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Comparative Study of Low Dose of Dexmeditomidine and Clonidine on the Characteristics of Intrathecal Bupivacaine - Prospective Randomized Study

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Abstract
Introduction: *Spinal Anaesthesia, most commonly used technique for lower abdominal surgeries as it is very economical and easy to administer. A number of adjuvants like midazolam, fentanyl, clonidine etc have been used to improve the quality of subarachnoid block. Dexmeditomidine an α2-adrenergic agonist which has α2/ α1 selectivity ratio eight times greater than Clonidine has been used recently as an adjuvant in various clinical trials. The aim of the study was to compare the Subarchnoid block characteristics with low dose dexmeditomidine or chlonidine added to intrathecal Bupivacaine.*
Methodology: *After institutional ethics committee approval and written informed consent, 60 ASA i-ii patients of both sexes included in the study. Patients allocated into three groups of 20 each randomly. Group B received 3ml of 0.5% Hyperbaric Bupivacaine with 0.2ml saline.Group C received 3ml of 0.5% Hyperbaric Bupivacaine with 0.2ml (30µg) of clonidine. Group D received 3ml of 0.5% Hyperbaric Bupivacaine with 0.2ml (5 µg) Dexmeditomidine. Total valume was made upto 3.2ml to achieve subarchnoid block. Sensory, motorblock characteristics, Haemodynamic parameters, adverse effects, duration of analgesia, Statistical analysis and results were noted in all the groups. Statistical analysis was done with one way analysis of variants (ANOVA).The duration of Sensory and Motor blockade were significantly longer in groups C & D than group B.(P<0.01). Time to 1st request for analgesia was significantly longer in Group D than Group C and Group B (P<0.01)*
Conclusion: *Addition of clonidine or dexmeditomidine to intrathecal bupivacaine significantly prolonged the duration of Sensory and Motor blockade , the duration of Post-Operative analgesia without causing significant side effects.*
Key Words: *Bupivacaine, Clonidine, Dexmedetomidine, effects of low dose Dexmedetomidine and clonidine on the characteristics of intrathecal Bupivacaine, Subarchnoid block*

I. Introduction

Spinal Anaesthesia is the most commonly used technique for lower abdominal surgeries as it is very economical easy to administer and safe. However local anaesthetics alone for Subarchnoid block is associated with relatively short duration of action.iAddition of adjuvants like Fentanyl, Midozolam,Ketamine,Clonidine etc., to intrathecal Bupivacaine significantly prolonged the duration of spinal anaesthesia and also improved the quality of spinal blockade in various clinical studies[1,2]. A common problem during lower abdominal surgeries under spinal anaesthesia is visceral pain, nausea and vomiting[3].This problem can be overcome by the addition of adjuvants to improve the quality of block[4]. Clonidine, an α2 agonist has been proved in various clinical studies to increase the duration of sensory and motor blockade, duration of analgesia and quality of subarchnoid blockade[5]. But Clonidine is associated with bradycardia and hypotension in the intra operative period[6]. Recently Dexmeditomidine , α2 agonist has been proved in various clinical studies to improve the quality of sensory and motor block characteristics when added to 0.5% hyperbaric bupivacaine for lower abdominal surgeries[7,8]. Its α2/ α1 selectivity ratio was 8 times higher than that of clonidine[9,10]. The aim of the study was to compare the characteristics of sensory and motor blockade, time to first request of analgesia, Hemodyanamic changes and adverse effects following intrathecal bupivacaine Vs intrathecal bupivacaine with low dose clonidine or Dexmedetomidine.

II. Methodoly:

After institutional ethics committee approval and written informed consent, 60 A S A – Grade_I – II patients of both sexes, aged between 20-50yrs were included in the prospective controlled and randomized study. This study was done in Government General Hospital, Vijayawada, Siddhartha Medical College. Randomization was done by using Computer generated Random number Tables.

Exclusion Criteria:

- ASA grade >III
- Patients below 20yrs and above 50yrs of age
- Patients with H/O any contraindications to spinal anaesthesia.
- Patients with severe systemic diseases, metabolic disorder, neurological, congenital and cardio vascular diseases.
- Patients with H/O allergy to study drugs i.e., Bupivacaine, Clonidine, Dexmedetomidine.

Two investigators were involved in the study. The observer anaesthesiologist who did intra operative and post operative monitoring was blinded to the study drug. Patients were randomized into three groups of 20 each into B,C&D groups.

Base line parameters like HR, NIPB, RR and SPO_2 were recorded in all the three groups. After shifting the patient to operating room routine monitors like NIBP, SPO_2 and electro cardiogram were applied to the patient. 18G IV canula was secured. All emergency resuscitative equipment was kept ready. All patients were preloaded with 500ml of Ringer's Lactate prior to spinal anaesthesia.

GROUP B : (n=20) patients received 3ml of 0.5% hyperbaric bupivacaine with 0.2ml of 0.9% saline.
GROUP C: (n=20) patients received 3ml of 0.5% hyperbaric bupivacaine with 30µg of clonidine.
GROUP D : (n=20) patients received 3ml of 0.5% hyperbaric bupivacaine with 5µg of Dexmedetomidine.
In all the groups the total volume administered was made upto 3.2ml to achieve subarchnoid block. Under strict aseptic conditions lumbar puncture was performed by midline approach by using disposable 25G Quinke Babcock needle at L_3-L_4 interspace. Intraoperatively bradycardia was treated with 1mg of IV atropine and Hypotension was treated with rapid boluses of IV fluids and increments of 6mg of Ephedrine.

The following parameters were observed.

1. Sensory block was assessed using pin-prick method. Onset time and duration of sensory blockade was recorded.
2. Motor blockade was assessed using Bromage Scale. Onset time and duration of motor blockade were noted between the three groups.
3. Haemodynamic parameters like Heart rate, Systolic Blood pressure, Mean arterial Blood Pressure and diastolic Blood Pressure were noted between the groups.
4. Time to1st request of analgesia (the duration of post operative analgesia) was compared between the groups.
5. Adverse effects were also noted between the groups. The possible adverse effects like nausea and vomiting, hypotension, Brodycardia, Respiratory depression, shivering, pruritus, motor weakness, drymouth, seizerus etc, were noted.

III. Statistical Analysis:

Demographic data was using fischers exart test. Sensory and motor block characteristics were analysed using one-way analysis of variance after Student-t test. Time to 1st request of analgesia was assessed using Student-t test. Data was expressed in mean, standard deviation, absolute numbers and percentage. $P<0.05$ was considered significant.

Table – 1: BROMAGE SCALE

	BROMAGE SCALE
0	Free movement of legs and feet, with ability to raise extended leg
1	Inability to raise extended leg and knee flexion is decreased but full flexion of feet and ankle is present
2	Unable to flex knees but some flexion of feet and ankle is possible
3	Unable to move feet, legs or toes

IV. Results:

60 Patients were included in the study. All patients completed the study. None of the patients had inadequate or failed block. All patients were comparable regarding demographic characteristics like age, height, weight, ASA status and duration of surgery.$P>0.05$ statistically not significant.(Table-2)

Table – 2: DEMOGRAPHIC DATA

	B (n=20)(control)	C (n=20) (Clonidine)	D (n=20) (Dexameditomidine)	P Value
Age in years	41.4 ± 7.49	39.8 ± 6.78	42.4 ± 8.54	0.398
Height in Cms	160 ± 4.5	162 ± 2.5	165 ± 1.2	0.35
Weight in Kgs	58 ± 9.8	62 ± 5.6	64 ± 9.4	0.06
ASA Status I/II	11/9	12/8	9/11	
Duration of Surgery (in mts)	75.5 ± 9.36	82.3 ± 0.5	80.17 ± 7.92	0.08

Data expressed in Mean, Standard Deviation and absolute numbers. P value insignificant

There were no significant differences in the baseline Haemodynamic parameters like PR, MAP and SBP in all the three groups. P>0.05, statistically not significant.

After intrathecal Bupivacaine there is invariable fall in systolic Blood pressure in all the three groups between first 15 to 20 minutes, followed by gradual recovery. The difference of fall in systolic Blood pressure between groups at different time intervals was statistically insignificant (P>0.05),(Table-3).

Table -3: PERIOPERATIVE SBP (SYSTOLIC BLOOD PRESSURE)

Time in mts	B(n=20)	C(n=20)	D(n=20)	PValue
0	124.3 ± 7.87	122.2 ± 14.55	126.2 ± 14.25	P>0.05
3	120 ±11.77	120.55 ± 19.71	126.4±15.37	P>0.05
6	111.9 ± 13.42	111.4 ± 25.28	122.85 ± 21.27	P>0.05
9	113.65 ± 15.37	113.75 ± 20.43	125.85 ± 21.49	P>0.05
12	110.9 ± 13.85	112.3 ± 14.04	112.4 ± 12.86	P>0.05
15	113.65 ± 12.1	107.8 ± 14.38	116.5 ± 11.7	P>0.05
20	111.5 ± 11.52	110.45 ± 12.47	111.35 ± 16.51	P>0.05
25	113.5 ± 9.38	109.5 ± 13.14	110.75 ± 13.49	P>0.05
30	112.35 ± 9.84	102.85 ± 13.46	112.01 ± 13.24	P>0.05
35	112.85 ± 10.30	105.5 ± 13.43	112.8 ± 10.54	P>0.05
40	111.7 ± 11.23	107.5 ± 12.71	111.8 ± 9.47	P>0.05
45	111 ± 12.86	109.9 ± 12.23	112 ± 10.55	P>0.05
60	120 ± 10.44	114.35 ± 14.33	115.85 ± 13.5	P>0.05
90	125.2 ± 10.7	117.3 ± 12.24	114.95 ± 12.55	P>0.05

Data expressed in Mean and standard deviation

Table – 4: PERIOPERATIVE PULSE RATE

Time in mts	B(n=20)	C(n=20)	D(n=20)	PValue
0	86.25 ± 13.84	87.05 ± 8.52	91.6 ± 8.21	P>0.05
3	91.8 ± 13.84	88.15 ± 7.66	92.8 ± 12.06	P>0.05
6	91.3 ± 12.48	85.1 ± 5.72	93 ± 12.08	P>0.05
9	92.75 ± 15.35	85.25 ± 7.55	93.15 ± 16.02	P>0.05
12	87.95 ± 11.99	84.45 ± 9.57	94.9 ± 16.24	P>0.05
15	87.6 ± 11.96	84.9 ± 6.91	91.3 ± 9.64	P>0.05
20	89.1 ± 11.51	85.1 ± 6.86	86.75 ± 11.21	P>0.05
25	87.9 ± 7.95	84.35 ± 5.68	85.05 ± 9.85	P>0.05
30	89.05 ± 10.27	87.2 ± 5.56	87.9 ± 8.97	P>0.05
35	86.85 ± 10.24	87.45 ± 4.86	86.4 ± 9.02	P>0.05
40	87.95 ± 11.83	86.3 ± 5.05	84.75 ± 7.29	P>0.05
45	85.8 ± 9.47	84.15 ± 4.6	84.6 ± 8.67	P>0.05
60	83.85 ± 8.92	83.9 ± 8.92	88.45 ± 11.64	P>0.05
90	80.7 ± 7.14	85.6 ± 7.14	88.55 ± 10.22	P>0.05

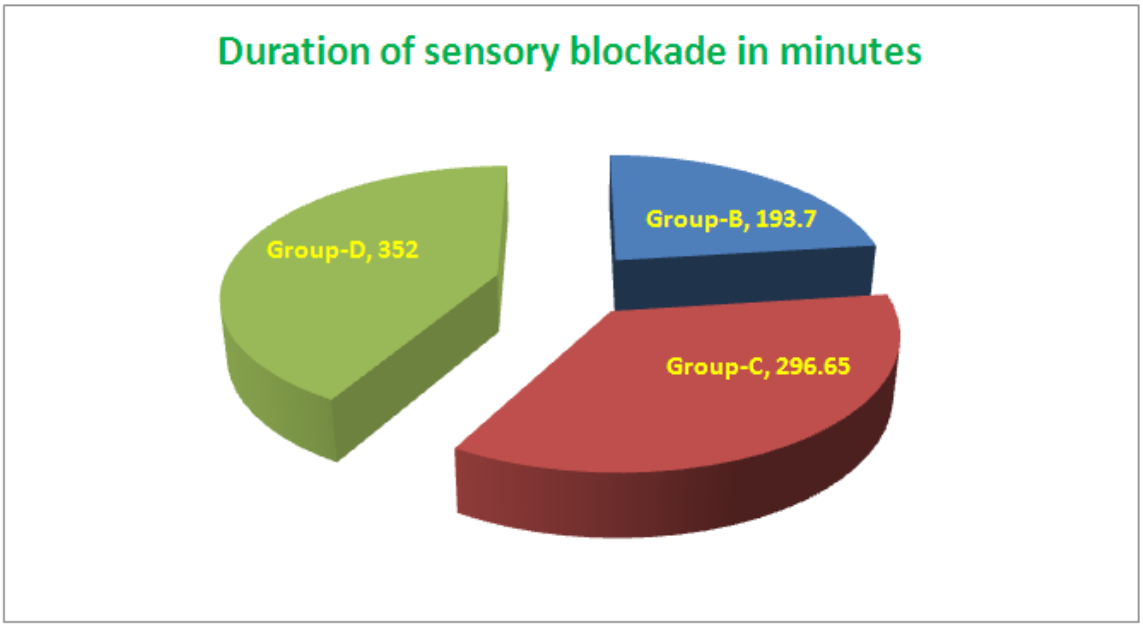
Data expressed in mean and standard deviation

The onset of Sensdory blockade was 3.95 ± 6.92 minutes in group B, 4.5 ± 1.36 minutes in group C, 4.2 ± 1.08 minutes in group D. The difference between the groups was statistically insignificant; (Table-5).

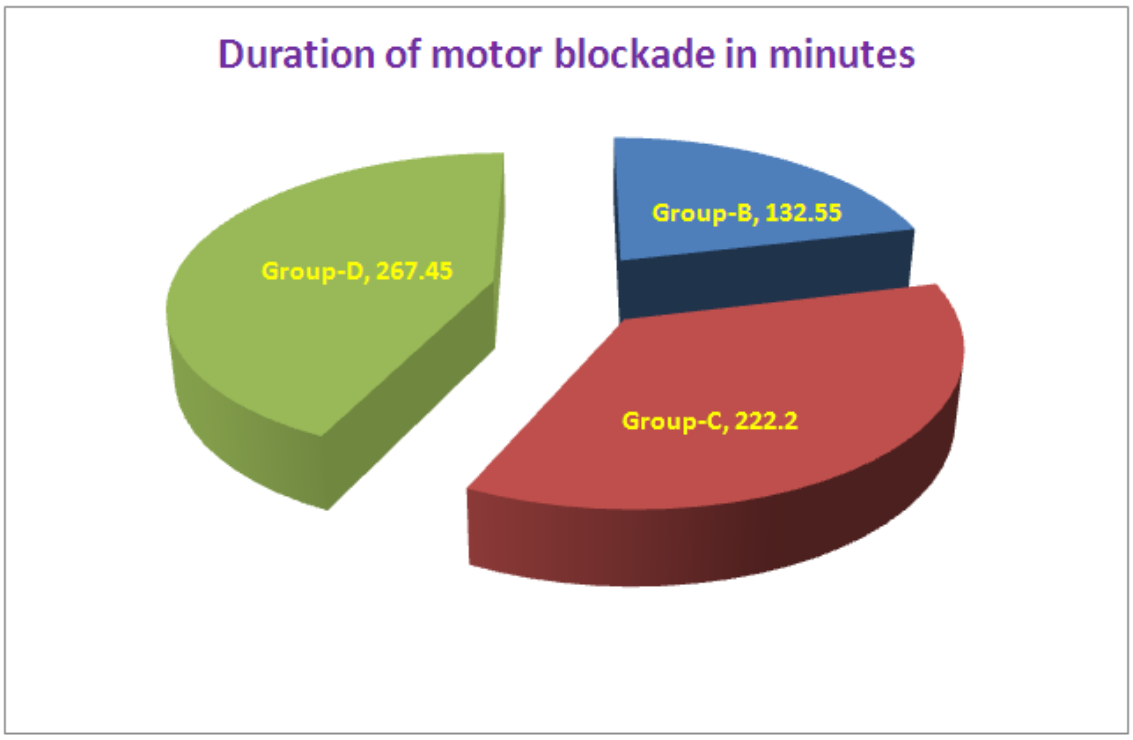
Table – 5: Sensory and Motor Block characteristics

	B	C	D	P Value
Onset of Sensory blockade	3.95 ± 0.92	4.5 ± 1.36	4.2 ± 1.08	P>0.05$^{(*)}$
Onset of Motor blockade	7.05 ± 1.69	6.95 ± 1.53	5.55 ± 1.36	P<0.01$^{(+)}$
Duration of Sensory blockade	193.7 ± 26.88	296.65 ± 38.8	352 ± 47.74	P<0.01 $^{(+)}$
Duration of Motor blockade	132.55 ± 23.81	222.2 ± 45.36	267.45 ± 49.22	P<0.01$^{(+)}$

Data expressed in mean and standard deviation.
(*) P>0.05 statistically insignificant
(+) P<0.01 satistically highly significant
Figure – 1: Duration of sensory blockade
The onset of motor blockade was 7.05 ± 1.69 minutes in group B, 6.95 ± 1.53 in group C and 5.55 ± 1.36 in group D. The difference between groups was statistically highly significant, P<0.01(Table-5).
The time for complete sensory recovery was 193.7 ± 26.88 minutes in group B, 296.65 ± 38.8 minutes in group C and 352 ± 47.74 minutes in group D. The difference between the groups was statistically highly significant, P<0.01(Table-5), (Figure 1).



The time for complete Motor recovery was 132.55 ± 23.81 in group B, 222.2 ± 45.36 minutes in group C and 267.45 ± 49.22 in group D. The difference between the groups was statistically highly significant, P<0.01, (Table-5), (Figure-2).



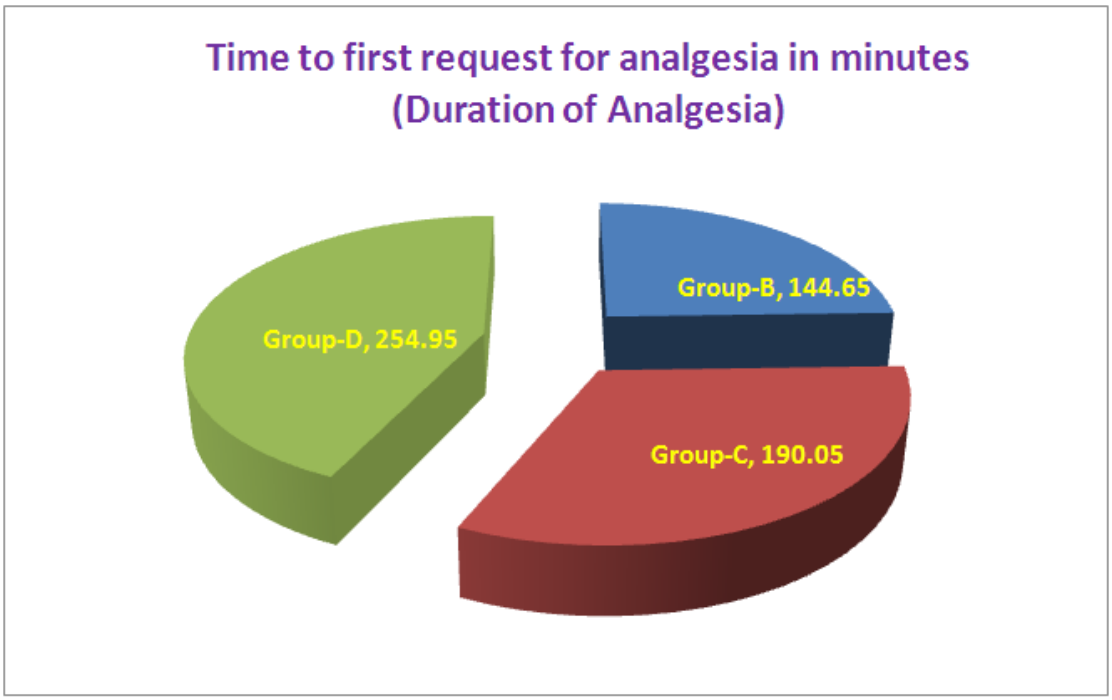
Time for 1st request of analgesic by the patients was 144.65 ± 26.39 minutes in group B, 190.05 ± 23.21 minutes in group C and 254.95 ± 57.27 minutes in group D. The difference between the group was statistically highly significant, P<0.01, (Tabel-6), (Figure-3).

Table – 6 : Time to first request of Analgesia

	B (n=20)	C (n=20)	D (n=20)	P Value
Time in minutes	144.65 ± 26.39	190.5 ± 23.21	254.95 ± 57.27	P<0.01

Data expressed in mean and standard deviation. P Value is highly significant.

Figure – 3



The incidence of hypotension was highest in group C (85%) and group D (65%) when compared to control group B (35%), P<0.05, statistically significant, (Table-7). There was no significant differences in the incidence of Bradycardia between three groups,P>0.05(Table-7). The requirement of Ephedrine was high in group C(85%) and group D(65%) the group B(35%). The incidence of side effects like Nausea and vomiting was not significant between the groups, P>0.05 (Table-7). None of the patients in all three groups had respiratory depression, pruritus and urinary retention.

Table – 7: Incidence of Side Effects

	B(n=20)	C(n=20)	D(n=20)
1.Hypotension	7(35%)	17(85%)	13(65%)
2.Brodycardia	0	1(5%)	2(10%)
3. Nausea & vomiting	0	1(5%)	1(5%)

V. Discussion:

Spinal Anaesthesia is the most commonly used regional anaesthesia technique especially for lower abdominal surgeries using local anaesthetics alone will provide less duration of analgesia. In order to improve the quality of analgesia aswellas to provide extended post operative analgesia various adjuvants are being added to entrathecal local anaesthetics, of which recently α_2 agonists have gained prominence due to their multiple beneficial effects, like prolonged post operative analgesia, opioid sparing effects, stable haemodynamics, reducing post operative analgesia requirements, facilitating early ambulation and reduction of hospital stay[12,13].

The principal mechanism by which intra thecal clonidine and dexmedetomidine provides analgesia is through α_2-agonistic action in the spinal cord. Dexmedetomidine is highly selective with a much greater affinity for α_2-receptors over α_1.receptors (1620:1) than clonidine(8:1). The α_2A receptors are located in the locus coeruleus and are responsible for sedation, anxiolysis and sympatholysis mediated by G-protein inhibition of α-

type calcium channels in the post-synaptic receptors. α_2B and α_2C receptors are located mainly in the dorsal horn of spinal cord and their activation inhibits nociception.

The patients studied across the three groups did not vary much with respect to demographic variables. In the present study, the incidence of hypotension was significantly high in group C and group D than group B. Similarly the incidence of fall of mean arterial pressure is more with clonidine-Bupivacaine group than dexmedetomidine-Bupivacaine and Bupivacaine alone in this study.

In a study conducted by B.S.Sethi, Mary et.al, who added intrathecal clonidine to Bupivacaine for gynaecological surgeries, concluded that patients in clonidine group had significant fall in MAP and heart rate than Bupivacaine group alone.

AM EL-HENNARY, A M Abd – Elwahab et.al, added clonidine or dexmedetomidine to caudal bupivacaine for lower abdominal surgeries in children. They concluded that the duration of analgesia was significantly prolonged with clonidine or dexmedetomidine without any significant haemodynamic and adverse effects[16].

Subhi M.Al-Ghanen, Islam M.Massad et.al, in their double blinded study on vaginal hysterectomies, evaluated the effects of intrathecal dexmedetomidine or fentanyl with 0.5% hyperbaric bupivacaine and concluded that patients of dexmedetomidine group had significantly prolonged durations of sensory and motor blockade[17].

The results of the above studies co-related with the observations of our study with respect to sensory and motor block characteristics and prolonged post-operative analgesia. In the present study, the onset times of sensory blockade between groups was statistically insignificant ($P>0.05$). The onset times of motor blockade was significantly less between groups in our study, it was shorter in dexmedetomidine and clonidine group when compared to control group.

Gecaj –Gashi A, Terziqui H,et.al; In their prospective double blinded study in patients posted for TURP surgical procedures, evaluated the efficacy of Bupivacaine versus Bupivacaine-clonidine intrathecally and concluded that Bupivacaine – clonidine combination improved the duration and quality of spinal anaesthesia while providing longer duration of post operative analgesia without significant side-effects[18].

In the present study; the duration of sensory blockade, the durations of motor blockade were significantly more in bupivacaine-clonidine and bupivacaine-dexmedetomidine groups when compared to bupivicaine group alone. This observation was similar to the observations of study mentioned above.

Al-Mustafa MM et.al, conducted study in patients who were assigned to receive a spinal bupivacaine versus bupivacaine – dexmedetomidine (5µg) or (10µg) and concluded that sensory and motor block duration were significantly prolonged with post operative analgesia with minimal side effects in dexmedetomidine – bupivicaine groups which correlated with the findings of our study[19]. In our study, the time to 1st request of analgesics by the patients was 144.65 ± 26.39 minutes in group B, 190.05 ± 23.21 minutes in group C and 254.95 ± 57.27 minutes in group D which was statistically highly significant.

None of the patients in this study had complications like respiratory depression, pruritus, shivering etc. The incidence of nausea and vomiting was only 5% in groups C and D which was statistically insignificant.

Number of patients requiring for ephedrine for hypotension were more in group C than in group D. Peri operative hypotension is not a problem as it can be treated with boluses of IV fluids and Vasopressors as proved in previous studies[20]. Over all the differences in the incidence of side effects was not clinically significant in this study.

VI. Conclusion:

We concluded that supplementation of intra thecal bupivacaine with either clonidine or dexmedetomidine improves the quality of spinal anaesthesia and increases the duration of post operative analgesia without significant side effects. The increase in the duration of post operative analgesia was higher in dexmedetomidine-bupivacaine group than clonidine-bupivacaine group.

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