SpO2 were recorded. Intravenous (IV) access was established with 18G cannula and fluids started at the rate of 10 ml kg^{-1} over 30 minutes and then at 5 ml kg^{-1} hr^{-1} for the rest of intra operative period. Subarachnoid block was given in the sitting position through midline approach at L3 – L4 intervertebral space using 26G spinal needle and 2.5 ml to 3 ml of 0.5% hyperbaric bupivacaine was given. Patient's position was kept supine after intrathecal injection. After assessing with hypodermic needle and achieving the sensory block up to T10 dermatome level and motor block of 3 on Bromage scale surgery was allowed to begin.

Intraoperative hypotension (defined by a decrease in MAP below 20% of baseline or systolic pressure ≤90 mmHg) was treated with intravenous ephedrine 5 mg and additional lactated Ringer's solution (200 mL over a 5 min period). Bradycardia (HR≤50 beats/min) was treated with intravenous atropine 0.3mg. No sedatives or analgesics were given during the intra-operative period. Intensity of pain was measured in the post-operative period on a 10-point visual analogue scale (VAS) at end of operation and then 1, 2, 4, 6, 12 and 24 h after the operation.

STATISTICALANALYSIS

Data were recorded in a Microsoft excel spread sheet and analysed using Statistical Package for the Social Sciences (SPSS Inc.; Version 23.0., Chicago, IL, USA). Quantitative data were expressed as means ± SD while qualitative data were expressed as numbers and percentages [%]. Student's 't' test was used to test significance of difference for quantitative variables (HR, BP) that follow normal distribution and chi square was used to test the significance of difference for qualitative variables. The significance of change in VAS score from first to final assessment was evaluated by repeated measures ANOVA. A probability value (p-value) <0.05 was considered statistically significant.

RESULTS

In this study 94 patients were assessed for eligibility, of which 3 patients were excluded for not giving consent and 1 patient was excluded for not meeting the inclusion criteria.

The demographic characteristics of patients in both the groups were comparable with respect to age, weight, sex, height and ASA status with no significant differences (p > 0.05). Table1.

The mean time to duration of surgery in Group A was 83.15±0.61, Group B was 87.33±1.23 and Group C it was 85.32±1.57min. On comparing the value of duration of surgery in group A, group B & Group C the significant difference was not found p Value = 0.847 (p > 0.05). Table2.

Comparing the intensity of post-operative pain through VAS score, p Value between oral clonidine and oral calcium group <0.05. p value between Pregabalin and oral calcium group <0.05. p value between the VAS score of pregabalin and clonidine group: 0 h p = 0.0013, 6th h; p = 0.0001, 1st h ; p=0.0001, 12th h; p=0.0001, 2nd h; p=0.507, 24th h, p=0.0001, 4th h; p=0.0824. Beyond 6th of observation the VAS scores were lower in the Pregabalin group. Table3.

Hemodynamic parameters i.e. heart rate (HR) and mean arterial pressure (MAP) were compared in both the groups, HR at 15 minutes and MAP at 5 minutes after spinal anaesthesia. The baseline values were comparable in both the groups and remained so till spinal anaesthesia was given. At 15 minutes, in group A the heart rate was 75.23±6.7, Group B the heart rate was 74.17±8.06 and in Group C was 76.1±3.52 beats per minute showing no significant difference among groups. The heart rate gradually returned to around baseline at 90 minutes, mean heart rate was 71.67±1.78 in Group A, 72.07±1.76 in Group B and 72.23±1.88 in Group C. Figure1.

Mean arterial blood pressure (MABP) were comparable in all the three groups. The mean basal MABP in Group A was 95.57±2.73, Group B was 95.27±2.70 and Group C was 95.97±2.61. MABP decreased at 5 & 15 minutes interval in three groups. The downward trend continued to 5 & 15 minutes to 90 minutes in three groups. Figure2.

No incidence of respiratory depression or dry mouth in the study groups A and B was observed. Episodes of post-operative nausea and vomiting were comparable in all the three groups and were not statistically significant.

Table1. Demographic profile of the participants. Data represented as Mean ± Standard Deviation.

Variables	Group A (n=30)	Group B (n=30)	Group C (n=30)	*p
GENDER (M/F)	18/12	21/9	17/13	0.203
AGE (YEARS)	42.92±13.38	40.70±13.13	36.83±11.51	0.135
Height (cm)	167.23±3.65	163.07±6.88	166.12±4.72	0.619
Weight (kg)	53.50±9.06	50.43±5.75	52.00±4.21	0.217

*Analyses done with Students t-test

Table 2. Duration of surgery (minutes). Test used to obtain p Value is t-test. Data in Mean± SD

	Group A	Group B	Group C	t-test	p-value
Duration of surgery (minutes)	83.15±0.61	87.33±1.23	85.32±1.57	1.1135	0.847

Table3. Comparison of post-operative visual analogue score. p value between oral clonidine and oral calcium group <0.05. p value between Pregabalin and oral calcium group <0.05. p value between the VAS score of pregabalin and clonidine group. 0 h p = 0.0013; 6th h p = 0.0001; 1st h p = 0.0001; 12th h p = 0.0001, 24th h p = 0.0001. Analyses done by ANOVA

Time (Hours)	Group A	Group B	Group C
0	0.51±0.50	0.38±0.55	0.78±0.73
1	2.58±0.56	2.55±0.85	4.87±1.09
2	5.33±0.93	4.93±1.33	6.46±0.62
4	4.51±0.99	4.09±0.86	4.46±0.79
6	4.83±0.52	4.12±0.83	5.28±0.77
12	5.61±0.80	3.52±0.89	6.58±1.12
24	4.52± 1.01	3.57±0.95	5.98±1.16

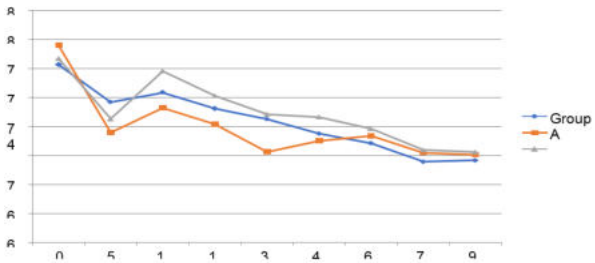

Figure1. Mean Heart Rate in study Groups at different time interval

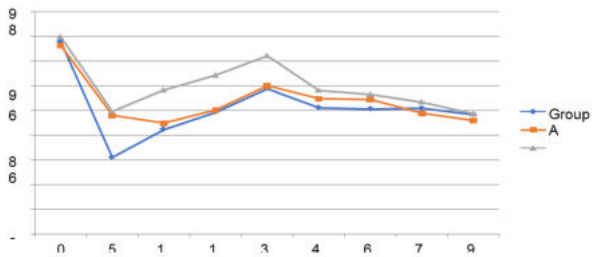

Figure2. MAP in study Groups at different time interval

DISCUSSION

Most important and most common complaint after operation is pain. In this study, 150 mcg oral clonidine and pregablin 300 mg was given 1.5 hours before spinal anaesthesia, which prolonged the duration of analgesia and maintained the VAS scores at 0, 1, 2, 4, 6, 12 and 24 h in the lower range in comparison with the placebo group (p < 0.05). Rescue analgesic doses required was less in the Group A and Group B than in the Group C (p< 0.05).

Clonidine is α2 adrenergic agonist that produces dose dependent analgesia at spinal and supraspinal sites. Oral clonidine is almost completely absorbed and peak plasma concentration is reached after 1-3 h of administration. It is highly lipid soluble, crosses the blood brain barrier easily. Clonidine inhibits neurotransmission in both A-delta and C fibres and potentiates inhibitory effect of the local anaesthetic on the C-fibre activity. Pregabalin is a GABA analog that binds to the α2-δ subunit of the pre-synaptic voltage-dependent calcium channels that are widely distributed throughout the central and peripheral nervous systems [9-10]It reduces the release of several neurotransmitters such as glutamate, norepinephrine, serotonin, dopamine and substance P.

Pregabalin is inactive at GABAA and GABAB receptors. Its elimination half-life is 5.5-6.7 h independent of dose and repeated administration. Side-effects of pregabalin include dizziness, somnolence, dry mouth etc.

We selected the dose of oral clonidine to be 150 mcg as the incidence of bradycardia and hypotension is more with higher doses during spinal anaesthesia. A test dose of 300 mg of pregabalin was based on the studies where such a dose produced no acute hemodynamic alterations

as well as sedation. [11]

Montazeri and Ghobadian found out that with oral clonidine in spinal anaesthesia, the mean duration of sensory and motor blockade was increased. [12] Liu et al., Ota et al. and Singh et al. observed that oral clonidine 150-200 mcg given 1-1.5 h before spinal anaesthesia caused significant prolongation of sensory analgesia. [13,14]

Joleka et al. found that there was a decreased post-operative requirement of analgesics in pregabalin (300 mg) group compared with those in the diazepam (10 mg) group with increased incidence of dizziness and blurred vision in the pregabalin group. [15] We also found that pregabalin had less incidence of post-operative complications but we compared it with clonidine in place of diazepam.

In our study, mean duration of sensory analgesia in Group A (238.41 ± 7.32 min) and in Group B was (252.14 ± 5.02 min), which was statistically significant ($P < 0.05$). The VAS score at rest was significantly different between Group A and Group B during the observations made at 0, 1 h and thereafter most of the patients demanded a rescue analgesic. After giving the rescue analgesic the VAS score was significantly lower in Group B ($P < 0.001$) than Group A beyond 6 hour of observation in the post-operative period.

Khetarpal et al. in their study concluded that Pregabalin 300 mg and gabapentin 1200 mg significantly reduce the need of postoperative rescue analgesia, epidural top-ups, and increase the duration of postspinal anesthesia without altering hemodynamics with sedation as a major side effect. [16]

Bafna et al. also concluded in their study that preemptive use of gabapentin 600mg and pregabalin 150 mg orally significantly reduces the postoperative rescue analgesic requirement and increases the duration of postoperative analgesia in patients undergoing elective gynaecological surgeries under spinal anaesthesia. [17]

Kohli et al. conducted a randomized trial on patients undergoing hysterectomy under spinal anaesthesia and concluded that oral pregabalin provides immediate post-operative analgesia by prolonging the neuraxial block and reduces the frequency of administration of parenteral analgesics.[18] Our study also had the same result.

All these studies suggest that both clonidine and pregabalin prolonged the duration of sensory analgesia after spinal blockade and reduce the analgesic requirement on the post-operative period. Their finding corroborates with our study.

CONCLUSION

We conclude that oral pregabalin in the dose of 300 mg prolonged the duration of spinal analgesia and provided better post-operative analgesia, less analgesic requirement and less sedation than oral clonidine in the dose of 150 µg in patients receiving spinal anaesthesia.

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