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"Dose related prolongation of hyperbaric bupivacaine by dexmedetomidinein lower abdominal and limb surgeries requiring spinal anaesthesia " A randomized double blind controlled study.

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Abstract :
Background and Aims: *This study aims to investigate the effect of intrathecal administration of dexmedetomidine on the duration of sensory and motor block and postoperative analgesic requirements produced by spinal bupivacaine.*
Materials and Methods: *Ninety patients scheduled for major surgeries under spinal anaesthesia were chosen for the study. All patients received drug volume of 3.5ml containing 3 ml of hyperbaric bupivacine (15 mg). The study groups received dexmedetomidine 5 μg (group B,n = 30) or 10 μg (group C,n =30) diluted to 0.5 ml with 0.9% saline, added to bupivacaine in the same syringe, the control group (group A, n= 30) received an identical volume of 0.9% saline added to bupivacaine. Heart rate, arterial blood pressure, sensory level, motor block, pain and level of sedation were assessed intraoperatively and upto 24 hrs after spinal anaesthesia. The incidence of adverse effects were recorded.*
Result: *Dexmedetomidine significantly prolonged time to two segment regression, sensory regression, regression of motor block to modified Bromage 0 and time to first rescue analgesic. In addition, it significantly decreased postoperative pain scores. The effects were greater in group C than in group B. In addition, group C patients had higher sedation scores and lower postoperative analgesic requirements than group B or A. Hemodynamic stability was maintained in all the groups.*
Conclusion: *Intrathecal dexmedetomidine in dose of 5 μg and 10 μg significantly prolonged the anesthetic and analgesic effects of spinal hyperbaric bupivacaine in a dose dependent manner. A 10 μg dose may be benefit for prolonged surgical procedure.*
Key words: *α 2 adrenoreceptor agonist, bupivacaine, dexmedetomidine, spinal anesthesia.*

I. Introduction

Subarachnoid blockade is the most commonly used regional anesthetic technique for below umbilical major surgeries. Various adjuncts are being used with local anaesthetics for prolongation of intraoperative and postoperative analgesia. However, their use in thwarted either due to the adverse effects of adjuvants or unreliable postoperative analgesia.

Most of the clinical studies about the intrathecal α2 adrenergic agonist are related to clonidine[1.]Dexmedetomidine[2] is a highly selective α2 adrenoreceptor agonist that has been recently evaluated as an adjuvant to intrathecal local anaesthesia. Based on previous studies[3], we hypothesized that intrathecal dexmedetomidine 5 μg and 10 μg would prolong bupivacaine sensory block in a dose dependent manner without major hemodynamic effects.

Thus prospective randomized double blinded controlled trial investigated the effects of adding dexmedetomidine 5 μg and 10 μg to hyperbaric bupivacaine in patients scheduled for below umbilicalmajor surgeries. Time to two segment sensory regression of spinal blockade was the primary outcome studied and time of sensory block to reach $T_{10,}$ sensory regression to S_1, motor regression to modified Bromage 0, time to first rescue analgesic, verbal rating pain scores, sedation scores, postoperative analgesic use and occurrence of adverse effects were the secondary outcomes.

II. Materials And Methods

After obtaining approval from the Research Ethics Committee and informed consent, 90 adult patients ASA physical status I and II age between 15-65 years of either sex presenting for major surgeries, below umbilical level under spinal anesthesia were enrolled in this prospective randomized double blinded study. Exclusion criteria included emergency surgery, deformities of the spine, hypersensitivity to any of the drugs in the study and contraindication to spinal anaesthesia, patients refusal, bleeding diathesis. Before surgery, patients were given instruction to use a 10 points verbal rating scale (VRS) with 0 indicating no pain and 10 indicating

the worst imaginable pain. Baseline VRS were recorded. In the operative room ECG, pulseoximetry and non invasive blood pressure were recorded. Following infusion of 1000 ml Lactated Ringer's solution and with the patient in the sitting position under strict asepsis, a Lumbar Puncture was performed at L_3- L_4 inter space through a midline approach using a 25 G Quincke needle.

Using a computer generated random list, patients were randomized to three groups: group A, B and group C (n= 30 for each group). All patients received drug volume of 3.5 ml containing 3 ml of hyperbaric bupivacaine hydrochloride (15 mg). The study groups received dexmedetomidine 5 µg (Group B) or 10 µg (Group C) diluted to 0.5 ml with 0.9% saline, added to bupivacaine in the same syringe, the control group (A) received an identical volume of 0.9% saline added to bupivacaine. Patients, attending anesthetist and operating room personnel were not aware of patients allocation. Thereafter, patients were placed in the supine position for surgery. All patients received antibiotic prophylaxis according to the hospital protocol. Patients were premedicated with Tab Rantac 150 mg and Tab Alprex0.5 mg H.S.

Heart rate (HR), Blood pressure (BP) and Oxygen saturation (SpO_2) were monitored and recorded after the block every 5 minutes for half an hour then every 15 minutes until the end of surgery. The sensory block level was assessed with pin prick method and the motor block was assessed with modified Bromage scale. Modified Ramsay sedation scale was used for intraoperative sedation.

After operation, HR, BP, Oxygen saturation, sedation score and VRS scores at rest and with movement (active knee flexion) were recorded during the first hour at 15, 30, 45 and 60 minutes, and thereafter every hour upto 8 hrs after spinal injection, then at 12 and 24 hours. The time from intrathecal injection to two dermatome sensory regression, sensory regression to S_1 dermatome and motor block regression to modified Bromage 0 were recorded. All duration were calculated in relation to the time of spinal injection. Duration of pain relief was defined as the time from spinal injection to the first request for rescue analgesics which consisted of intravenous infusion of diclofenac 75 mg.

Occurrence of nausea, vomiting, pruritis and respiratory depression were recorded throughout the study duration Hypotension (defined as a decrease in systolic blood pressure > 30% of the baseline value or systolic blood pressure < 90 mm Hg) was treated with intravenous boluses of 6 mg ephedrine. Bradycardia defined as a pulse rate of < 50 beats/ min was treated withboluses of 0.3 - 0.5 mg atropine. Respiratory depression (RR< 8 or SpO_2< 95%) was treated with oxygen supplementation and respiratory support if required. All data collection was performed by a blinded observer.

Statistical analysis

Statistical analysis was performed with the SPSS, version 20 for Windows statistical software package (SPSS inc., Chicago,il, USA). The categorical data were presented as numbers (percent) and were compared among groups using Chi square test. The quantitative data were presented as mean and standard deviation and were compared using by ANOVA (Analysis of variance test).The post HOC Test Tukey Test was used for further analysis in the significant groups. Probability was considered to be significant if less than 0.05.

III. Results

Total 90 adults consented patients undergoing surgeries under spinal anaesthesia were randomized to three equal groups of 30 patients.

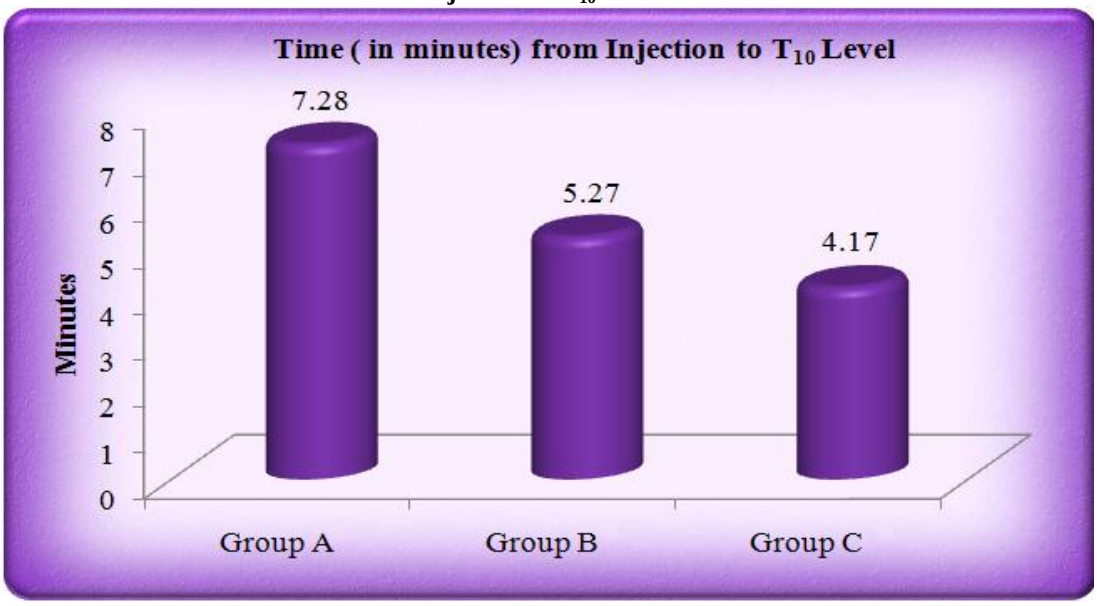
The mean age of the patients among groups was comparable and is shown in table 1.

Table No. 1: Age Wise Distribution of The Cases

Mean Age (in years)						
Age	**N**	**Mean**	**Std. Deviation**	**Minimum**	**Maximum**	**P Value LS**
Group A	30	35.2	13.278	18	64	
Group B	30	30.8	12.299	18	63	0.28 NS
Group C	30	30.87	10.76	18	59	

Distribution of the cases according to time form injection to T_{10} level (in minutes) in all groups is shown in figure 1.

Figure 1: Distribution of The Cases According to Time (minutes) from Injection to T_{10} Level



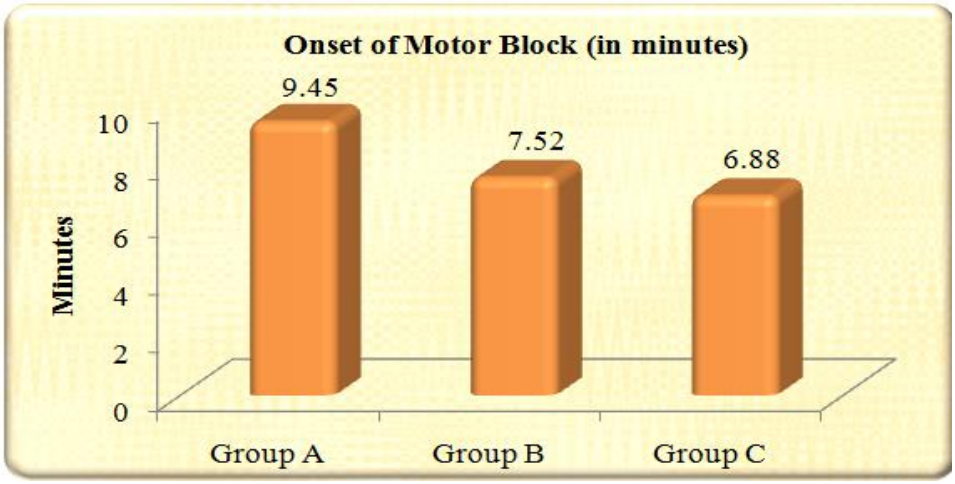
Significant difference was observed in mean time (in minutes) from injection to T_{10} level of the patients among all the groups. On applying post hoc Test Tukey Test, it was observed that the mean time was significantly higher in group A as compared to group B and C, and also group B and C was significantly differ i.e. (mean of group A> B > C).
The highest sensory level (in minutes) in all the groups is shown in Table 2.

Table 2: The Highest Sensory Level (in minutes) in All The Groups

Groups	N	Mean Time (in minutes)	Std. Deviation	ANOVA Test P Value	Significant groups
Group A	30	10.78	1.20		1 vs 3
Group B	30	7.97	1.25	<0.001 s	1 vs 2
Group C	30	6.33	1.18		2 vs 3

Significant difference in time was observed to achieve highest sensory level in all the groups. It was higher in group A as compared to group B and C, and also Group B and C differed significantly i.e. (mean of group A > B > C).
The onset of motor block (in minutes) in all groups is shown in figure 2.

Figure 2:The Onset of Motor Block (in minutes) in All Groups



Significant difference in time was observed to the onset of motor block in patients of all the groups. It was observed that the mean time was significantly higher in group A as compared to Group B and C, and Group B and C also differed significantly i.e. (mean of group A > B > C).

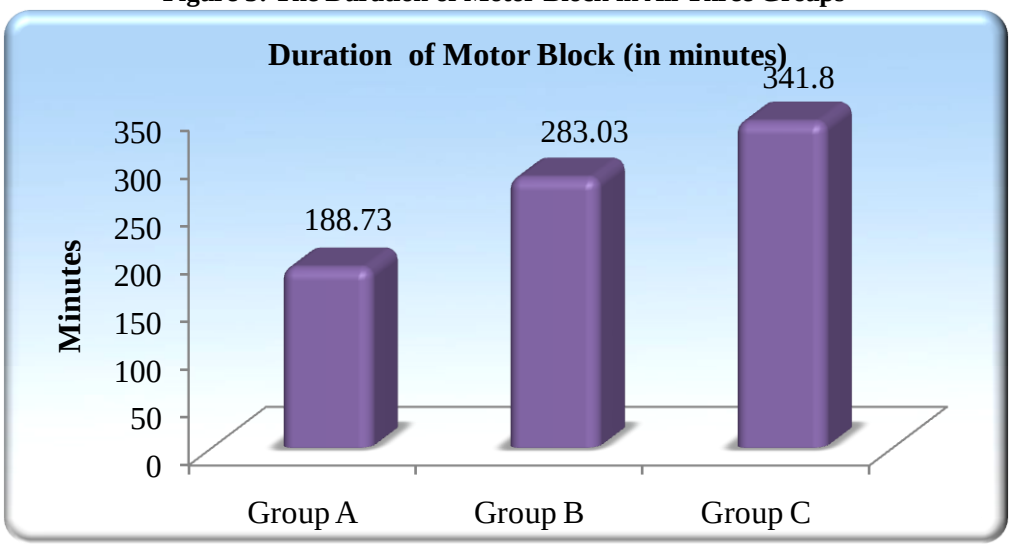
Significant difference in time of duration of analgesia (in minutes) was observed in all patients of the three groups as shown in Table 3.

Table No 3: The Duration of Total Analgesia in All Groups

Groups	N	Mean Time (in minutes)	Std. Deviation	ANOVA Test P Value	Significant groups
Group A	30	210.33	15.79		3 vs 1
Group B	30	308.90	38.03	<0.001 s	3 vs 2
Group C	30	416.47	37.96		2 vs 1

It was observed that the mean time was significantly higher in group C as compared to Group B and A, and Group A and B had significant difference in mean time i.e. (mean of group C > B >A).
The duration of motor block in all the three groups is shown in figure 3.

Figure 3: The Duration of Motor Block in All Three Groups



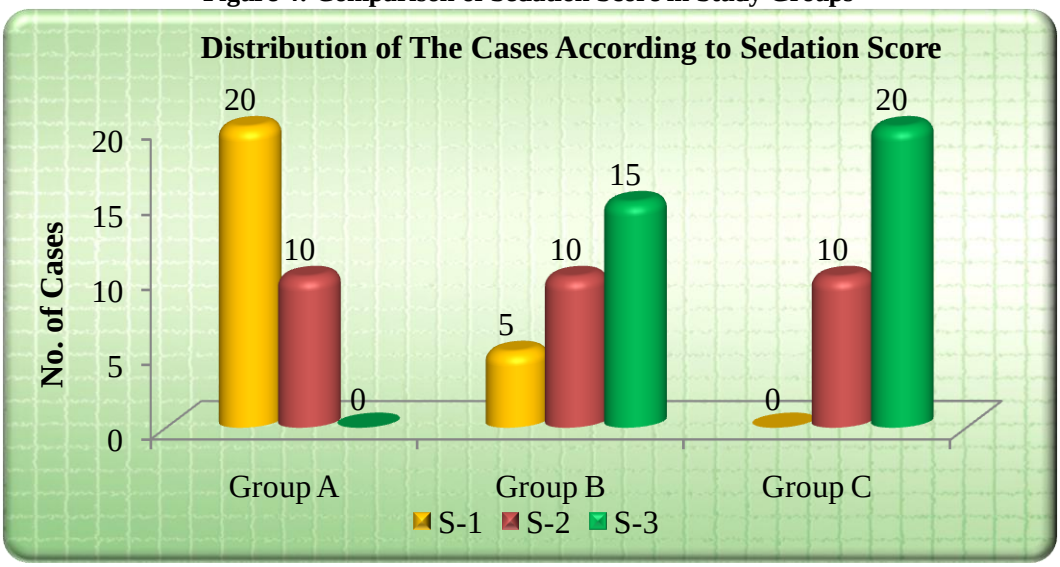
It was observed that the mean time was significantly higher in group C as compared to Group B and A, and Group C and B were also significantly different in total duration of motor block i.e. (mean of Group C > B > A).
Comparison of patients achieving maximum dermatome level done in all three study groups as shown in Table 4.

Table No 4: Comparison of Patients Achieving Maximum Dermatome Level

	Group A		Group B		Group C		Total
	No.	%	No.	%	No.	%	No.
T 4	1	7.69	4	30.77	8	61.54	13
T 5	4	25	4	25.00	8	50.00	16
T 6	9	32.14	8	28.57	11	39.29	28
T 7	7	46.67	8	53.33	0	0.00	15
T 8	9	52.94	5	29.41	3	17.65	17
T-10	0	0	1	100.00	0	0.00	1

It was found that T_4 dermatome level was achieved more (61.54%) in group C as compared to other Groups and least (7.69%) cases were in group A. Comparison of all patients to achieve maximum sedation score during study showed that sedation was significantly higher (57.14%) in group C as compared to other groups and least (0%) was in group A as shown in figure 4.

Figure 4: Comparison of Sedation Score in Study Groups



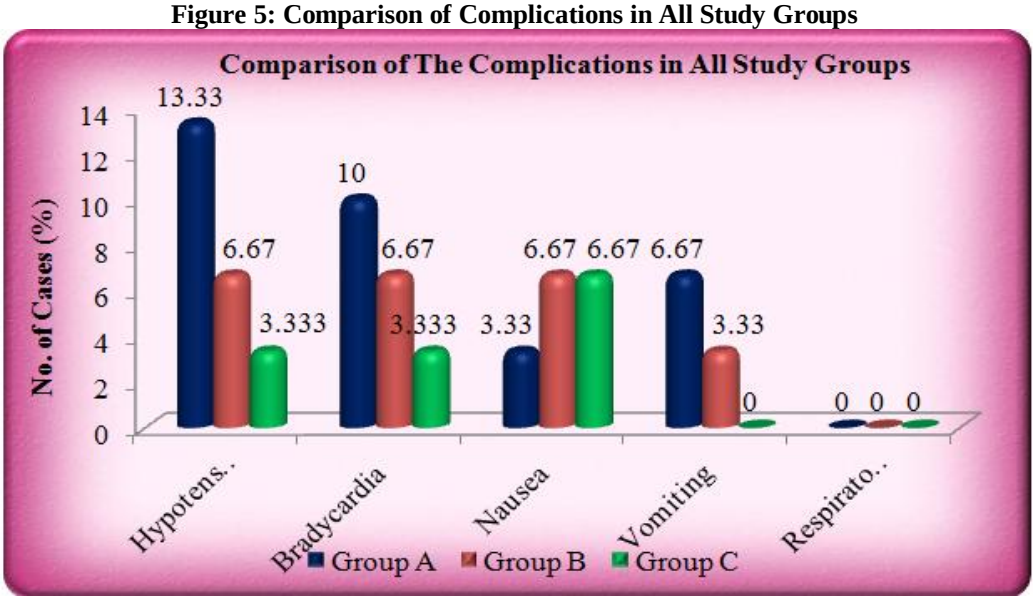
Significant difference in requirement of rescue analgesia (in minutes)was observed in patients of all the groups. On applying post Hoc Test Tukey Test, it was observed that requirement of rescue analgesia was significantly higher in group A as compared to Group B and C, and Group C & B also differed significantly i.e. (mean of group C >B >A) as shown in Table 5.

Table No. 5: Comparison of Requirement of Rescue Analgesia (in minutes)

Groups	N	Mean Time (in minutes)	SD	ANOVA Test	Significant groups
Group A	30	237.80	17.688	<0.001 S	3 vs 1
Group B	30	331.03	41.517		3 vs 2
Group C	30	433.30	51.817		2 vs 1

No significant mean difference was observed in baseline hemodynamic par meters, mean arterial pressure, mean heart rate and mean SpO_2at different time interval among the groups.
Comparison of the complication in all study groups as shown in figure 5 revealed no significant complication in all the groups. Hypotension (13.3%) followed by bradycardia (10%)was observed in group A and same pattern was observed in group B, and Nausea(6.67%)was common in group C. No cases had respiratory depression.

Figure 5: Comparison of Complications in All Study Groups



IV. Discussion

a) Spinal anaesthesia is the most preferred regional anaesthesia technique as it is easy to perform, produces rapid onset ofanaesthesia and complete muscle relaxation andis also economical. These advantages are sometimes offset by a relatively short duration of action.
b) Hyperbaric bupivacaine is the most commonly used intrathecal local anesthetic. Various adjuvants have been added to bupivacaine to shorten the onset of block and prolong the duration of block.
c) Dexmedetomidine has been used intrathecally in varying doses ranging from 3 µg to 15 µg[3,4,5]. The optimal dose of intrathecal dexmedetomidine has not been established.
d) This study shows significant prolongation of the duration of spinal blocked by intrathecal administration of dexmedetomidine as an adjunct to hyperbaric bupivacaine for patients undergoing lower abdominal and limb surgeries. Patients in the groups that received dexmedetomidine had reduced post operative pain score and a longer analgesic duration than those who received spinal bupivacaine alone. This effect appears to be dose dependent and more pronounced with the dose of 10 µg.
e) 10 µgdexmedetomidine but not 5 µg was associated with lower 24 hours analgesic requirements and desirable level of sedation. No hemodynamic instability or increased side effects were reported.

Dexmedetomidine, the pharmacologically active d-isomer of medetomidine is a highly specific and selective α2adrenoreceptor agonist with α2 : α1 binding selectivity ratio of220 : 1 for clonidine, thus decreasing the unwanted side effects of α1 receptors.

Presynaptic activation of α2 adrenoreceptor in central nervous system inhibits the release of norepinephrine, terminating the propagation of pain signals and their post synaptic activation inhibit sympathetic activity, thereby decreasing HR and BP. Baroreceptor reflex and HR response to pressure agent is well preserved with the use of dexmedetomidine, thus hypotension and bradycardia are easily treatable conferring hemodynamic stability. High selectivity for α2 adrenoreceptorsmediate analgesia, sedation and anxiolysis. In our study, we observed that onset of sensory block was earlier in study group of dexmedetomidine 10 µg having a mean value of 4.17 ± 1.132 minutes in comparison with study group of dexmedetomidine 5 µg having mean value of 5.27 ± 0.833 minutes and with control group of bupivacaine alone having mean value of 7.28 ± 1.080 minutes which is statistically significant (P = < 0.001). This observation well matches with study of Abdul KadirYektas, Enver Belli [6] and Hala EA Eid MD et al [7]and SusantaHalder, Anjan Das et al[8]. Onset of motor block was earlier in study group of dexmedetomidine 10 µg having the mean value of 6.88 ± 0.887 minutes and in comparison the study group of dexmedetomidine 5 µg had a mean value of 7.52 ± 0.725 minutes and control group bupivacaine alone had a mean value of 9.45 ± 1.262 minutes which is statistically significant.Abdul KadirYektas, Enver Belli [6] and RamilaH Jamaliya et al [9] observed that bupivacaine alone group had faster onset of motor block than group receiving dexmedetomidine as adjuvant. In another study done by Hala E.A.Eid MD et al [7], stated that patients receiving dexmedetomidineintrathecally as an adjuvant had faster onset of motor block than patients receiving bupivacaine alone.

Rachna Joshi, Jignesh Mori et al [10,] observed in their study that patients receiving bupivacaine alone intrathecally had mean time of onset of motor block of 5.2 ± 0.8 minute, which is faster than patients receiving bupivacaine with dexmedetomidine 5 µg (8.45±1.0 minute).Total duration of motor block was found to be 341.80 ± 41.71 min in study group of dexmedetomidine 10 µg compared to study group B having 282.03 ± 28.03minutes and control group of bupivacaine alone having mean value of 188.73 ± 18.64 min and this difference was statistically significant (p = <0.001). This observation well matches with study of Hala E A Eid MD et al [7] andRamila H Jamaliya et al [9,] and Abdul Kadir, Yektas, Enver Belli[6]

The mean time of total duration of analgesia was 416 ± 37.96 minutes in study group of dexmedetomidine 10 µg and 308.90 ± 38.03 minutes in group receiving dexmedetomidine 5 µg and 210.33 ± 15.79 minutes in control group of bupivacine alone, which is statistically significant (p = < 0.001). Our study matches with the study of Hala E A Eid MD et al [7] and Ramila H Jamaliya et al [9]and Rachana Joshi, Jignesh Mori et al [10] The mean time from onset of motor block to request of analgesia is taken as rescue analgesia. It was 433.30 ± 51.817 minutes in dexmedetomidine 10 µggroup, 331.03 ± 41.517 minutes in dexmedetomidine 5 µg group and 237.80 ± 17.688 minutes in control group which is statistically significant (P= <0.001)

Abdel Hamid and El lakany[5]and Hala EA Eid MD et al[7] concluded in their study that dexmedetomidine significantly decreases the requirement of post operative analgesia in dose dependent manner and it is beneficial to decrease the requirement of rescue analgesia significantly.During our study we noticed a decrease in systolic, diastolic as well as mean arterial blood pressure in group C but none of the patients had hypotension and maintained the hemodynamic parameters well within the normal range as compared to dexmedetomidine 5 µg and control group of bupivacaine alone. In our study we recorded decrease in pulse rate though it was not statistically significant. Hala EA Eid MD et at [7] and Rachana Joshi, Jigneshmori et al [10], Abdul KadirYektas, Enver Belli [6], Ramila H Jamaliya et al [9]observed that dexmedetomidine as an adjuvant to intrathecal anaesthetic agent provides excellent hemodynamic stability including BP, HR, S_PO_2

In this study we compared all patients to achieve the maximum dermatome level and found that dexmedotomidine 10 µggroup has 61.54% patients reaching to maximum dermatome level (T_4) which was significantly more as compared to group receiving dexmedetomidine 5 µg (30.77%) and bupivacaine alone (7.69%) Rachana Joshi, Jignesh Mori et al [10], Abdul KadirYektas, Enver Belli [6], Ramila H Jamaliya et al [9], Hala EA Eid MD et al [7] observed in their respective studies that intrathecal administration of dexmedetomidineas an adjuvant provides ability to reach maximum dermatome level and provide excellent muscle relaxation for surgery. In our study we observed that dexmedetomidine has sedative property as it provides good sedation when used intrathecallyas an adjuvant. No respiratory depression was noted among the patients.

There is decrease in systolic, diastolic as well as mean arterial blood pressure in group C but only one patient had hypotension and bradycardia as compared to other groups though was not significant.

To conclude, dexmedetomidine in different doses (5 µg and 10 µg) when added to hyperbaric bupivacaine for subarachnoid block, shortens the onset times for sensory and motor block and prolongs their duration (10 µg> 5 µg). The significantly prolonged duration of analgesia obviated the need for any additional analgesics. The added advantage of conscious sedation, hemodynamic stability and minimal side effects make it a potential adjuvant for subarachnoid blocks.

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