Comparison of Intravenous Dexmedetomidine Versus Midazolam for Sedation and Post-operative Analgesia with Spinal Anesthesia

Ganorkar Prachi D.*, Dalvi Naina**, Tendolkar Bharati***

Abstract

Background: Central neuraxial anaesthesia may need to be supplemented with benzodiazapines, alpha$_2$ blockers etc. for sedation and analgesia. In the present study, we compared the effects of intravenous dexmedetomidine and midazolam on sedation, post-operative analgesia, and spinal block duration in lower abdominal surgeries like inguinal hernias and appendicectomies performed under spinal anaesthesia. *Methods:* This prospective randomized controlled double blind study was carried out in 60 patients. Group D (n=30) received IV premedication with Dexmedetomidine 0.5mcg/kg while Group M (n=30) received IV Midazolam 0.05mg/kg fifteen minutes prior to subarachnoid block with bupivacaine 0.5% 3.5ml. Onset and duration of sensory and motor blockade, level of sedation, cardiorespiratory parameters and quality of post-operative analgesia were recorded.

Results: The duration of sensory blockade was significantly prolonged in group D (280.00 ± 31.62 minutes) as compared to group M (263.00 ± 30.30 minutes) (p<0.05). The duration of analgesia was significantly prolonged in group D (261.50 ± 90.85minutes) than group M (213.67 ± 49.02minutes). The sedation scores were higher in group D as compared to group M in the beginning but comparable later on. The pulse rate was significantly decreased in group D than in group M. The systolic, diastolic and mean arterial pressures were significantly decreased in group M. There was no significant difference in respiratory rates in both the groups. *Conclusion:* IV premedication with dexmedetomidine 0.5 mcg/kg prolongs the duration of sensory blockade as compared to IV midazolam 0.05 mg/kg. Dexmedetomidine produces sedation with easy arousability, and provides better analgesia than midazolam.

Keywords: Dexmedeto-Midine; Midazolam; Premedication; Sedation; Spinal Anesthesia.

Introduction

In 1898, August Bier first used spinal anaesthesia as an anaesthetic technique for surgery, since then spinal anaesthesia is a preferred method of anaesthesia for surgeries on lower half of the body[1]. This is due to its efficacy, rapidity, minimal side effects on mental status, reduction of blood loss and protection against thrombo-embolic episodes. However, it may be associated with stress and anxiety leading to various manifestations like increasing oxygen consumption, respiratory rate and heart rate due to circulating level of endogenous catecholamines and their untoward effects. Hence, some patients require sedatives to limit discomfort. Also, surgery represents a form of premeditated injury to the body stimulating free nerve endings and specific nociceptors, and leads to post-operative pain. Adequate control of pain in the perioperative period may improve the post-operative outcome and shorten the hospital stay. Thus to make patients under central neuraxial blockade comfortable during surgery and for adequate post-operative analgesia, different supplements may be required.

Midazolam, an ultra-short acting benzodiazepine has amnesic, anxiolytic and sedative properties[2]. However its intravenous use is associated with cardio-respiratory side effects causing oxygen desaturation and occasionally, a cardiopulmonary

Author's Affiliation:
*Ex-resident, Department of Anesthesiology, ***Professor and Head, Department of Anaesthesia, LTMMC & LTMGH, Sion, Mumbai. **Additional Professor, Dept. of Anaesthesia, HBTMC & Dr R N Cooper Hospital, Juhu Mumbai 400 056.

Corresponding Author:
Ganorkar Prachi D., No.170, "Kruthika", 7th cross, 4th main, Saraswathi Nagar, Vijayanagar, Bangalore-560040.
E-mail: prachi_2509@yahoo.co.in

complication.

Dexmedetomidine is a highly selective alpha$_2$-adrenoreceptor agonist with sedative, analgesic and antisialagogue effects [3]. Dexmedetomidine offers hemodynamic stability, diminished sympathetic response to stress, has minimal effects on respiration and has only minor effects on cognitive functions.

To our knowledge, little information is available in literature about the effects of IV dexmedetomidine used in single dose as an adjunct to spinal anaesthesia. In the present study, we hypothesize that intravenous dexmedetomidine is better than midazolam for intraoperative sedation and post-operative analgesia in lower abdominal surgeries under spinal anaesthesia. Also we plan to compare their effects on the onset, duration of sensory and motor blockade, and their cardiorespiratory endpoints.

Materials and Methods

The study protocol was approved by Instituitional Ethics Committee, and written informed consent was obtained from each patient. This study was carried out in 60 adult patients of either sex between 18-60 years of age, classified as American Society of Anesthesiologists' (ASA) physical status I-II, undergoing lower abdominal surgeries: appendicectomy and unilateral inguinal hernia repair, under sub-arachnoid blockade. The patients with body mass index >30kg/m^2, height <145 cm or >160 cm, known contraindication to spinal anaesthesia (eg. coagulation disorders, infection at puncture site, hypovolemia, pre-existing neurological deficits in lower extremities), hemodynamic instability, therapy with pain perception modifying drugs, pregnant and lactating mothers, use of sedative medications within a week prior to surgery, were excluded. Patients were randomly divided into two groups of 30 each, using computerized randomization table in a double blind manner. Patients receiving premedication with IV dexmedetomidine 0.5 mcg/kg were termed as group D while those receiving IV midazolam 0.05 mg/kg were in group M.

After confirming adequate starvation, patients were wheeled in the operating theatre and monitors including cardioscope, pulse-oximeter and non-invasive blood pressure cuff were attached and baseline values were recorded. A 20G IV cannula was secured in upper limb and patients were preloaded with Ringer's lactate 10 ml/kg.

The study drug was pre-mixed with normal saline

to a total volume of 10ml and was infused IV over a period of 10 minutes using infusion pump. Five minutes after the end of infusion, subarachnoid block with Inj.Bupivacaine 0.5% (heavy) 3.5 ml, was given in left lateral position with midline approach in L$_3$-L$_4$ interspace using 25-G Quincke needle. Oxygen was supplied via face mask with flow rate of 6 L/min, throughout the procedure. Both the patient and the anaesthesiologist administering the drug were blinded to the treatment group, and all recordings were performed by this anaesthesiologist.

The time of onset and duration of sensory block was noted. The highest level of sensory blockade was checked by pinprick method from caudal to cephalad direction every 2 minutes after the subarachnoid block and time taken to achieve this was noted as time of onset. Duration of sensory blockade was defined as the time from injection of subarachnoid drug till the level of regression up to L$_5$- S$_1$ level assessed by re-appearance of sensation on heel and sole of foot.

The time of onset of motor blockade was the time taken to achieve the highest level of motor blockade checked by Modified Bromage Scale (0 - full flexion of hip, knee and ankle,1 - unable to raise extended leg, 2 - unable to flex knee, 3 - unable to flex ankle). Duration of motor blockade was defined as the time from injection of subarachnoid drug till return to modified bromage scale 0 [4].

Intra-operative sedation was graded by Ramsay Sedation Score (RSS) (1- anxious and agitated, 2- co-operative and oriented, 3- drowsy but responsive to commands, 4- asleep but with a brisk response to glabellar tap or loud auditory stimuli, 5- asleep but with a sluggish response to tactile stimuli, 6- asleep and no response)[5].

Postoperative pain was assessed by 10cm Visual analogue scale (VAS) (0=no pain, 10=worst possible pain) [6]. Duration of analgesia was considered as interval from time of intrathecal injection to time of first rescue analgesic demanded or when VAS > 4. Inj. diclofenac 75 mg intravenously was used as a rescue analgesic. The total number of analgesic doses in the first 24 hours was noted.

Vital parameters like heart rate (HR), mean arterial blood pressure (MAP), peripheral oxygen saturation (SpO2) and respiratory rate (RR) were noted every 2 minutes for first 10 minutes, every 5 minutes till the end of surgery, every 30 minutes for next 4 hours and thereafter at 2 hours interval for 24 hours. The level of sensory blockade, motor blockade, VAS and RSS score were noted every 15 minutes for first 2 hours, every 30 minutes for next 4 hours and thereafter at 2 hours interval for 24 hours.

Ganorkar Prachi D. et. al. / Comparison of Intravenous Dexmedetomidine Versus Midazolam
for Sedation and Post-operative Analgesia with Spinal Anesthesia

201

Duration of surgery was noted at the end of surgery. No prophylactic pain relief was given. Patients were transferred to post-operative anaesthesia care unit and monitoring was continued for 24 hours. All the patients were observed for following side effects:

Nausea, vomiting, excessive sedation (RSS>5), hypotension (fall in blood pressure > 20% from baseline) treated with intravenous additional 200ml RL and ephedrine 6 mg, respiratory depression (RR < 12 breaths/min), bradycardia (fall in HR < 60/minute) treated with IV atropine 0.01mg/kg, high spinal level treated with general anaesthesia, resuscitation if required.

Statistical Analysis

Considering the power at 80% and confidence interval at 95%, to detect at least 15% difference in duration of analgesia, the minimum sample size required was 16 patients in each group. However we included 30 patients in each group for better validation of results. Data analysis was done using SPSS software version 15. The data was statistically analysed using unpaired student's 't 'test for continuous variables (age, height, duration of surgery/analgesia, pulse, BP, RR, RSS, VAS etc). Chi square test was used to analyse demographic data for categorical variables (sex, type of surgery, ASA grade) and treatment factors (number of analgesics required in 24 hours, peak sensory level etc). Descriptive statistics are summarized as

mean ± standard, whereas categorical variables are expressed in percentages.

The 'p' value of < 0.05 was considered as statistically significant.

Results

The study was completed in all the patients. The demographic data did not differ between the two groups (Table 1).

RSS ranged from 2-4 in both the groups. RSS in group D were statistically higher between 4 and 10 mins, i.e. immediately after giving SAB in the early period, while that in group M were higher in the later period, $1^{1}/_{2}$ to $2^{1}/_{2}$ hrs and then between 4 to 5 hrs. The maximum mean score of sedation (3.17) was achieved 35 min after starting dexmedetomidine infusion (20 min after SAB), while it took 55 min for midazolam infusion (40 min after SAB) to achieve maximum mean score (3.53) (Figure 1).

The 24-hr VAS scores were similar in both groups. Time of rescue analgesia was later in group D than in group M (p<0.05). Analgesic requirement during 24 hours (post-SAB) among both the groups was comparable (Table 2) (Figure 2).

There was no significant difference in the two groups in terms of onset of sensory block, and onset and duration of motor block. However, the duration of sensory block was statistically prolonged in group D than in group M (p<0.05).

Table 1: Demographic data

	Group D	Group M	P Value
Age (yr)	31.67±8.75	32.57±9.62	0.706
Weight (kg)	59.33 ± 5.96	60.47 ± 4.45	0.407
Height (cm)	160.2 ± 3.22	159.2 ± 3.04	0.237
Sex (M/F)	23/7	22/8	0.736
ASA (I/II)	26/4	26/4	1.00
Surgery (Appendicectomy/Hernia)	16/14	15/15	
Duration of surgery (min)	73.17 ± 15.23	73.67 ± 15.81	0.901

(Values are expressed as mean ± standard deviation or numbers.)

Table 2: Data regarding onset and duration of sensory and motor block, and postoperative analgesia. (Values are expressed as mean ± standard deviation)

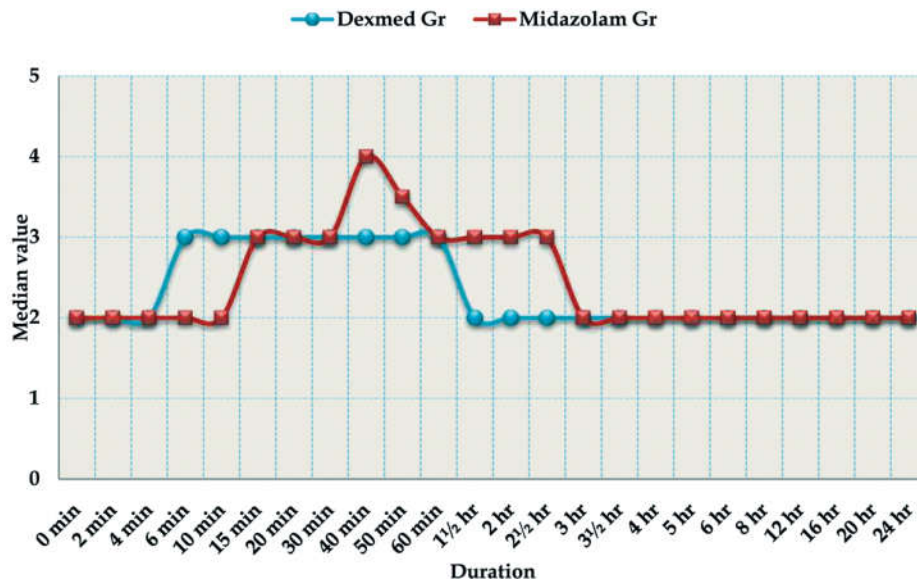|		Group D	Group M	p value
Sensory block (min)	Onset	1.37 ± 0.56	1.47 ± 0.51	0.470
	Duration	280.00 ± 31.62	263.00 ± 30.30	0.038
Motor block (min)	Onset	2.47 ± 0.78	2.60 ± 0.62	0.466
	Duration	217.67 ± 24.02	210.33 ± 23.27	0.235
Time of rescue analgesia (min)		261.50 ± 90.85	213.67 ± 49.02	0.014
Number of analgesics in 24-hr		2.30 ± 0.53	2.47 ± 0.51	0.221

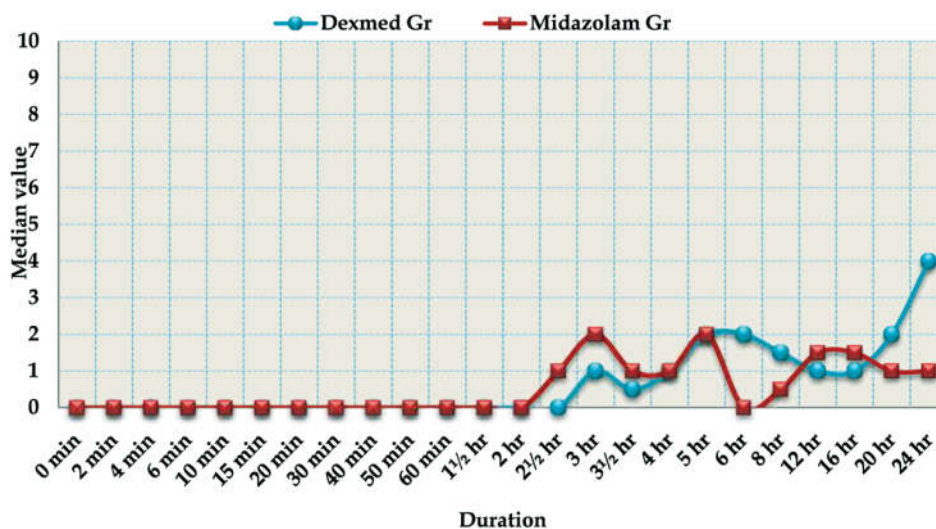**Fig. 1:** Comaprison of Sedation score at various interval among study group

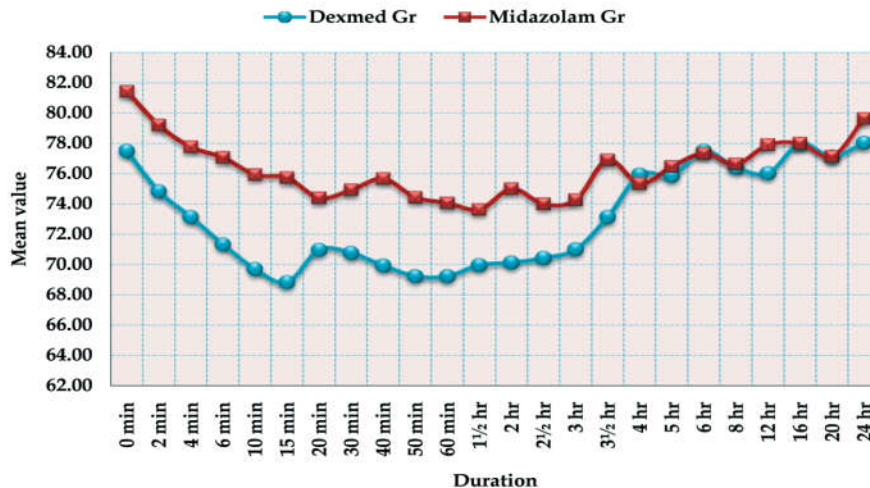**Fig. 2:** Comaprison of VAS score at various interval among study group

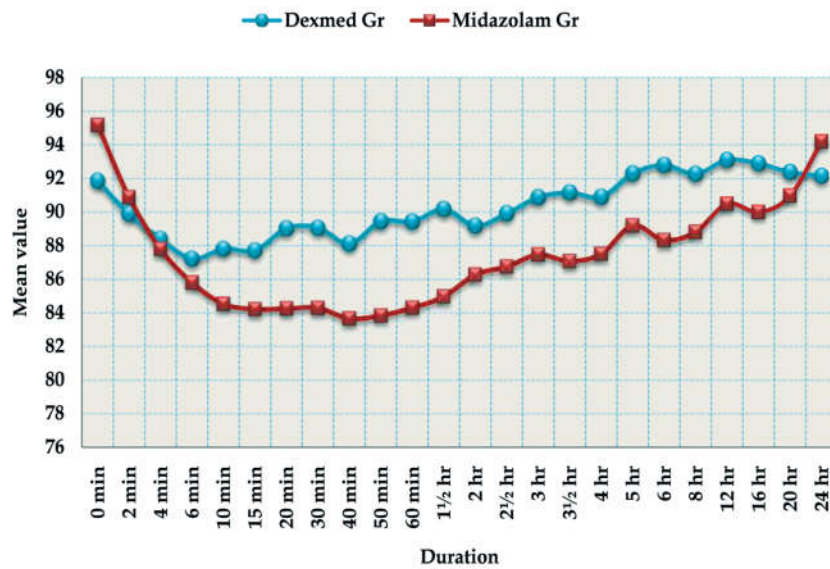**Fig. 3:** Comaprison of Pulse Rate at various interval among study group

Fig . 4: Comaprison of Mean Arterial Pressure (mmHg) at various interval among study group

There was decline in pulse rate from the baseline in both groups, significant in first 3½ hours (post SAB) in group D (p < 0.05) than group M. Nine patients in group D presented with bradycardia (and were treated for the same), while none in group M (p<0.001) (Figure 3).

A fall in mean arterial pressure (MAP) from the baseline has been observed in both the groups, significant in group M (p<0.05) as compared to group D. But none in either group required treatment for hypotension. The variations in respiratory rates and SpO2 were negligible in both the groups (Figure 4).

No other complications attributable to the drugs and procedure were noted.

Discussion

The aim of intra-operative and post-operative relief of anxiety and pain is to provide comfort and to inhibit trauma induced nociceptive impulses, thereby blunting autonomic and somatic reflex responses to pain. Postoperative analgesia plays a pivotal role in medical practice enabling faster restoration of physiological functions.

Spinal anesthesia is a popular and preferred anesthetic technique for surgeries on abdomen and lower limbs. But some drawbacks are linked with it, eg. fear of needles, pain at puncture site, recall of events, stress, anxiety etc. This emphasizes the importance of sedation that offers anxiolysis, analgesia and amnesia. The ideal sedative agent

should have minimal side-effects, particularly a lack of hemodynamic impairment and respiratory depression.

Dexmedetomidine, an alpha-2 receptor agonist has sedative, analgesic, sympatholytic properties with minimal respiratory depression[3]. Its half-life is 2 hours. Midazolam belongs to benzodiazepine group, with elimination half-life of 1-4 hours [2]. It acts on the benzodiazepine binding site of $GABA_A$ receptors by facilitating its action, and thus mediates sedation and anxiolysis.

According to previous studies, supplement of intravenous dexmedetomidine as loading dose followed by infusion, in patients receiving epidural anesthesia and spinal anesthesia provided good sedative effect and postoperative pain management without any clinically important untoward cardiorespiratory reactions [7-9]. The present study demonstrated similar results following use of single dose of dexmedetomidine (0.5 mcg/kg) intravenously as an adjunct to spinal anesthesia.

The present study was conducted in patients undergoing appendicectomy or unilateral inguinal hernia repair as the estimated duration of these surgeries is usually < 1½ hours, which is no longer than the half-lives of any of our study drugs, if used as a single dose. Dexmedetomidine may cause bradycardia, hypotension if rapidly administered, hence recommended to be infused slowly over a period of 10 minutes[10]. In our pilot study infusing different doses of midazolam or dexmedetomidine for induction of sedation, we found that 0.05 mg/kg

of midazolam or 0.5 μg/kg of dexmedetomidine provided sedation with RSS ≥ 3. Thus we chose the initial doses used in the present study.

It was noticed that clinically, the patients in dexmedetomidine group were more comfortable and at the same time easily arousable than the midazolam group while giving subarachnoid block. This arousable sedation is preferred during spinal puncture as patients can inform any paresthesia caused which can be associated with postoperative neurologic deficit. The sedation scores were higher in the early period (4 to 10 min post SAB) in dexmedetomidine group, and in the later period ($1^1/_2$ to 5 hrs) in midazolam group. Since, the half-life of midazolam is longer than dexmedetomidine, the sedation lasted longer in group M than in group D. However, as none of our surgeries lasted longer than 1 ½ hrs, patients in group D were equally comfortable as those in group M, even during the later part of intra-operative and early post-operative course. In dexmedetomidine group, 10 patients reached RSS=2, one patient RSS =4 and none reached RSS>4 anytime during the observation period. In midazolam group, 17 patients reached RSS= 5, but none with RSS>5. Thus in our study, dexmedetomidine provided intra-operative sedation which was comparable to midazolam, and also prevented the risk of prolonged sedation in post-operative period. In addition, dexmedetomidine provided easy arousability. Similar results were found in studies conducted by M.Celik et al [7] and other authors [8,10,11].

In central nervous system, the locus ceruleus is the site of origin for the descending medullospinal noradrenergic pathway, known to be an important modulator of nociceptive neurotransmission. Dexmedetomidine acts as an agonist to α_2 receptors present on this site in brain and spinal cord[12]. Thus its analgesic effects could be mediated through supraspinal, spinal and peripheral actions. A study performed by J-Y. Hong et al [13] described improved post-operative analgesia in patients premedicated with IV dexmedetomidine 1mcg/kg. In our study, the duration of post-operative analgesia was prolonged in group D as compared to group M. But the total number of analgesics required in 24 hours was comparable in both the groups. This indicates that the patients from dexmedetomidine group remained pain-free for longer duration than the patients of midazolam group in the immediate post-operative period but dexmedetomidine did not offer any advantage over midazolam with respect to analgesia in a 24 hours period because of its shorter half life.

The present study suggested that use of single dose of 0.05 mcg/kg dexmedetomidine intravenously prolonged the duration of sensory blockade without affecting the duration of motor blockade. Kaya F.N. et al[11] also observed similar finding in their study. However, in studies conducted by Al-Mustafa MM et al[14] and K. Elcicek et al[10], prolongation of motor along with sensory blockade was noted with use of dexmedetomidine as 1 mcg/kg loading dose followed by maintenance infusion. This can be attributed to continuous infusion following loading dose in their studies. The prolonged duration of sensory block of spinal anaesthesia, by intravenous dexmedetomidine can be attributed to its supra-spinal and direct analgesic actions. Clonidine, an alpha-2 agonist, inhibits impulse conduction more in the large, myelinated Aα fibers than the small, unmyelinated C fibers. Thus conduction of motor nerve fibers is less inhibited than sensory nerve fibers at the same concentration of clonidine [15]. This same theory might explain the sensory but not motor block prolongation with dexmedetomidine as well.

The ideal sedation provides patient comfort and maintenance of spontaneous respiration without altering airway function. Dexmedetomidine is known to cause no or minimal respiratory depression. However, midazolam can cause apnea and arterial desaturation in sedative doses. Yongskin Liang et al [8] observed respiratory depression and intervention in midazolam group but not in dexmedetomidine group. There was no evidence of respiratory depression in any patients of either group in our study. Also the respiratory rates in both the groups were comparable at any time during the observation period.

In the present study, decrease in pulse rate and mean arterial pressures from the baseline were observed in both the groups after infusion of respective drugs, because of release of anxiety and sympathetic blockade. But, the decrease in heart rate was more significant in dexmedetomidine group. This could be explained by further decreased sympathetic outflow and circulating levels of catecholamines that are caused by dexmedetomidine [3]. Nine (30%) patients out of 30 in group D developed bradycardia and were given atropine while none in midazolam group had bradycardia. The fall in mean arterial pressure was statistically more significant in midazolam group. However, none of the patients in either group required treatment with ephedrine. This might be attributed to sufficient preoperative hydration in both the groups. Thus clinically the difference in the two groups with regards to mean arterial pressures was not significant, though

Ganorkar Prachi D. et. al. / Comparison of Intravenous Dexmedetomidine Versus Midazolam
for Sedation and Post-operative Analgesia with Spinal Anesthesia

205

statistically significant.

In conclusion, a single dose of intravenous dexmedetomidine 0.5 mcg/kg when given intravenously as premedication for bupivacaine-induced spinal anesthesia provides arousable and stable sedation, without affecting respiratory parameters, and better post-operative analgesia, as compared to intravenous midazolam 0.05 mg/kg. It also prolongs the duration of sensory blockade. However bradycardia needs to be taken care of.

Conflicts of Interest

None

References

1. McLeod G. Spinal anaesthesia - Intradural and extradural. In: Davies NJS and Cashman JN editors. Lee's synopsis of anaesthesia. 13th ed. New Delhi. Elsevier. 2006. p.471- 538.

2. Robert K Stoelting, Simon c Hillier. Pharmacology and physiology in anesthetic practice 2006. 4th edition.142-147.

3. Kamibayashi T, Maze M. Clinical uses of alpha-2 adrenergic agonists. Aneslhesiology. 2000;93:1345-9.

4. Bromage PR, Burfoot MF, Cromwell DE, Pettigrew RT. Quality of epidural blockade. I. Influence of physical factors. Br J Anaesth 1964;36: 342-52.

5. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974;2:656-9.

6. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain.

J Pain 2003; 4:407-14.

7. M. Celik, N. Koltka, B. Cevik, H. Baba. Intraoperative sedation during epidural anesthesia: DexmedetomidineVs Midazolam. The Internet Journal of Anesthesiology. ISSN:1092-406X.

8. Y Liang, M Gub, S Wanga, H Chua. A Comparison of Dexmedetomidine and Midazolam for Sedation in Gynecologic Surgery Under Epidural Anesthesia. Journal of Current Surgery. 2011;1:12-18.

9. M Korkmaz , A Gurbet, S [a]ahin , O OPurcu.. Comparison of the sedative effects of midazolam and dexmedetomidine during regional anaesthesia. Dicle Medical Journal. 2011;38(2):148-154.

10. K Elcicek, M Tekin, I Kati. The effects of intravenous dexmedetomidine on spinal hyperbaric ropivacaine anesthesia.J Anesth. 2010;24:544-548.

11. Kaya FN, Yasvascaoglu B, Turker G, Yildirim A, Gurbet A, Mogol EB, Ozcan B. Intravenous dexmedetomidine, but not midazolam, prolongs bupivacaine spinal anesthesia. Can J Anesth. 2010;57:39-45.

12. Jorm CM, Stamford JA. Actions of the hypnotic anaesthetic , dexmedetomidine, on noradrenaline release and cell firing in rat locus coeruleus slices. Br J Anaesth 1993;71:447-9.

13. J-Y.Hong, W. O. Kim, Y. Yoon, Y. Choi, S-H. Kim, H. K. Kil. Effects of intravenous dexmedetomidine on low-dose bupivacaine spinal anaesthesia in elderly patients.Acta Anaesthesiologica Scandinavica. 2012;56:382–387.

14. Al-Mustafa MM, Badran IZ, Abu-Ali HM, Al-Barazangi, Massad IM, Al-Ghanem SM., Intravenous Dexmedetomidine prolongs bupivacaine spinal analgesia. Middle East Journal of Anesthesiology. 2009 Jun20;(2):225-231.

15. Rhee K, Kang K, Kim J, Jeon Y. Intravenous clonidine prolongs bupivacaine spinal anesthesia. Acta Anaesthesiol Scand 2003;47:1001-5.