Effect of addition of Midazolam, Fentanyl or Dexmedetomidine to 0.5% Hyperbaric Bupivacaine Given Intrathecally in patients undergoing Lower Abdomen and Lower Limb Surgeries.

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Abstract

Background : Various adjuvants are being used with local anesthetics for prolongation of intraoperative and postoperative analgesia. Our research mainly focused on the additive action of 3 drugs (Midazolam, Fentanyl or Dexmedetomidine) when administered intrathecally as adjuvant to 0.5% Bupivacaine (H).Materials and Methods: 90 patients, scheduled for elective lower abdominal, lower limb and gynecological procedures were selected to participate in this prospective, randomised, double-blind study. Approval from the institutional ethical committee and written informed consent from patients involved in this research was taken.

These patients were randomly divided into three groups of 30 each by a lottery method. Patients in group BM received 3 ml of 0.5% Bupivacaine (heavy) and 0.5 ml 2.5 mg preservative free Midazolam(total volume made 3.5 ml of drug). Patients in group BF received 3 ml of 0.5% Bupivacaine (heavy) and 0.5 ml 25 mcg preservative free Fentanyl (total volume made 3.5 ml of drug) and patients in group BD received 3 ml of 0.5% Bupivacaine (heavy) and 0.5 ml 10 mcg Dexmedetomidine diluted in 0.5 ml distilled water (total volume made 3.5 ml of drug) intrathecally. The onset and duration of sensory and motor blockade, time to reach peak sensory and motor level and the sensory and motor regression times were recorded. Hemodynamic changes and time to use first rescue analgesia, Diclofenac sodium 75 mg IM, were also recorded.Results: The time of two dermatomal regression of sensory block was prolonged in Group BD Dexmedetomidine 10 mcg (145.43 ± 8.705mins.), as compared to group BF Fentanyl 25 mcg (131.93 ± 12.616mins.), and Group BM Midazolam 2.5mg (125.67 ± 10.568mins).The duration of sensory and motor block was significantly prolonged (clinically and statistically) in Group BD (502.27 ± 20.495 mins, 483.50 ± 19.244 mins, respectively) as compared to Group BF (373.97 ± 17.026 mins,321.60 ± 18.144 mins. respectively) and least in Group BM (288.33 ± 15.749 mins.,269.43 ± 13.221mins.respectively). The duration of sensory block was more prolonged than the duration of motor block and no patient complained of urinary retention in all three groups.The mean duration of onset of severe pain (VAS>7) was significantly prolonged(clinically and statistically) in Group BD (556.17 ± 20.487 mins.) than in Group BF and Group BM (450.63 ± 19.632 mins. and 301.40 ± 14.857 mins. respectively).The duration of effective analgesia (time of rescue analgesia) was significantly prolonged (clinically and statistically) in Group BD (577.70 ± 18.039 mins.) as compared to Group BF (465.17 ± 18.903 mins.) and Group BM(313.93 ± 13.866 mins).Conclusions: Dexmedetomidine in a dose of 10 mcg is found to be more potent than Fentanyl 25 mcg and Midazolam 2.5 mg intrathecally with hyperbaric Bupivacaine, with less side effects and significantly prolongs the duration of post-operative analgesia.Keywords: Midazolam, Fentanyl, Dexmedetomidine, 0.5% Bupivacaine (H), Intrathecally, lower abdomen and lower limb surgeries.

Introduction : Pain is the expected outcome of surgery. The sole essence of anaesthesia is pain relief. Many people experience sub-optimally managed post-operative pain and it is a personal sensory experience, unique for specific individual. In the evaluation of any pain relieving measures, the nature of the pain must be considered. Spinal anaesthesia has many advantages over general anaesthesia which makes it the anaesthesia of choice in the present surgical practice.

Spinal anaesthesia has emerged as an important technique, with simplicity, effectiveness, safety and a successful history since late nineteenth century. To improve the effect and duration of spinal anesthesia, various drugs are used as an adjuvant to hyperbaric Bupivacaine[1,2]. The search continues for the better adjuvants and lead to the discovery of intrathecal benzodiazepines, opiates and alpha receptors agonists. Our objectives were to compare onset & duration of sensory analgesia, onset & duration of motor block achieved with the use of individual drug, hemodynamic changes, depth of sedation, side effects related to drugs under study and postoperative assessment of pain by VAS (Visual Analogue Scale).

Aims And Objectives : To compare the effects of addition of Midazolam, Fentanyl or Dexmedetomidine as adjuvants to 0.5% Bupivacaine (heavy) with each other on:-

a) Quality of blockade (Time of onset of sensory blockade, Time of peak sensory blockade, Time of onset of motor blockade, Time of peak motor blockade).

b) The hemodynamic responses (effect on blood pressure, heart rate) after adding of these drugs as adjuvants intrathecally with 0.5% Bupivacaine (heavy).

Methodology : A total of 90 patients, scheduled for elective lower abdominal, lower limb and gynecological procedures were selected to participate in this prospective, randomized, double-blind study.

Approval from the institutional ethical committee and written informed consent from patients involved in this research was taken.

Patients were divided on the basis of computer generated random number table into three groups as follows:

GROUP 1-: That is group BM-n=30

They were administered intrathecally 3 ml of Bupivacaine 0.5% (H) plus injection Midazolam 2.5 mg in 0.5 ml distilled water.

GROUP 2-: That is group BF-n=30

They were administered intrathecally 3 ml of Bupivacane 0.5% (H) plus injection Fentanyl 25 microgram in 0.5 ml distilled water.

GROUP 3-: That is group BD-n=30

They were administered intrathecally 3 ml of Bupivacaine 0.5% (H) plus injection Dexmedetomidine 10 microgram in 0.5 ml distilled water.

All the patients were premedicated with oral Alprazolam (0.25 mg) and Ranitidine (3 mg/kg) the night before surgery. In the operating room, standard monitors (electrocardiogram, non invasive blood pressure and pulse oximeter) were attached to the patient, and baseline vitals were recorded. An 18G intravenous line was secured and preloaded with Ringers lactate 10 ml/kg. Patients and assessing anaesthesiologists were blinded to the test drug. The drugs were administered intrathecally in sitting position in L3-4 or L4-5 space with a 26 gauze spinal needle. The study solution, prepared by another researcher who was not involved in the patients care, was injected through the spinal needle over a period of ten seconds with no barbotage.

- After injecting the drug, time was noted (T0) and the patient was put in supine position.
- Following observations were recorded:
  - Onset time of sensory block (T1) (defined as the time interval between the completion of intrathecal drug injection to the onset of complete loss of pinprick sensation at T8).
  - Level of sensory block (LMAX) (defined as the highest dermatomal level of sensory blockade by pinprick testing).
  - Time to achieve maximum sensory block level (T3).
  - Onset of motor block (T2). (Onset of motor block is defined as time taken from injection of drug, score 0 to start of motor block, score 1of Bromage score).
  - Peak level of motor blockade (T4) assessed by using Bromage score. (Peak level of motor block is defined as time taken from injection of drug, score 0 to development of complete motor block, score 3).
  - Duration of sensory block (T5) (defined as the interval from completion of intrathecal drug injection and 2-segment regression of sensory block by pinprick method).
  - Duration of motor block (T6) (defined as the time taken from onset of complete motor block, score 3 to complete recovery of motor block, score 0).
  - Time of rescue analgesia (defined as the time interval between administration of intrathecal drug to the time of administration of first rescue analgesia).

    Pain was assessed using the Visual Analogue Score (VAS)

    (0: no pain, 10: maximum pain).

Pulse rate and blood pressure was monitored every five minutes intra-operatively and every ten minutes subsequently till 2-segment regression of block. Hypotension (< 20% decrease in systolic blood pressure from baseline) was managed with intravenous fluid (20 ml/kg) initially and then with Mephentermine 3 mg IV in incremental boluses. Adverse effect such as nausea, vomiting, sedation, pruritus and urinary retention were recorded. Intraoperative rescue analgesia was administered with Fentanyl (1 microgm/kg) intravenously, when required. If the pain was not relieved, the patient was given general anaesthesia and excluded from the study. Postoperatively, rescue analgesic medication with Diclofenac sodium (1.5 mg/kg) was administered intramuscularly, if VAS was found to be $\geqslant$ 5. Dermatomal sensory block up to T10 was considered adequate for surgery. The maximum height of sensory

blockade was noted at 20 minutes.

Motor block was assessed by the Bromage score.

The level of sedation of the patients was assessed by the Ramsay sedation score.

Observation and Results-

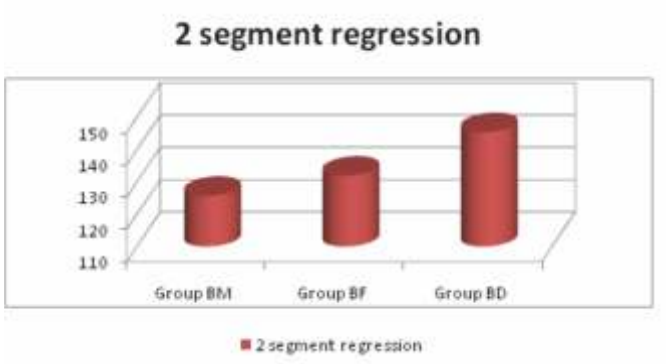
Comparison of mean age, sex wise distribution of cases among groups and ASA grade wise distribution showed no statistical significant results between three groups.

P value showed no significant difference.

Groups	Group BM	Group BF	Group BD	P value
Onset sensory blockage (sec)	56.43 ± 12.294	53.50 ± 10.741	52.47 ± 11.389	0.386
Onset motor blockade	72.17 ± 11.951	72.43 ± 10.718	72.37 ± 11.996	0.996
Peak sensory blockade (min)	7.47 ± 1.737	7.87 ± 1,655	7.37 ± 1.671	0.482
Peak motor blockade	8.73 ± 1.760	9.00 ± 1.722	8.83 ± 1.802	0.839

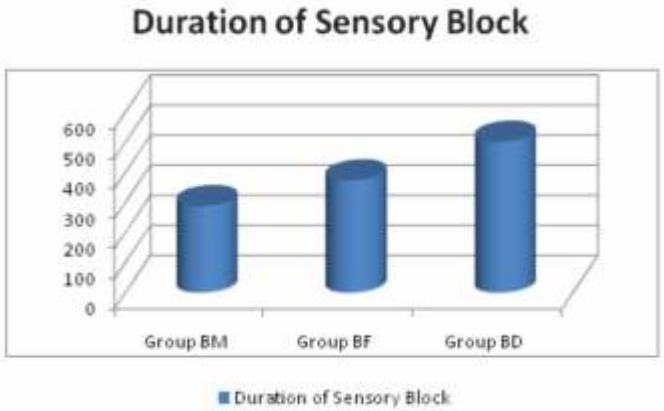
- **P value showed no significant difference**
- Onset of sensory blockage- In this study, Midazolam, Fentanyl and Dexmedetomidine group, the onset of sensory blockade was 56.43 ± 12.294 secs.,53.50 ± 10.741 secs., 52.47 ± 11.389 seconds respectively, and all three groups are comparable and there was no significant difference between the time of onset of sensory blockade.
- Onset of motor blockade-In Midazolam, Fentanyl and Dexmedetomidine group, the onset of motor blockade 72.17 ± 11.951 secs, 72.43 ± 10.718 secs, 72.37 ± 11.996 secs respectively are comparable and there was no significant difference in the time of onset of motor blockade.
- Peak sensory blockade-In Midazolam group peak sensory blockade was 7.47 ± 1.737 minutes, in Fentanyl group it was 7.87 ± 1.655 minutes, and in Dexmedetomidine group, 7.37 ± 1.671 minutes.
- Peak motor blockade-In Midazolam group peak motor blockade was 8.73 ± 1.760 minutes, in Fentanyl group it was 9.00 ± 1.722 minutes, and in Dexmedetomidine group 8.83 ± 1.802 minutes.

This shows that addition of Midazolam, Fentanyl or Dexmedetomidine are comparable and there is no significant difference in the time of onset of sensory and motor block and also in the time of onset of peak sensory and motor block.

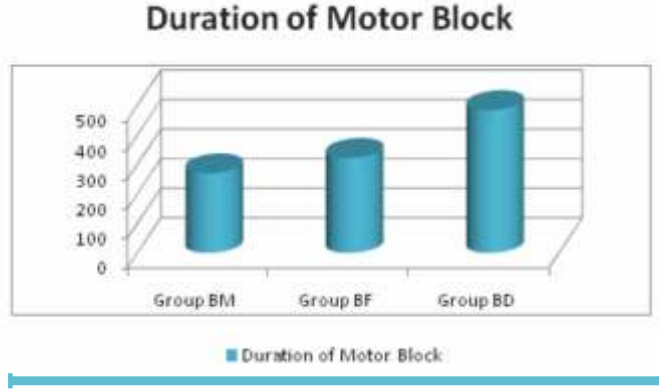


The time for two segment regression of sensory block was shorter in group BM (125.67 ± 10.568 min) compared to group BF (131.93 ± 12.616 min) and group BD (145.43 ± 8.705 min).

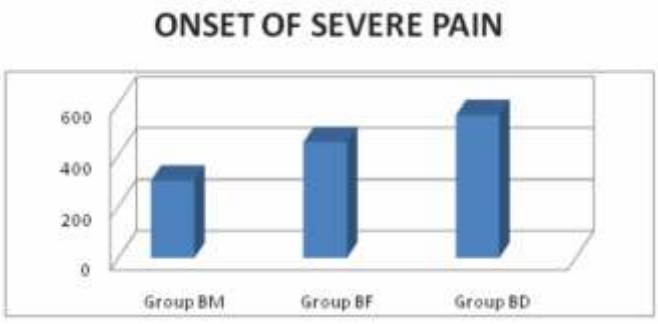
Analysis was done using ANOVA test which showed statistically significant difference between the three groups.



ANOVA test showed that the duration of sensory block was significantly prolonged in group BD (502.27 ± 20.495min) as compared to group BF (373.97 ± 17.026 min) and group BM (288.33 ± 15.749 min).



ANOVA test showed that the duration of motor block was significantly prolonged in group BD (483.50 ± 19.244 min) as compared to group BF (321.60 ± 18.144 min) and group BM (269.43 ± 13.221min).



ANOVA test showed time of onset of severe pain was significantly prolonged in group BD (556.17 ± 20.487min) as compared to group BF (450.63 ± 19.632 min) and group BM (301.41 ± 14.857min).

Side effects	Group BM (n=30)	Group BF (n=30)	Group BD (n=30)
Bradycardia	02	06	08
Hypotension	04	05	10
Others (nausea, itching, vomiting)	01	04	00
None	23	15	12

Groups	Group BM	Group BF	Group BD	P value
2 segment regression (min)	125.67 ± 10.568	131.93 ± 12.616	145.43 ± 8.705	0.000
Duration of sensory block	288.33 ± 15.749	373.97 ± 17.026	502.27 ± 20.495	0.000
Duration of motor block	269.43 ± 13.221	321.60 ± 18.144	483.50 ± 19.244	0.000
Time of rescue analgesia	313.93 ± 13.866	465.17 ± 18.903	577.70 ± 18.039	0.000

P value showed significant results.

The time of two dermatomal regression of sensory block was prolonged in Group BD Dexmedetomidine 10 mcg (145.43 ± 8.705 mins.), as compared to group BF Fentanyl 25 mcg (131.93 ± 12.616 mins.) and Group BM (125.67 ± 10.568 mins).

The duration of sensory and motor block was significantly prolonged (clinically and statistically) in Group BD (502.27 ± 20.495 mins, 483.50 ± 19.244 mins, respectively) as compared to Group BF (373.97 ± 17.026 mins. 321.60 ± 18.144 mins., respectively) and least in Group Bm (288.33 ± 15.749 mins., 269.43 ± 13.221 mins., respectively). The duration of sensory block was more prolonged than the duration of motor block and no patient complained of urinary retention in all three groups.

The mean duration of onset of severe pain (VAS>7) was significantly prolonged (clinically and statistically) in Group BD (556.17 ± 20.487 mins.) than in Group BF and Group BM (450.63 ± 19.632 mins and 301.40 ± 14.857 mins respectively).

The duration of effective analgesia (time of rescue analgesia) was significantly prolonged (clinically and statistically) in Group BD (577.70 ± 18.039 mins.) as compared to Group BF (465.17 ± 18.903 mins.) and Group BM (313.93 ± 13.866 mins).

With respect to quality of block, patients who were calm, oriented and co-operative were considered to have the best quality of block followed by patients who were responsive to commands only (deeply sedated) and anxious and agitated or restless or both, patients were considered to have least quality.

On comparison, significant improvement in quality (calm, oriented and co-operative) of the block was found more in patients in Group BD Dexmedetomidine 10 mcg (10 patients) when compared to Group BF Fentanyl 25mcg (5 patients) and Group BM Midazolam 2.5mg (3 patients).

Discussion :

The importance of post operative analgesia has been well understood. " Failure to relieve pain is morally and ethically unacceptable". Severe postoperative pain is known to adversely affect patient outcome after surgical procedures. Uncontrolled post operative pain may produce a range of detrimental acute and chronic effects. The attenuation of perioperative pathophysiology that occurs during surgery through reduction of nociceptive input to the CNS and optimization of perioprative analgesia may decrease complication and facilitate recovery during the immediate post operative period and after discharge from the hospital. The goal of post operative pain management is to reduce pain to a tolerable level with minimal or no associated suffering or distress. Post operative pain management in an individual relies heavily on pharmacological interventions. In order to maximize post operative analgesia, a number of adjuvants have been added to spinal anaesthesia like Ketamine,Neostigmine, Clonidine, etc;[3,4,5,6].

Our study compared three drugs in comparison to studies of other investigators who have compared Dexmedetomidine with either one of the adjuncts only. We also evaluated the analgesic efficacy of intrathecal Dexmedetomidine which has been hitherto reported in literature previously by only one study[7].

In this study, Midazolam, Fentanyl or Dexmedetomidine were added as adjuvants intrathecally along with 0.5% hyperbaric Bupivacaine and their effects on quality of blockade and duration of post operative analgesia were compared with each other.

Midazolam- belongs to benzodiazepine group of drugs. It was found to exhibit anti nociceptive action when administered intrathecally by binding to GABA-a receptors[8]and also it was found that it has action on delta and kappa opioid receptors which are involved in action of Midazolam given intrathecally.

Fentanyl- It is a phenyl-piperidine derivative synthetic opioid agonist which is 75-125 times more potent than morphine. It is more lipid soluble than morphine, which makes it more effective, when given intrathecally. It acts by directly inhibiting ascending transmission of information from spinal cord dorsal horn and also activating pain controlling circuit that descend from midbrain via rostral ventromedial medulla[9].

Dexmedetomidine showed protective or growth promoting properties in tissues, including nerve cells from cortex and has a neuroprotective effect similar to methylprednisolone in spinal cord injury when used intrathecally[10,11].

In this study, we compared the following parameters after adding Midazolam, Fentanyl or Dexmedetomidine to 0.5% (H) Bupivacaine given intrathecally with each other. Most of the clinical experience gained in the use of intrathecal α2 adrenoreceptor agonists has been described with Clonidine[12,13,14,15]and there has been a need for clinical studies related to intrathecal Dexmedetomidine to prove its efficacy, safety, and the suitable dose for supplementation to spinal local anesthetics. In our study, the intrathecal dose of Dexmedetomidine selected was based on previous human studies wherein no neurotoxic effects have been observed[16,17,18].The 15 mcg intrathecal dose of Dexmedetomidine used by Hala EA Eid et al.,(19) showed significantly higher sedation scores which can be beneficial for patients undergoing lengthy complex surgeries as an alternative to epidural or prolonged general anesthetics and can preclude the use of IV sedative.

Local anesthetics act by blocking sodium channels. α2 adrenoreceptor agonists act by binding to the presynaptic C-fibers and postsynaptic dorsal horn neurons. They produce analgesia by depressing release of C-fiber transmitters and by hyperpolarization of post synaptic dorsal horn neurons[16,17,20]. The complementary action of local anesthetics and α2 adrenoreceptor agonists accounts for their profound analgesic properties. The prolongation of the motor block of spinal anesthetics may be the result of binding of α2 adrenoreceptor agonists to the motor neurons in the dorsal horn[16,17]. Dexmedetomidine is eight times more specific and highly selective α2 adrenoreceptor agonist compared to Clonidine, thereby making it a useful and safe adjunct in diverse clinical applications [21,22] and therefore we strived to explore its usefulness and also compare this new α2 adrenergic agonist with the previously established and widely used adjuncts Midazolam and Fentanyl on the spinal block characteristics in patients scheduled for lower limb surgery.

Conclusion :

We thus conclude that, the addition of Dexmedetomidine 10 mcg to hyperbaric Bupivacaine 0.5% for spinal anaesthesia:-

Does not clinically significantly affect the onset of sensory and motor block as compared to Fentanyl and MIdazolam when added intrathecally. Increases the time of 2 segment dermatomal regression of sensory block.

Provides a better and longer lasting post operative analgesia. Improves quality of sedation intra-operatively. Provides better anaesthesia intra-operatively with minimal side effects (mild hypotension and bradycardia).

We also conclude from our study that intrathecally Dexmedetomidine potentiates the Bupivacaine induced sensory and motor block compared to Midazolam and Fentanyl without causing urinary retention (due to prolongation of motor blockade) and reduces the analgesic requirement in the early post-operative period without any major side effects.

Dexmedetomidine in a dose of 10 mcg is found to be more potent than Fentanyl 25 mcg and Midazolam 2.5 mg intrathecally with hyperbaric Bupivacaine, with less side effects and significantly prolongs the duration of post-operative analgesia.

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