



RESEARCH ARTICLE

COMPARISON OF THE EFFECTS OF INTRAVENOUS DEXMEDETOMIDINE WITH INTRAVENOUS MIDAZOLAM ON THE CHARACTERISTICS OF BUPIVACAINE SPINAL BLOCK

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ABSTRACT

Introduction: Different adjuvants have been used to extend spinal anesthesia, with probable benefits of late commencement of postoperative pain and reduced analgesic requirements. Midazolam has only sedative property. However, dexmedetomidine has both analgesic and sedative properties that may prolong the duration of sensory and motor block obtained with spinal anesthesia. This study was designed to compare intravenous dexmedetomidine with midazolam and placebo on spinal block duration, analgesia and sedation.

Method: Single blinded randomized study was carried out on 75 patients undergoing surgeries in spinal anesthesia at General Surgery OT in Civil hospital Ahmedabad. Patients were randomly divided into 3 groups

D-received Dexmedetomidine 0.5 µg/kg i.v.

M-received Midazolam 0.05 mg/kg i.v.

S-received Normal Saline i.v.

After 5 min all patients were induced under spinal anesthesia with 0.5% bupivacaine heavy 3 ml intrathecaly. Time taken for highest level and duration of sensory and motor block of bupivacaine spinal block was noted. Duration of analgesia and sedation were recorded.

Result: Highest upper level of sensory block were higher in D($T_{560} \pm 1.73$) than in M($T_{784} \pm 1.99$) ($p < 0.001$) or with S($T_{8.48} \pm 1.75$) ($p < 0.001$). Time for sensory regression of two dermatomes was 154 ± 9.89 min in D while 112 ± 10.31 min in M ($p < 0.001$) and 96.4 ± 10.94 min in S ($p < 0.001$). Duration of motor block was higher in D(194 ± 9.94 min) compared to M(169 ± 11.38 min) and S(169 ± 18.38 min)

Patients in D had 24 hrs mean VAS score < 3 while patients in M and S needed rescue analgesic after 12 hr and 8 hr respectively as their VAS score were > 3 . The median of RAMSAY sedation score was 2(2-5) in D, 3(2-5) for M and 1(1-2) for S.

Conclusion: Dexmedetomidine prolonged highest upper level, duration of sensory blockade of bupivacaine induced spinal anesthesia with effective analgesia and sedation compared to intravenous midazolam.

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INTRODUCTION

Spinal anesthesia is the technique for regional anesthesia obtained by blocking the spinal nerves. The anesthetic agents are deposited in the subarachnoid space and act on the spinal nerve roots. One of the main advantages of spinal over general anesthesia is effective post operative pain relief. Local anesthetic agents usually have short duration of action and

higher volume of local anesthetics are associated with more side effects. Adjuvants from different pharmacological classes of drugs are used to enhance and prolong analgesia, to lower the dose requirements and to reduce dose dependent side effects. Opioids have attained an integral role as a spinal anesthetic adjuvant to local anesthetic. However these solution have disadvantages such as pruritus and respiratory depression. Dexmedetomidine, a highly selective α_2 agonist, has been used for premedication and as an adjuvant to general anesthesia. Its unique properties render it suitable for sedation and analgesia during the whole perioperative period. US-FDA has approved

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use of intravenous Dexmedetomidine for sedation in non intubated patients during intraoperative period. Although there was data regarding intrathecal dexmedetomidine prolonging bupivacaine spinal block but by using intravenous dexmedetomidine, its effects on duration of sensory & motor blockage and analgesia will be dealt with this study. Midazolam has sedative property but no analgesic property while dexmedetomidine has both sedative as well as analgesic property so to determine analgesic property of dexmedetomidine, we have taken three groups midazolam, dexmedetomidine and placebo.

Aims and objectives

- To compare the highest upper level and duration of sensory and motor block of bupivacaine spinal block after intravenous Dexmedetomidine versus intravenous Midazolam
- To compare the duration of effective analgesia of Bupivacaine spinal block.
- To compare the effective sedation after intravenous Dexmedetomidine versus intravenous Midazolam.
- To compare hemodynamic changes.
- To study the side effects if any.

Inclusion criteria

- ASA I and II
- Age 18-70 years

Exclusion criteria

- Patient refusal
- Extremes of ages
- Body weight of more than 100kg
- Height less than 150cms
- Allergy to drugs
- Patient using α_2 adrenergic receptor antagonists, calcium channel blockers, angiotensin converting enzyme inhibitors long term beta blocker users.
- History of drug or alcohol abuse.
- Uncontrolled systemic disease.

Procedure

75 patients were randomly divided into three groups having 25 patients each. All the patients were assessed a day before surgery. Routine investigations were done.

- Group – DReceived Inj. Dexmedetomidine 0.5 μ g/kg i.v.
- Group – MReceived Inj. Midazolam 0.05 mg/kg i.v.
- Group – SReceived Inj. Normal Saline i.v.

Informed and written consent was taken from all patients. On arrival to the operation theater, intravenous line secured with 18 gauge cannula in the non-dominant forearm. Routine & standard monitoring like ECG, pulse oximetry, NIBP applied & baseline values were noted. All patients received preloading with crystalloid (Ringer Lactate) 10-15 ml/kg. Each group premedicated with the study drug 5 minutes before spinal

anesthesia. The study drugs will be premixed to total volume of 5ml in 5ml syringe and were administered intravenously over 10 minutes. 5 minutes after the end of study drug, spinal anesthesia given in left lateral position with 23 G quincke needle in L3-L4 subarachnoid space under all aseptic precautions after local infiltration with 2ml of 2% lignocaine. Bupivacaine 0.5% heavy 3ml was injected intrathecally in all patients. Then the patient turned supine.

- The onset of sensory blockade was assessed by pinprick method in midclavicular line.
- Time to reach highest sensory blockade was recorded. Time for two segment regression of sensory block was recorded.
- The time to onset of complete motor blockade was recorded as the time to achieve Bromage scale III. The duration of motor blockade was time taken to be Bromage scale I.
- The duration of effective analgesia was counted from the time of injection of drug to the time first rescue analgesic drug required.
- Postoperative pain assessment was carried out by Visual Analogue Score (VAS) at 4, 8, 12 and 24 hrs.(VAS; 0-no pain; 10-worst possible pain). Patient with a VAS score of 3 or more received inj.Diclofenac 1.5 mg/kg IV.
- Perioperative degree of sedation was assessed by using Ramsay hund sedation score. It was re-evaluated every 10 minutes for up to 120 minutes.
- Recording of HR, BP and O2 saturation, RR was done first at the time of premedication with study drug, 2min after end of premedication, at the time of performing spinal block than every 5min for 30min, every 15min up to 120min, every 30min up to 180min after giving study drug.
- Episode of perioperative hypotension defined as 0.4 MAP below 20% of baseline or systolic pressure <90 mmHg, Bradycardia (HR <50/min), perioperative emesis, respiratory depression, pruritus and any other side effects were noted and treated accordingly.

Statistical methods

The demographic data of patients was studied for each group. The means of the continuous variables (Age and duration of surgery) were compared between the three groups using analysis of variance ANOVA, The demographic data for the categorical variables (sex, ASA class) were compared using chi-square test.

OBSERVATION AND RESULTS

1) Demographic data:

	GROUP D	GROUP M	GROUP S
Age(yr)	58.12±11.68	54.16±18.31	56.64±15.39
Weight(kg)	69.12±6.01	68.58±6.57	67.84±4.54
Height(cm)	159.9±7.89	161±7.67	158±7.88
Sex(male/female)	13/12	12/13	13/12
ASA(I/II)	18/7	22/3	20/5

Patients in all three groups are statistically comparable (p value>0.5)

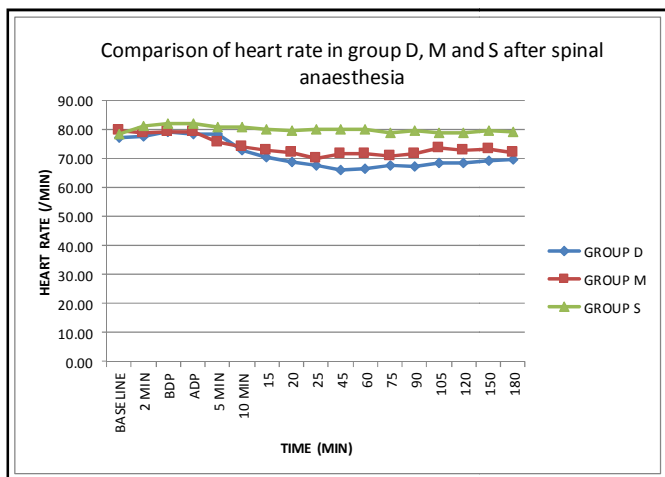
2) Hemodynamic parameters:

(a) Baseline hemodynamic parameters

BASELINE	GROUP D	GROUP M	GROUP S
Heart rate(/min)	77.16±10.88	79±11.86	78.48±8.58
Systolic BP(mm Hg)	119.7±11.68	124.8±10.26	121.4±13.49
Diastolic BP(mm Hg)	78.16±6.5	81.4±4.90	80.33±4.92

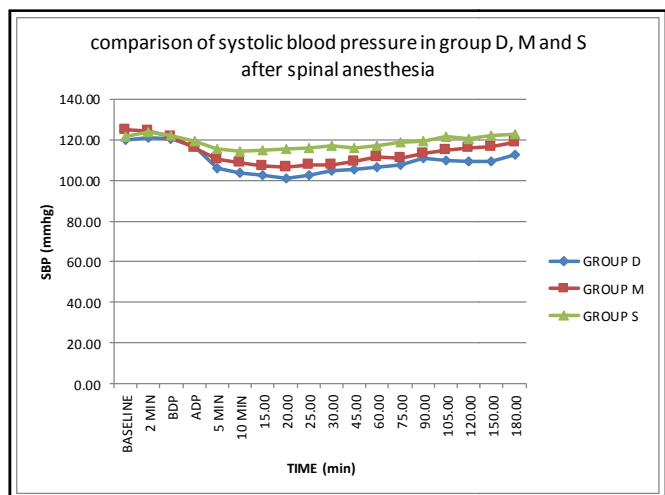
Patients in all the three groups are having statistically comparable baseline hemodynamic parameters (p>0.05)

(b) Heart rate during intraoperative and postoperative period



In patients receiving Dexmedetomidine or Midazolam, the decrease in heart rate were highly significant as compared to normal saline group. (p value <0.001).

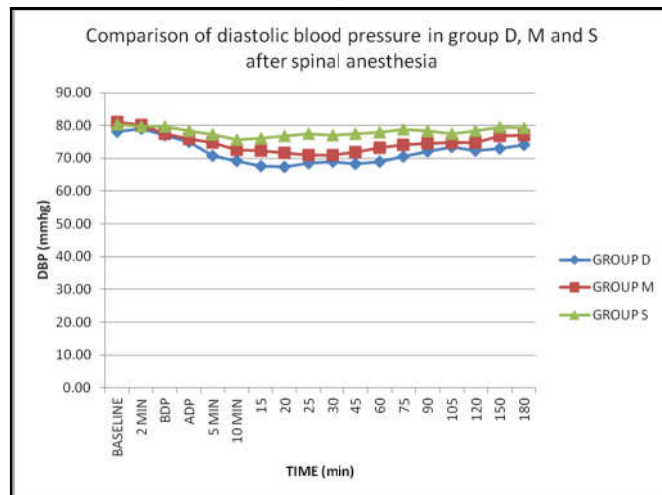
(C) Systolic blood pressure during perioerative period



The mean values of systolic blood pressure in the first 120 min after performing the spinal anaesthesia are comparable between the two groups (p value > 0.01)

(d) Diastolic blood pressure during perioerative period

The mean values of diastolic blood pressure in the first 120 min after performing the spinal anaesthesia are comparable between the three groups (p-value >0.05).



3) Analgesia

VAS SCORE	GROUP D	GROUP M	GROUP S
4 HR	0	0.4	0.88
8 HR	1.24	2.48	2.6
12 HR	2.16	3.12	3.56
24 HR	2.76	3.56	3.8
OVERALL	1.232	1.912	2.2

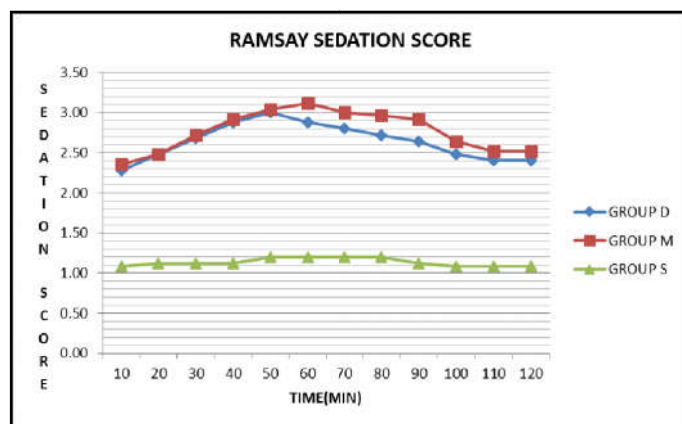
First request for analgesia made by all 25 patients in group S, 23 patients in group M while only 7 patients in group D. All these patients received analgesia in form of Inj. diclofenac sod. 75mg IM. This observation suggests significant reduction in need of additional analgesic among patients receiving dexmedetomidine compared to midazolam and saline.

4) Effect on bupivacaine spinal block

	GROUP D	GROUP M	GROUP S
Highest level of sensory block	T5.60±1.73	T7.84±1.99	T8.48±1.75
Duration of sensory block(min)	154±9.89	112±10.31	96.4±10.94
Duration of motor block(min)	194±9.94	169±11.38	169±18.38

Values expressed in above table are MEAN± S.D. for patients in each group.

5) Sedation score



The sedation score was higher in patients receiving dexmedetomidine or midazolam compared to patients receiving saline (p<0.001). Excessive sedation (Ramsay

score \geq 5) was observed in 2 patients in group D and 4 patients in group M.

6) Complications

	GROUP D	GROUP M	GROUP S
Hypotension	3	1	3
Bradycardia	3	1	-
Excessive Sedation	2	4	-

DISCUSSION

It is recommended to administer dexmedetomidine slowly over 10 minutes. Rapid administration might produce bradycardia and hypertension. Furthermore, different doses of intravenous dexmedetomidine (0.25, 0.5 and 1 μ g/kg) in healthy volunteer demonstrated moderate analgesia with ceiling effect at 0.5 μ g/kg. With this in mind, dexmedetomidine 0.5 μ g/kg was given over 10 min in this study. Bolus administration of midazolam 0.05 mg/kg was reported to give enough sedation and amnesia without any side effect on hemodynamic and respiration in patients under spinal anesthesia. Therefore, midazolam 0.05 mg/kg was administered in this study.

Heart Rate

It was observed that the heart rate decreased in all the groups immediately after spinal anesthesia. The heart rate started to return to normal values at the end of observation period. Base line heart rate of all patients of all the groups were comparable to each other and there is no statistical difference between them (p value $>$ 0.05). After intravenous Dexmedetomidine the decrease in heart rate was highly significant in group D as compared to group S (p value $<$ 0.001). Intravenous midazolam also decreases heart rate of patients in group M compared to group S(p $<$ 0.001) probably by its sedative and anxiolytic action. The lower HR observed in group D could be explained by the decreased sympathetic outflow and circulating levels of catecholamine that are caused by Dexmedetomidine. These observations are comparable with studies by Berrin Naydin *et al.* (2004), Judith E. Hall *et al.*, Bajwa *et al.*, Mahmoud M Al-Mustafa *et al.* (2009) and Harsoor *et al.* (2013).`1`

Blood Pressure

Systolic blood pressure

Baseline blood pressure in all the groups were comparable (p-value $>$ 0.05). It was observed that the systolic blood pressure decreased in all the groups. Decrease in blood pressure was due to spinal anesthesia. The mean values of systolic blood pressure in the first 120 min after performing the spinal anesthesia were comparable between the groups (p-value $>$ 0.05).

Diastolic blood pressure

Baseline blood pressure in all the groups were comparable (p-value $>$ 0.05). It was observed that the diastolic blood pressure decreased in all the groups. Decrease in blood

pressure was due to spinal anesthesia. The mean values of diastolic blood pressure in the first 120 min after performing the spinal anesthesia and were comparable in all the three groups (p-value $>$ 0.05).

These observations are comparable with studies by Berrin G. Naydin *et al.* (2004), Judith E. Hall *et al.*, Bajwa *et al.*, Mahmoud M Al-Mustafa *et al.* (2009) and Harsoor *et al.* (2013)

Analgesia

Majority of patients all the three groups had VAS score below 3 up to 8 hr. Majority of patients receiving dexmedetomidine had 24 hr pain score $<$ 3, while majority of patients in group M and S needed rescue analgesic after 12 hr and 8 hr respectively as their VAS score were $>$ 3. The first request for analgesia by the patients in all 25 patients of group S, 23 patients in group M and 7 patients in group D. These data suggest that dexmedetomidine provide statically significant analgesia than midazolam and saline. Based on previous studies, the effects of dexmedetomidine is not dependent on the route of the administration. Midazolam has been reported to have an antinociceptive effect through neuroaxial pathway as analgesia with midazolam observed after spinal or epidural application, but not after systemic administration. Also in our study, intravenous midazolam did not enhance the analgesic effect of intrathecal injection. Finally, the use of dexmedetomidine premedication before spinal anesthesia seems to offer clinical advantage over midazolam premedication by providing additional analgesia. These observations are comparable to study done by Fatma Nur kaya *et al.* (2010) comparing intravenous dexmedetomidine 0.5 μ g/kg with midazolam 0.05mg/kg as premedication during spinal anesthesia.

Effect on bupivacaine spinal block

Highest upper level of sensory block were higher with group D(T 5.60 \pm 1.73) than with group M (T 7.84 \pm 1.99) (p $<$ 0.001) or with group S (T8.48 \pm 1.75) (p $<$ 0.001). The time for sensory regression of two dermatomes was 154 \pm 9.89 min in group D, longer than in the group M (112 \pm 10.31 min, p $<$ 0.001) or with group S (96.4 \pm 10.94 min; p $<$ 0.001). The difference between extension or duration of sensory block between the midazolam and saline group was not statistically different. Duration of motor block was higher in group D(194 \pm 9.94 min) compared to group M(169 \pm 11.38 min) and group S(169 \pm 18.38 min) but statically non-significant. This study showed that the intravenous dexmedetomidine prolonged the sensory block of bupivacaine spinal anesthesia and increased the maximum upper levels of sensory block, the underlying mechanism of this effect unclear. The supra-spinal, direct analgesic, and/or vasoconstricting actions of dexmedetomidine are suggested to be involved in this mechanism. Duration of motor block was not affected, which could be explained by that conduction of sensory nerve fiber might be more inhibited than motor nerve fiber at the same concentration of dexmedetomidine, as similarly reported with clonidine. These observations are comparable to study done by Mahmoud M Al-Mustafa *et al.* (2009) and Fatma Nur kaya *et al.* (2010) comparing

intravenous dexmedetomidine 0.5µg/kg with midazolam 0.05mg/kg as premedication during spinal anesthesia.

Sedation

During lumbar puncture procedure and intra operative period, it is preferable that patients remain sedated but arousable and cooperative. The median of the RAMSAY sedation score was 2(2-5) in group D, 3(2-5) for group M and 1(1-2) for group S. The sedation score was higher in patients receiving dexmedetomidine or midazolam compared to patients receiving saline ($p < 0.001$). These observations are comparable to studies done by Fatma Nur kaya *et al.* (2010) and Harsoor *et al.* (2013) comparing intravenous dexmedetomidine 0.5µg/kg with midazolam 0.05mg/kg as premedication during spinal anesthesia.

Complications

Bradycardia observed in 3 and 1 out of 25 patients in patients receiving dexmedetomidine and midazolam respectively in our study which was treated with inj. atropine i.v. Hypotension observed in 3, 1 and 3 out of 25 patients in patients receiving dexmedetomidine, midazolam and saline respectively in our study which was treated with inj. mephentermine i.v. This might be attributed to sympathetic blockade associated with spinal anesthesia. Excessive sedation (i.e. RAMSAY sedation score ≥ 5) observed in 2 and 4 out of 25 patients in patients receiving dexmedetomidine and midazolam respectively in our study. There was no other complications like nausea, vomiting, pruritus or respiratory depression seen during this study. Fatma Nur kaya *et al.* (2010) observed similar kind of complications while comparing intravenous dexmedetomidine 0.5µg/kg with midazolam 0.05mg/kg as premedication during spinal anesthesia.

Conclusion

A single dose of intravenous dexmedetomidine given as premedication prolonged the highest upper level and duration of sensory blockade of bupivacaine induced spinal anesthesia with effective analgesia and sedation compared to intravenous midazolam without significant hemodynamic disturbances and complications.

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