

## Original Research Article

# Clinical benefits of preemptive oral clonidine versus oral tramadol for abdominal hysterectomy conducted under subarachnoid block with 0.5% hyperbaric bupivacaine: a comparative evaluation

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## ABSTRACT

**Background:** Neuraxial techniques possess many benefits for elective abdominal hysterectomy due to profound surgical anesthesia and muscle relaxation. The present study was aimed to compare the clinical benefits of preemptive oral clonidine with oral tramadol for abdominal hysterectomy conducted under subarachnoid block with 0.5% hyperbaric bupivacaine.

**Methods:** Sixty adult female patients of American Society of Anaesthesiologists (ASA) physical status I and II, aged 42 to 65 years, were randomized into two groups of 30 patients each to receive either oral clonidine, 100 µg (Group C) or oral tramadol 50 mg tramadol (Group T), 90 min before initiation of subarachnoid block with 3.5 mL of 0.5% hyperbaric bupivacaine. Intraoperative hemodynamic changes, duration of analgesia and incidence of shivering were recorded as primary end points. Drug related effects of pruritus, sedation, nausea, vomiting, and respiratory depression were recorded as secondary outcomes.

**Results:** The onset of sensory and motor block was comparable between the groups but the time to two dermatome regression were prolonged in patients of Group C with statistical significant difference ( $p=0.05$ ). Duration of analgesia was also enhanced in patients of Group C ( $268.27 \pm 12.18$  min versus  $223.15 \pm 14.31$  min in Group T) with statistically highly significant difference ( $p=0.000$ ). The incidence of shivering was lower in the patients of clonidine group. The heart rate was lower in patients of clonidine throughout intraoperative period and no incidence of bradycardia, hypotension or sedation occurred in any patient.

**Conclusions:** Both drugs showed clinical benefits as pre-emptive oral medication for abdominal hysterectomy conducted under subarachnoid block but oral clonidine (100 µg) proved to be more beneficial.

**Keywords:** Abdominal hysterectomy, Clonidine, Tramadol, Subarachnoid Block, Shivering

## INTRODUCTION

Subarachnoid block is commonly used regional anesthetic technique for abdominal surgeries due to their

higher level of safety. It may be more useful in patients who suffer from co-morbidities of severe respiratory disease or a difficult airway. Spinal anesthesia covering the mid-thoracic level yields a contracted small intestine

to provide superior surgical conditions in combination with profound muscle relaxation of abdominal muscles.

Local anesthetics reversibly block the nerve conduction by blocking sodium and potassium ion channels in the nerve membrane. Blockade of neural transmission in the posterior nerve root fibres interrupts somatic and visceral sensation and blockade of anterior nerve root fibres prevents efferent motor and autonomic outflow. Thus local anesthetic progressively inhibits the transmission of autonomic, sensory and motor impulses, resulting in sympathetic blockade, analgesia and anesthesia.

Subarachnoid blockade with 0.5% hyperbaric bupivacaine provides sensory and motor blockade for surgeries lasting for about 2 hours. Several adjuvants such as opioids and alpha-2 agonists are used to enhance the onset and duration of spinal anesthesia, the surgical level of anesthesia, and postoperative analgesia.<sup>[1]</sup> Oral premedication with clonidine and tramadol may be advantageous for prolonging the duration of sensory analgesia, less hemodynamic changes and prevention from post spinal shivering.<sup>2,3</sup>

Clonidine is a centrally acting selective partial  $\alpha_2$  adrenergic agonist and acts on pre-junctional and post-junctional  $\alpha_2$  adrenoreceptors in the dorsal horn of spinal cord. It prolongs the duration of sensory and motor blockade by virtue of its ability to decrease sympathetic nervous system outflow, thus it may cause hypotension and bradycardia.<sup>4</sup> Additionally, clonidine has thermoregulatory effect and exerts its antishivering effect at the level of hypothalamus, locus coeruleus and spinal cord.<sup>5</sup>

Tramadol has  $\mu$  agonist activity as well as acts as inhibitor of serotonin and norepinephrine uptake at the synapse to produce the analgesic and antishivering effect. It also activates the monoaminergic receptors of the descending spinal cord, inhibiting pain pathway. Tramadol is mainly used as opioid analgesic but its role as an antishivering agent is well established.<sup>6,7</sup>

The present prospective randomized double blind study was aimed to compare the clinical benefits of preemptive oral clonidine with oral tramadol on subarachnoid block characteristics, post spinal shivering and intraoperative hemodynamic changes during abdominal hysterectomy, conducted under subarachnoid block with 0.5% hyperbaric bupivacaine.

## METHODS

After approval from Institutional Ethical and Research Committee and written informed consent, 60 adult female patients of American Society of Anaesthesiologists (ASA) physical status I and II, aged 42 to 65 years, weighing 55-85 kg with height of 150-175 cm, scheduled for elective abdominal hysterectomy conducted under

subarachnoid block, were enrolled for present prospective randomized double blind study.

The patients with history of severe cardiac or pulmonary disease, poorly controlled hypertension, morbidly obese patients, neurologic disease, hepatic or renal dysfunction, metabolic disorders, atrioventricular block, and deformity of spinal column, bleeding or coagulation disorder, known sensitivity to clonidine or tramadol, autonomic neuropathy, or using any drug that modifies pain perception or infection at site of lumbar puncture were excluded from study. Refusal to technique and uncooperative patients were also excluded from study. All patients were admitted prior to day of surgery and 6 hours fasting was ensured before the surgery.

All selected sixty patients were randomized into two equal groups of 30 patients each according to computer generated random number, each receiving a sealed envelope of an oral medication. Patients of Group C were given oral Clonidine (100  $\mu$ g) and patients of Group T were given Tramadol (50 mg), 90 minutes before schedule time of surgery. Study medication was given by the resident who was neither aware of study protocol nor further involved for data collection. Anaesthesiologist recording the data and caring for the patient was also unaware of study protocol to ensure the blindness of study.

After arrival in the operation theatre, standard monitors for heart rate, electrocardiogram, pulse oximetry and non-invasive blood pressure were attached and intravenous line with 18 G intracath was secured. All patients were preloaded with lactate Ringer solution at rate of 10 mL/kg over 15 minutes, before initiation of subarachnoid block.

The subarachnoid block was carried out under all strict aseptic precaution in sitting position by midline approach at L2-3 or L3-4 intervertebral space using the 25 G Quincke's spinal needle with 3.5 ml of 0.5% hyperbaric bupivacaine and they were immediately aligned into a supine position with 10° Trendelenberg tilt of table to achieve the adequate level of surgical anesthesia. Patients were supplemented with 100% oxygen at the rate of 4L/min via venti face mask.

### *Subarachnoid block characteristics*

The sensory and motor block characteristics were assessed at 2 minute interval till the surgical anesthesia was achieved. The segmental level of sensory block was assessed by pin prick method bilaterally along the mid clavicular line using short bevelled 26 G hypodermic needle. The motor block of the lower extremities was evaluated bilaterally by modified Bromage Scale (0-3): 0 = full movement and able to raise straight leg against resistance; 1= unable to raise extended leg at the hip but able to flex knee; 2= unable to flex the knee but able to

move ankle joint; 3= unable to move hip, knee or ankle (no motor activity).

All time intervals were calculated from the time of end of intrathecal injection. The complete onset time of sensory blockade, maximum cephalic dermatome level, and time taken to two dermatome regression of sensory analgesia were recorded. Time taken to achieve complete motor blockade and total recovery time from motor blockade was also recorded. The surgical anesthesia was considered when T8 dermatome was anesthetized.

### ***Hemodynamic parameters***

The hemodynamic parameters of systemic arterial pressure, heart rate, pulse oximetry and electrocardiography (ECG) were recorded preoperatively and then at every 5 minute intervals after initiation of subarachnoid block, till end of surgery and followed by at every 15 minutes interval in postoperative room. For the present study, hypotension was defined as systolic blood pressure of less than 20% of base line value or less than 100 mm Hg. It was treated primarily by increasing the rate of intravenous fluid and additionally with bolus of mephenteramine 6 mg intravenously. Bradycardia was defined as heart rate less than 60 beats per minute and was treated with intravenous atropine 0.6 mg.

### ***Adverse events***

All patients were observed for shivering, pruritus, sedation, nausea, vomiting, respiratory depression (defined as respiratory rate less than 10 breaths/ minute), or any other adverse effects. Respiratory discomfort was managed by increasing the flow of oxygen. Nausea and vomiting was treated by intravenous ondansetron (4 mg).

### ***Postoperative care***

After the end of surgery, the patients were shifted to the recovery room and monitored for any changes in vital signs. The sensory and motor block levels were assessed at 30 minutes intervals until normal sensations were returned. Duration of sensory analgesia was taken from onset of spinal anesthesia to time of administration of first rescue analgesic, diclofenac sodium 75 mg, reflected on visual analogue scale (VAS >3), which is a continuous line between two endpoints of 0 to 10, where 0=no pain to 10=worst possible pain.

### ***Study population size and statistical analysis***

The sample size was calculated with standard computer programme which computed that approximately 23 to 25 patients should be included in each group in order to detect at least clinically significant difference of 30 min in mean duration of analgesia between the groups for type 1 error of 0.05 with power of 80% and 95% confidence limit. Assuming a 5% drop out rate, the final

sample size was set at 60 patients for better validation of results.

All data was tabulated and expressed as Mean  $\pm$  Standard Deviation (SD) considering the later as the best predictor for statistical analysis. Data was analyzed using Stat graphic centurion, version 16 (Stat point Technologies INC, Warrenton). The demographic data for categorical variables were compared using chi-square test and statistical significance in mean difference was done by using analysis of variance (ANOVA). A  $p < 0.05$  was considered to indicate statistical significance.

## **RESULTS**

The present study compared the clinical benefits of preemptive oral clonidine with oral tramadol for abdominal hysterectomy performed under subarachnoid block with 0.5% hyperbaric bupivacaine on 60 adult consenting female patients. There was no protocol deviation and study was successfully completed. Data of all patients were included for statistical analysis.

The demographic data for age, weight, height, BMI, American Society of Anaesthesiologist physical status, and duration of surgery were comparable between the groups (Table 1).

### ***Sensory blockade profile***

The mean time required to achieve complete sensory blockade, the time required to achieve Bromage score of 3 (no motor activity) and mean maximal cephalic dermatome level were comparable between the groups. Mean time for two segment regression was  $218.36 \pm 14.31$  min in patients of Group C and  $179.27 \pm 12.35$  min in patients of Group T. The duration of two segment regression varied significantly between the groups ( $p=0.05$ ).

Mean duration of sensory analgesia was  $268.27 \pm 12.18$  min in patients of Group C and  $223.15 \pm 14.31$  min with in patients of Group T with statistically significant difference ( $p=0.000$ ). Mean duration of complete motor block was  $196.53 \pm 19.32$  min in patients of Group C and  $146.50 \pm 18.06$  min in patients of Group T with statistically significant difference ( $p=0.05$ ) (Table 2). Rescue analgesia was not required in any patient till 3 hours after subarachnoid blockade.

### ***Hemodynamic profile***

The hemodynamic parameters of mean blood pressure, mean heart rate, respiratory rate and oxygen saturation at baseline were comparable. After 5 min of subarachnoid block (SAB), the mean heart rate and mean systolic blood pressure showed gradual decline in patients of both group until after 30 min of SAB. Later on, the mean systolic blood pressure became stable in patients of both groups and the difference between the groups was comparable (Table 3).

The heart rate was lower in patients of clonidine group throughout the study period when compared to tramadol group, but there was no incidence of bradycardia. There was insignificant intragroup variation with respect to

blood pressure, respiratory rate and peripheral oxygen saturation during intraoperative period and no patient require any medical intervention. All patients were calm and easily arousable.

**Table1: Demographic profile.**

Demographic data	Group C	Group T	P value
Age (year)	45.83±6.7	43.96±11.5	0.209
Weight (kg)	55.23±10.65	54.06±9.4	0.655
Height(cm)	164.6±5.37	162.2±6.58	0.128
BMI (kg/m <sup>2</sup> )	21.35 ± 2.51	20.47 ± 2.88	0.894
ASA(I/II)	21/9	22/8	0.640
Duration of abdominal hysterectomy (min)	127.14± 6.53	124.71±9.82	0.652

Data are expressed as Mean and Standard deviation (SD) or numbers.

**Table 2: Sensory and motor blockade profile.**

Parameter/ Groups	Group C	Group T	P value
Onset of complete sensory blockade (min)	3.49±1.06	3.57±1.78	0.394
Maximal cephalic dermatome level	7.1±1.06	7.6±1.58	0.157
Mean time of two segment regression(min)	218.36±14.31	179.27±12.35	0.05*
Duration of sensory analgesia (min)	268.27±12.18	223.15±14.31	0.000**
Onset of complete motor block (min)	4.84±3.23	5.15±2.06	0.711
Duration of motor blockade (min)	196.53±19.32	146.50±18.06	0.05*

Data are expressed as Mean and Standard deviation (SD); \*p<0.05 is statistically significant; \*\* p<0.001 is statistically highly significant.

**Table 3: Hemodynamic parameters of heart rate and systolic blood pressure.**

Parameters	Heart rate (beats/min)		SBP ( mm Hg)	
	Group C	Group T	Group C	Group T
Preoperative	97.3±8.16	104.5±3.95	135.2±1.92	129.5±3.97
5min after SAB	71.7±6.34	95.3±4.78	118.5±2.72	117.2±4.78
10 min	70.8±7.21	94.5±2.43	115.6±3.71	117.3±2.75
15 min	65.4±4.28	95.2±3.45	110.4±2.64	114.4±4.70
20 min	61.5±3.45	87.6±1.98	112.3±1.68	112.7±3.76
25 min	63.2±4.67	82.4±1.76	106.8±1.60	111.9±2.74
30 min	59.8±2.38	79.7±2.57	103.7±3.60	107.3±4.73
45 min	63.1±3.47	77.2±5.21	103.3±4.61	109.2±5.67
60 min	60.3±7.61	79.6±3.89	108.9±2.93	108.4±6.62
75 min	61.4±6.36	72.4±6.38	104.4±1.65	110.7±3.68
90 min	65.7±4.93	71.3±4.78	106.5±1.76	118.1±8.72
Postoperative	66.9±5.69	74.9±7.18	109.3±2.67	112.5±9.75

SAB- Subarachnoid blockade, SBP- systolic blood pressure, \*p value <0.05 significant.

### Adverse events

The incidence of shivering was significantly lower in the patients of Group C (4 patients) when compared to Group T (7 patients) at 30 min. Mild pruritus was observed in 5 patients of Group T which resolved by assurance. Three patients of Group T suffered from nausea and vomiting while none such episode occurred in patients of Group C.

None of the patient needed supplemented analgesia during surgery.

### DISCUSSION

Subarachnoid blockade is widely used as safe anesthetic technique and preferred for abdominal hysterectomy due to its rapid onset of surgical anesthesia and complete

muscular relaxation. It is beneficial in patients suffering from comorbid conditions such as respiratory diseases or anticipated difficult airway. The technique is simple, economical, and reproducible with reduction in the incidences of venous thrombosis.

The present study evaluated the clinical efficacy of preemptive oral clonidine and oral tramadol for abdominal hysterectomy performed under subarachnoid anesthesia with 17.5 mg 0.5% hyperbaric bupivacaine, proving their efficacy might incorporate the use of this enteral medication in future as oral tablets are economical when compared to their intravenous formulations.

The present study showed that prophylactic oral clonidine was clinically more beneficial than oral tramadol for enhancing the duration of analgesia and reducing the incidences of post spinal shivering, nausea and vomiting. The onset of sensory and motor blockade showed no significant difference between the groups. Intraoperative variation in systolic blood pressure, heart rate, respiratory rate and peripheral oxygen saturation were also comparable.

In the present study, 17.5 mg hyperbaric bupivacaine was used to establish the subarachnoid block because 10 mg or less hyperbaric bupivacaine carry a risk of inadequate block as proven by Pederson *et al* while generous dosages guaranteed the effective surgical anesthesia.<sup>8</sup>

The clonidine is centrally acting  $\alpha$ -2 adrenergic agonist and used in premedication for anxiolysis, sedation, analgesia, and to reduce sympathetic activity. It easily penetrates the blood-brain barrier to provide effective and prolonged duration of subarachnoid blockade, which may be due to synergism between bupivacaine and clonidine. Clonidine is known to induce bradycardia and hypotension however, in the present study the incidence of bradycardia and hypotension did not occur in any patient. Clonidine reduces the thermoregulatory threshold hence incidences of perioperative shivering.<sup>2,5</sup>

Tramadol is a  $\mu$ -receptor agonist opioid and exerts its affect by combining with opioid receptors in the dorsal horn of spinal cord with supraspinal spread to provide good perioperative analgesia.<sup>9</sup> It activates the monoaminergic receptors of the descending spinal cord inhibiting pain pathways as well as inhibit the uptake of adrenaline and serotonin at the synapse, thus extends the analgesic effect.<sup>7</sup>

In present study, the sensory blockade profile was significantly better in patients with clonidine when compared to tramadol and it is in concurrence with various other studies which also showed the enhanced duration of analgesia with clonidine.<sup>10,11</sup> The prolongation of the motor block may be the result of binding of  $\alpha$ 2 adrenoceptors agonists to the motor neurons in the dorsal horn. The complementary action of local anesthetics and  $\alpha$ 2 adrenoceptors agonists accounts for their profound analgesic properties.

In various studies, the prevalence of shivering in subarachnoid block was suggested as 40% to 70%. Hypothermia during central neuraxial block is common and rapid infusion of cold intravenous fluids can be involved for producing shivering.<sup>12</sup> Hypothermia causes bradycardia, reduced cardiac output and peripheral vasoconstriction. In a study by Wason *et al*, the prevalence of shivering was 54% in patients during neuraxial anesthesia.<sup>13</sup> Many other studies have shown that clonidine and tramadol can be effective in preventing the incidence, severity and duration of perioperative shivering and its adverse effects but not the subarachnoid block induced hypothermia.<sup>14,15</sup> Despite premedication with these drugs, it would still be essential to adopt measures to maintain normothermia. In the present study, all patients were draped with blanket and the temperature of intravenous fluids, medication, and operating room were controlled. In the present study, 4 patients of clonidine group and 7 patients of tramadol suffered mild shivering. The result of present study supports the results of other studies which showed that clonidine and tramadol are effective to prevent post spinal shivering.

Hemodynamic changes were comparable between the groups which could be due to adequate preloading prior to subarachnoid block. Bradycardia did not occur in either group reflecting the safety of low doses of oral premedicants. No significant changes in the respiratory rate and oxygen saturation were observed in patients of both the groups. All patients were calm and arousable. Tramadol is known to cause pruritus, nausea and vomiting. In the present study, the 5 patients of tramadol group suffered from pruritus and vomiting occurred in 3 patients. Patients of clonidine group were free from these adverse effects.

## CONCLUSION

Prophylactic oral clonidine (100  $\mu$ g) was clinically more beneficial than tramadol 50 mg for potentiating the subarachnoid block characteristics and enhancement of postoperative analgesia during abdominal hysterectomy. The incidences of shivering, hypotension or bradycardia were comparable and needed no medical intervention. All patients were calm and arousable.

Limitation of study was conducted on patients with stable cardiorespiratory status (ASA I and II).

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