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**ORIGINAL RESEARCH**

# Comparative Study of Intrathecal Dexmedetomidine and Fentanyl as Adjuvants to Bupivacaine Regarding Onset of Sensory, Duration of Motor Blockade and Requirement of Post-Operative Analgesia.

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## ABSTRACT

**Background:Sub Arachnoid block is the safe, satisfactory and most commonly used technique for lower abdominal, pelvic and lower limbs surgeries. The duration of action of Bupivacaine is prolonged; it may not produce adequate post-operative analgesia. Hence adjuvants were used for producing prolonged post-operative analgesia. The aims and objective is to Compare the onset, duration of sensory and motor blockade and requirement of post-operative analgesia with dexmedetomidine vs fentanyl as adjuvants to intrathecal 0.5% hyperbaric bupivacaine Secondary Objectives were compare the hemodynamic effects of adding dexmedetomidine vs fentanyl as adjuvants to intrathecal bupivacaine.**

**Materials and Methods: Patients were allocated into one of the three groups of 50 each using computer generated random number. Patients were counselled regarding the procedures.**

**Results: The Onset of Sensory Block amongst the groups was statistically insignificant with P-Value of 0.279.), The mean duration of motor block was 231.16±68.56, 263±64.46 and 178.52±26.60 mins in Groups A, B and C respectively. The prolonged motor block in Group B (Dexmedetomidine) was statistically significant with P-Value of <0.0001. The mean time for first rescue analgesia was 323.44±116.29 mins in Group A, 391.52±105.63 mins in Group B and 311.80±99.15 mins in Group C. Better post-operative analgesia in Group B, P value of <0.0001.**

**Conclusion: From this study it can be concluded that the use of intrathecal dexmedetomidine as an adjuvant to bupivacaine seems to be a better alternative to fentanyl for long duration surgical procedures due to its prolonged duration of sensory and motor block combined with minimal side effects. However, prolonged duration of motor blockade with dexmedetomidine may be undesirable for shorter surgical procedures or ambulatory surgeries.**

**Keywords: Spinal Anesthesia ,Dexmedetomidine,Fentanyl**

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## INTRODUCTION

Sub Arachnoid block is the safe, satisfactory and most commonly used technique for lower abdominal, pelvic and lower limbs surgeries. Spinal anesthesia requires a small volume of local anaesthetic, virtually devoid of systemic pharmacologic effect, to produce profound, reproducible sensory analgesia.[1]

There are two groups of local anaesthetics, esters and amides. The amides include Lignocaine, Prilocaine, Bupivacaine and all share a common basic structure termed aminoacylamide. Earlier intrathecal lignocaine was the choice for short surgical procedures.Transient neurological symptoms' may be associated with all local anaesthetics, but it is 7-9 times more common with lignocaine than bupivacaine.[2] Because of this controversy use of spinal lignocaine is replaced by 0.5%(Hyperbaric) bupivacaine as the gold standard drug for the safe conduct of spinal anaesthesia. Sensory and motor blockade is satisfactory, duration of action, longer than that of lignocaine.Though the duration of action of Bupivacaine is prolonged, it may not produce adequate post-operative analgesia. Hence adjuvants were used for producing prolonged post-operative analgesia.

Many studies have shown that opioids produce intense, prolonged and segmental analgesic action without gross autonomic changes, loss of motor power or impairment of sensation other than pain when injected into subarachnoid or epidural space.[3]Neuraxial administration of opioids along with local anaesthetics improves the quality of intra-operative analgesia and also provides post-operative pain relief for longer duration.[4]Fentanyl, a highly lipophilic opioid has rapid onset of action following intrathecal administration. Dexmedetomidine, a highly selective α-2 agonist. Its use is often associated with a decrease in heart rate and blood pressure.[5-7]

This study had been conducted to compare the effects of adding dexmedetomidine and fentanyl as adjuvants to intrathecal 0.5%hyperbaric bupivacaine.

### Aims and objectives

Primary Objective were to compare the onset, duration of sensory and motor blockade and requirement of post-operative analgesia with dexmedetomidine vs fentanyl as
adjuvants to intrathecal 0..5% hyperbaric bupivacaine

Secondary Objectives were comparing the hemodynamic effects of adding dexmedetomidine vs fentanyl as adjuvants to intrathecal bupivacaine and to find out adverse effects of dexmedetomidine and fentanyl as adjuvants to intrathecal bupivacaine.

## MATERIALS & METHODS

**Study Design:** A comparative, prospective, randomized and controlled study.

**Sample size:** The study was conducted on 150 patients who were randomly divided by computer generated series into three groups of 50 each. To calculate sample size, a power analysis of α=0.05 and β=1.00 showed that minimum 36 patients were needed per study group.

$$N = 2 \times \left( \frac{z_{1-\frac{\alpha}{2}} + z_{1-\beta}}{\delta} \right)^2 \times s^2$$

$$N = 2\left(\frac{1.96 + 0.84}{4}\right)^2 \times 6^2$$

N=36

N=size per group, Z=standard normal deviate, S2=polled standard deviation, δ= clinically admissible margin.

**The groups received the drugs as follows:**

Group "A" - Bupivacaine plus fentanyl (25µg) group.

Group "B" - Bupivacaine plus dexmedetomidine (05µg) group.

Group "C" – Bupivacaine plus Normal Saline group.

Total Volume 3.5ml (3ml Bupivacaine+0.5ml Fentanyl/ Dexmedetomidine/ Normal Saline).

**Methodology**

I. This study was conducted at a tertiary care service hospital between Apr 2014 and Sep 2015 after approval from hospital ethical and scientific committee. During this period 150 patients of ASA physical status I and II in the age group of 18 years to 60 years, of either sex, posted for elective lower limb, lower abdominal, gynecological and urological surgeries of less than three hours duration under spinal anaesthesia were recruited in the study after obtaining written informed consent. Patients belonging to ASA grade III and IV, physically dependent on narcotics, history of drug allergy, gross spinal abnormality, localized skin sepsis, hemorrhagic diathesis or neurological involvement / diseases, Head injury cases, Patients with cardiac, pulmonary, hepatic or renal disorders, peripheral neuropathy were excluded in our study.

Patients were allocated into one of the three groups of 50 each using computer generated random number. Patients were counselled regarding the procedures and informed consent taken.

**Preoperative period**

All standard monitoring like ECG, NIBP, HR, SPO2 were attached and all basal parameters were recorded. Intravenous line was secured and the patients were preloaded with 10 ml/kg Ringer lactate. Spinal anaesthesia was performed under strict aseptic precautions by inserting 25 gauge Quincke's spinal needle into subarachnoid space at L2–3 or L3-4 intervertebral space with patient in sitting position and the study solution was injected as per the allocated group.

GROUP A: 3.0 ml of 0.5% bupivacaine heavy +25µg fentanyl made to a total of 3.5 ml.

GROUP B: 3.0 ml of 0.5% bupivacaine heavy + 5 µg dexmedetomidine and made to total of 3.5 ml by adding preservative free normal saline.

GROUP C: 3.0 ml of 0.5% bupivacaine heavy + 0.5 ml preservative free normal saline. Total volume 3.5 ml.

Immediately after the injection patient was made supine and standard monitoring was carried out. Pulse rate, respiratory rate, blood pressure and oxygen saturation were recorded every 3 minutes till fifteen minutes and then at 15-minute interval till one hour and every 30 minutes till 3 hours intra operatively. Bolus doses of injection mephenteramine IV 0.1 mg/kg were given whenever required to maintain blood pressure within 20% of base line and injection atropine 0.6 mg IV was given if the patient developed symptomatic bradycardia (HR < 45 beats/min)

The following parameters were recorded in all patients

**Extent of sensory block –**The highest level of sensory blockade was checked by using pin prick every minute. The maximum level was recorded after three consecutive pin pricks didn't show progression of block.

**Time of onset of sensory block –**The time for onset of sensory block was defined as the time from injection of intrathecal anesthetic to time taken to attain highest level of sensory block.
**Duration of sensory block –**The duration of sensory was defined as time for two segment regression of sensory blockade from the maximum level, which was noted using pin prick.
Degree of motor blockade according to bromage score was recorded every 2 minutes till maximum score was achieved.

**Table: Bromage Score**

| Scale | Criteria | Degree of block |
|---|---|---|
| 0 | Free movement of legs and feet, with ability to raise extended leg | None |
| 1 | Inability to raise extended leg and knee flexion is decreased, but full flexion of feet and ankles is present | Partial, 33% |
| 2 | Inability to raise leg or flex knees, flexion of ankle and feet present | Partial, 66% |
| 3 | Inability to raise leg, flex knee or ankle, or move toes | Complete Paralysis |

Duration of motor blockade – duration of motor block was defined as the time from intrathecal injection till the time when the patient was able to move both legs and feet freely (Bromage score 0).
Time for first rescue analgesia- was defined as the time from intrathecal injection to the time of first recue analgesia given. Injection diclofenac 1 mg/kg 1M was used for used for rescue analgesia. Injection paracetamol 15 mg/kg IV was used if diclofenac was contraindicated.
Any adverse effects like bradycardia, hypotension, nausea, vomiting, shivering, pruritus, pain, dry mouth were observed.

**Statistical Analysis**
The data obtained were tabulated and analyzed using Statistical Package for Social Science (SPSS version 18.0). For categorical covariates Pearson chi-square/Fisher exact test was used as appropriate. Continuous covariates were compared using ANOVA and was followed by suitable post hoc test for multiple comparison (Tukey HSD).

**RESULTS**
All the demographic data (age, sex, weight and ASA) were comparable in groups P>0.05 shows statistical insignificant.

**Table 1: Demographic Data**

| Demographic Data | P value |
|---|---|
| Age | 0.998 |
| Weight | 0.9 |
| Sex | 0.06 |
| ASA | 0.942 |

The Onset of Sensory Block amongst the groups was statistically insignificant with P-Value of 0.279. The mean time for onset of sensory block was 5.82±1.335 min in Group A (Fentanyl), 6.1±1.374 min in Group B (Dexmedetomidine), 6.24±1.287 in Group C (Bupivacaine) as shown in [Table 2].

**Table 2: Onset of sensory block**

| Onset of sensory block | | | | | |
|---|---|---|---|---|---|
| | Sum of squares | df | Mean square | f | Sig. |
| Between groups | 573 | 2 | 2.287 | 1.288 | 0.279 |

| | | | | | |
|---|---|---|---|---|---|
| Within groups | 261 | 147 | 1.776 | | |

The meantime for 2 Segment Regression among the groups was 91.52±12.86 min for Group A (Fentanyl), 143.02±17.86 min for Group B (dexmedetomidine) and 76.52±5.94 min for Group C (bupivacaine).This difference was statistically significant with P-Value of <0.001as shown in [Table 3].

**Table 3: Time for 2 Segment Regression**

| | | Sum of squares | df | Mean square | f | Sig. |
|---|---|---|---|---|---|---|
| Time for 2 segment regressi | Between groups | 121658.3 | 2 | 60829.17 | 351.186 | <0.001 |
| | Within groups | 25461.94 | 147 | 173.21 | | |
| | Total | 147120.3 | 149 | | | |

The mean duration of motor block was 231.16±68.56, 263±64.46 and 178.52±26.60 mins in Groups A, B and C respectively. The prolonged motor block in Group B (Dexmedetomidine) was statistically significant with P-Value of <0.0001 as shown in [Table 4].

**Table 4: Duration of Motor Block**

| | | Sum of squares | df | Mean square | f | Sig. |
|---|---|---|---|---|---|---|
| Duration of motor block | Between groups | 184052.3 | 2 | 92026.16 | 28.871 | <0.001 |
| | Within groups | 468565.7 | 147 | 3187.522 | | |
| | Total | 6526618 | 149 | | | |

The mean time for first rescue analgesia was 323.44±116.29 mins in Group A, 391.52±105.63 mins in Group B and 311.80±99.15 mins in Group C. The prolonged duration in Group B was statistically significant with P value of <0.0001 as shown in [Table 5].

**Table 5: Time for First Rescue Analgesia**

| | | Sum of squares | df | Mean square | f | Sig. |
|---|---|---|---|---|---|---|
| Time for first rescue Analgesia | Between groups | 185427.6 | 2 | 92713.79 | 8.059 | <0.001 |
| | Within groups | 1691105 | 147 | 11504.11 | | |
| | Total | 1876532 | 149 | | | |

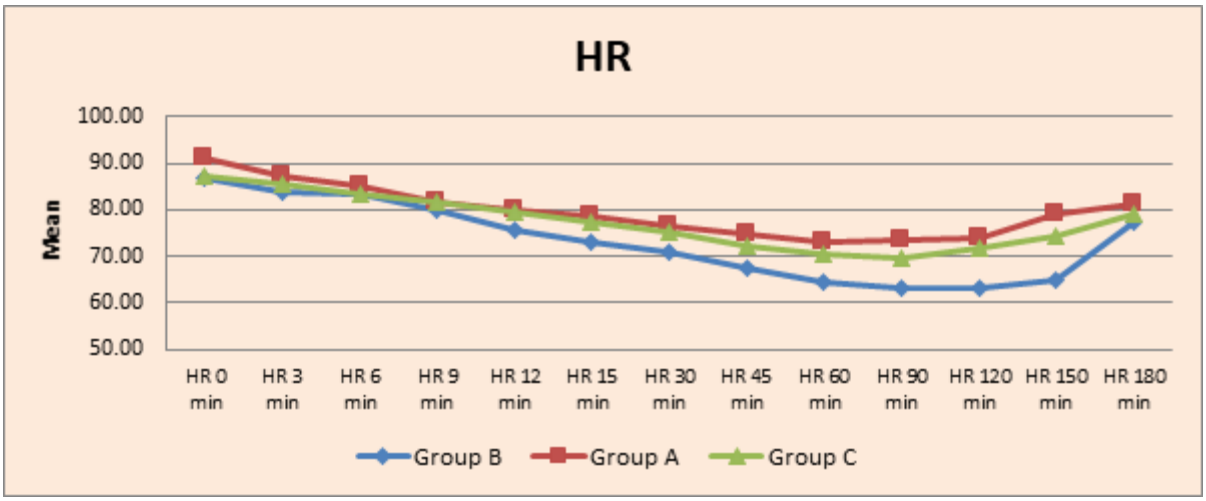


**Figure 1: Changes in Heart Rate**

The baseline heart rate was comparable among groups with mean of 91.06±12.04 bpm in Group A, 86.86±8.34 bpm in Group B and 87.46±11.18 bpm in Group C with the P value of 0.106. Heart rate was comparable among the groups from 0 to 12 minutes and 150 to 180 minutes with P value of >0.05, there was statistically no difference between the groups during these time intervals.The decrease in heart rate from 15 to 120 minutes was greater in Group B (dexmedetomidine group) compared to other groups with a P value of < 0.05, hence the difference was statistically significant as shown in [Figure 1].

The baseline SBP, DBP was comparable among the groups repectively with mean of 131.02±11.27mm of hg in Group A, 126.2±11.97 mm of Hg in Group B and 126.32±12.48 mm of hg in Group C with p value of 0.073.

The baseline DBP was comparable among the groups with mean of 85.52±8.21 mm of hg in Group A, 80.06±10.4 mm of hg in Group B and 80.2±9.13 mm of hg with a P-value of 0.323. There was no significant change from the baseline value in the groups. The mean DBP was comparable throughout 180 minutes with P Value of >0.05, hence the variation in mean DBP was statistically insignificant between the groups as shown in figure 2 and 3.

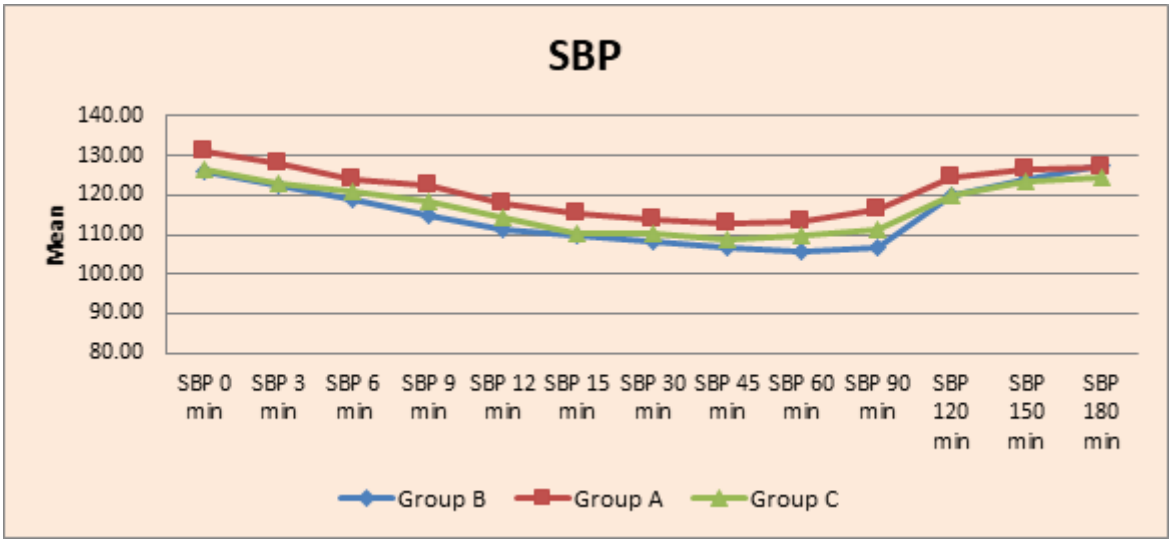


**Figure 2: Changes in Systolic Blood Pressure**

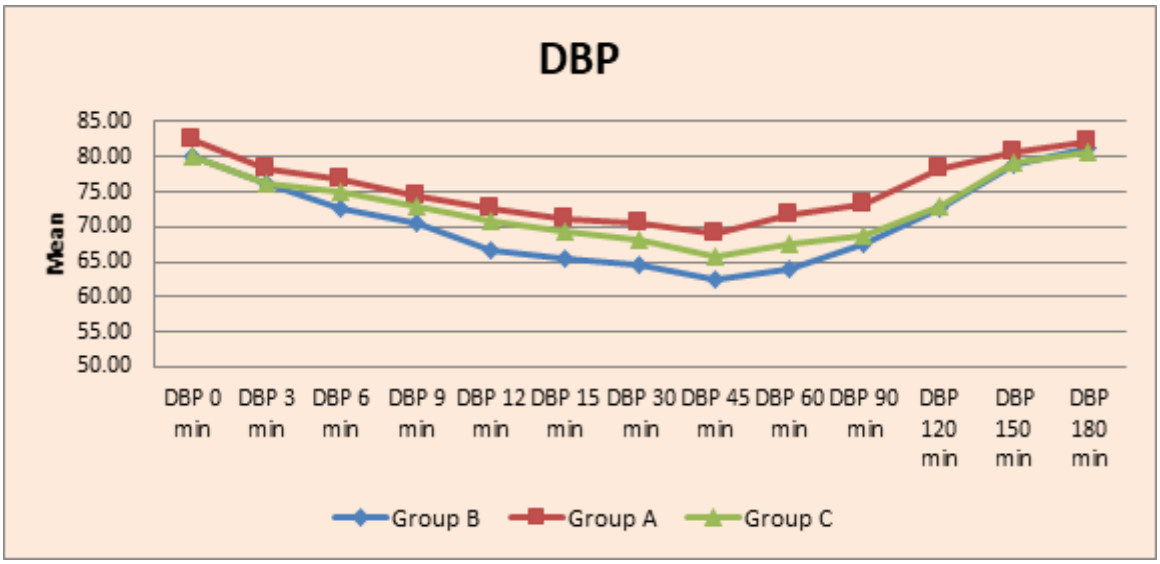


**Figure 3: Changes in Diastolic Blood Pressure**

## DISCUSSION

Sub arachnoid block is the preferred mode of anaesthesia for surgeries of lower abdomen, pelvic organs and lower limbs. Neuraxial blockade is preferred mode of anaesthesia because of its rapid onset, superior blockade, and low risk of infection, less failure rate and cost effectiveness. One of the major limitations for sub arachnoid block is its short duration of block and limited post-operative analgesia. To overcome this limitation various adjuvants are being used with local anaesthetics, their use is thwarted either due to the adverse effects or unreliable post-operative analgesia.[8-10]

In our study dexmedetomidine was compared with fentanyl as adjuvant to intrathecal 0.5%hyperbaric bupivacaine in sub arachnoid block for surgeries below the umbilicus, shows that supplementation of spinal bupivacaine with 5 µg dexmedetomidine significantly prolonged both sensory and motor block compared with fentanyl.[11,12]

In our study there was statistically no significant difference in age, sex, weight distribution and ASA physical status among the three groups.[13]

5µg dexmedetomidine or 25µg fentanyl were used as adjuvants to 10mg intrathecal hypobaric bupivacaine by Al Ghenem SM et al,[14]and they concluded that 5µg dexmedetomidine produces prolonged sensory and motor blockade when compared to 25µg of fentanyl.[15] Gupta R et al,[16] in their studies also came to the same conclusion, they also used 5µg dexmedetomidine or 25µg fentanyl as adjuvants to intrathecal hyperbaric bupivacaine.

Based on the above studies we conclude that 5µg dexmedetomidine is safe and appropriate, when compared with 25µg fentanyl as adjuvant to 0.5% hyperbaric intrathecal bupivacaine.

The mechanism by which intrathecal α2 adrenoceptor agonists prolong the motor and sensory block of local anaesthetics. It may be an additive or synergistic effect secondary to the different mechanism of action of the local anaesthetics and α2 adrenoceptor agonists. Bupivacaine acts by blocking sodium channels, α2 adrenoceptor agonists act by binding to the presynaptic C-fibers and post synaptic dorsal horn neurons. They produce analgesia by depressing release of C-fiber transmitters and by hyperpolarization of post synaptic dorsal horn neurons.[9-13] The complementary action of local anaesthetics and α2 adrenoceptor agonists accounts for their profound analgesic properties. Clinical studies exhibit potentiation of Neuraxial local anaesthetics and post-operative analgesia when intrathecal dexmedetomidine was used in conjunction with local anaesthetics.[8,15,16,17]Fentanyl which is lipophilic opioid and µ-receptor agonist exerts its effect intrathecally by combining with opioid receptor in the dorsal horn of the spinal cord and may have supra spinal spread and action.[5,6]

Time of onset of sensory block was comparably similar among all groups The mean time in group A (fentanyl) was 5.82±1.3 mins, group B (dexmedetomidine) was 6.1±1.37 mins and group C (bupivacaine) was 6.24±1.28 mins with a P value of >0.05. These findings were in concordance with the results of Al Ghanem SM et al,[14] who observed no difference in the time for onset of sensory block, in patients receiving dexmedetomidine (5.5±1.4min) and fentanyl (5.4±3.3min) as adjuvants to isobaric bupivacaine. Similarly, comparable time of onset of sensory block among study groups was also observed by Gupta R et al,[19] on comparison of 5 µg dexmedetomidine with 25 µg fentanyl.

In our study the time for 2 segment regression of sensory blockade was compared between group. It was found that the mean time for 2 segment regression in Group A was 91.52±12.86 mins, Group B was 143.02±17.8 mins and Group C was 76.52±5.94 mins with P Value of<0.001. This difference was statistically significant suggesting prolongation of sensory block by dexmedetomidine. These findings were concurring with the studies of Mahendru V et al,[17] Gupta R et al,[16]Kanazi et al,[14] Al Ghanem SM et al,[14] who also observed significantly prolonged two segment regressions.

Gupta R et al, [19] in their study found that time for 2 segment regression in dexmedetomidine group was prolonged with 120±22.2mins compared to fentanyl group with 76±20.3mins.Kanazi et al in their study found that time for 2 segment regression was prolonged in dexmedetomidine group 122±37mins as compared to fentanyl group 101±37mins and it was 80±28mins with bupivacaine alone.

The intrathecal 5µg dexmedetomidine used in our study has shown significantly prolonged duration of motor block (263±64.46 P<0.001), which was also observed by other investigators in comparison to various adjuvants (clonidine, fentanyl) used in their studies.[17]

In our study patients in all the groups had attained bromage score of 3 suggesting there was no significant difference in the motor blockade which concurred with the studies conducted by Al Ghanem SM et al,[14] Gupta R et al,[16] and MahendruV et al.[17]

The average duration of motor block in our study among the three groups was 263±64.46 in dexmedetomidine group, 231.16±68.56 in fentanyl group and 178.52±26.60 in bupivacaine group. This shows the motor blockade was prolonged in dexmedetomidine group, which was statistically significant with P- value of <0.001. Similar duration of motor block was also observed in studies by Mahendru V et al,(273.3 ± 24.6 min P<0.001) and Kanazi et al, (250 ± 76 min P, 0.001).

We observed significantly delayed requirement of rescue analgesia and prolonged duration of analgesia, which was calculated when the first dose of rescue analgesia was administered post operatively. The total duration of analgesia was found to be 391.52±105.63mins in Group B (dexmedetomidine), 323.44±116.29mins in Group A (fentanyl) and 311.8±99.15mins in Group C with P-value of <0.001. This difference was statistically significant.Similarly, significantly prolonged duration of analgesia was seen by Gupta R et al,on comparison of dexmedetomidine and fentanyl as intrathecal adjuvant (P < 0.001).[18]

Gupta R et al,[16] in their study observed prolonged duration of analgesia with dexmedetomidine in comparsion to fentanyl as intrathecal adjuvant (P<0.001), Mahendru V et al,[17]observed prolonged duration of analgesia with dexmedetomidine, incomparison to fentanyl, clonidine as intrathecal adjuvant (P<0.001). Halder S et al,[18]also observed prolonged duration of analgesia with dexmedetomidine in their studies.

The most significant side effects reported about the use of intrathecal α2 agonists are bradycardia and hypotension.In our study the changes in heart rate were compared between three groups. The changes in mean heart rate was similar upto 12 min in three groups with P>0.05 with no significant difference. From 15 min onwards till the end of 120 min there was gradual fall in the heart rate in Group B(Dexmedetomidine) as compared to other two groups with P<0.001, which was statistically significant. The base line mean was comparable across groups with P>0.05. The changes in systolic blood pressure were similar intraoperatively across the groups with P>0.05, which was statistically not significant.

The changes in diastolic blood pressure which were similar to changes in systolic blood pressure. The base line reading was comparable among groups with no statistically significant difference. The changes in diastolic blood pressure were similar in three groups with no significant difference introperatively with P>0.05. These hemodynamic findings were similar to findings in other similar studies like Mahendru V et al,[17]Halder S et al,[18] Al-Mustafa MM et al,[15] Gupta R et al,[16]Kanzi et al,[8] Al Ghanem SM et al.[14]

The SpO2 were not statistically significant among groups with P>0.05 which concurred with findings of other similar studies. None of the patients in our study had respiratory depression and fall in saturation.

Patients in both groups were evaluated for common adverse events like nausea, vomiting, hypotension, bradycardia, shivering, desaturation and dry mouth. Six (12%) patients had pruritus in fentanyl group which is known to occur with fentanyl, this was not statistically

significant (P=0.10). One patient each in Group B and Group C had bradycardia requiring atropine. This was statistically not significant (P=0.184).

Although this study adds to the current knowledge on dexmedetomidine, the results should be considered taking into consideration the obvious limitations: The population involved includes the young and otherwise healthy patients and the effect in older patients with cardiovascular comorbidities are yet to be invest Thus, as the renewed interest in regional anesthesia techniques grows, especially for the prolongation of excellent quality of intraoperative and postoperative analgesia with minimal side effects, use of intrathecal dexmedetomidine as an adjuvant to local anesthetics is evolving gradually and further clinical studies are proving its efficacy and safety and will be determining the suitable dosages of dexmedetomidine required for supplementation of spinal local anesthetics.

## CONCLUSION

From this study it can be concluded that the use of intrathecal dexmedetomidine as an adjuvant to bupivacaine seems to be a better alternative to fentanyl for long duration surgical procedures due to its prolonged duration of sensory and motor block combined with minimal side effects. However, prolonged duration of motor blockade with dexmedetomidine may be undesirable for shorter surgical procedures or ambulatory surgeries.

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**CONFLICT OF INTEREST**-There is no conflict of interest.

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