http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v8i9.31

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Dexmedetomidine for Sedation during Total Abdominal Hysterectomy under Spinal Anesthesia

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Abstract

Background: *Intravenous Dexmedetomidine is associated with stable cardiovascular profile and less associated with fear, anxiety and agitation. Spinal anesthesia offers many advantages over general anesthesia, like providing analgesia and muscle relaxation in a conscious and compliant patient and an uneventful postoperative recovery.*

Objective: *To evaluate the efficacy of dexmedetomidine in attenuation of haemodynamic stability and sedation during total abdominal hysterectomy under spinal anesthesia.*

Materials and Methods: *This prospective study work was conducted during 8th June 2017 to 7th December 2017, in Dhaka Medical College Hospital, Dhaka, Bangladesh. Total 60 patients were recruited as study population under two groups of group D of dexmedetomidine and M of midazolam who classified by American Society of Anesthesiologists (ASA- I, II). Random sampling methods was followed. Subarachnoid anaesthesia was performed in all patients with 0.5% hyperbaric bupivacaine intrathecally, at L3-L4 interspinous spaces, with 25G Quinke's spinal needle. The patients of group D) was administrated with an intravenous loading dose of 0.5 µg.kg-dexmedetomidine and group M 0.04 µg.kg- midazolam via a syringe infusion. Changes of BP, pulse and any complication was recorded. Collected data were analyzed by SPSS software, version 22.0.*

Results: *According to the study, majority of the patients 66.6% (n=40) were between 50-60 years, mean age was 53.3±11.5 years. The difference was not statistically significant (p>0.05) between two groups. The baseline mean heart rate was found 90.2±7.3 and 93.1±8.2 beat/min in group Mand D. At 5 minute after, mean heart rate was 92.9±7. and 93.7±9.4 beat/min. At 30 minute after mean heart rate was 100.4±9.1 and 93.5±9.1. At 45 minute, mean heart rate was 103.0±8.9 and 87.7±17.7. At 60 minutes,104.5±7.7 and 92.7±8.2. At after 30 minute, 45 minute and 60-minute difference was statistically significant (p<0.05) between two groups. On evaluation of systolic blood pressure, baseline, mean systolic BP was found*

89.6±6.3 mmHg and 84.3±5.0 mmHg. At 10 minute after, was 95.3±7.1 and 85.5±5.1 mmHg. At 45 minute, was 94.6±15.6 and 84.3±5.0. At 10, 15, 30 and 45 minute after difference was statistically significant (p<0.05) between two groups. After 30 minute, mean sedation was found 4.13±0.32 and 3.89±0.5. After 60 minute, mean sedation was found 4.38±0.57 score in group D, but in group M score is reduced and found 3.52±0.27. Mean difference was statistically significant (p<0.05) between two groups.

Conclusion: *In this study, intraoperative Ramsay sedation scores were significantly higher in dexmedetomidine group. When compared with intravenous (IV) midazolam, administration of IV dexmedetomidine during spinal anesthesia provides a longer duration of postoperative analgesia, with satisfactory arousable sedation and minimal side effects.*

Keywords: *Dexmedetomidine, spinal anaesthesia, statistically significant, baseline.*

Introduction

The indications for hysterectomy are varied and greatly influenced by the patient's age, pathology, diagnosis, and reproductive status. Popular and common anaesthetic technique used for abdominal hysterectomy is spinal anaesthesia which is best to control intraoperative pain.[1] Spinal anesthesia is associated with significantly reduced blood loss and good control of hemodynamics and respiratory parameters both intra operatively and perioperatively and results in reduced pain and a faster postsurgical recovery.[2] But patients express many apprehensions about anesthesia, including the fear, being probed with needles, smothered with the anesthesia mask, awakening during the procedure and vomiting postoperatively. Some believe that regional anesthetics (spinals, epidurals) frequently result in paralysis. These apprehensions, often magnified by public misinformation, are heightened during the preoperative period.[3] So sedation plays a major role during the surgical procedure. In a bid to improve regional anesthesia techniques, many drugs have been tried as sedative agents in patients undergoing lower abdominal surgeries under subarachnoid block. All these agents have their own integral merits and demerits, and none of them can be considered as an ideal agent for sedation during spinal anesthesia. Sedation may be defined as the use of pharmacological agents to produce depression of the level of consciousness sufficient to result in drowsiness and anxiolysis without loss of verbal communication. The difference between sedative and anaesthetic drugs is largely one of usage. Many anaesthetic drugs may be used at reduced dosage to produce sedation. Drugs more usually used as sedatives produce a form of anaesthsia if given in high enough doses. There exists a seamless progression from so-called 'conscious' sedation to deep sedation where verbal contact and protective reflexes are lost, a state indistinguishable from general anaesthsia. The ability of the patient to maintain a patent airway independently is one characteristic of conscious sedation, but even at this level of sedation it cannot be assumed that protective reflexes are intact[2]. Numerous trials of different techniques and drugs for postoperative pain control of abdominal surgeries has been conducted but none of them has ever emerged with overwhelming advantage.[1] Various drugs such as opioids, beta blockers and centrally acting sympatholytics have been tried to attenuate such stress response. Many drugs are used intrathecally like adrenaline, fentanyl, buprenorphine to prolong the duration of sensory block and achieve longer perioperative analgesia.[4] Continuous infusions of propofol is a useful method for sedation because of the easy titratibility and rapid emergence.[5] Intravenous (i.v.) dexmedetomidine prolongs the duration of spinal anesthesia, provides sufficient sedation with fewer side effects.[6,7] Clonidine and dextmedetomedine have been used intrathecally[8] and also intravenously to prolong the duration of spinal anaesthesia using various local ansthetics. Recently dexmedetomidine, a newer α2 agonist has been introduced. Dexmedetomidine was initially permitted to use in the intensive care unit sedation, but now it is commonly used as an

anesthetic adjuvant due to its distinct properties. Dexmedetomidine is more selective to the α-$_2$adrenoceptors than clonidine and shows potent sedative analgesia-sparing properties. At therapeutic doses, dexmedetomidine is not related to respiratory depression in spite of often-times profound levels of sedation. Because of these properties (sedation, analgesia, and respiratory-sparing), dexmedetomidine is used for sedation during regional anesthesia.[6,9] In a study shows, a significant decrease in mean HR with dexmedetomidine was observed at 5 min of starting the infusion. This difference persisted throughout the procedure and could be attributed to sympatholytic properties and vagal mimetic effects of dexmedetomidine[5]. Dexmedetomidine has been used in routine anesthesia practice and studies have shown that there is a reduction of requirement of induction agents and opioids during perioperative period. In a study, there was statistically difference in the onset as well as in the duration of sensory block was found in dexmedetomidine group. The onset of sensory block was earlier in dexmedetomidine group and duration of sensory blockade was significantly prolonged.[10] These effects can be explained on the basis of site of action of dexmedetomidine which is locus coeruleus and is mediated by hyperpolarization of noradrenergic neurons thus inhibiting noradrenaline release and inhibiting activity in descending medullospinal noradrenergic pathways.[11] Analgesic effects are mainly meted by α-2C and α-2A receptors present on the neurons of the superficial dorsal horn in lamina II, by inhibiting the release of pronociceptive transmitters namely substance P and glutamate and by hyperpolarization of spinal interneurons. These similar mechanisms also possibly explain the motor blockade augmentation effects. In a study,[10] there was a significant difference in time taken for motor blockade to reach modified Bromage scale 3 in dexmedetomidine. The regression time to reach the modified Bromage scale 0 was significantly prolonged in dexmedetomidine group. Mean arterial BP shows biphasic variations with an initial transient rise with a reflex fall in HR brought about by stimulation of α-2B subtypes of receptors present in vascular smooth muscles. This is followed by fall in BP and HR due to inhibition of central sympathetic outflow and stimulation of presynaptic α-2 receptors cause decreased release of noradrenaline leading to further fall in the BP.[11] These findings are on expected lines as dexmedetomidine is known to cause bradycardia and hypotension. Another important adjuvant drug is midazolam. Midazolam is a medication classified as a short-acting benzodiazepine (anxiolytic) that depresses the central nervous system. In a primary choice, the drug for conscious sedation since midazolam causes patients to have no recollection of the medical process. In over-all, midazolam has a fast-acting, short-term sedative result when given intravenously, attaining sedation within one to five minutes and peaking within 30 minutes. When given intravenously, it starts working, characteristically, within five minutes. Effects last for between one and six hours.[12] While midazolam is thought to cause minimal hemodynamic effects, it does have the potential to cause loss of airway reflexes, respiratory depression, and even apnea.[13]Like all benzodiazepines, midazolam also induces muscle relaxation. The mode of action of the benzodiazepines appear to increase the physiological inhibitory mechanisms mediated by gamma-aminobutyric acid (GABA), which is the most common inhibitory neurotransmitter in the brain. Midazolam may cause a diffident decrease in mean through pressure. Baroreceptor response is not affected and decreases in arterial pressure are accompanied by increases in heart rate.[14] If an effective, reliable and safe sedative could be used in general practice, this would benefit a wide range of patients, especially those who are frail, anxious, severely phobic or uncooperative. Hence we designed this study to evaluate the sedative, hemodynamic and side effects of i.v. dexmedetomidine and midazolam when used for

intraoperative moderate sedation along with spinal anesthesia.

Materials and Methods

This prospective study work was conducted during 8th June 2017 to 7th December 2017, in Dhaka Medical College Hospital, Dhaka. Sample was selected by random sampling in two groups distributed as- group D (dexmedetomidine), group M (midazolam). Sequence of study were pretesting of questionnaire, finalization of questionnaire, sampling, consent talking, data collection with detailed history, physical examination etc. Total 60 patients, classified by American Society of Anesthesiologists (ASA- I, II).Listed for operative procedure under spinal anaesthesia were randomized by card method in two groups of 30 patients each. Subarachnoid (spinal) anaesthesia was performed in all patients with 0.5% hyperbaric bupivacaine intrathecally, at L3 - L4 interspinous spaces, with 25G Quinke's spinal needle. The patients in the first group (group D) was administrated with an intravenous loading dose of 0.5 µg.kg-dexmedetomidine and the second group (group M) administrated 0.04 µg.kg-midazolam via a syringe infusion. Changes of BP, pulse and any complication was recorded. All the information recorded in data collection sheet. All collected questionnaire checked very carefully to identify the error in the data and analyzed by computer based software SPSS, version 22.0.

Results

Table- 1: Age distribution of the patients (N=60)

Age (years)	Number of patients		Total	p-Value
	Group D(%)	Group M(%)	N(%)	
<50	7(23.3%)	4(13.4%)	11(18.4%)	
50-60	19(63.3%)	21(70.0%)	40(66.6%)	
61-70	4(13.4%)	5(16.6%)	9(15.0%)	0.471ns
Mean ± S.D.		53.3±11.5		

ns= not significant

P value reached from chi square test.

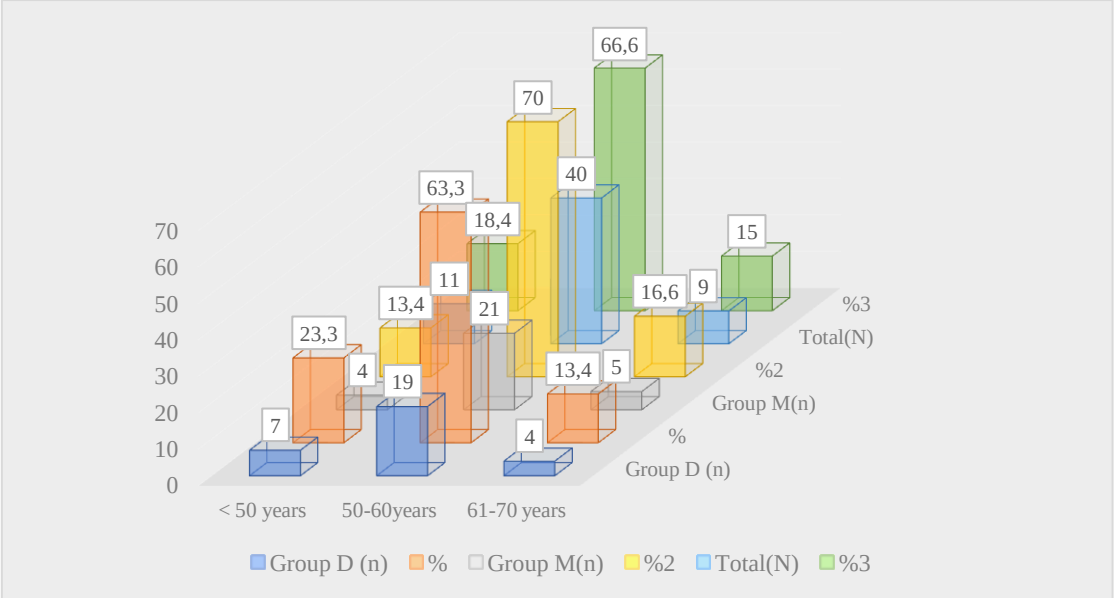

Figure I: Group wise Patients Age Distribution

Table- 2: Distribution of the study patients according to types of heart rate (N=60)

Heart rate (beat/min)	Group D (n=30)	Group M (n=30)	p-Value
	Mean ±SD	Mean ±SD	
Baseline	93.1±8.2	90.2±7.3	0.184[ns]
Range (min-max)	80 -110	80 -100	
5 minute after	93.7±9.4	92.9±7.1	0.231[ns]
Range (min-max)	80 -110	81 -105	
10 minute after	94.2±7.8	96.9±7.4	0.206[ns]
Range (min-max)	80 -110	86 -110	
15 minute after	102.2±6.3	105.5±6.0	0.182[ns]
Range (min-max)	90 -100	95 -110	
30 minute after	93.5 ±9.1	100.4±9.1	0.008[s]
Range (min-max)	80-115	89 -120	
45 Minute after	87.7±17.7	103.0±8.9	0.001[s]
Range (min-max)	45 -110	90 -120	
60 minute after	92.7±8.2	104.5±7.7	0.001[s]
Range (min-max)	80-110	92 -120	

s= significant, ns= not significant

P value reached from unpaired t-test.

Table-2 stated that, at baseline, mean heart rate was found 90.2±7.3 beat/min in group M and 93.1±8.2 beat/min in group D. At 5 minute after, mean heart rate was 92.9±7.1 beat/min and 93.7±9.4 beat/min in group M and group D respectively. At 10 minute after, mean heart rate was found 96.9±7.4 beat/min in group M and 94.2±7.8 beat/min in group D. At 15 minute after, mean heart rate was found 105.5±6.0 beat/min in group M and 102.2±6.3 beat/min in group D. At 30 minute after mean heart rate was 100.4±9.1 beat/min and 93.5±9.1 beat/min in group M and group D respectively. At 45 minute, mean heart rate was 103.0±8.9 beat/min in group M and 87.7±17.7 beat/min in group D. At 60 minutes, mean heart rate was 104.5±7.7 beat/min and 92.7±8.2 beat/min in group M and group D respectively. At after 30 minute, 45 minute and 60-minute difference was statistically significant ($p<0.05$) between two groups.

Table- 3: Distribution of the study patients according to types of systolic blood pressure (N=60)

Systolic BP (mmHg)	Group D (n=30)	Group M (n=30)	p-Value
	Mean ±SD	Mean ±SD	
Baseline	84.3±5.0	89.6±6.3	0.271[ns]
Range (min-max)	80 - 95	80 -100	
5 minute after	81.4±9.2	92.5±6.8	0.083[ns]
Range (min-max)	62 - 95	80 -105	
10 minute after	85.5±5.1	95.3±7.1	0.001[s]
Range (min-max)	80 -110	86 -110	
15 minute after	84.3±4.8	95.6±11.2	0.001[s]
Range (min-max)	80 -95	85 -110	
30 minute after	84.3±5.0	97.9±4.7	0.001[s]
Range (min-max)	80 - 95	45 -105	
45 Minute after	84.3±9.4	94.6±15.6	0.002[s]
Range (min-max)	80 - 95	90 -105	
60 minute after	61.2±9.4	59.6±6.0	0.467[ns]
Range (min-max)	80 - 95	45 -110	

Table-3 stated that, systolic blood pressure during follow up it was observed that at baseline, mean systolic BP was found 89.6±6.3 mmHg in group M and 84.3±5.0 mmHg in group D. At 5 minute after, mean systolic blood pressure was 92.5±6.8 mmHg and 81.4±9.2 mmHg in group M and

group D respectively. At 10 minute after, mean systolic blood pressure was 95.3±7.1 mmHg in group M and 85.5±5.1 mmHg in group D. At 15 minute after, mean systolic blood pressure was 95.6±11.2 mmHg and 84.3±4.8 mmHg in group M and group D respectively. At 30 minute after, mean systolic BP was 97.9±4.7 mmHg in group M and 84.3±5.0 mmHg in group D. At 45 minute after, mean systolic blood pressure was 94.6±15.6 mmHg and 84.3±5.0 mmHg in group M and group D respectively. At 60 minutes after, mean systolic blood pressure was 59.6±6.0 mmHg in group M and 61.2±9.4 mmHg in group D. At 10, 15, 30 and 45 minute after difference was statistically significant ($p<0.05$) between two groups.

Discussion

This prospective randomized double blind study was conducted in Department of Anaesthesia, Analgesia, Palliative & Intensive Care Medicine, Dhaka Medical College Hospital, Dhaka from 8th June 2017 to 7th December 2017. Total of 60 patients fulfilling inclusion/exclusion criteria were studied to determine the effectiveness between Dexmedetomidine and Midazolam in attenuation of haemodynamic stability and sedation during total abdominal hysterectomy under spinal Anesthesia. While studying the distribution of cases by age it was found that majority of the patients i.e. 66.6% (n=40) were between 50-60 years, mean age was found to 53.3±11.5 years. The difference was not statistically significant ($p>0.05$) among two groups. Central neuraxial blockade is a widely used anesthetic procedure. However, may promote some type of discomfort caused by the procedure itself or by a prolonged perioperative period, requiring the simultaneous administration of hypnotic, sedative and amnesic drugs. Benzodiazepines, propofol and opioids have these properties and provide some comfort to patients. However, these agents may cause respiratory depression, with consequent hypercarbia and hypoxemia. A promising alternative to these drugs is the alpha2-adrenergic agonists, which have excellent sedative and analgesic properties without respiratory depression. Dexmedetomidine (D) is a α2 agonist, has anesthetic and analgesic-sparing property. I.V. dexmedetomidine significantly prolongs the duration of sensory and motor block of bupivacaine in spinal anesthesia. Dexmedetomidine provides an excellent sedation during surgery.[10] Various studies have demonstrated that intravenous infusion of dexmedetomidine prolongs the sensory and motor blockade with intrathecal bupivacaine. Its effects are readily reversible with atipamezole, an α-2 adrenoceptor antagonist. Prospective anticipated effects include decreased requirements of anesthetics and analgesics, a reduced sympathetic response to stress, and the impending for cardioprotective effects against myocardial ischemia with nominal effects on respiration.[6] In this study at baseline, mean heart rate was found 90.2±7.3 beat/min in group M and 93.1±8.2 beat/min in group D. At 5 minute after, mean heart rate was 92.9±7.1 beat/min and 93.7±9.4 beat/min in group M and group D respectively. At 30 minute after mean heart rate was 100.4±9.1 beat/min and 93.5±9.1 beat/min in group M and group D respectively. At 45 minute, mean heart rate was 103.0±8.9 beat/min in group M and 87.7±17.7 beat/min in group D. At 60 minutes, mean heart rate was 104.5±7.7 beat/min and 92.7±8.2 beat/min in group M and group D respectively. At after 30 minute, 45 minute and 60-minute difference was statistically significant ($p<0.05$) between two groups. On evaluation of systolic blood pressure during follow up it was observed that at baseline, mean systolic BP was found 89.6±6.3 mmHg in group M and 84.3±5.0 mmHg in group D. At 10 minute after, mean systolic blood pressure was 95.3±7.1 mmHg in group M and 85.5±5.1 mmHg in group D. At 45 minute after, mean systolic blood pressure was 94.6±15.6 mmHg and 84.3±5.0 mmHg in group M and group D respectively. At 10, 15, 30 and 45 minute after difference was statistically significant ($p<0.05$) between two groups. Regarding diastolic

blood pressure during follow up, after 15 minute, mean diastolic blood pressure was found 67.6±7.4 mmHg in group M and 61.5±9.7 mmHg in group D. After 45 minute, mean diastolic blood pressure was 66.0±6.8 mmHg in group M and 61.2±9.4 mmHg in group D. Which statistically significant ($p<0.05$) between two groups but other follow up were not significant ($p>0.05$) between two groups. All findings accordance with result of other studies. In a study shows basal hemodynamic parameters were comparable between the groups. Intraoperatively, there was significant decrease in heart rate in group D after 10 min of loading dose and persisted to be lower for 45 min after spinal anesthesia. None of the patients in either group developed clinically significant bradycardia. Mean arterial pressure (MAP) remained comparable throughout the study ($p> 0.05$) except at 120 min and 180 min, where significant decrease in MAP was observed in group D when compared with group M ($p< 0.001$)[6]. In this study two patients from each group developed a single episode of hypotension (blood pressure < 80 mm of Hg) intraoperatively, which was treated by rapid infusion of Ringer's lactate solution and single bolus of inj. ephedrine (6 mg IV).A significant decrease in pulse rate and MAP were observed when compared with baseline in both the groups throughout the surgery. But the fall in pulse rate was greater with dexmedetomidine infusion up to 45 min after spinal anesthesia when compared with midazolam infusion. ($p< 0.05$). Most studies have noted fall in pulse rate and MAP when compared with baseline value with both dexmedetomidine and midazolam infusion without significant difference between the groups.[24-26] Many studies have noted bradycardia as a prominent side effect following dexmedetomidine infusion.[6,9] However, we did not note any incidence of bradycardia in our study. Incidence of hypotension was comparable with other studies.[24-26]The lower heart rate and MAP observed with dexmedetomidine infusion could be explained by the decreased sympathetic outflow by activation of postsynaptic α2-A receptor in central nervous system and decreased circulatory levels of catecholamines caused by dexmedetomidine.[6] Duration of postoperative analgesia was longer with dexmedetomidine infusion when compared with midazolam infusion. Celik et al[25] and Kaya et al.[24]also had similar observation regarding duration of analgesia in their study. Intraoperative sedation provided by dexmedetomidine or midazolam eliminates the need of additional sedatives. Dexmedetomidine produces sedation by its central effect and seems to be dose-dependent. Most of the patients were sedated in both the groups but easily arousable. Respiratory rate and oxygen saturation were maintained within normal range in both the groups.Immediate after SA, mean sedation score between groups were non-significant and was found 1.39±0.47 score in group D and 1.46±0.51 score in group M. After administration of tested medication anxiety and agitation begins to reduce and desired level of sedation established. After 30 minute, mean sedation was found 4.13±0.32 score in group D and 3.89±0.51 score in group M. The quality of pleasant and adequate sedation varied between groups, and it was maintained properly in group D in whole time. After 60 minute, mean sedation was found 4.38±0.57 score in group D, but in group M score is reduced and found 3.52±0.27. Mean difference was statistically significant ($p<0.05$) between two groups. So precise control of the depth of sedation is managed by group D or intravenous Dexmedetimidine.In a study[6] found that dexmedetomidine infusion prolonged the duration of sensory and motor blockade during bupivacaine spinal anesthesia. In addition, it also increased the time until first request of analgesic for postoperative pain relief. It also provided sedation comparable to midazolam infusion. As rapid administration might produce tachycardia, bradycardia, and hypertension, because of direct action on peripheral α_2 receptor[6]. Al-Mustafa et al.[27]reported prolonged duration of motor block following use of 1 μg/kg initial bolus dose, followed by 0.5 μg/kg/h infusion. Elcicek et

al.[28]observed that dexmedetomidine bolus of 1 μg/kg, followed by infusion at 0.4 μg/kg/h prolonged the duration of sensory and motor regression following spinal anesthesia with ropivacaine. Lugo et al.,[29] in their study noted prolongation of sensory block and duration of analgesia without significant effect on motor block while using 1 μg/kg bolus, followed by 0.5 μg/kg/h infusion of dexmedetomidine. Administration of single bolus of 1 μg/kg and 0.5 μg/kg also were reported to prolong the duration of analgesia and sensory blockade. However, in a study by Kaya et al.,[24] use of a single dose of 0.5 μg/kg of dexmedetomidine did not affect the duration of motor block. Harsoor et al.[30] observed that loading dose of dexmedetomidine at 0.5 μg/kg, followed by 0.5 μg/kg/h produce longer duration of analgesia and motor blockade.The effect of dexmedetomidine on spinal anesthesia is not dependent on the route of administration. Midazolam has been reported to show an antinociceptive effect through the neuroaxial pathway. However, the effects of midazolam on nociception may depend on the route of administration, with analgesia observed after spinal or epidural application but not after systemic administration of this agent. This may be the reason why in our study the duration of sensory and motor blockade and postoperative analgesia was longer with dexmedetomidine infusion when compared with midazolam. Subjective compliance & satisfaction revealed that total 27(90.0%) of patients in group D and 22(73.3%) in group M patients were satisfied regarding remission of anxiety and agitation with maintenance of pleasant asleep (hypnosis) during operation.

Conclusion

In this study, it was found that intravenous Dexmedetomidine is associated with stable cardiovascular profile and less associated with fear, anxiety and agitation. I conclude that, during spinal anesthesia, IV supplementation of dexmedetomidine is more effective than midazolam infusion, as it provides longer duration of sensory and motor blockade and postoperative analgesia with minimal and similar side effects. It provides satisfactory arousable sedation without respiratory depression. Haemodynamic changes observed in our patients were very small and could be ignored. Patient remained stable haemodynamically throughout the intra-operative period. So dexmedetomidine seems to be a good choice for sedation in spinal anesthesia (SA).

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