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# "A RANDOMIZED CONTROLLED DOUBLE BLIND STUDY TO EVALUATE THE EFFICACY OF PROPHYLACTIC DOSE OF ORAL CLONIDINE VS ORAL TAPENTADOL FOR PERIOPERATIVE SHIVERING AND POST OPERATIVE ANALGESIA IN ELECTIVE INFRAUMBILICAL SURGERIES UNDER SPINAL ANAESTHESIA."

Anesthesiology

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## ABSTRACT

**AIM:** The aim of this study was to evaluate the efficacy, hemodynamic effects, complications and side effects of oral Clonidine as compared to oral Tapentadol for perioperative shivering and postoperative analgesia.

**MATERIAL AND METHODS:** Total 120 adult patients (randomly divided into three groups with 40 patients in each group) of either sex belonging to American Society of Anaesthesiologists (ASA) physical status I-II, aged 18 to 60 years, scheduled for elective infra umbilical surgeries. Group A : Oral Clonidine (100 mcg) 60 minutes prior to Subarachnoid block Bupivacaine hyperbaric 0.5% (12.5 mg). Group B : Oral Tapentadol (50 mg) 60 minutes prior to Subarachnoid block Bupivacaine hyperbaric 0.5% (12.5 mg). Group C : Oral Placebo 60 minutes prior to Subarachnoid block Bupivacaine hyperbaric 0.5% (12.5 mg). Data recordings were done for time to reach sensory and motor block, hemodynamic changes, shivering, duration of sensory and motor block and duration of postoperative analgesia.

**RESULTS:** Incidence of grade III shivering was less with addition of oral Clonidine (5%) and oral Tapentadol (10%) with intrathecal Bupivacaine as compared to oral placebo (20%) with intrathecal bupivacaine. Duration of analgesia (requirement for first analgesic dose) showed statistical difference between three groups ($P < 0.01$) [Group I - 341.75 ± 22.970 minutes, Group II - 301.5 ± 18.334 minutes and Group III - 273.75 ± 23.390 minutes]. Both Clonidine and Tapentadol increased post operative analgesic time and decreases incidence of shivering than control group without causing any side effects.

**CONCLUSION:** Oral Clonidine and oral Tapentadol increases the duration of analgesia and decreases incidence of shivering as compared to control group without increasing side effects or complications and hemodynamic changes. Overall Clonidine has better results as compared to Tapentadol and Placebo group.

## KEYWORDS

Clonidine, Tapentadol, Shivering, Postoperative analgesia, Spinal anaesthesia, Hyperbaric Bupivacaine.

## INTRODUCTION

Lower abdominal and lower limb surgeries may be performed under local, regional (spinal or epidural) or general anaesthesia, but neuraxial blockade is the preferred mode of anaesthesia. Shivering is known to be a frequent complication, reported in 40 to 70% of patients undergoing surgeries under regional anaesthesia[1,2]. Shivering is an involuntary, oscillatory muscular activity, due to physiological response to core hypothermia in an attempt to raise the metabolic heat production. Shivering is a potentially serious complication, resulting in :

- Increased metabolic rate,
- Increased oxygen consumption (up to 100-600%),
- Increased carbon dioxide ($CO_2$) production,
- Increased ventilation,
- Increased cardiac output,
- Adverse postoperative outcomes, such as increased surgical bleeding, increased wound pain, delayed wound healing and morbid cardiac events[3].
- Arterial hypoxemia, lactic acidosis, increased intraocular pressure (IOP), increased intracranial pressure (ICP) and interferes with pulse rate, blood pressure (BP) and electrocardiographic (ECG) monitoring.
- May be detrimental to the patient with low cardiorespiratory reserve.

There are various methods available to control shivering during spinal anaesthesia, which include non pharmacological methods and pharmacological methods using drugs which have anti-shivering properties.

Non Pharmacological methods include radiant heat warmers, warming the operation theatre, blankets, warm IV fluids. Non-pharmacological method using equipment to maintain normothermia are effective but may be expensive and are not practical in all settings.

Pharmacological methods using drugs like Pethidine, Tramadol, Doxapram, Ketanserin, Nefopam, Granisetron, Alfentanyl, Butorphanol etc[4,5].

**Tapentadol** provides analgesia through two mechanisms of action, μ opioid receptor agonism and Noradrenaline reuptake inhibition. It binds to μ opioid receptor selectively, with ≥ ten times affinity as compared with delta- and kappa- opioid receptors. Noradrenaline reuptake inhibition increases levels of Noradrenaline, which in turn leads to analgesia through activation of inhibitory α-2 receptors. This dual mechanism of action contributes to its opioid sparing effects[6,7,8].

**Clonidine** is also a potent sedative and analgesic and can prevent post-operative shivering in intensive and post-operative care. Clonidine exerts its anti-shivering effects at three levels: Hypothalamus, Locus Coeruleus and Spinal cord. At the Hypothalamic level, it decreases thermoregulatory threshold for vasoconstriction and shivering, because hypothalamus has high density of α2 adenoceptors and hence is effective in treating the established post-anaesthetic shivering[9,10]. It also reduces spontaneous firing in Locus Coeruleus — a pro-shivering centre in Pons. At the Spinal Cord level, it activates the α2 adrenoreceptors and release of Dynorphine, Norepinephrine and Acetylcholine.

**Bupivacaine** is available as racemic mixture of R- & S- enantiomers for clinical use. Mechanism of action of bupivacaine is similar to that any other local anaesthetics as follows:

a. Local anaesthetics in the cationic form act on the receptors within the sodium channels, on the cell membrane and block it. The local anaesthetic can reach the sodium channel either via the lipophilic pathway directly across the lipid membrane, or via the axoplasmic opening. This mechanism accounts for 90% of the nerve blocking

effects of amide local anaesthetics.

b. The second mechanism of action is by membrane expansion. This is a nonspecific action in contrast to the more specific drug-receptor interaction.

## MATERIAL AND METHODS

After approval from ethical committee, the study was conducted at S.R.N. Hospital, associated to Moti Lal Nehru Medical College, Prayagraj (formerly Allahabad) over a period of one year. During pre-anaesthetic visit, a complete pre-anaesthetic checkup was done. All patients were visited one day before surgery and all patients were explained the purpose of the study along with the procedure and thereafter a valid, informed and written consent was taken from all the patients undergoing study. This prospective study was conducted on 120 adult patients (40 patients in each group) of either sex belonging to American Society of Anaesthesiologists (ASA) physical status I-II, aged 18 to 60 years, scheduled for elective infra umbilical surgeries. Patients who refused, ASA Class III & IV, age < 18 or > 60 yrs, having BMI >35 kg/$m^2$, patients with cardiovascular disease, hypotension and hypertension, compromised reserves of respiratory system, endocrine disease, metabolic disorders, hepatic or renal impairment, prior history of allergy to any of the drugs used in this study, or drug abuse, use of analgesics or central nervous system depressants over the previous 24 hrs, neurologic, psychiatric disease, contraindication to regional anaesthesia, Emergency cases and patients for lower segment caesarean section were excluded from the study.

After randomization and blinding, patients allocated into one of the following groups :

**Group A :** Patients who received single dose of Tab. Clonidine (100 µg) orally 60 minutes prior to Subarachnoid Block alone with Bupivacaine (0.5% hyperbaric – 12.5 mg).

**Group B :** Patients who received single dose of Tab. Tapentadol (50 mg) orally 60 minutes prior to Subarachnoid Block alone with Bupivacaine (0.5% hyperbaric – 12.5 mg).

**Group C :** Patients who received single dose of Tab. Placebo orally 60 minutes prior to Subarachnoid Block alone with Bupivacaine (0.5% hyperbaric – 12.5 mg).

Patients were randomly allocated into three groups, each receiving a sealed envelope of an oral formulation 60 minutes prior to the subarachnoid block.

On arrival in operation theatre, venous cannulation was done and intravenous line was secured. In the operation theatre continuous ECG monitoring, pulse oximetry (SPO2), non invasive blood pressure and Skin temperature (axillary temperature) were instituted and initiated monitoring.

Under all aseptic precautions, Subarachnoid block was given with Bupivacaine (0.5% hyperbaric – 12.5 mg) administered using 25 gauge Quincke's spinal needle at L2-3 and L3-4 interspace through midline approach in sitting position. Immediately, patients were turned supine following the block with 10° Trendelenburg position.

On completion of spinal injection, all patients were monitored for the following :

I). Heart rate, Oxygen saturation ($SPO_2$) and non-invasive blood pressure (mean arterial pressure) was measured at every 5 minutes for first 15 minutes and then every 15 minutes for the rest of surgery. Heart rate < 50 beats/min was considered bradycardia and treated with incremental doses of Inj. Atropine 0.4 mg I/V. A decrease in mean arterial pressure >20% of the baseline blood pressure is considered hypotension and treated with incremental doses of Inj. Mephentermine 6 mg I/V. Oxygen supplementation was given if oxygen saturation falls below 92%.

II). Baseline value for temperature is before subarachnoid bupivacaine was administered. Skin temperature recorded after every 5 minutes for first 15 minutes and then after every 15 minutes for the rest of the surgery. All operations performed in the operation theatre, which maintained at constant ambient temperature. No means of active warming used. Patients are covered with drapes but not actively warmed. Intravenous fluids administered at room temperature.

III). Grades of shivering recorded as per Wrench grading. Grading of shivering done as per Wrench[11] , which is as follows:

Grade 0: No shivering
Grade 1: One or more of the following:
Piloerection,
Peripheral vasoconstriction,
Peripheral cyanosis with, but without visible muscle activity

Grade 2: Visible muscle activity confined to one muscle group
Grade 3: Visible muscle activity in more than one muscle group
Grade 4: Gross muscle activity involving the whole body

Peri Operative Shivering checked as per Wrench grading and was given rescue drug with Inj. Pethidine 25 mg Intravenous bolus when shivering grade is ≥3 occured.

IV). Onset of sensory block was determined by the time from administration of drug to loss of pinprick sensation till $T_6$ level and the highest level of sensory block achieved was noted down (checked every 30 seconds from administration of drug till 15 minutes by loss of sharp sensation to atraumatic pinprick with a 26 gauge blunt tip needle in midclavicular line bilaterally).

V). Onset of motor block was determined by the time from administration of drug to motor block upto Bromage score 3 (checked every 30 seconds from administration of spinal anaesthetic drug till 15 minutes assessed by Modified Bromage Motor score.)

**MODIFIED BROMAGE SCALE[12] :**

| Score | Response |
|---|---|
| 0 | No motor block |
| 1 | Inability to raise extended leg able to move knees and feet. |
| 2 | Inability to raise extended leg and move knees, able to move feet |
| 3 | Complete block of motor limb. |

VI). Sedation score was evaluated using Ramsay sedation scale as mentioned below [13]:

1 - Anxious, agitated or restless or both.
2 - Co-operative, oriented and tranquil.
3 - Responding to commands only.
4 - Brisk response to light glabellar tap or loud auditory stimulus.
5 - Sluggish response to light glabellar tap or loud auditory stimulus.
6 - No response to light glabellar tap.

VII). Duration of sensory block was defined by the time taken by sensory block to regress from maximum sensory block level upto S2 dermatome level (assessed by pin prick method every 15 minutes following intrathecal injection).

VIII). Duration of motor block was defined by the time taken by motor block to recover upto Bromage score 1 (was assessed every 15 minutes following intrathecal solution injection).

IX). Post Operative analgesia checked with help of VAS (visual analogue scale) score and will give rescue analgesia with Inj. Diclofenac 75 mg Intravenous in 100 ml Normal Saline when VAS score is ≥4. Duration of analgesia [time from completion of administration of drug to first requirement of analgesic supplement (VAS ≥4). The VAS score of ≥4 constituted the end point of the study. Visual Analogue Score [14] (VAS- consisting of score 0 to 10 with score 0 – no pain to score 10 – worst possible pain) was explained to every patient preoperatively].

X). Complications, if any – Nausea, Vomiting, Bradycardia, Hypotension, Sedation, Pruritus, Shivering, Hypoxemia.

### Statistical Analysis

Statistical analysis was performed using Microsoft Excel 2010 and statistical software plug-ins. Continuous data was analyzed by ANOVA. Data are being represented as mean ± SD. $P < 0.05$ was considered statistically significant and $P < 0.001$ was considered statistically highly significant. All times were recorded from injection of the spinal anaesthetic.

## RESULTS

The three groups analysed were similar in terms of demographic profile including pateint's age, sex, weight and height with no statistically significant difference (Table 1).

The changes in hemodynamics were similar (P>0.05). Mean arterial pressure, heart rate and axillary temperature gradually fall in all three groups for first 15 to 30 minutes after spinal anaesthesia with slight increase towards the end of surgery as the effect of drugs begin to wear

down. (Table 2 – 4). There was occurrence of intraoperative hypotension and bradycardia in all the groups but the difference was statistically insignificant.

The mean time to reach sensory block till T6 dermatome (I - 4.975 ± 0.775 minutes, II - 5.137 ± 0.854 minutes, III - 5.175 ± 0.944 minutes), onset of motor block till Bromage scale 3 (I - 5.84 ± 0.806 minutes, II - 5.9 ± 0.885 minutes, III - 5.937 ± 0.968 minutes) and duration of surgery (I - 72.875 ± 14.671 minutes, II - 74.625 ± 13.839 minutes, III - 75.25 ± 15.930 minutes) respectively (Table 5), during intra-operative period between groups I, II & III were statistically insignificant ($p > 0.05$).

Duartion of sensory block (regression from maximum block height to S2 dermatome) is 127.875 ± 12.241 minutes for group I, 125.625 ± 12.567 minutes for group II, and 123.375 ± 12.929 minutes for group III and showed no statistical difference. Duration of motor block (recovery upto Bromage score 1) showed no statistical difference (Group I - 112.875 ± 10.183 minutes, Group II - 110.25 ± 11.544 minutes and Group III - 109.875 ± 10.947 minutes). Duration of analgesia (requirement for first analgesic dose) showed statistical difference between three groups ($P < 0.01$) [Group I - 341.75 ± 22.970 minutes, Group II - 301.5 ± 18.334 minutes and Group III - 273.75 ± 23.390 minutes] (Table 5).

There was no significant difference in shivering in group I as compared to group II and there was less shivering in group I & group II than group III as $P<0.05$ which was statistically significant. Incidence of Grade III shivering is least in group I (5%) as compared to group II (10%) and group III (20%). (Table 6)

There was more sedation in group I as compared to group II which was statistically ($P < 0.05$) significant. There was no difference in sedation between group II and group III. Sedation was not associated with any respiratory depression and all the patients were arousable.

## DISCUSSION

In our study, we found that oral clonidine (100 mcg) and oral tapentadol (50 mcg) 60 minutes prior to subarachnoid block is better than oral placebo for intraoperative shivering and prolongs postoperative analgesia period without causing any hemodynamic changes and adverse effects.

**Table 1: Demographic profile of patients (n = 120)**

| | Group I | Group II | Group III | P value (ANOVA) |
|---|---|---|---|---|
| Age (in years) | 39.5 ± 13.210 | 38.75 ± 13.796 | 37.175 ± 11.515 | 0.713 |
| Height (in cms) | 166.4 ± 7.252 | 167.125 ± 7.064 | 166.725 ± 6.625 | 0.898 |
| Weight (in kg) | 63.625 ± 9.742 | 64.825 ± 10.250 | 65.05 ± 9.768 | 0.788 |

**Table 2: Mean Heart Rate**

| Heart rate (per minute) | Group I (n=40) | Group II (n=40) | Group III (n=40) | P Value (ANOVA) |
|---|---|---|---|---|
| Baseline | 77.6 ± 9.673 | 78.1 ± 10.267 | 77.05 ± 6.563 | 0.872 |
| 5 minute | 74.05 ± 9.813 | 74.85 ± 10.915 | 74.1 ± 8.063 | 0.918 |
| 10 minute | 70.9 ± 10.396 | 71.45 ± 11.493 | 71.5 ± 9.508 | 0.961 |
| 15 minute | 69.8 ± 9.146 | 70.6 ± 11.306 | 70.65 ± 7.888 | 0.905 |
| 30 minute | 69.15 ± 6.852 | 70.55 ± 6.808 | 70.5 ± 4.568 | 0.517 |
| 45 minute | 71.4 ± 6.628 | 72.5 ± 6.879 | 72.75 ± 4.017 | 0.563 |
| 60 minute | 72.606 ± 7.026 | 74.324 ± 7.623 | 74.111 ± 4.274 | 0.436 |
| 75 minute | 72.666 ± 7.052 | 74.636 ± 8.973 | 74.916 ± 4.968 | 0.316 |
| 90 minute | 74.857 ± 7.104 | 77.142 ± 8.858 | 76.833 ± 5.149 | 0.309 |

**Table 3 : Mean Arterial Pressure (mm Hg) {MAP =DBP +1/3 (SBP – DBP)}**

| MAP (mm Hg) | Group I (n=40) | Group II (n=40) | Group III (n=40) | P Value (ANOVA) |
|---|---|---|---|---|
| Baseline | 92.575 ± 3.037 | 92.625 ± 2.647 | 93.075 ± 2.453 | 0.665 |
| 5 minute | 89.375 ± 2.733 | 89.4 ± 2.216 | 89.675 ± 2.268 | 0.827 |
| 10 minute | 85.275 ± 3.218 | 85.075 ± 2.324 | 86.1 ± 2.687 | 0.218 |
| 15 minute | 82.575 ± 3.781 | 83.15 ± 2.983 | 83.75 ± 3.143 | 0.290 |
| 30 minute | 81.8 ± 3.890 | 81.975 ± 2.796 | 82.7 ± 3.267 | 0.446 |
| 45 minute | 84.4 ± 3.028 | 85.05 ± 2.183 | 85.3 ± 2.821 | 0.310 |
| 60 minute | 86.272 ± 2.295 | 87.054 ± 1.597 | 87.111 ± 2.387 | 0.147 |
| 75 minute | 88 ± 2.121 | 88.454 ± 2.501 | 88.708 ± 2.493 | 0.405 |
| 90 minute | 89.714 ± 2.429 | 90.142 ± 2.911 | 90.333 ± 1.669 | 0.497 |

**Table 4: Axillary temperature (in Fahrenheit)**

| Axillary temperature (in Fahrenheit) | Group I (n=40) | Group II (n=40) | Group III (n=40) | P Value (ANOVA) |
|---|---|---|---|---|
| Baseline | 98.48 ± 0.195 | 98.472 ± 0.196 | 98.435 ± 0.192 | 0.545 |
| 5 minute | 98.197 ± 0.232 | 98.157 ± 0.176 | 98.107 ± 0.167 | 0.119 |
| 10 minute | 97.845 ± 0.312 | 97.792 ± 0.245 | 97.732 ± 0.205 | 0.151 |
| 15 minute | 97.452 ± 0.418 | 97.365 ± 0.330 | 97.3 ± 0.297 | 0.158 |
| 30 minute | 97.162 ± 0.574 | 97.155 ± 0.552 | 97.127 ± 0.415 | 0.950 |
| 45 minute | 97.127 ± 0.615 | 97.167 ± 0.545 | 97.21 ± 0.347 | 0.772 |
| 60 minute | 97.342 ± 0.590 | 97.291 ± 0.528 | 97.238 ± 0.339 | 0.647 |
| 75 minute | 97.523 ± 0.569 | 97.345 ± 0.555 | 97.333 ± 0.304 | 0.158 |
| 90 minute | 97.585 ± 0.484 | 97.5 ± 0.529 | 97.5 ± 0.262 | 0.610 |

**Table 5**

| Parameter | Group I (n = 40) | Group II (n = 40) | Group III (n = 40) | P value |
|---|---|---|---|---|
| TTHSB (min) | 4.975 ± 0.775 | 5.137 ± 0.854 | 5.175 ± 0.944 | 0.377*, 0.850**, 0.303*** |
| TTBS3 (min) | 5.84 ± 0.806 | 5.9 ± 0.885 | 5.937 ± 0.968 | 0.752*, 0.858**, 0.627*** |
| TDOS (min) | 72.875 ± 14.671 | 74.625 ± 13.839 | 75.25 ± 15.930 | 0.584*, 0.851**, 0.490*** |
| DOSB (min) | 127.875 ± 12.241 | 125.625 ± 12.567 | 123.375 ± 12.929 | 0.419*, 0.432**, 0.114*** |
| DOMB (min) | 112.875 ± 10.183 | 110.25 ± 11.544 | 109.875 ± 10.947 | 0.284*, 0.881**, 0.208*** |
| DOA (min) | 341.75 ± 22.970 | 301.5 ± 18.334 | 273.75 ± 23.390 | 0.0001*, 0.0001**, 0.0001*** |

*Group I vs II, **Group II vs III, ***Group I vs III.

Abbreviation : TTHSB–Time to highest sensory block (T6), TTBS3-Time to Bromage scale 3, TDOS–Total duration of surgery, DOSB – Duration of sensory block, DOMB – Duration of motor block, DOA–Duration of Analgesia.

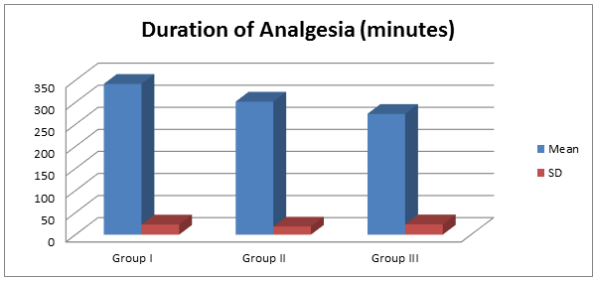
**Table 6: Comparison of shivering grades in three groups**

| N = 40 | Group I | Group II | Group III | P value (ANOVA) |
|---|---|---|---|---|
| Mean ± SD | 0.775 ± 0.861 | 0.975 ± 1.025 | 1.475 ± 1.061 | 0.347*(NS), 0.035**(S), 0.001***(HS) |
| Range (grades of shivering) | 0-3 | 0-3 | 0-3 | |
| Incidence of grade III shivering | 2 (5%) | 4 (10%) | 8 (20%) | |

*Group I vs II, **Group II vs III, ***Group I vs III.

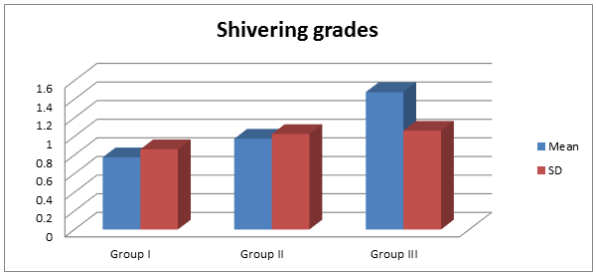
S – Significant, NS – Non Significant, HS – Highly Significant

**Bar Diagram 1 - Comparison of duration of analgesia (minutes) between three Groups (Table 5)**




- SD – Standard Deviation

**Bar Diagram 2: Distribution of Shivering grades in three groups (Table 6)**




- SD – Standard Deviation

In the study conducted by Buggy D et al, Clonidine 150 mcg iv at induction of anaesthesia reduces the incidence of shivering and patient's subjective perception of cold on emergence from general anaesthesia. Another study conducted by Mao CC et al, showed incidence of post-spinal shivering after oral clonidine vs placebo as a premedication, which was graded as none, mild, moderate, and severe, showed statistically significant differences ($p < 0.05$) between clonidine 150 micrograms and placebo (83% vs. 42%, 10% vs. 6%, 10% vs. 19%, 0% vs. 33%, respectively) during the 30 min immediately after spinal anesthesia. Tewari A., et al conducted study to compare the efficacy of prophylactic dose of oral clonidine 150 mcg, vs oral tramadol 50 mg vs oral starch tablet in geriatric male patients scheduled for elective TURP under SAB. In Group I (clonidine), in 95% patients shivering not occurred. In Group II (Tramadol), in 92.5% patients shivering not occurred. In the group III (Starch), 60% patients did not experience shivering. The results of our study were consistent with these above mentioned studies as there was no significant difference in shivering in group I as compared to group II and there was less shivering in group I & group II than group III as $P<0.05$ which was statistically significant. Incidence of Grade III shivering is least in group I (5%) as compared to group II (10%) and group III (20%).

Singh S., et al evaluated the effects of oral clonidine premedication on hemodynamic response and modulation of post-operative pain in patients undergoing laparoscopic surgeries. The administration of oral clonidine 150 $\mu$g results in improved perioperative hemodynamic stability and reduction in anaesthetic requirements. The another study conducted by Yadav G., et al to assess the preemptive role of tapentadol in reducing postoperative analgesic requirements after laparoscopic cholecystectomy. The time to first analgesia in post anesthesia care unit (PACU) was significantly longer in Group A (Tapentadol) as compared to Group B (control) ($P < 0.001$). Our study showed duration of analgesia (requirement for first analgesic dose) statistical difference between three groups ($P <0.01$) [Group I - 341.75 ± 22.970 minutes, Group II - 301.5 ± 18.334 minutes and Group III - 273.75 ± 23.390 minutes]. Both Clonidine and Tapentadol increased post operative analgesic time than control group but maximum increased with Clonidine.

## CONCLUSION

Conclusion of our study is that oral Clonidine and oral Tapentadol increases the duration of analgesia (time to first rescue analgesia) and decreases incidence of shivering as compared to control group without increasing side effects or complications and hemodynamic changes. Overall Clonidine has better results than Tapentadol and control group.

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