Original article:

A Comparative Clinical Study of the Effects of Intrathecal Injections of Dexmedetomidine and Fentanyl in Combination with Bupivacaine on Analgesia and Haemodyanamic Changes

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ABSTRACT

Introduction: Various adjuvants have been used with local anaesthetics in spinal anaesthesia to avoid intraoperative visceral and somatic pain and to provide prolonged postoperative analgesia. Dexmedetomidine, the new highly selective α_2-agonist drug, is now being used as a neuraxial adjuvant. The aim of this study was to evaluate the onset and duration of sensory and motor block, haemodynamic effect, postoperative analgesia, and adverse effects of dexmedetomidine or fentanyl given intrathecally with hyperbaric 0.5% bupivacaine.

Method: Ninety patients classified in ASA class 1 and 2 scheduled for lower limb and lower abdominal surgeries were studied in S.P. Medical College & A.G. of Hospitals, Bikaner after the permission of ethical committee of the institution. Patients were randomly allocated in three groups to receive intrathecal 12.5mg hyperbaric bupivacaine plus 25 µg fentanyl (group 1, n=30), 12.5 mg hyperbaric bupivacaine plus 5 µg dexmedetomidine (group 2, n=30) or 12.5 mg hyperbaric bupivacaine plus normal saline 0.5ml (group 3, n=30).

All the patients were evaluated for haemodynamic changes, block characteristics (onset and duration of motor and sensory blockade), duration of analgesia and complications.

Result: Patients in dexmedetomidine group (group 2) had a significantly faster onset and longer duration of sensory and motor block than patients in fentanyl group (group 1). The mean times of onset of sensory and motor block were 3.98 ± 1.28 and 8.02 ± 1.53 minutes in group 1, 2.63± 0.64 and 5.78±0.88 minutes for group 2 and 5.98±0.99 and 10.77±1.13 minutes in group 3 with CD values 0.51 and 0.68 respectively. Regression of sensory block to S1 and motor block to reach modified Bromage 0 was also prolonged with dexmedetomidine (441.40±77.36; 349.67±61.66 respectively) more than fentanyl (312.47±46.32; 221.43±44.10 respectively) with CD values 26.89 and 22.74 respectively. Duration of analgesia was also significantly increased (CD value 22.77) with dexmedetomidine (382.70±61.15) more than fentanyl (261.00±45.51) when compared to bupivacaine alone (175.67±10.32).

Conclusion: Group 2 (dexmedetomidine) showed faster onset and maximum duration of motor and sensory block and duration of analgesia. There were no significant differences in pulse rate and mean arterial pressure among all three groups but dexmedetomidine caused maximum fall in pulse and MAP when compared to other groups.

Keywords: Dexmedetomidine,Fentanyl,Intrathecal,Spinal Anaesthesia, Analgesia, Heamodynamic, Bupivacaine.

INTRODUCTION

Spinal anesthesia is the technique of choice for lower limb and lower abdominal surgeries as it is inexpensive, easy to administer and provide good postoperative analgesia. The major limitation is duration of post-operative analgesia with single shot injection. With the use of longer acting local anesthetic and various adjuvants (opioids, midazolam, ketamine, α_2 agonist like clonidine etc.) has significantly improved the quality of anesthetic effect as well as prolonged the duration of post-operative analgesia.

Most frequently used opioid adjuvant fentanyl, provides prolonged perioperative analgesia and stable hemodynamics[1-4]. Newer and more selective α_2 agonist Dexmedetomidine, also provides prolonged postoperative analgesia[5-7]. Various studies[32-35] are undertaken to study the effects of fentanyl and Dexmedetomidine have found that both increased the duration of local anesthetic action and provide good post-operative pain relief. Dexmedetomidine being a less studied drug, has an unknown safety profile when given intrathecally. We studied the effects of fentanyl and Dexmedetomidine as an adjuvant to bupivacaine in spinal anesthesia given for lower limb and lower abdominal surgeries for prolongation of motor and sensory block, post-operative analgesia, and perioperative hemodynamic changes. A follow-up of all the patients was done before discharge and thereafter at every fortnight till 3 months for any late neurological sequel.

METHOD

After getting clearance from institutional ethics committee and informed/written consent from patients,90 patients of either sex, aged between 18 to 60 years, belonging to American Society of Anesthesiologist (ASA) physical status 1 or 2 and scheduled to undergo either lower abdominal or lower limb surgery under spinal anesthesia were enrolled. Patients having history of cardiac, respiratory, hepatic, renal and central nervous system diseases; contraindications to regional anesthesia such as local infections or bleeding disorders; history of long term opioid use or chronic pain; history of taking drugs that affect central nervous system e.g. MAO inhibitors, Carbamazepine, Quinidine, Cimetidine etc.; known allergic or hypersensitivity to any drug and uncooperative patients were excluded.

All the patients were examined the day before surgery. Detailed history and thorough examination including general physical, systemic, airway and spine were carried out. Routine lab investigations like haemogram, blood sugar, blood urea, serum creatinine, chest X-ray and ECG were done. The procedure of spinal anesthesia was explained to each patient and a written informed consent was taken from the patient in presence of independent witness.

Randomization was done with the help of computer generated randomization tables and all patients were evenly assigned into three groups. A person not participating in the study kept the computer generated table of random numbers and prepared all medications. According to the randomizing table, the volume to be injected was prepared in syringes with labels indicating only the serial number of the patient. Neither patients nor the anesthetist giving spinal and recording observations were aware of the group allocation.

In the operation room standard monitoring including noninvasive blood pressure (NIBP), continuous electrocardiography (ECG) for heart rate (HR)and plethysmography for

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Oxygen Saturation (SpO_2) were attached and baseline vital parameters were recorded. Intravenous (IV) access was secured and Ringer's Lactate solution 10ml/kg was started for preloading. Spinal anesthesia was administered under strict aseptic precaution after giving proper sitting position, using 25 G Quincke's spinal needle, lumbar interspaces were identified and drug was injected through L3-L4 interspaces according to the group allocated.

Group 1- Patients received 0.5% hyperbaric Bupivacaine 2.5 ml and Fentanyl 25 µg (0.5ml).

Group 2- Patients received 0.5% hyperbaric Bupivacaine 2.5 ml and Dexmedetomidine 5 µg (diluted in 0.5 ml normal saline).

Group 3- Patients received 0.5% hyperbaric Bupivacaine 2.5 ml and 0.5 ml normal saline.

After the block, time (T_0) was noted, patients were placed in the supine position and supplemental oxygen 3 L/min through a face mask was started. Assessment of block characteristics (sensory and motor) was performed every minute till ten minutes. Sensory block was evaluated {0- no block; 1- analgesia (touch sensation); 2- anaesthesia (no sensation)} by pin prick method with a 25 gauge needle. Motor block was evaluated using modified Bromage score (0- No motor loss; 1- Inability to flex the hip; 2- Inability to flex the knee; 3- Inability to flex the ankle). Onset of sensory block was defined as time required to achieve sensory score of 2 up to the T6 dermatome level. Onset of motor block was defined as time required to achieve modified Bromage score of 3.

Surgery was permitted after 10 minutes. Intraoperative HR, mean arterial pressure (MAP), respiratory rate (RR) and SpO2 were recorded every 5 min for 30 min and then every 15 min till the end of the surgery.

At the end of the surgery, duration of surgical time was noted and patient was shifted to post anesthesia care unit (PACU). Postoperative monitoring including HR, MAP, RR and SpO_2 were recorded at every 15 min. Sensory and motor blocks were assessed every hour till 6 hour and then every 3 hour till 24 hour.

Postoperative recording of vital parameters (HR, MAP and SpO_2), block characteristics, assessment of postoperative pain using the visual analogue scale (VAS) score with its 0-10 score range and postoperative sedation using Ramsay Sedation Scale were done every hour till 6 hour, every 3 hour till 12 hour, and every 6 hour till 24 hour. The duration of adequate postoperative analgesia (from the time of onset of the sensory block to time at which VAS score was 4 or more) was recorded, and IV tramadol 100 mg was administered at VAS pain score ≥4, also total doses of rescue analgesic administered in observation period were recorded. Duration of motor block (from the time of onset of the motor block to time at which patient began to move his leg) was also recorded.

Adverse effects such as nausea, vomiting, respiratory depression, bradycardia, hypotension, and urinary retention were looked for, recorded, and treated accordingly. Postoperative respiratory depression was defined as a decrease in SpO2 of <95% requiring supplementary oxygen. Fall in BP and HR by >20% from the preoperative value was defined as hypotension or bradycardia, respectively, and was treated by fluid bolus, ephedrine, or atropine, as necessary. Nausea and vomiting was treated with IV ondansetron.

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Statistical analysis:

The data was subjected to statistical analysis by using INDOSTAT software. ANOVA (one factor) was applied for all qualitative parameters and critical difference (CD) was calculated. The means were compared for their statistical difference using CD values.The frequency data was subjected to χ^2 test and p values calculated using MSTAT software.

RESULTS:

All three groups were comparable in terms of age,sex, ASA class and duration of surgery (Table-1). Hemodynamic parameters (HR and MAP) remained stable in all three groups but lowest value was observed in group 2 followed by group 1 and group 3 respectively..

Onset of sensory and motor block was significantly faster in group 2 (2.63± 0.64, CD value 0.51 and 2.63± 0.64, CD value 0.68 respectively) compared to group 1(3.98 ±1.28 and 8.02 ± 1.53 respectively) and group 3 (5.98 ± 0.99 and 10.77 ± 1.13 respectively) (Table -2).Duration of sensory and motor block was significantly more within group 2 (441.40 ± 77.36, CD value 26.89 and 349.67 ± 61.66, CD Value 22.79 respectively) compared to group 1 (312.47 ± 46.32 and 221.0 ± 44.10 respectively) and group 3 (200.50 ± 10.28 and 164.93 ± 12.05 respectively)(Table -2). Duration of analgesia was significantly longer in group 2(382.70 ± 61.15, CD Value 22.77) compared to group 1 (261.00 ± 45.51) and group 3(175.67 ± 10.32)(Table -2).

Hypotension was observed in 3 patients in group 2 and 1 patient each in group 1 and 3.Three patients in group 2 and 1 in group 1 had bradycardia. Other side effects noted were nausea, vomiting, pruritus, urinary retention and respiratory depression (Table-3).

On follow-up of patients for one year we found no neurological sequelae like paresthesia, abnormal sensations or motor weakness in all three groups.

	Group 1	Group 2	Group 3
Mean age (Years) ±SD	31.77 ± 10.78	34.33± 10.68	41.73 ± 15.45
Male : Female	18 : 12	16 : 14	17 : 13
ASA 1: ASA 2	25 : 5	24 : 6	21 : 9
1. Type of surgery			
a. Orthopaedic (lower limb & Hip) surgery	21	20	20
b. Hysterectomy			
c. Skin Grafting	6	10	5
d. Inguinal Hernia	1	0	0
e. Haemorrhoidectomy	1	0	5
	1	0	0

Table 1: Demographic characteristics

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	Group 1	Group 2	Group 3	CD
Time to reach T10 sensory level (min)	3.98 ±1.28	2.63± 0.64	5.98 ± 0.99	0.51
Time to reach Bromage 3 motor block (min)	8.02 ± 1.53	3.78 ± 0.88	10.77 ± 1.13	0.68
Time to regress to S1 sensory level (min)	312.47 v 46.32	441.40 ± 77.36	200.50 ± 10.28	26.89
Time to regress Bromage 0 motor block (min)	221.0 ± 44.10	349.67 ± 61.66	164.93 ± 12.05	22.79
Duration of analgesia (min)	261.00 ± 45.51	382.70 ± 61.15	175.67 ± 10.32	22.77

Table 2:Characteristics of spinal block in all three groups

Complications	**GROUP 1**	**GROUP 2**	**GROUP 3**
Hypotension	1	3	1
Bradycardia	1	2	-
Nausea	-	2	1
Vomiting	-	-	-
Pruritus	1	-	-
Respiratory Depression	-	-	-
Urinary Retention	1	2	-

Table 3: Complications observed in all three groups.

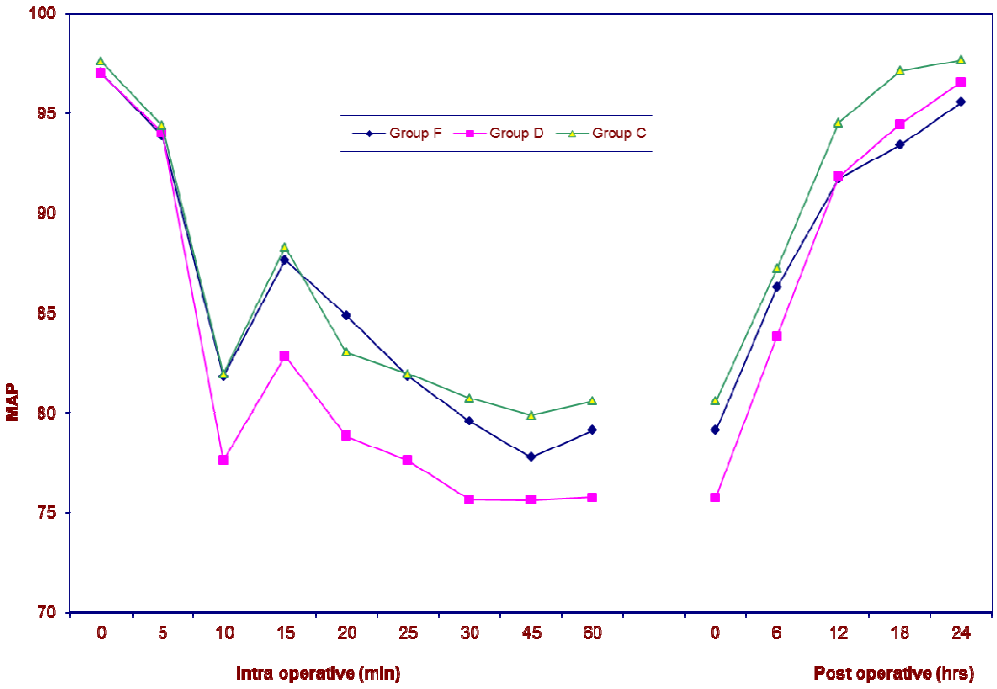

Figure 1 : Graph showing mean Arterial Pressure in different groups

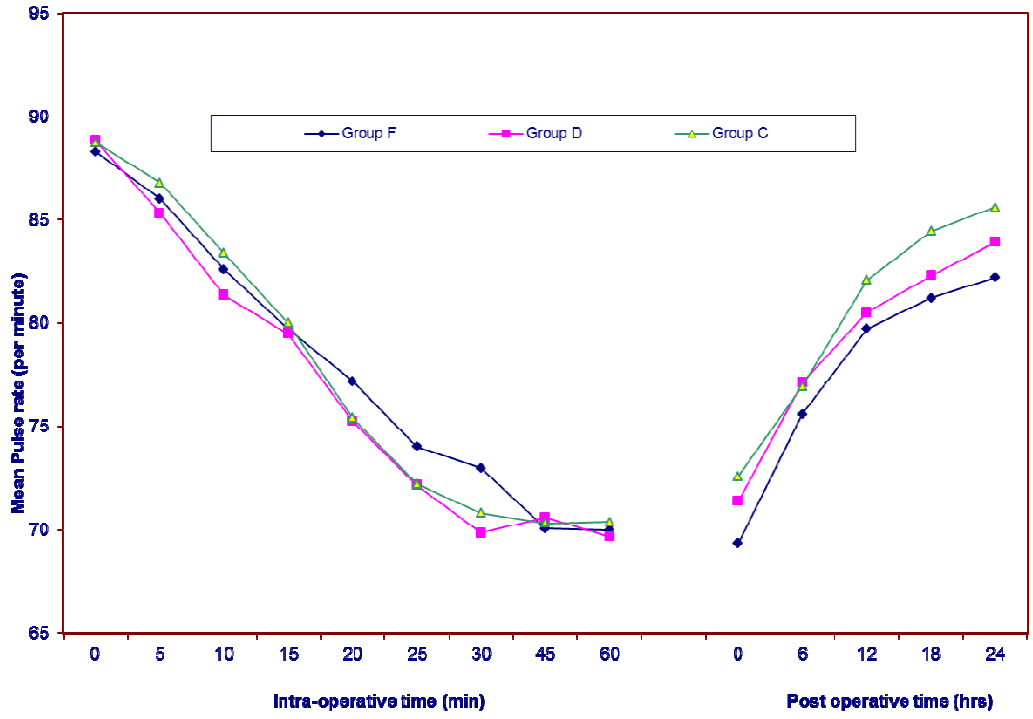

Figure 2 : Graph showing mean Pulse Rate at different time intervals in all groups

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DISCUSSION

Intrathecal α2-adrenoceptor agonists prolong the motor and sensory block of local anaesthetics by mechanisms not very well known. They bind to presynaptic C-fibers and postsynaptic dorsal horn neurons. Their analgesic action is a result of depression of the release of C-fiber transmitters and hyperpolarization of postsynaptic dorsal horn neurons[12]. Local anaesthetic agents act by blocking sodium channels. The prolongation of effect may result from synergism between local anaesthetic and α 2-adrenoceptor agonist, while the prolongation of the motor block of spinal anaesthetics may result from the binding of α2-adrenoceptor agonists to motor neurons in the dorsal horn[13]. Intrathecal α 2-receptor agonists have been found to have anti nociceptive action for both somatic and visceral pain. Fentanyl is a lipophilic μ-receptor agonist. Intrathecally, fentanyl exerts its effect by combining with opioid receptors in the dorsal horn of spinal cord and may have a supraspinal spread and action[14-16]. The use of intrathecal clonidine has been studied with local anaesthetics. A number of animal studies conducted using intrathecal dexmedetomidine at a dose range of 2.5–100 μg did not report any neurologic deficits with its use. Fukushima et[17] al administered 2μg/kg epidural dexmedetomidine for postoperative analgesia in humans but did not report neurologic deficits.

Intrathecal fentanyl prolongs the duration of spinal anaesthesia produced by bupivacaine and lignocaine and this effect has been shown in obstetric and non-obstetric patients undergoing various surgeries[1,18]. The prolongation of the duration of spinal analgesia produced by intrathecal fentanyl is not dose related. Seewal et al[19] found a significant improvement in the duration and quality of analgesia produced by intrathecal fentanyl and bupivacaine compared to intrathecal bupivacaine alone, meanwhile, the author found no further increase in the duration of analgesia when the dose of fentanyl was increased from 10 μg to 20, 30, or 40 μg.

In this comparative clinical study, 90 patients of ASA grade 1 or 2 were posted for lower abdominal or lower limb surgery under spinal anaesthesia were divided into 3 groups of 30 each. Group 1 patients received 2.5 ml hyperbaric bupivacaine 0.5% + inj. fentanyl 25 μg intrathecally. Group 2 patients received bupivacaine 0.5% heavy 2.5 ml + inj. Dexmedetomidine 5μg while group 3 patients received bupivacaine heavy 0.5% 2.5 ml + inj. Normal saline 0.5ml.

All the patients were evaluated for block characteristics and duration of analgesia as primary outcomes and haemodynamic changes, complications as secondary outcomes.

All the groups were comparable in distribution of patients regarding age, sex and ASA grade. There was no significant difference regarding type and duration of surgery.

Although patients in all three groups remained haemodynamically stable perioperatively but fall in pulse rate and Mean Arterial Pressure (MAP) was maximum in group 2 patients followed by group 1 and 3 respectively, but the fall in pulse and MAP was statistically insignificant. Maximum fall in pulse and MAP were noted between 20-30 minutes with dexmedetomidine. These finding correlate well with Al-Ghanem et al[8].

Mean onset of sensory block was assessed by pin prick method and was 3.98±1.28 min for group 1, 2.63±0.64 min for group 2 and 5.98±0.99 min for group 3. The statistical analysis showed significant difference between all the 3 groups in the onset of sensory blockade. This shows that the addition of dexmedetomidine leads to faster onset of sensory blockade in comparison to fentanyl.

Onset of motor block was also hastened by addition of dexmedetomidine and fentanyl but it was faster with dexmedetomidine than fentanyl. Mean time for onset of motor block was 8.02±1.53, 5.78±0.88 and 10.77±1.13 minutes for group 1, 2 and 3 respectively. There was statistically significant difference in onset of motor block among all the 3 groups. This shows that both dexmedetomidine and fentanyl leads to significant faster onset of motor block but dexmedetomidine causes faster onset of motor block than fentanyl and plain bupivacaine.

Al-Ghanem et al[8] and Gupta et al[10] observed no significant changes in onset of sensory and motor blockade among intrathecal dexmedetomidine and fentanyl while our study in contrast shows significant difference in onset times of sensory and motor blockade.

The mean duration of sensory block (regression time to S-1 dermatome level) was 312.47±46.32, 441.40±77.36 and 200.50±10.28 minutes in group 1, 2 and 3 respectively. Addition of dexmedetomidine caused maximum duration of sensory blockade followed by fentanyl and bupivacaine. The difference in duration of sensory block was statistically significant among all three groups.

The mean duration of motor block to reach Bromage 0 level was 221.43 ± 44.10, 349.67 ± 61.66 and 164.43 ± 12.05 minutes for group 1,2 and 3 respectively with dexmedetomidine causing maximum prolongation of motor block followed by fentanyl and bupivacaine plain. The difference in prolongation of duration of motor blockade was statistically significant among all three groups.

These findings of prolongation of duration of sensory and motor blockade correlate well with Al-Ghanem et al[8] and Gupta et al[10].

The mean duration of analgesia was maximum with group 2 (382.70 ± 61.15 min) followed by group 1 (261.00 ± 45.51 min) and group 3 (175.67 ± 10.32 min). Hence both dexmedetomidine and fentanyl caused significant prolongation of duration of analgesia when compared to bupivacaine alone but it was significantly more with dexmedetomidine than fentanyl also.

Bano and Sabbar[16] concluded that addition of Fentanyl to intrathecal Bupivacaine results in faster onset with improved perioperative anaesthesia without increasing side effects.

Fairbanke and Wilcox[20] concluded that intrathecal Dexmedetomidine combined with bupivacaine prolongs the sensory block.

Our current study correlates well with all the above authors, with significant increase in duration of analgesia with addition of dexmedetomidine and fentanyl.

The most significant side effects reported about the use of intrathecal α 2 adrenoreceptor agonists are bradycardia and hypotension, and pruritus along with bradycardia and hypotension with intrathecal fentanyl. In our current study we observed

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hypotension, bradycardia, nausea, vomiting, pruritus, respiratory depression and urinary retention as complications. Maximum incidence of bradycardia and hypotension was observed with group 2 (dexmedetomodine) (2 and 3 patients respectively) followed by fentanyl (1 each for bradycardia and hypotension) and bupivacaine (1 case of hypotension). One patient had pruritus in group 1 while urinary retention was observed in 1 and 2 patients respectively in group 1 and 2. No any patient was observed having respiratory depression in any group in our study.

There was no neurological sequalae at the end of one year after surgery. There is no follow up study present till date who have followed up for such a long period. Option of multiple agents which can be used as adjuvants in spinal anaesthesia in very useful for different group of patients. Alpha 2 agonists, specially Dexmedetomidine is very useful in this context. It hastens the onset as well as prolongs the duration of the block and duration of analgesia more than fentanyl and any other agents available. This makes possible surgeries of upto 3-4 hours duration to be done under spinal anaesthesia alone which reduces cost of anaesthesia which is a major limitation in developing world.

Many studies are available in literature to compare effectiveness of Dexmedetomidine and Fentanyl as adjuvants to intrathecal local anaesthetics and they suggest that both are safe agents when used intrathecally but there is no any systemic review available till date. So there is a need of a systematic review to be done for intrathecal administration of Dexmedetomidine which will further authenticate the usefulness of the drug.

CONCLUSION

The effects of subarachnoid block with bupivacaine heavy (0.5%, 2.5 ml) plus fentanyl (25µg), bupivacaine heavy (0.5%, 2.5 ml) plus dexmedetomidine (5µg) and bupivacaine heavy (0.5%, 2.5 ml) alone were studied and following conclusions were drawn:

1. Surgeries in all the three groups were performed without difficulty. There was good analgesia and muscle relaxation.
2. All three groups remained haemodynamically stable but there was slightly more fall in pulse rate and MAP with dexmedetomidine group which was found to be statistically insignificant.
3. The onset of sensory as well as motor block was significantly faster with dexmedetomidine when compared to other groups.
4. The duration of sensory and motor block was significantly prolonged in both group 1 and group 2 when compared to control group but it was longer in dexmedetomidine (441.40 min, 349.67 min.) group than fentanyl (312.47min, 221.43min) and control (199.41min, 162.82min) respectively.
5. There was significant prolongation of duration of analgesia in both study groups but it was more with dexmedetomidine (382 min.) than fentanyl (261min.) compared to control (173min.).
6. There were more incidences of hypotension and bradycardia with dexmedetomidine (3, 2) than fentanyl (1, 1) and control (1, 0)

groups but intergroup comparison showed that it was not significant.

7. There were no neurological sequalae in any group after one year of surgery.

The results of this study concluded that the patients receiving addition of dexmedetomidine to intrathecal bupivacaine had faster onset and longer duration of sensory and motor blockade as well as longer duration of post-operative analgesia with acceptable haemodynamic stability. Dexmedetomidine is a better adjuvant in our study but more studies and systematic reviews are required to confirm the results.

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