

Comparison of Dexmedetomidine and Clonidine Added To Hyperbaric Bupivacaine in Spinal Anaesthesia for Vaginal Hysterectomy: A Prospective Randomized Controlled Double Blinded Study

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Abstract: Many adjuvants are being tried with local anaesthetics for prolongation of intra-operative and post-operative analgesia. Dexmedetomidine, the highly selective alpha2 adrenergic agonist is a newer neuraxial adjuvant gaining popularity nowadays. The purpose of this study was to compare the onset, duration of sensory motor blockade, hemodynamic effects and adverse effect of dexmedetomidine, clonidine with bupivacaine and bupivacaine with normal saline for spinal anaesthesia. The study was conducted in prospective, controlled randomized, double blind manner after approval from hospital ethical committee with written and informed consent of the patients. The patients were randomly allocated into three groups (30 patients each). 15 mg of hyperbaric bupivacaine was given to all patients with normal saline to group N, with 30 µg clonidine to group C and with 5 µg dexmedetomidine to group D patients. The onset time, regression time and peak levels of sensory and motor blockade, hemodynamic changes and side effects were recorded. Patients in group D had significantly longer duration of sensory and motor blockade than patients of group C and N. Mean duration of analgesia among the group N, D and C was 211.1±30.47, 386.83±58.43 and 296.53±57.19 minutes respectively (p <0.001). The regression time of motor blockade to reach modified bromage scale to zero was 181.03±20.83, 253.37±48.87 and 269.77±51.95 minutes in group N, D and C respectively (p<0.001). The difference in onset time and mean peak sensory level between three groups was statistically not significant (p>0.05). There was no significant sedation and hemodynamic variability between three groups. Intrathecal dexmedetomidine is associated with prolonged and sensory and motor block in comparison of clonidine. In low dose of dexmedetomidine and clonidine used for spinal anaesthesia in our study have minimal hemodynamic instability and does not cause any sedation intraoperative and post-operatively.

Keywords: Dexmedetomidine, clonidine, bupivacaine, spinal anaesthesia, vaginal hysterectomy.

INTRODUCTION

“For all the happiness that mankind can gain, is not the pleasure, but in rest from pain” John Dryden (1631-1701). Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage [1,2] and is associated with neuroendocrine response and muscle spasm. Anaesthesiologists have succeeded to a considerable extent, in rendering the patient pain free during surgery, but once the surgery is over, the patient might face the misery of postoperative pain. Post-operative pain relief reduces the complications associated with the surgery. It allows early mobilization, ambulation and

prevents deep vein thrombosis. Post-operative pain management has now become an integral part of modern anaesthesia. Various techniques and methods of post-operative pain relief have been advocated such as analgesic agents, regional nerve blocks, acupuncture, cryoanalgesia etc. The most widely used method of post-operative pain relief are pharmacological drugs especially opioids and NSAIDs. Nerve blocks using local anaesthetics alone are of limited value in specific surgeries, because of the short duration of action and need for repeated injections.

In spite of all these methods, the problem of postoperative analgesia awaits a radical new approach. Many studies were done to find new approaches and adjuvant drugs with local anaesthetics in central neuraxial and regional anaesthesia. Starting with the use of morphine in 1979, the use of additives for prolongation of duration of analgesia has been a key area of interest. Epidural and subarachnoid adjuvants have provided means of prolong post-surgical pain relief and subsequent patient satisfaction.

Clonidine an imidazoline derivative with partial alpha - 2 adrenergic receptor agonist activities, which has a variety of different actions, including the antinociceptive effects of its action on the alpha2adrenoreceptors in the dorsal horn of spinal cord was tried along with local anaesthetic drugs. Numerous previous reports indicate that systemic as well as regional administration of clonidine has anaesthetic advantages which include reduction of anaesthetic requirements improving hemodynamic instability and providing analgesia [3-6].

Dexmedetomidine and clonidine increases the duration of analgesia when used as adjuvants in intrathecal anaesthesia. Dexmedetomidine is 8-10 times more specific for alpha2 receptors than clonidine [7,8], and inhibits the release of norepinephrine[9,10]. Post synaptic activation of alpha2 receptors in the CNS however, inhibits sympathetic activity and thus can decrease blood pressure and heart rate.

In view of above scientific evidences, the present randomised prospective study was to compare the prolongation in duration of analgesia when dexmedetomidine and clonidine used as adjuvant with 0.5% heavy bupivacaine in spinal anaesthesia for vaginal hysterectomy.

AIM AND OBJECTIVES

The aim of the study was to compare dexmedetomidine and clonidine added to hyperbaric bupivacaine in spinal anaesthesia for vaginal hysterectomy in the terms of:

Primary outcomes like a) onset and duration of sensory block, b) onset and duration of motor block, 3) duration of analgesia 4) hemodynamic changes if any. Secondary outcomes like adverse effects and any other complications.

MATERIALS AND METHODS

After approval from institutional ethical Committee, a prospective, hospital based, double blinded, randomised, controlled, comparative study was planned on 90 patients. Study period was from July 2016 till completion of the desired number of cases in Umaid Hospital, Jodhpur.

In this study participating patients were randomly selected from gynaecology department posted

for vaginal hysterectomy. All patients were between ages 40-70 yrs., height 140-180 cms and weight 40-80 kgs., belong to ASA class I and II. Exclusion criteria include all the contraindications for spinal anaesthesia, allergy to study drugs and any comorbidity.

A written informed consent was taken from all the patients for spinal anaesthesia and other procedures after complete explanation about the study protocol, anaesthetic technique, merits and demerits of the procedure and perioperative course of anaesthesia. A detailed pre anaesthetic check-up was done one day before surgery.

Sample size calculation

Considering a mean difference of 30 minutes in duration of analgesia, alpha error at 5% and statistical power of 80%, sample size was calculated as 30 per group, hence finally a sample size of 30 was taken for each group. We have taken duration of analgesia equivalent to time taken for sensory regression to S1 as in reference study [11].

Randomization

The patients were randomly allocated into three predefined groups by chit in box method. Group N: patients received 3 ml (15mg) of 0.5% bupivacaine heavy and 0.5 ml normal saline intrathecally. Group D: patients received 3 ml (15mg) of 0.5% bupivacaine heavy+ dexmedetomidine 0.5 ml (5mcg) intrathecally. Group C: patients received 3 ml (15mg) of 0.5% bupivacaine heavy+ clonidine 0.5 ml (30mcg) intrathecally.

Technique

All patients were kept nil by mouth for 6 hours before the scheduled time of surgery. Patient was taken on operation table and monitors for ECG, non-invasive blood pressure and oxygen saturation were applied. Then pulse rate, blood pressure, respiratory rate, SpO2 readings were taken and recorded as basal parameters. An 18 G intravenous line was established and preloading started with 15 ml/kg body weight of Ringers solution about 15 minutes before intended time of intrathecal drug administration.

Patients were positioned in sitting posture. Patient's back painted with betadine solution and draped with sterile towel. Lumbar puncture was performed at L3-4 intervertebral space using midline approach with a 25 gauge Quincke spinal needle. After ensuring a free flow of CSF, the drugs according to the group allocated were injected. The patient were made to lie supine position and oxygen was administered through face mask (flow of 4-5 lit per minute) during the surgery. Drug to be given in spinal anaesthesia was loaded and approximate mixture prepared by assistant and a coding done by same assistant, 0.9% normal saline used as diluent for dexmedetomidine and clonidine. The blinding code retained by the nursing

staff was opened after completion of study. For the reasons of patient's safety, a sealed envelope containing the treatment assigned was kept with the patient in recovery room and ward.

The vital parameters were recorded at baseline, 1 min after spinal anaesthesia and after every 5 minutes till 1 hour(intraoperative period) then at every 15 minutes for next 1 hour and then at 3 hours(post-operative period). Respiratory rate, sedation score and oxygen saturation was recorded at baseline, 30 minutes, 1,1.5,2,3,4,6 and 8 hours.

Onset of sensory block and peak level was assessed by pinprick method, after 3 minutes of spinal anaesthesia and then after every minute till T10 level of sensory blockade achieved, after that assessment continued at every 5 min till 30 min after spinal anaesthesia and peak sensory level achieved was noted. Onset of motor blockade was assessed by modified bromage scale. Time to reach modified bromage scale 3 was taken as motor block onset time and assessment after 3 min of spinal anaesthesia and then after every min till modified bromage 3 blocks achieved. Duration of motor block was considered as time from motor block onset to reach modified bromage scale zero. Duration of analgesia was considered as first complaint of pain VAS score 3/10), and analgesia supplement done with diclofenac 75 mg IM.

During surgery, IV fluids (crystalloids, colloids, blood) were administered as required. A record was also made of blood loss, urine output and IV fluid input. Patients were observed for any discomfort, nausea, vomiting, shivering, pain, bradycardia, hypotension or any other side effects and the need for any additional medications were recorded.

During monitoring the parameters, pulse rate less than 60/min was graded as bradycardia and greater

than 100/min as tachycardia. Atropine 0.6 mg was administered in cases of bradycardia. Systolic blood pressure less than 20% of baseline or less than 90 mm Hg was taken as hypotension; it was treated with IV fluids and/or by mephenteramine sulphate 3 mg. A respiratory rate of less than 10/min was taken as respiratory depression.

Duration of surgery was taken as time period from skin incision to skin closure after completion of surgical procedure. Patients were closely observed in the intraoperative and post-operative period for any complications and/or side effects.

Statistical Analysis

Continuous variables like age, BMI, onset of sensory and motor block, duration of sensory and motor block, peak sensory level, heart rate, mean blood pressure, sedation score and respiratory rate are expressed as mean± SD and compared across the groups using one way ANOVA test.

Categorical variables ASA grade and incidence of adverse events are expressed as number and percentage of patients and compared across two groups using Pearson's Chi square test for independence of attributes.

The statistical software SPSS version 16 has been used for the analysis. An alpha level of 5% has been taken, i. e. If any p value is less than 0.05, it has been considered as significant and p value of <0.001 was considered highly significant for the entire test.

OBSERVATIONS

The differences in all demographic data and ASA grade in three groups are statistically not significant (Table 1,2).

Table-1: Age distribution

Age(in years)	Group N	Group D	Group C	Total	Percentage
40-50	7	8	7	22	24.44%
50-60	15	14	14	43	47.78%
60-70	8	8	9	25	27.78 %
Total	30	30	30	90	100%

Table-2: Distribution of demographic data

Variable		Group N	Group D	Group C	P value		
					N & D	N & C	D & C
BMI (Mean±SD)		27.42±3.01	26.63±3.07	26.7±3.02	0.322	0.361	0.933
ASA	I	22(73%)	20(67%)	19(63%)	0.573	0.405	0.787
	II	8(27%)	10(33%)	11(37%)			

As shown in table 3, mean time to achieve T10 sensory level among the groups N,D and C were 5.40±1.38,4.87±0.73 and 5.20±1.40 minutes

respectively. It appears that dexmedetomidine may causes faster onset of sensory block but the difference between group N and D, N and C, D and C were

statistically not significant ($p > 0.05$). So it implies that addition of low dose dexmedetomidine and clonidine

with bupivacaine in spinal anaesthesia did not affect the onset of sensory block.

Table-3: Characteristics of spinal block

Variable		Group N	Group D	Group C	P value		
					N & D	N & C	D & C
Onset of sensory block (In minutes)	(Mean±SD)	5.40±1.38	4.87±0.73	5.20±1.40	0.07	0.58	0.25
Onset of motor block (In minutes)	(Mean±SD)	8.97±0.96	8.33±1.56	8.80±1.46	0.06	0.64	0.27
Duration of analgesia (in minutes)	(Mean±SD)	211.1±30.47	386.83±58.43	296.53±57.19	<0.001	<0.001	<0.001
Duration of motor block (in min.)	(Mean±SD)	181.03±20.83	353.37±48.87	269.77±51.95	<0.001	<0.001	<0.001
Side Effects (number of patients)	Bradycardia	1(3%)	1(3%)	0(0%)	0.303	0.083	0.355
	Hypotension	2(7%)	1(3%)	0(0%)			
	Shivering	3(10%)	0(0%)	0(0%)			
	None	24(80%)	28(93%)	30(100%)			
Peak level of sensory block(in minutes)	Mean	6.07	5.83	6.13	0.586	0.863	0.481

Mean time to achieve motor block to modified Bromage scale level 3 among the groups N, D and C was 8.97±0.96, 8.33±1.56 and 8.80±1.46 min respectively (Table 3). The difference in mean time for motor block onset between group N and D, N and C, D and C is statistically not significant ($p > 0.05$). Mean duration of analgesia among the group N, D and C was 211.1±30.47, 386.83±58.43 and 296.54±57.19 respectively (Table 3). Addition of clonidine to bupivacaine in spinal anaesthesia significantly increases the mean duration of analgesia in comparison to control group, on comparison of group D and C it is found that addition of dexmedetomidine increases the mean duration of analgesia significantly than addition of clonidine to bupivacaine in spinal anaesthesia.

Mean time to achieve motor block from Bromage scale level 3 to 0 level among the group N, D and C was 181.03±20.83, 353.37±48.87 and 269.77±51.95 min respectively (Table 3). So addition of clonidine increases mean duration of motor block

significantly in comparison to normal saline (control group). On comparison of group D and C it is found that addition of dexmedetomidine increases the mean duration of motor blockade significantly than addition of clonidine to bupivacaine in spinal anaesthesia.

The mean of peak level of sensory block achieved among the group N, D and C was 6.07, 5.83 and 6.13 respectively (Table 3). The difference in mean peak level of sensory block between group N v/s D, N v/s C and C v/s D is statistically not significant ($p > 0.05$). So it concludes that addition of low dose of clonidine and dexmedetomidine with bupivacaine in spinal anaesthesia does not affect peak level of sensory block.

Table 3 shows that in patient of group D and C were less likely to experience shivering than group N. In group D and C no statistically significant difference were found for bradycardia, hypotension and shivering ($p > 0.05$).

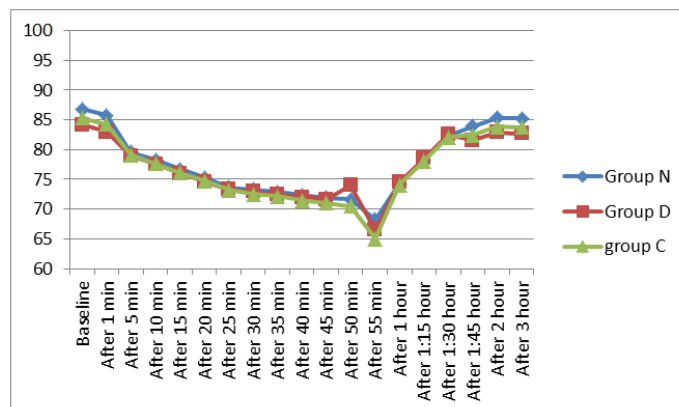


Fig-1: Distribution of Heart rate (beats per min)

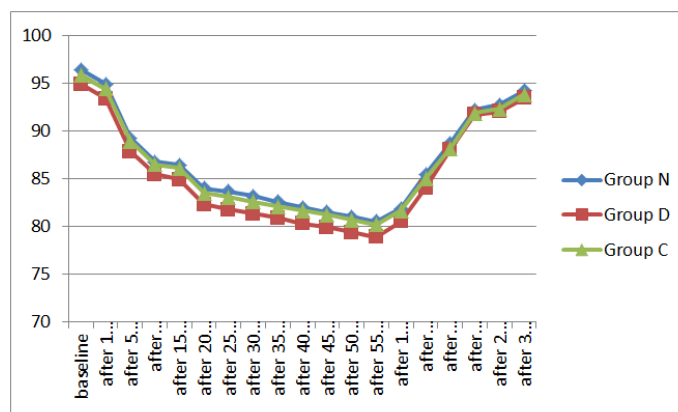


Fig-2: Distribution of Mean Blood Pressure (mm Hg)

Figure 1 and 2 shows that difference in mean heart rate and mean blood pressure (intraoperative and

postoperative period) in all three groups is not significant.

Table-4: Sedation score

Time	Group N	Group D	Group C	P value		
	Mean ±SD	Mean ±SD	Mean ±SD	N & D	N & C	D & C
Baseline	2.03±0.18	2.17±0.38	2.07±0.25	0.088	0.561	0.235
After 0.5 hour	2.03±0.18	2.1±0.31	2.07±0.25	0.309	0.561	0.647
After 1 hour	2.17±0.38	2.27±0.45	2.23±0.43	0.356	0.527	0.770
After 1.5 hour	2.1±0.31	2.2±0.41	2.17±0.38	0.286	0.456	0.744
After 2 hour	2.1±0.31	2.2±0.41	2.13±0.35	0.286	0.694	0.497
After 3 hour	2.07±0.25	2.17±0.38	2.1±0.31	0.235	0.647	0.456
After 4 hour	2.03±.18	2.13±0.35	2.07±0.25	0.167	0.561	0.398
After 6 hour	2.07±0.25	2.13±0.35	2.1±0.31	0.398	0.647	0.694
After 8 hour	2.03±0.18	2.1±0.31	2.03±0.18	0.309	1.000	0.309

Table 4 shows that maximum sedation score is in group D that is 2.27±0.45, in group N it is 2.17±0.38 and in group C it is 2.23±0.43. This difference is statistically not significant (p>0.05).

DISCUSSION

In modern anaesthesia post-operative analgesia became an integral part of anaesthesia. Many advances have occurred in this field, yet more efforts are required. In our study we have compared hyperbaric bupivacaine with saline (group N), with dexmedetomidine (group D) and with clonidine (group C). We compared the demographic data among three groups to verify the comparability of three groups. It was found that all demographic data (age, BMI, ASA grade) are comparable (table 1&2). We compared the mean time taken to achieve sensory block. It appears that dexmedetomidine might cause faster onset of sensory block but the difference between group N and D, N and C and D and C is statistically not significant (p >0.05). So it may be concluded that addition of low dose dexmedetomidine with bupivacaine and clonidine with bupivacaine in spinal anaesthesia didn't affect the onset of sensory block (table 3).

On comparison of motor block onset in three study groups, we found that dexmedetomidine causes faster onset of motor block but the difference between group N and D, N&C, D&C is statistically not significant (p >0.05) (table 3). These findings of onset of motor and sensory block were in concordance with results of Van Tuiji *et al.* [12] Kanazii *et al.* [13] and Al Ghenem *et al.* [11]. Al Ghenem *et al.* observed no significant difference in the onset time in the patients receiving dexmedetomidine and clonidine as adjuvant to isobaric bupivacaine. The onset times observed in the study conducted by us were relatively shorter than those observed by Al Ghenem *et al.* [11] which can be attributed to differences in patients positioning (lithotomy v/s supine).

We compared the mean time to achieve motor block from bromage scale level 3 to level zero (motor block duration). The difference in the motor block duration between group N v/s D, N v/s C and D v/s C was found to be highly significant statistically (p <0.001, table3). So addition of dexmedetomidine or clonidine to bupivacaine in spinal anaesthesia can be said to significantly increase the duration of motor blockade in comparison to addition of normal saline (control group). It was also found that the addition of

dexmedetomidine could significantly increase the duration of motor block in comparison to clonidine group. This duration of motor block as observed in our study, was markedly prolonged when compared to duration of motor block of 250 ± 76 min in study by Kanazi *et al* ($p<0.001$) and 240 ± 64 min in a study by Al Ghenem *et al.* ($p<0.001$), which could be attributed to higher intrathecal volume of drug (3ml used in our study as compared to 1.9 and 2.5 ml used in the respective studies) [13, 11].

The comparison of mean duration of analgesia among the group N v/s D, D v/s C showed highly significant difference ($p<0.001$) in our study (table 3). So hereby we infer that addition of dexmedetomidine to bupivacaine in spinal anaesthesia significantly increase the mean duration of analgesia in comparison to control group and group C. Addition of clonidine to bupivacaine in spinal anaesthesia also significantly increase the duration of analgesia in comparison to addition of normal saline, but on comparison of group D and C it is found that addition of dexmedetomidine increases the mean duration of sensory blockade significantly than addition of clonidine. The duration of analgesia as observed in our study in group D and C, was markedly lengthened when compared to the duration of analgesia of 303 ± 75 min and 272 ± 38 respectively in a study by Kanazi *et al.* ($p<0.001$), which could be attributed to higher intrathecal volume of drug (3ml) used in our study as compared to 2.5 ml used in their study [13]. The duration of analgesia as observed in our study in group D was also prolonged in comparison of study by Mustafa *et al*, they found 277.1 ± 23.2 min, which could be attributed to difference in definition of duration of analgesia and sensory regression to S1 and due to higher intrathecal volume of drug (3ml) in our study as compared to 2.5 ml used in reference study [14]. Our findings are also supported by similar studies done by B S Sethi *et al.* [15] and Dobrydnjov *et al.* [16], wherein it was concluded that there is significant prolongation of analgesia and motor blockade with intrathecal clonidine.

Intrathecal use of clonidine has a well-established synergistic effect with local anaesthetics [17]. The mechanism by which alpha-2 adrenergic agonist prolong the motor and sensory block of local anaesthetics is not clear. Intrathecal alpha2 adrenergic agonist produces analgesia by depressing the release of C- fibre transmitters and by hyperpolarization of post synaptic dorsal horn neurons [18]. The anti-nociceptive effect may be of possible explanation for the prolongation of sensory block when added to local anaesthetics. The prolongation of motor block in spinal anaesthesia may result from the binding of alpha 2 adrenergic agonists to motor neurons in dorsal horn [19].

In our study patients of D group experience higher level of sensory block than group C and N, but the difference in mean of peak level of sensory block between groups is statistically not significant ($p>0.05$). Our findings were in concordance with findings of Kanazi *et al.* [13]. So in conclusion it can be assumed that addition of low dose Dexmedetomidine and clonidine with bupivacaine in spinal anaesthesia does not affect peak level of sensory block. We also observed that peak motor blockade achieved on modified Bromage scale is same (level 3) in all groups, so it can be stated that the two drugs used in our study were equally efficacious.

Vital parameters observed in present study i. e. Pulse rate, mean BP do not show any significant change ($p>0.05$)(fig1&2). These findings are consistent with the finding of Gabriel JS and Gordin V [20], Kaabachi *et al.* [21], Dobrydnjov I *et al.* [16], Stephen Strebel *et al.* [17], Van Tuijl *et al.* [12] and B S Sethi *et al.* [15], who studied with clonidine and also with Kanazi *et al.* [13] and Mustafa *et al.* [14] who used dexmedetomidine in spinal anaesthesia.

On observing and analysing sedation score in present study (table 4), we found that sedation score are comparable at all intervals on intergroup comparison. This finding is consistent with the findings of studies done by Strebel S *et al.* [17], Mustafa *et al.* and Kanazi *et al.* [13]. Small dosages of adjuvants used in our study may be the reason for minimal or no sedation observed in any of the groups in our study. The intrathecal dose of dexmedetomidine used by Hala EA *et al.* (15ug) showed significantly higher sedation scores [22].

The most important side effects reported about the use of intrathecal alpha2 adrenoreceptor agonists in literature are bradycardia and hypotension [23]. In our present study, these side effects were not significant, the probable reason being the small doses of intrathecal dexmedetomidine, clonidine.

Most of the clinical experience gained in the use of intrathecal alpha-2 adrenoreceptor agonists has been described with clonidine [24-26]. There is a need for more and detailed clinical studies related to intrathecal dexmedetomidine with a larger patients pool, to prove its efficacy, safety and the suitable dose for supplementation to spinal anaesthetics and demarcate its side effect profile.

The present clinical study had the following limitations

- The effect of drug in older patients and in patients with comorbidities like cardiovascular system is not to be inferred from this study and needs further study.

- Oxygen at 4 litres per hour started immediately after spinal anaesthesia, so oxygen saturation data not analysed.

CONCLUSION

After analysing the results of present study with previous studies we conclude that use of low dose of dexmedetomidine (5ug) as an adjuvant to bupivacaine in spinal anaesthesia prolongs the duration of analgesia and motor blockade in comparison to clonidine (30ug) but effect on the onset of sensory and motor blockade, peak level of sensory blockade are similar. Low doses of dexmedetomidine and clonidine used for the spinal anaesthesia have minimal hemodynamic instability and do not cause any significant sedation intra and post-operative period.

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