Original Research Article

Indian Journal of Anesthesia and Analgesia
July – August 2020;7(4)
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.7420.22

Changes in Hemodynamic Parameters in Patients Undergoing TURP and TURBT Due to Additive Intrathecal Clonidine

Putta Vinod Kumar[1], Krishna Diddi[2], TVL Tanuja[3]

[1,2]Assistant Professor, Department of Anesthesiology, Government Medical College and General Hospital, Mahabubnagar, [3]Post Graduate, Department of Anesthesiology, Sri Venkateswara Medical College and Hospital, Tirupathi, Andhra Pradesh 517501, India.

How to cite this article:
Putta Vinod Kumar, Krishna Diddi, TVL Tanuja. Changes in Hemodynamic Parameters in Patients Undergoing TURP and TURBT Due to Additive Intrathecal Clonidine. Indian J Anesth Analg. 2020;7(4):1004–1010.

Abstract

Introduction: Clonidine has been used by anesthesiologists as an anesthetic adjunct to provide increased perioperative cardiovascular and sympathoadrenal stability, to enhance general and regional anesthesia, as well as sedation and analgesia.

Materials and Method: This randomized prospective double blind study conducted at MIOT hospitals, Chennai, from October 2014 – December 2015, evaluated the effective dose of clonidine with 10 mg of 0.5% heavy bupivacaine in 80 patients posted for these surgeries and also to find the effect of various doses of clonidine on various subarachnoid block characteristics. Patients of either physical status ASA 1 or ASA 2 admitted for elective TURP and TURBT.

Results: There were statistically significant differences in the heart rate between the groups from 30 min onwards but none of the patients in any group needed atropine to treat bradycardia (ie., heart rate did not fall below 60 beats per minute). There was a significant fall in MAP (mean arterial pressure) at 10-20 minutes in all the 4 groups following the subarachnoid block. The mean dose of ephedrine given was 10 mg in group NS, 10 mg in group BC25, 15 mg in group BC35 which was significant.

Conclusion: Addition of 35 mcg of clonidine to bupivacaine when compared to 25 mcg/15 mcg clonidine significantly prolongs the duration of analgesia without affecting the onset and maximum level achieved of sensory block.

Keywords: Hemodynamic parameters, intrathecal clonidine,TURP, TURBT.

Introduction

Clonidine was synthesized in 1962 as nasal decongestant, and marketed as antihypertensive in 1972. Bloor and Flacke in 1982 demonstrated in mongrel dogs that intravenous clonidine 5 and 20 μg/kg decreased halothane MAC by 42% and 48% respectively.[1] Since then, clonidine has been used by Anesthesiologists as an anesthetic adjunct to provide increased perioperative cardiovascular and sympathoadrenal stability, to enhance general and regional anesthesia, as well as sedation and analgesia.[2,3]

Transurethral resection of the prostate (TURP) are largely restricted to the geriatric population. They have a high incidence of anesthesia-related complications, especially hypotension increasing the risk of ischemia to various vital organs.[4] Bupivacaine, most commonly used the drug for subarachnoid block produces hypotension and bradycardia.[5] High doses of bupivacaine may lead to myocardial depression, heart blocks and dysrhythmias. The addition of certain adjuvants can counter balance these side effects of the subarachnoid block with bupivacaine. There

Corresponding Author: **Putta Vinod Kumar,** Assistant Professor, Department of Anesthesiology, Government Medical College and General Hospital, Mahabubnagar, India.
E-mail: assignmentandthesis@gmail.com

are a number of studies on the use of intrathecal clonidine or fentanyl with bupivacaine in various lower abdominal surgeries.[6–8]

Materials and Method

This randomized prospective double blind study conducted at MIOT hospitals, Chennai, from October 2014 – December 2015, evaluated the effective dose of clonidine with 10 mg of 0.5% heavy bupivacaine in 80 patients posted for these surgeries and also to find the effect of various doses of clonidine on various subarachnoid block characteristics. Patients of either physical status ASA 1 or ASA 2 admitted for elective TURP and TURBT.

Formula used for the sample size n:

$n = (Z\alpha_{/2} + Z\beta)^2 * 2 * \sigma^2 / d^2$,

where Zα /2 is the critical value of the Normal distribution at α/2 (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Zβ is the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value is 0.84), σ2 is the population variance, and d is the difference you would like to detect.

Patients of ASA physical status 1 and 2, were included in the study. while the patients of ASA physical status 3 and above, allergic to any of the study drugs, undergoing treatment with α2 agonists, patients refusing for the trial, coming with emergency bladder outlet obstruction, Patients with Absolute contraindication for spinal anesthesia-Raised ICT, Bleeding disorders, and Infection at the site, Neurological deficit were excluded from the study.

After institutional ethics committee approval and informed consent 80 patients were included in the study. Patients were randomized to one of the four groups according to a computer generated randomization list:

- Group BN: 10 mg (2 ml) 0.5% hyperbaric bupivacaine + normal saline (0.24 ml)
- Group BC15: 10 mg (2 ml) 0.5% hyperbaric bupivacaine + 15 μg clonidine (diluted with normal saline to 0.24 ml).
- Group BC25: 10 mg (2 ml) 0.5% hyperbaric bupivacaine + 25 μg clonidine (diluted with normal saline to 0.24 ml).
- Group BC35: 10 mg (2 ml) 0.5% hyperbaric bupivacaine + 35 μg clonidine

Routine preanesthetic check was done and advice regarding medications for associated disease was given. Each patient was advised to fast after 10 pm and diazepam [5-10 mg] given orally night before surgery and 2 hrs before surgery.

In the operating room standard monitors such as Electrocardiogram (ECG) Pulse oximeter (SpO_2) Noninvasive blood pressure (NIBP) were connected and the basal pulse rate and Blood Pressure were recorded.

Subarachnoid block was performed under aseptic conditions with patient in sitting position. All patients [i.e; patients in group BN BC15 BC25 BC35] received 2 ml bupivacaine(+additive normal saline/clonidine) intrathecally over 1 minute after ensuring free flow of cerebro spinal fluid (CSF). The patient was then positioned supine and the level of sensory and motor blockade were assessed. The cephalad spread of anesthesia and the degree of motor block was assessed every 5 min. The level of sensory block was assessed by pin prick using 25G needle. The onset of motor blockade noted as the time taken for loss of knee reflex. [Modified bromage score 3]. The maximum height of the blockade was determined by the sensory level achieved at 20 min.

Heart rates (HR), MAP, SpO_2 were monitored continuously and noted every 5 min. Bradycardia defined as heart rate <60 beats per minute (bpm) and was treated with IV atropine. Fall of Mean arterial pressure i.e., MAP <60 Millimeters of mercury (mm of hg) was treated with rapid infusion of IV fluids (normal saline/ringer lactate) at 10 ml/kg and IV ephedrine (3-6 mg boluses). All patients received oxygen by facemask at the rate of 6 L/min.

All patients were observed intraoperatively for any complaints of pain, discomfort, restlessness or for other symptoms or TURP syndrome. All patients were monitored in PACU after the Surgery for a period of 24 hr.

The severity of postoperative pain was assessed using 10 point visual analog scales every 30 min by postoperative ward nurses who were blinded to the study. Time for 1st analgesic requirement noted. Duration of pain relief = time from intrathecal injection to first analgesic request. Rescue analgesia (injection Diclofenac 1.5 mg/kg upto maximum of 75 mg) was administered when VAS score was ≥4 and when the patient complained of pain.

Any symptom of TURP Syndrome like restlessness was noted. Time for catheter sensation was noted. Urinary retention was defined as inability to void spontaneously by 8 hr postoperatively. Adverse effects were noted finally

Results

The mean age of patients(+SD) in group BN was 44.95+15.34 years compared to 47.15+15.15 years in group BC15, 45.10+14.46 years in group BC25 and 43.20+16.67 years in group BC35. The difference in age between the groups was not significant. The gender distribution was comparable between the groups.

The distribution of patients according to ASA physical status between the groups was also comparable. 7 patients in group BN, 7 patients in group BC15, 11 patients in group BC25 and 8 patients in group BC35 belonged to ASA physical status 2 and mainly had controlled essential hypertension.

The mean weight in kilograms of patients in group BN was 77.50±15 as compared to 72.50±8 in group BC15, 75.85±11.47 in group BC25 and 72.05±9.19 in group BC35. The difference in weight between the groups was not significant.

The duration of surgery between the 4 groups was of mean duration of 42.60±5.67 min in group BN, 46±6.58 mins in group BC15, 46.85±7 mins in group BC25 and 52±7.17 mins in group BC35 (Table and Fig. 1).

Heart Rate

The heart rate (mean+SD) was compared between the 4 groups. The baseline heart rate per minute was 82.95+7.17 in group BN, 86.80+5.83 in group BC15, 85.70+5.95 in group BC25 and 83.50+5.37 in group BC35 which was comparable. There was fall in the heart rate from baseline in all the groups. There were statistically significant differences in the heart rate between the groups from 30 min onwards but none of the patients in any group needed atropine to treat bradycardia (ie., heart rate did not fall below 60 beats per minute). (Table and Fig. 2).

Mean Arterial Pressure (MAP)

The mean MAP(mean arterial pressure) of all the 4 groups was compared the baseline MAP was 84.25±3.11 in group BN, 86.45±4.28 in group BC15. 85.7±5.54 in group BC25, 88.95±8.32 in group BC35 and were all comparable. There was a significant fall in MAP at 10-20 minutes in all the 4 groups following the subarachnoid block.

All the groups had a fall in the mean arterial pressure to less than 20% of the baseline after the subarachnoid block. The difference was statistically significant between the groups NS and BC35 (P=0.000). It was not statistically significant between the groups BC15 and BC25 and between BC25 and BC35.

On comparison of the MAP trends within each group a significant fall in MAP was observed starting from 5-10 min following administration of subarachnoid block. Subgroup analysis was done to determine the significant between the groups. A highly significant difference in MAP was observed between the group NS AND BC35 (P=0.000). There

Table 1: Demographic data

Parameters	Group BN	Group BC15	Group BC25	Group BC35	P Value
Age	44.95±15.34	47.15±15.15	45.10±14.46	43.20±16.67	NS
Gender (M/F)	2/10	2/10	2/10	2/10	NS
ASA (1/2)	13/7	13/7	9/11	12/8	NS
Weight	77.50±15	72.50±8	75.85±11.47	72.05±9.19	NS
Surgical duration (min)	42.60±5.67	46±6.58	46.85±7	52±7.17	0.000

P value<0.05 significant, NS: not significant.

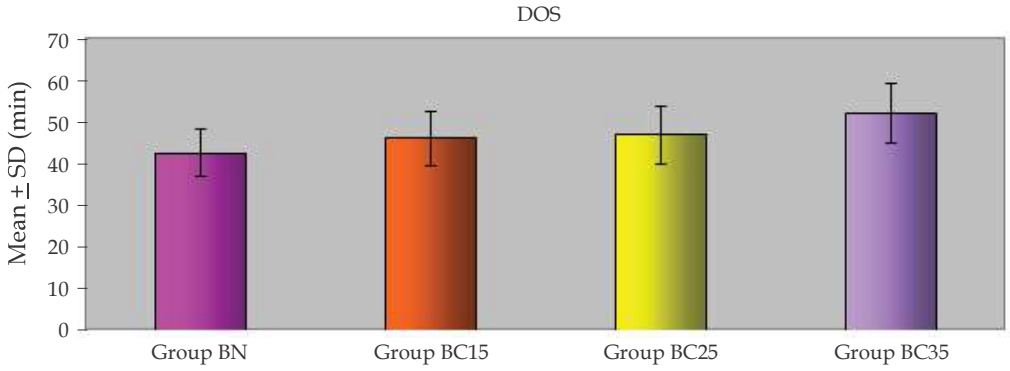

Fig. 1:

were no significant differences in MAP between BC15 and BC25 and between BC25 and BC35 groups. The mean arterial pressure (mean±SD) is shown in the Table 7 and displayed graphically in (Table and Fig. 3).

Ephedrine Requirement

3 Patients in group NS, 3 Patients in group BC25 and 2 patients in group BC 35 had a MAP <60 mm hg and received intravenous ephedrine boluses.

Table 2: Heart Rate

HR(min)	Group BN	Group BC15	Group BC25	Group BC35	P Value
0	82.96±7.17	86.8±5.83	85.7±5.95	83.5±5.37	0.162
5	84.7±9.14	85.2±6.05	84.6±5.64	82.15±5.78	0.495
10	83.9±11.08	84.4±5.67	83.6±6.17	80.45±6.12	0.350
15	80.45±9.85	82.55±6.6	83.05±5.84	78.7±5.4	0.202
20	81.65±12.51	80.95±6.57	81.65±5.91	78.05±5.88	0.458
25	81.05±11.58	79.6±6.36	80.45±5.6	80±5	0.488
30	82.1±9.41	79.7±6.35	79.75±6.66	75.55±6.27	0.046
35	81.15±9.37	79.2±6.31	79.2±6.37	75.4±7.14	0.106
40	81.53±9.53	79.39±7.08	77.75±6.73	74.45±6.21	0.035
45	82.25±10.41	80.69±6.48	78.13±6.83	74.28±6.23	0.027
50	79.6±8.32	80±6.48	75.4±7.74	73.75±6.37	0.121
55	84.5±13.43	80.57±6.65	78.8±4.32	75.25±6.6	0.208
60			82±1.73	75.5±4.5	0.042

P Value <0.05 significant, NS – Not significant.

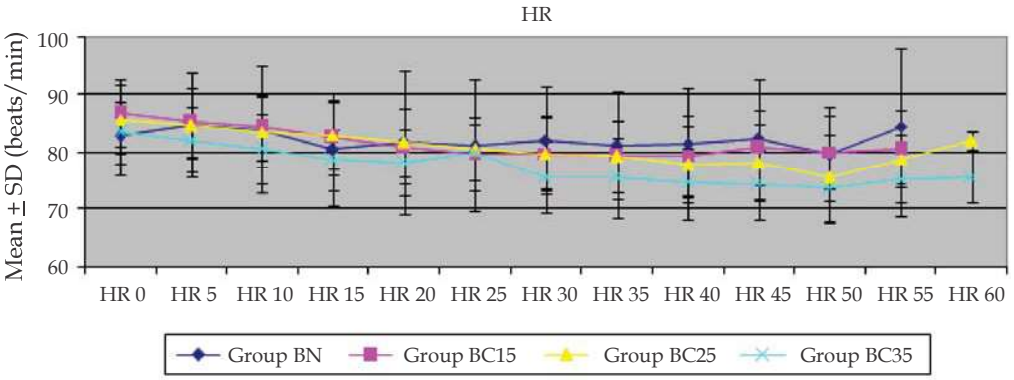

Fig. 2:

Table 3: Mean Arterial Pressure

MAP	Group BN	Group BC15	Group BC25	Group BC35	P Value
0	84.25±3.11	86.45±4.28	85.7±5.54	88.95±8.38	0.075
5	74.65±9.01	83.8±4.21	83.85±5.43	86±7.72	0.000
10	72.9±8.65	82.16±4.71	82±5.52	83.8±7.42	0.000
15	71.15±7.47	80.55±4.62	79.95±5.32	81.4±7.15	0.000
20	69.4±6.2	78.55±5.03	77.95±5.21	79±7.06	0.000
25	68.3±5.24	77.25±4.54	75.95±5.2	77.1±6.91	0.000
30	68.85±4.45	76.6±4.76	74.3±5.01	75.1±6.95	0.000
35	65.15±4.46	78.45±5.13	74.9±4.52	76.1±7.54	0.000
40	68.41±4.62	81.21±4.79	77.6±4.5	78±7.21	0.000
45	71.23±4.4	82.15±3.53	79.44±4.77	79.44±5.97	0.000
50	74.33±2.16	83.4±3.53	81.75±5.1	81.67±5.59	0.004
55	78±2.82	83±2.3	83±5.93	85.13±6.4	0.390
60			81.67±5.77	84±7	0.679

P Value <0.05 significant, NS – Not significant.

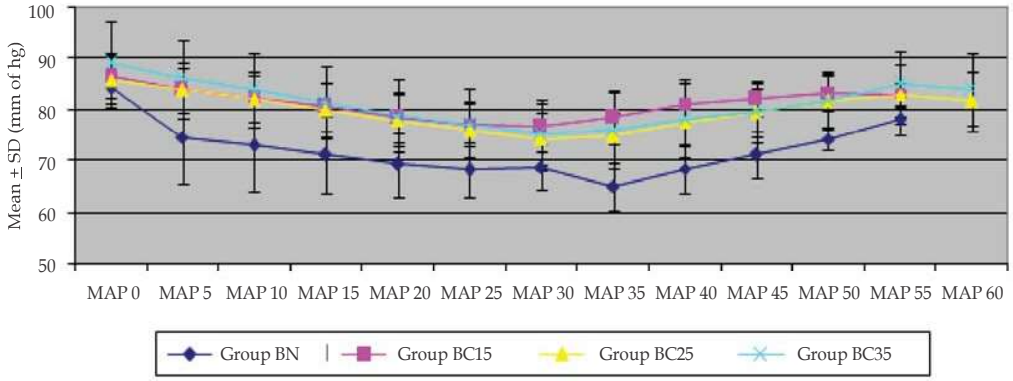

Fig. 3:

Table 4: Ephedrine Requirements

Parameter	MEAN±SD		
	BN	BC25	BC35
Ephedrine(mg)	10±1.73	10±1.73	15±0.00
No of patients	3	3	2

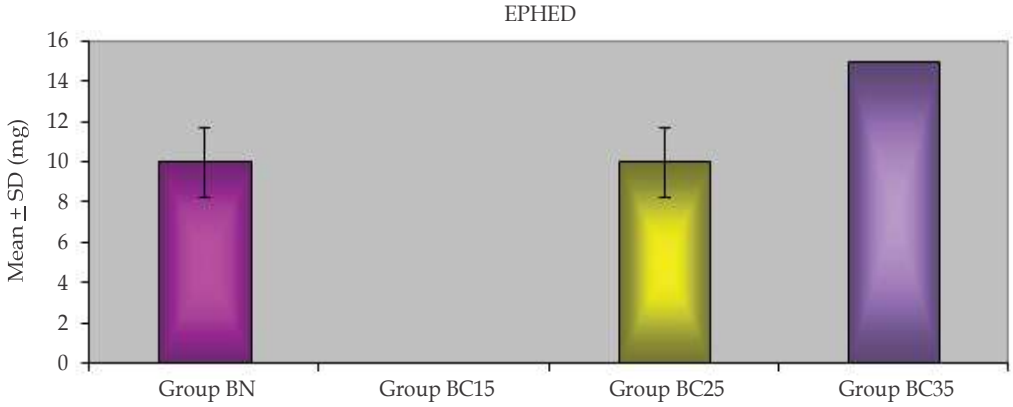

Fig. 4:

The mean dose of ephedrine given was 10 mg in group NS, 10 mg in group BC25, 15 mg in group BC35 which was significant.

Subgroup analysis showed a significant difference in ephedrine requirement between groups NS and BC35, BC25 and BC35 (Table and Fig. 4).

Oxygen Saturation

The oxygen saturation (SpO_2) (Mean±SD) was compared between the 4 groups. The baseline SpO_2 was 99.95±0.22 in group BN, 100±0.00 in group BC15,100±0.00 in group BC25, and 99.95±0.22 in group BC35 which were comparable.

All patients received oxygen by face mask at 6L/min. There was no significant change in SpO_2 (mean±SD) between the groups during the procedure.

Discussion

The addition of clonidine to intrathecal bupivacaine prolongs the duration of motor block by 30-50%.[9] The mechanism is due to the alpha 2 adrenoreceptor induced hyperpolarisation of motor neurons in the ventral horn of spinal cord.[10] However these studies have used higher doses of local anesthetics (15 mg) along with higher doses of clonidine (75 mcg) for patients undergoing lower limb and lower abdominal surgeries.[9]

The most common adverse effects noted with the use of intrathecal clonidine are hypotension and bradycardia. Maximal incidence of hypotension was seen with doses more than 75 mcgs of clonidine.[11] Alpha2 adrenergic agonists like clondine produce sympatholysis and decreased blood pressure by their action on brainstem nuclei and on sympathetic preganglionic neurons

in the spinal cord. This effect overrides the direct vasoconstriction that would have resulted from their action on adrenergic receptors in the peripheral vasculature.[12] The hypotensive effect produced by clonidine can last upto 2 hr. Different criteria have been used for defining hypotension following intrathecal administration of clonidine with bupivacaine. Some studies have defined significant hypotension as a 20% to 30% fall in systolic blood pressure (SBP), while others have used criteria such as SBP <90 mm of hg. Or fall in MAP more than 20% of the base line value. We also defined hypotension as SBP<90 mm of hg or fall in MAP more than 20% of baseline value. The difference was statistically significant between the groups NS and BC35 (P=0.000). It was not statistically significant between the groups BC15 and BC25 and between BC25 and BC35.

Patients in group BC35 had severe fall in blood pressure (MAP<60 mm of hg) and received more number of intravenous ephedrine boluses to increase the blood pressure. Subgroup analysis showed a significant difference in ephedrine requirement between groups NS and BC35. The amount of hypotension and the required dosage of ephedrine was more in patients receiving 35 mcg of clonidine compared to control group.

Most of the studies have reported a significant fall in blood pressure when 150 mcg clonidine was added to the local anesthetic for patients undergoing lowerlimb orthopedic and abdominal surgeries. In contrast, when clonidine is added to a low dose of bupivacaine it results in a greater decrease in mean arterial pressure than that observed with bupivacaine alone. In this study 10 mg of hyperbaric bupivacaine was used in patients of all groups with various doses of clonidine. Addition of 35 mcg clonidine to hyperbaric bupivacaine resulted in hypotension in patients who were hypertensive and on multidrug therapy.

Kothari and coworkers observed an increased incidence of hypotension in those who received 12.5 mg of 0.5% hyperbaric bupivacaine (72%) compared to 8 mg (57%) or 10 mg (35%) of 0.5% hyperbaric bupivacaine with 50 mcg clonidine.[13] In conclusion increasing the dose of bupivacaine increases the incidence of hypotension significantly. In this study the dose of bupivacaine remained the same (10 mg) in all the four groups but varying doses of clonidine were used. There were more episodes of significant hypotension in patients whom 35 mcg clonidine was used than in other groups.

Heart rate in this study was found decreased in all the 4 groups. However, the change was comparable between groups. This might be because of the use of low doses of clonidine along with low dose of hyperbaric bupivaciane in all the patients. None of the patients in any group required atropine to treat bradycardia which was defined as heart rate below 60 beats per minute.

Satish Dhasmana and coworkers found that with the addition of clonidine, there was a decrease in the heart rate from the baseline in their study on effects of addition of fentanyl or clonidine to intrathecal ropivacaine in patients undergoing anorectal surgeries.[14]

In a study in patients undergoing cesarean section Kothari and coworkers observed an increased incidence in bradycardia (22.85%) in patients who received a higher dose of hyperbaric bupivacaine (12.5 mg) as compared to who received lower doses of bupivacaine (8 mg) with 50 mcg clonidine (7.14%).[13] There was no difference in bradycardia between patients who received 50 mcg clonidine with 8 mg (7.14%) or 10 mg of 0.5% hyperbaric bupivacaine (14.28%). They explained that use of higher doses of bupivacaine (12.5 mg) resulted in higher level of block and contributed to bradycardia.

In contrast we found a lower incidence of bradycardia in this study. This could be due to use of low doses of clonidine as well as bupivacaine in this study. In this study there was no difference in the oxygen saturation between the four groups at any time during the procedure. None of the patients in any group had nausea, vomiting or pruritis.[15] This is similar to the effects observed in other studies.

Conclusion

There is good evidence from literature that clonidine has an antinociceptive effect at spinalcord and brainstem level. This is borne out in our study which concludes that addition of 35 mcg of clonidine to bupivacaine when compared to 25 mcg/15 mcg clonidine significantly prolongs the duration of analgesia without affecting the onset and maximum level achieved of sensory block.

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