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Comparison of Effects of 35µg Clonidine and 5µg Dexmedetomidine on Characteristics Of 0.5% Hyerbaricbupivacaine Subarachnoid Block.A Prospective, Randomised, Double-Blind Study.

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Abstract:
Background:*Alpha-2agonists like clonidine and dexmedetomidine are used as neuraxial adjuvants. They potentiate the effect of local anaesthetics and allow a decrease in required doses. They prolong the duration of both motor and sensory spinal blockade.*
Aims & Objectives:*This study is designed to compare the onset, duration of sensory and motor block and haemodynamic characteristics and side effects of addition of clonidine (35µg) and dexmedetomidine (5µg) to intrathecal 0.5% bupivacaine.*
Materials & Methods: *Sixty American Society of Anesthesiologists(ASA) grade I and II patients were randomized into two groups, 30 patients in each. : Group C (n=30) received 3.5 ml [3ml (15mg) of 0.5% bupivacaine + 0.5ml (35µg) of clonidine] and Group D received 3.5ml [3ml (15mg) of 0.5% bupivacaine + 0.5ml(5µg) of dexmedetomidine] of study drug. All the drugs used in this study were preservative free. The intrathecal injections were prepared by an anaesthesiologist who was not involved in the study. The investigator performing the block and recording the observations of the study parameters was blinded to the intrathecal drug administered. Lumbar puncture was performed in lateral position at L3-L4 intervertebral space using a 25 gauge, Quincke Babcock's spinal needle and intrathecal injection was administered after aspiration of cerebrospinal fluid.*
Results:*The two groups were comparable with respect to age, weight, height, gender, ASA status. The mean times of onset of sensory block (loss of cold sensation at T10), maximum height of block, time to reach maximum height and regression time to S1 were comparable in between the 2 groups. The motor block onset and duration of block were comparable in between the 2 groups. Haemodynamic parameters were well maintained in both the groups. Heart rate was compared between the groups at regular intervals. The results did not show any statistical significant difference. Mean arterial pressure compared in between the 2 groups. A statistically significant difference was observed at 2min, 60min and 3hr. No statistical significant difference in the incidence of adverse events is observed between 2 groups. The mean doses of ephedrine and atropine and total amount of I.V fluid given to the patients were comparable between the groups.*
Conclusion: *In our study we concluded that addition of clonidine 35µg or 5µg dexmedetomidine produced similar characteristics of sensory and motor block with maintenance of haemodynamic stability.*
Keywords*: Clonidine, Dexmedetomidine, Bupivacaine, Subarachnoid block*

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I. Introduction

Central neuraxial blockade (CNB) can provide excellent intraoperative anaesthesia and prolonged and satisfactory postoperative analgesia in many cases. Adequacy of spinal anaesthesia with bupivacaine for lower limb and lower abdominal surgeries is limited by fixed duration of action.Single dose spinal anaesthesia is associated with haemodynamic instability especially when high doses were used in order to achieve longer duration of block. Severalneuraxial adjuvants are used most commonly with hyperbaric bupivacaineto minimize the instability in haemodynamics.

Alpha-2agonists like clonidine and dexmedetomidine are used as neuraxial adjuvants. They potentiate the effect of local anaesthetics and allow a decrease in required doses[1, 2]. They prolong the duration of both motor and sensory spinal blockade [1,2,3]. This study is designed to compare the onset, duration of sensory and

motor block and haemodynamic characteristics and side effects of addition of clonidine (35µg) and dexmedetomidine (5µg) to intrathecal 0.5% bupivacaine.

II. Material And Methods

After obtaining the Institutional Ethics and Research Committee approvals,60 American Society of Anesthesiologists (ASA)[4] physical status I/II patients aged 18-60 years who were scheduled for elective infra umbilical surgery under spinal anaesthesia were included in this prospective, randomised, double-blind study. Patients with contraindication to central neuraxial blockade, neurological and psychiatric disorders,obesity [body mass index >30kg/m^2], hypersensitivity to study drugs, pregnant and lactating women and patients who were not willing to participate in the study were excluded. Patients were kept fasting as per the guidelines[7]. Patients were premedicated with tab alprazolam 0.5mg and ranitidine 150mg on the night and morning before surgery. On arrival in the operation theatre, routine monitoring with electrocardiogram (ECG), non-invasive arterial pressure and pulse oximetry were done and preloaded with 10ml/kg ringer's lactate after securing an intravenous access over 20min before surgery. The patients were randomly allocated into one of the two groups of 30 patients each using a computer generated randomization code and sealed opaque envelope technique. The patients were given intrathecal study drug as follows: Group C (n=30) received 3.5 ml [3ml (15mg) of 0.5% bupivacaine + 0.5ml (35µg) of clonidine] and Group D received 3.5ml [3ml (15mg) of 0.5% bupivacaine + 0.5ml(5µg) of dexmedetomidine] of study drug. All the drugs used in this study were preservative free. The intrathecal injections were prepared by an anaesthesiologist who was not involved in the study. The investigator performing the block and recording the observations of the study parameters was blinded to the intrathecal drug administered. Lumbar puncture was performed in lateral position at L3-L4 intervertebral space using a 25 gauge, Quincke Babcock's spinal needle and intrathecal injection was administered after aspiration of cerebrospinal fluid. Patients were administered oxygen with a face mask at the rate of 6L/min. Crystalloid solutions were administered during anaesthesia and the rate was adjusted depending on the haemodynamic response.

The haemodynamic parameters like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) were recorded at baseline (at the time of injection of study drug), 2 min, 3 min, 6 min, 10 min, 15 min, 30 min, 45 min, 60 min, 2 hours, 3 hours, 6 hours, 8 hours after injection of study drug. Hypotension was defined as a drop in systolic blood pressure below 90mmHg or more than 30% of the baseline and initially treated with 200 ml IV fluid bolus over 10min, if not corrected then was treated with IV ephedrine 0.06mg/kg bolus.Bradycardia was defined as decrease in heart rate below 50 beats per minute and was treated with IV atropine 0.04mg/kg bolus. The number of incidences of hypotension and bradycardia of each patient was used for statistical analysis.

The subarachnoid block characteristics were assessed like sensory onset time (time between the injections of intrathecal anaesthetic to loss of cold sensation at T10 dermatome), maximum height of sensory block attained, time to reach maximum height and regression to S1. The motor level was assessed according to modified Bromage score: (0= no motor loss; 1= inability to flex hip; 2= inability to flex the knee joint; 3= inability to flex the ankle)[6]. Onset of motor block (modifiedBromage I), time to achieve complete motor block (modified Bromage III), and time to regression(modified Bromage 0) from the completion of intrathecal injection were assessed.

STATISTICAL ANALYSIS

Data was presented as mean (SD), or frequencies as appropriate. Normality was tested by Shapiro-Wilk test. Continuous variables between the groups were compared using student T test or Mann Whitney U test as appropriate. Nominal categorical data between the groups were compared using the Chi-square test. A p-value of <0.05 was considered statistically significant.

III. Results

In our study 60 patients undergoing elective infra umbilical surgeries under subarachnoid block were randomised into 2 groups (Group C and Group D) of 30 patients each. The groups were comparable with respect to age, weight, height, gender, ASA status (Table 1)

Table 1: Comparison of demographic characteristics between two groups

Variables	Group C	Group D	p value
Age(years)*	41.8±11.72	43.2±10.30	0.62
Ht(cm)*	163.26±8.63	161.26±8.69	0.37
Wt(kg)*	62.23±11.37	61.18±11.46	0.72
Gender (Male/Female)	24/6	22/8	0.76
ASA status(I/II)	18/12	22/8	0.41

*data are presented as mean± standard deviation, ASA = American society of Anesthesiologists

The mean times of onset of sensory block (loss of cold sensation at T10), maximum height of block, time to reach maximum height and regression time to S1 were comparable in between the 2 groups. The motor block onset and duration of block were comparable in between the 2 groups. (Table 2)

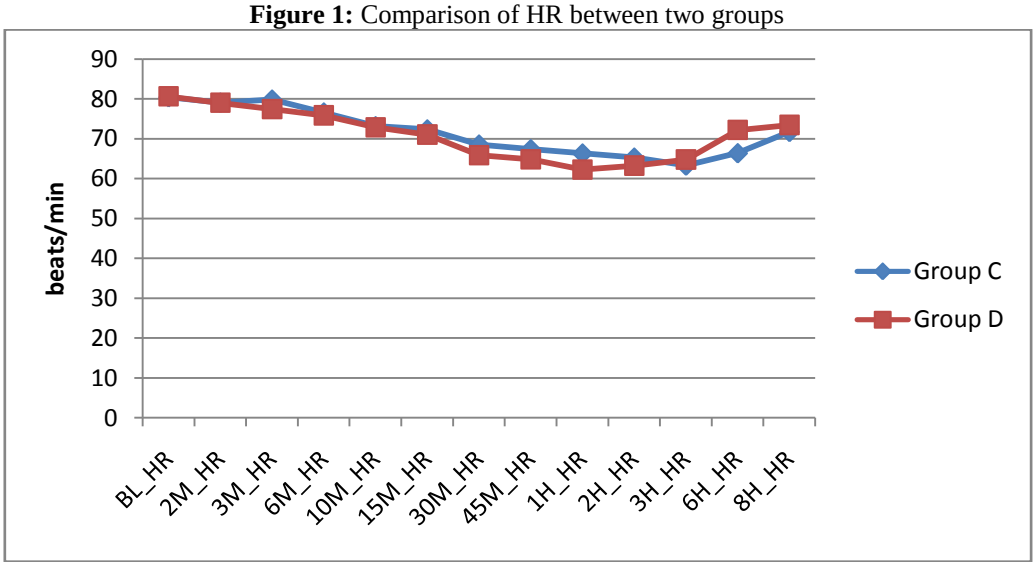
Table 2: Comparison of block characteristics between 2 groups

Variables	Group C	Group D	p value
Onset time of block toT10(sec)	152.4±77.81	141.7±84.48	0.48
Time to reach max height(min)	5.41±2.58	5.95±2.82	0.46
Regression time S1(min)	372.33±69.31	395.33±63.77	0.10
Onset of motor block(min)	3.45±2.08	3.28±1.81	0.81
complete motor block(min)	9.71±4.01	9.13±3.06	0.52
Resolution of motor block (min)	309.5±59.99	338.16±61.62	0.07

Data expressed as mean±standard deviation

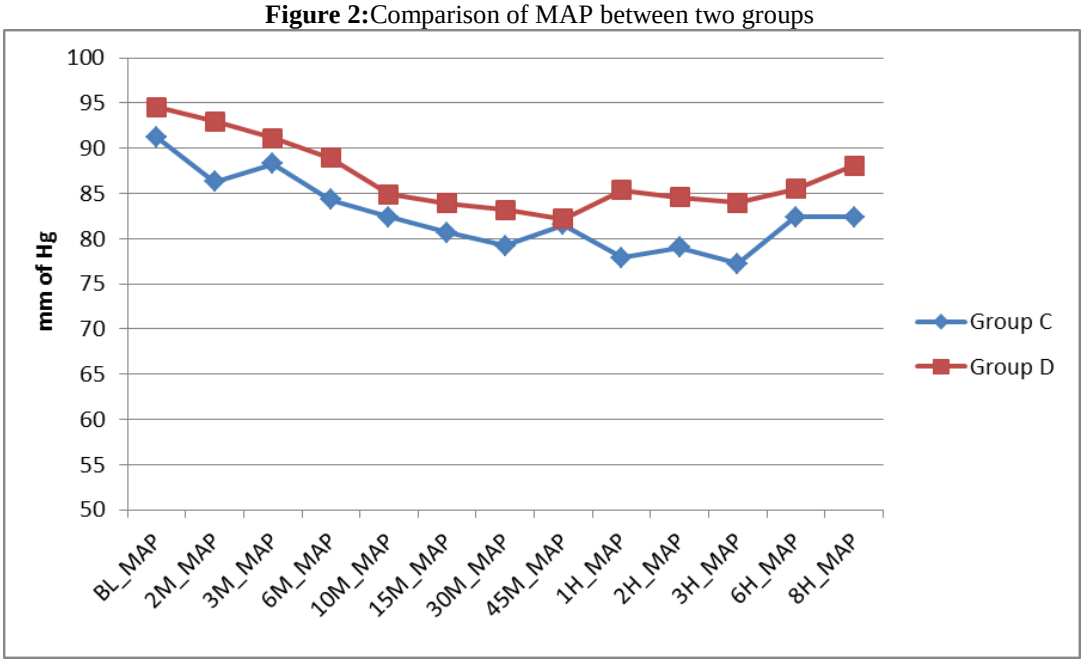
Haemodynamic parameters were well maintained in both the groups. Heart rate (figure 1) was compared between the groups at regular intervals. The results did not show any statistical significant difference.

Figure 1: Comparison of HR between two groups



Mean arterial pressurecompared in between the 2 groups. A statistically significant difference was observed at 2min, 60min and 3hr

Figure 2: Comparison of MAP between two groups



Hypotension was observed in 4 out of 30 patients in Group C and 6 out of 30 in Group D.Bradycardia was observed in 4 out of 30 patients in both Group C and D. No statistical significant difference is observed between 2 groups.

Table 3: Comparison of adverse effects between two groups

Adverse effects (Qualitative data)	Group Cn (%)	Group Dn (%)	p value
Hypotension	4 (13.3%)	6 (20%)	0.731
Bradycardia	4 (13.3%)	4 (13.3%)	1
Nausea/Vomiting	Nil	Nil	-

Data expressed as frequency (n) and percentage (%)

The mean doses of ephedrine and atropine and total amount of I.V fluid given to the patients were comparable between the groups

Table4: Comparison of ephedrine and atropine doses required between two groups

Adverse effects Quantitative data	Group Cmean±SD	Group Dmean±SD	p value(Mann Whitney U)
Total dose Ephedrine given (mg)	0.70±1.8	0.60±1.2	0.632
Total dose of Atropine given (mg)	0.05±0.13	0.05±0.13	1
Total I.V fluid administered(ml)	2186.33±238.73	2148.66±166.87	0.922

IV. Discussion

Adjuvants for spinal anaesthesia are intended to improve the success of regional anaesthesia by prolonging the analgesia of local anaesthetics and preventing the deleterious clinical effects of their toxic doses. Interest in the alpha-2 agonists has been rising in the field of regional anaesthesia given their ability to enhance neuraxial analgesia without the respiratory depression and pruritis common to opioids.Intrathecal α2-adrenoceptor agonists produce analgesia by binding and depressing the release of pre-synaptic C-fibre neurotransmitters and also by hyperpolarisation of post-synaptic dorsal horn neurons[7].This anti nociceptive effect may explain the prolongation of the sensory block while prolongation of motor block may be due to the binding of α2-adrenoceptor agonists to motor neurons in the dorsal horn. The present study has been undertaken to compare the effects of addition of clonidine or dexmedetomidineintrathecally to bupivacaine.

Kanazi et al.,[8]showed that dexmedetomidine (3µg) and clonidine (30µg) in a dose ratio1:10 produced an equipotent effect on the characteristics of the block. In our study, 35µg of clonidine and 5 µg of dexmedetomidine were used, as it was found that the incidence of side effects increased with larger doses.

Results of our study showedaddition ofdexmedetomidine resulted in mean onset of sensory block in 141.7 sec and motor block in 3.283 min that is comparable to 2.3 min and 3.4 min from the study performed bySamantaray et al. ,[9] in which 5µg dexmedetomidine is added to 0.5% hyperbaric bupivacaine. Similarly addition of clonidine resulted in sensory blockade within 152.4 sec and motor block in 3.45 min that is comparable to 2.06 min and 3.29 min from the study performed by Ranjusingh et al.,[10] by addition of 50µg clonidine to 0.5% hyperbaric bupivacaine.

Times for the complete sensory and motor block in clonidine group are about 5.417±2.58 min and 9.71±4.01min respectively and in dexmedetomidine are 5.95±2.82 min and 9.13±3.08 min. The times for complete sensory and motor block are less in Group D when compared to Group C but the difference is not statistically significant.

Mahmoud M. Al-Mustafa[11] added different doses of dexmedetomidine to spinal bupivacaine for urological procedurefound that the mean time of sensory block to reach T10 dermatome was 6.3±2.7 minute with addition of 5µg dexmedetomidine. The time of onset of peak in clonidine group can be comparable with a study byManish Sapate et al.[12] in below knee orthopaedic surgeries the addition of 50µg clonidine to 12.5mg hyperbaric bupivacaine resulted in peak sensory block within 4.7±1.32 min. Time of onset of complete motor block can be comparable with a similar study by Sarma J et al.[13] i.e.,addition of 50µg clonidine group to hyperbaric bupivacaine resulted in complete motor block within 9.52±1.87 min and by addition of 5µg dexmedetomidine to bupivacaine resulted in motor block in 10.76±1.74 min.

The time for the regression of sensory block to S1 dermatome is 372.33±69.31 minute in clonidine group and 395.33±63.77 min with dexmedetomidine.The time for regression of sensory block is less in Group C than in Group D but the difference is not clinically significant. In a study conducted by Sarma J et al.[13] the addition of similar doses of clonidine and dexmedetomidine to 0.5% bupivacaine resulted in sensory block time of 278.60±26.20 min in clonidine group and 306.60±50.56 min in dexmedetomidine group. The time taken to resolution of motor block (to modified Bromage 0) in clonidine group is 309.5±59.99 min and in

dexmedetomidine group is 338.16±61.62 min .The duration of motor block is more in the dexmedetomidine group than the clonidine group but the difference is statistically not significant.

In our study patients remained hemodynamically stable both indexmedetomidine and clonidine group. Few patients required therapeutic interventions but it was not statistically significant. Similar results were also observed to study byG.E.Kanaziet al.[8] who compared 3µg dexmedetomidine with 30µg clonidine intrathecally with hyperbaric bupivacaine in patients undergoing Trans urethral resection of prostate (TURP)/Trans urethral resection of bladder tumour (TURBT) under spinal anaesthesia. The MAP and HR are comparable in all three groups –control, clonidine and dexmedetomidine groups in their study.

The adverse effects observed in the study are bradycardia, hypotension and nausea & vomiting.None of the 60 patients complained nausea and vomiting. The incidence of hypotension and bradycardia did not show any statistically significant difference in between the groups.The total I.V fluid given to the patient intraoperatively and post operatively upto 8 hour after giving the spinal drug was comparable in between the groups.

The limitations of the present study are the small sample size and absence of control group presence of which would have been useful to evaluate the effectiveness of dexmedetomidine and clonidine.

V. Conclusion

The addition of 35 µg clonidine and 5 µg dexmedetomidine to 0.5% bupivacaine produced effective sensory and motor block in all the patients participated in our study. In our study we concluded that addition of clonidine 35µg or 5µg dexmedetomidine produced similar characteristics of sensory and motor block with maintenance of haemodynamic stability.

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Conflicts of Interest: None

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