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Effect of Dexmeditomidine and Clonidine as Spinal Adjuvant in TURP – A Comparative Study

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Abstract
Background: *The standard anaesthetic technique for TURP (Transurethral Resection of Prostate) is subarachnoid block. Bupivacaine is the local anaesthetic drug used to achieve the subarachnoid block. Adjuvants are used to enhance analgesia, to lower the bupivacaine dosage and to reduce the dose dependent side effects. Effects of Clonidine and Dexmedetomidine on subarachnoid block in TURP are compared in this study.*
Aim: *Aim of this study is to compare Dexmedetomidine and Clonidine as spinal adjuvant with Bupivacaine in TURP surgeries.*
Settings and Design: *This is a randomized double blinded study conducted in 60 patients of ASA I and II undergoing elective TURP surgeries. Patients were allocated in three groups. Group A (Bupivacaine + sterile normal saline as placibo) Group B (Bupivacaine + Clonindine 30µg) Group C (Bupivacaine + Dexmedetomidine 5µg).*
Materials and Methods: *After getting the ethical committee approval the study was conducted in 60 patients undergoing elective TURP surgeries. It was a double blinded study in which patients were randomly allocated into three groups by using the computer based randomization Group A- Inj. 0.5% Bupivacaine 2.0 cc + Normal saline 0.5cc = 2.5cc ,Group B (clonidine)Inj. 0.5% Bupivacaine 2.0 cc + Inj.Clonidine (30µg) 0.5cc = 2.5 cc ,Group C (dex) Inj. Bupivacaine 2.0 cc+ Inj. Dexmedetomidine (5µg) 0.5cc= 2.5 .*
Statistical Analysis Used: *Data analysis was done with Epidemiological Information Package (EPI 2008). ANNOVA t test was used to test the significance of difference between quantitative variables.*
Results: *Time to peak sensory level and time for Modified Bromage scale – 3 motor block were earlier and statistically significant in Dexmeditomidine group. Time for 2 segment regression, time to regress Modified Bromage 0, time to regress to S1 level, rescue analgesia duration were significantly more in Dexmeditomidine group*
Conclusion: *Adding 30µg Clonidine or 5µg Dexmedetomidine to 10mg of Bupivacaine significantly prolongs the duration of post operative analgesia when compared to Bupivacaine alone in elective transurethral resection of prostate (TURP) surgeries, without any side effect.*
Keywords: *Dexmedetomidine, clonidine, adjuvant, bupivacaine, subarachnoid block.*

INTRODUCTION

Transurethral Resection Of Prostate (TURP) is the surgical procedure done for benign prostatic hypertrophy. The standard anaesthetic technique for TURP is subarachnoid block using Bupivacaine.

Out of the many drugs that has been tried as spinal adjuvants, Clonidine and Dexmedetomidine used in this study are α2 agonists. They cause sedation and analgesia, in that Dexmedetomidine produces more analgesia and sedation because of its high selectivity to α2A receptor compared to Clonidine.

Initially opioids were used as spinal adjuvants, but since there were many side effects and complications like early and late depression of ventilation, pruritus, nausea, vomiting, urinary retention, central nervous system excitation, delayed gastric emptying and ocular dysfunction, there is an active search for an alternative ideal adjuvant which is devoid of these side effects and complications.

The mechanism of action of Dexmedetomidine is by selective alpha 2-adrenoceptor agonism. The three subtypes of α2 receptors are α2a, α2b, α2c. α2a receptors mediate sedation, analgesia, and sympatholysis. α2b receptors mediate vasoconstriction and anti- shivering.Activation of post synaptic alpha 2 receptors in the substantia gelatinosa of the spinal cord is the presumed mechanism by which it produces analgesiaClonidine hydrochloride is an imidazoline compound and exists as a mesomeric compound. The chemical name is 2- (2, 6-dichlorophenylamino) -2- imidazoline hydrochloride. Clonidine is a centrally acting selective partial α2 adrenergic agonist[1] with a selectivity ratio of 220: 1 in favour of α2 receptors.

MATERIALS AND METHODS

After getting the ethical committee approval the study was conducted in 60 patients undergoing elective TURP surgeries. It was a double blinded study in which patients were randomly allocated into three groups A, B and C by using the computer based randomization. After getting informed consent and explaining the procedure details to the patients, the anaesthetic technique was performed.

ASA I and II, Grade I prostatic hypertrophy with duration of surgery less than one hour, and Age 50 – 70 years patients were selected for the study.Patient who are refusing to undergo study , ASA III & IV patients, Known case of diabetics mellitus and hypertension, Spinal deformity, and patients with H/o drug allergy are excluded from the study. Patients were divided into the following three groups.Group A Inj. 0.5% Bupivacaine 2.0 cc + Normal saline 0.5cc = 2.5cc, Group B (clonidine)Inj. 0.5% Bupivacaine 2.0 cc + Inj.Clonidine (30µg) 0.5cc = 2.5 cc , Group C (dex) Inj. Bupivacaine 2.0 cc+ Inj. Dexmedetomidine (5µg) 0.5cc= 2.5 cc.

On the day of surgery, preoperative baseline parameters like Pulse Rate, Blood Pressure, and Respiratory Rate were recorded. Intravenous line started with 18 gauge intravenous cannula in right dorsum of hand. All the patients were preloaded with 500 ml of Lactated Ringer solution.

Emergency drugs and equipments were kept ready before anaesthesia intervention. Boyles machine with oxygen cylinder, Oxygen source, Laryngoscope with various blades, Airway in all sizes, and Suction apparatus were checked and kept ready. Emergency drugs like ephedrine, dopamine, atropine and adrenaline were kept ready.

Inj. Clonidine[150 µg/1 ml amp] was diluted to 2.5cc with sterile normal saline and made into 60µg /ml. Inj. Dexmedetomidine[100 µg/ml -2ml amp] diluted to 10cc with sterile normal saline and made into 10µ/ml. Drug was diluted and was loaded by another person as per randomization and this diluted blinded drug was given to the performer as 20units in a insulin syringe.

Patients were positioned in the right lateral position. With strict aseptic precautions, after infiltration of 2ml of 2% lignocaine, lumbar puncture was done with Quincke standard 25 guage spinal needle. In all patients, in L3-L4 interspinous space. After ensuring free flow of CSF, first 0.5 ml (20units) of testing drug was injected, following which 2ml of 0.5% hyperbaric Bupivacaine was injected.

After the injection, patients were placed in supine position, The level of sensory block was assessed by pin prick sensation using 25G needle along the mid

clavicular line bilaterally. The onset and duration of motor blockade was assessed by using modified bromage scale. Time to peak sensory level is defined as the time to reach T 10 dermatome (the highest dermatome).

The onset and duration of motor blockade was assessed by using modified bromage scale. The scale is:

0 – patient able to move the hip, knee and ankle.

1 - Patient unable to move the hip. But able to move knee and ankle.

2 - Patient unable to move the hip and knee. But able to move ankle.

3 - Patient unable to move the hip, knee and ankle

Time to peak sensory level is defined as the time to reach T 10 dermatome (the highest dermatome).

Intra operative mean arterial blood pressure (MAP) was recorded by placing blood pressure cuff in the left arm. The pulse rate (PR) and the oxygen saturation were recorded using pulse oxymeter. 5-lead ECG monitored continuously using Philips MP 40 machine. The parameters were recorded every 2 minutes for 10 minutes followed b y every 5 minutes for first hour, then every 15 minutes for second hour and every hourly till the first rescue analgesia after spinal block post operative intensive care unit.

Hypotension is defined as decrease in systolic blood pressure by 30% from baseline or systolic blood pressure lower than 90 mmHg. Hypotension is treated with 6mg of intravenous ephedrine

Bradycardia is defined as pulse rate <50 beats/minute .Level of sedation was evaluated intraoperatively and post operatively every 15 minutes for first three hours then hourly for next 8 hours by using Ramsay sedation score.

Pain was assessed by the verbal rating score every 15 minutes for 3 hours then every hourly for 8 hours.

All the patients received oxygen through face mask with 5 liter per minute. After 5 minutes patients were positioned in lithotomy and then the surgeon was asked to proceed.

STATISTICAL ANALYSIS

The information collected from the study was documented in a Master Chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2008).

Using this software range, frequencies, percentages, means, standard deviations and 'p' values were calculated. ANNOVA t test was used to test the significance of difference between quantitative variables. A 'p' value of less than 0.05 is taken to denote significant relationship. The results are expressed as mean (SD).

RESULTS

All three groups were statistically identical in age, height, weight and ASA classes. Time to peak sensory level in group A mean is 4.5 minutes with standard deviation of 0.2 minutes. In group B (clonidine) mean time to reach peak sensory level is 3.5 minutes with standard deviation of 0.3 minutes. In group C (dex) mean time to reach peak sensory level is 3.5 minutes with standard deviation of 0.3 minutes P value shows there is significant change in the time for peak sensory level among the three groups.

In group A mean time for motor block to reach modified Bromage scale 3 is 5.3 minutes with standard deviation of 0.3 minutes. In group B (clonidine) mean time to reach for motor block to modified Bromage 3 is 4.4 minutes with standard deviation of 0.3 minutes. In group C (dex) mean time to reach for motor block to modified Bromage 3 is 2.9 minutes with standard deviation of 0.4 minutes. P value shows there is significant change in the time for motor block to modified bromage 3 among the three groups.

In group A mean time to sensory level to regress two dermatome level is 59.3 minutes with standard deviation of 10.3 minutes. In group B (clonidine) mean time to sensory level to regress two dermatome level is 91.5 minutes with standard deviation of 9.6 minutes. In group C (dex) mean time to sensory level to regress two dermatome level is 105 minutes with standard deviation of 9.7 minutes. P value shows there is significant change

in the time for peak sensory level among the three groups.

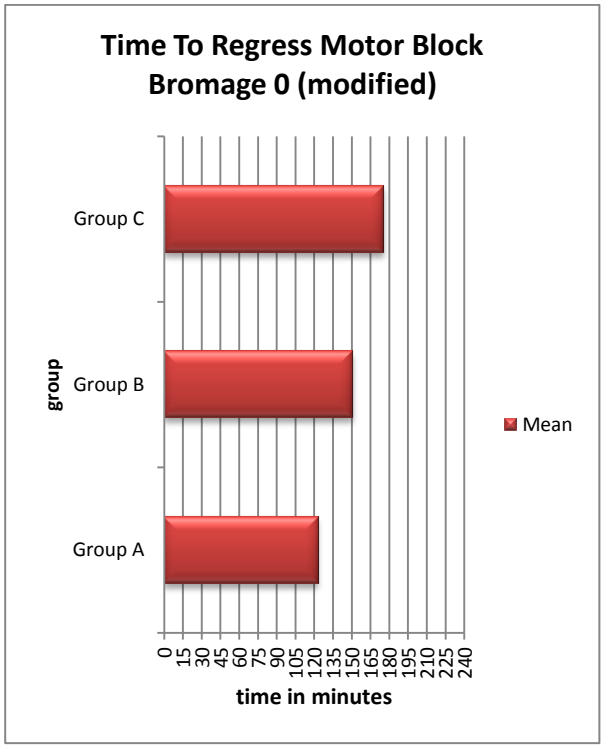
In group A mean time to regress motor block to modified bromage 0 level is 123 minutes with standard deviation of 14.3 minutes. In group B (clonidine) mean time to regress motor block to modified bromage 0 level is 150.8 minutes with standard deviation of 11.4 minutes. In group C (dex) mean time to regress motor block to modified bromage 0 level is 175.5 minutes with standard deviation of 13.0 minutes. P value shows there is significant change in the time to motor block to regress modified bromage 0 level among the three groups.

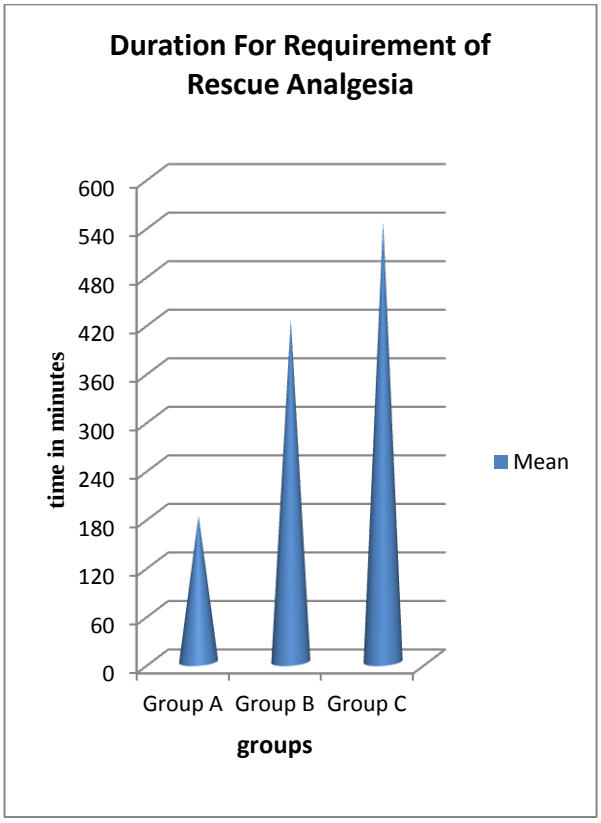
In group A mean time to regress sensory level to S1 is 119.3 minutes with standard deviation of 11.4 minutes. In group B (clonidine) mean time to regress sensory level to S1 is 147 minutes with standard deviation of 13.4 minutes. In group C (dex) mean time to regress sensory level to S1 is 169.5 minutes with standard deviation of 8.6 minutes. P value shows there is significant change in the time to motor block to regress bromage 0 level among the three groups.

In group A mean time for requirement of analgesia is 180.5 minutes with standard deviation of 10 minutes. In group B (clonidine) mean time for requirement of analgesia is 423 minutes with standard deviation of 16.6 minutes. In group C (dex) mean time for requirement of analgesia is 544.5 minutes with standard deviation of 17.6 minutes. P value shows there is significant change for time for requirement of analgesia among the three groups.P value shows there is significant change in the time for peak sensory level, Time for Modified Bromage scale – 3 motor block Time for 2 segment regression, Time to regress Modified Bromage 0 Time to regress to S1 level, Durarion for requirement of rescue analgesia were statistically significant among the three groups.(Table1- Results)

Table 1 RESULTS (in mins)

	Group A (Bupi)	Group B (Bupi+Clo)	Group C (Bupi+Dex)	P value
Time to peaksensory level	4.5±0.2	3.5±0.3	2.1±0.5	0.001
Timefor Modified Bromage score 3	5.3±0.3	4.4±0.3	2.9±0.4	0.001
Time for 2 segment regression	59.3±10.3	91.5±9.6	105±9.7	0.001
Time to regress Modified Bromage 0	123±14.3	150.8±11.4	175.5±13	0.001
Time to regress to S1 level(min)	119.3±11.4	147±13.4	169.5±8.6	0.001
Rescue analgesia(min)	180.5±10	423±16.6	544.5±17.6	0.001





DISCUSSION

The doses of Dexmedetomidine and of Clonidine used in our study were 5µg and 30µg respectively, as additive to spinal Bupivacaine. There were very few studies done using Dexmedetomidine as an additive in spinal anaesthesia[1]. Eisenach et al[2] had done animal studies with spinal Dexmedetomidine in the dose of 100µg. Kanzai et al[3] did an early human study with 3 µg of Dexmedetomidine and he found it is equipotent to 30µg of Clonidine (1:10 ratio). Subhi et al[4] chose 5µg of Dexmedetomidine as spinal additive in his studies. In both the above studies low dose of 3µg and 5µg of Dexmedetomidine were effective as an additive to spinal anaesthesia with least complication.

In our study when 10 mg of 0.5% Bupivacaine is added with 5µg of Dexmedetomidine it significantly prolongs the duration of sensory blockade, motor blockade and duration of post operative analgesia when compared to 30µg of Clonidine when added with 10mg of 0.5% Bupivacaine

In Kanzai et al[3], Khalifa et al[5] and Subhi et al[4] studies, they all have used Dexmedetomidine as spinal additive. The above three studies have compared Dexmedetomidine as spinal additive to Clonidine 30µg or sufentanil 5µg or Fentanyl 25µg, and they found in common, that Dexmedetomidine prolongs the spinal anaesthesia more when compared to all other three additives mentioned above.In Mustafa et al[6] they compared two doses of spinal Dexmedetomidine as spinal additive (5µg and 10µg). In that 10µg Dexmedetomidine group had prolonged sensory blockade, motor blockade and post operative analgesia compared to 5 µg Dexmedetomidine group.

The mechanism by which intrathecal α2 adrenoceptor agonists prolong the motor sensory block of local anaesthetics is not well understood. It may be an additive or synergistic effect secondary to a different mechanism of action of the local anaesthetic. The local anaesthetic acts by blocking the sodium channels, whereas the 2adrenoceptor agonist acts by binding to pre-synaptic C- fibers and post-synaptic dorsal horn neurons[7,8,9,10]. These antinocieptive effects explain the prolongation of the sensory block when added to spinal anaesthsia. The prolongation of the motor block of spinal anaesthetics may result from the binding of α2 adrenoceptor agonists to motor neuron in the dorsal horn[11] in the spinal cord.

In our patients the addition of Dexmedetomidine or Clonidine to Bupivacaine causes initial fall in the blood pressure especially in Clonidine group. But fall is not clinically significant and they did not require vasopressor intra operatively or post operatively. An Intrathecal local anaesthetic blocks the sympathetic outflow and reduces the blood pressure. The sympathetic block is usually near maximal with the doses used for spinal anaesthesia. The addition of low dose of α2 agonist to a high dose of local anaesthetics does not further affect the near maximal sympatholysis[12].

In our study none of our patients were drowsy. All the patients were co-operative, oriented and calm.Intrathecally administered α2 agonists have a dose dependent sedative effect[13]. The doses of Clonidine and Dexmedetomidine selected in our study were at the lower end of dosing spectrum. This explains the lack of sedative effect in the study groups.

CONCLUSION

We would like to conclude addition of 30µg Clonidine or 5µg Dexmedetomidine to 10mg of Bupivacaine significantly prolongs the duration of post operative analgesia when compare to Bupivacaine alone in elective transurethral resection of prostate (TURP) surgeries. Bupivacaine with Dexmedetomidine prolongs significantly the duration of post operative analgesia when compared to Bupivacaine with Clonidine in spinal anaesthesia. Bupivacaine when used alone or with adjuants like Clonidine (30µg) or Dexmedetomidine (5µg) does not produce any appreciable side effects.

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