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Study of Efficacy and Safety of Dextmedetomidine Vs Midazolam in Gynacological Laproscopic Surgery

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Abstract

Background: Laparoscopic surgeries under are associated with unique hemodynamic changes thus a basic need is felt among the anaesthesiologist fraternity for the desired availability of a drug that effectively suppresses all the hazardous responses to obnoxious stimuli with a maximum safety margin. Dexmedetomidine due to its distinct sedation, analgesia and sympatholytic properties can be used as an anaesthetic adjuvant in anaesthesia for Laparoscopic surgeries. Thus we undertook this double blind, prospective comparative study. *Methods*: Fifty women undergoing Laparoscopic gynaecological Surgeries divided randomly by a computer generated table into two groups of 25 each. D group - Dexmedetomidine loading dose 1µg/kg followed by maintenance infusion of Dexmedetomidine at 0.4µg/kg/hr M Group – Midazolam loading dose 0.03 mg/kg followed by maintenance infusion of saline. Both the group were given Fentanyl citrate 1ug/kg. We undertook this double blind, prospective comparative study to evaluate efficacy and safety and its effect on sedation, hemodynamic, anaesthesia and analgesia requirement and recovery characteristics. *Results*: Baseline Mean degree of sedation was same but after 5 min study drug it was 2 for group D compared to group M -1.32 and postoperative 1.16 for group D and 1.08 for group M. Mean heart rate was 73.84 for group D and 74.52 for group M. Mean blood pressure was 100.84 for group D and 102.56 for group M. Same trend observed at the time of induction, intubation, mean during pneumoperitonium and mean value in PACU. Mean dose of fentanyl required was less 65µg compared to 93.4µg in group M. *Conclusion*: This randomised, double blind study demonstrated that when compared to Midazolam Dexmedetomidine is more effective anaesthetic adjuvant that causes adequate sedation without respiratory depression, decreases requirement of anaesthetic and opioid, attenuate sympathoadrenal response, maintains stable haemodynamics perioperatively at the same time provide excellent recovery profile without any adverse events but continuous monitoring for hypotension and bradycardia is essential during first two hours of postoperative period if higher infusion rate are used.

Keywords: Midazolam Dexmedetomidine; Anaesthesia; Laparoscopic Surgeries.

Introduction

There are many class of drugs that can be used for to relieve anxiety and provide sedation. Among these most frequently used drugs are benzodiazepines like Midazolam and opioids like Fentanyl. Dextmedetomidine is alpha 2 receptors agonist are being increasingly used in anaesthesia as they not only decrease sympathetic tone and attenuate stress response to anaesthesia and surgery but also cause sedation and analgesia and attenuates sympathoadrenal response to noxious stimuli encountered during anaesthesia and surgery thus providing improved haemodynamics, metabolic, and hormonal stability [1,2]. Laparoscopic surgeries under anaesthesia are associated with unique hemodynamic changes in the form of increased systemic vascular resistance leading to hypertension thus a basic need is continuously felt among the anaesthesiologist fraternity for the desired availability of a drug that effectively suppresses all

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the hazardous responses to obnoxious stimuli with a maximum safety margin [3].

General anaesthesia with Midazolam as sedation agent and Fentanyl as opioids is standard practice of anaesthesia for Laparoscopic surgeries in our institution. Dexmedetomidine due to its distinct sedation, analgesia and sympatholyticproperties we undertook this double blind, prospective comparative study to evaluate efficacy and safety of Dexmedetomidine verses Midazolam in Gynaecological Laparoscopic surgery. We studied its effect on sedation, hemodynamic, anaesthesia and analgesia requirement and recovery characteristics.

Materials and Methods

After institutional medical ethics committee approval written informed consent was obtained from all patients. Patient were included in study if they are between18-40, ASA1 and ASA 2, Gynaecological laparoscopy procedurs of anticipated duration < 2hrs and patient requiring one day post-op stay in hospital. patient excluded from study if ASA 3 and more, body weight ≥ 25% of recommended height, contraindication to the use of Dexmedetomidine e.g. Liver, kidney and cardiac disorder, History of severe adverse reaction or allergy to any drug, if patient has taken any sedative analgesic within 24hrs. This study was carried out in 50 women undergoing Laparoscopic gynaecological Surgeries like chromopertubation, Ovariancystectomy, ovarian drill and other short procedure. They will be divided randomly by a computer generated table into two groups of 25 each.

D group - Dexmedetomidine loading dose 1µg/kg followed by maintenance infusion of Dexmedetomidine at 0.4µg/kg/hr M Group – Midazolam loading dose 0.03 mg/kg followed by maintenance infusion of saline.

Double Blind Design Employed as Follows

Drug was prepared in two syringes by senior anaesthetist who was not a part of the anaesthesia team and not the investigator. patient randomized into 2 groups – group Dexmedetomidine (D) and Midazolam (M) by using a computer generated randomization. In group M loading dose of drug was prepared in 20cc syringe with normal saline containing Midazolam 0.03mg/kg and group (D) loading dose of drug was prepared in 20cc syringe with normal saline containing Dexmedetomidine 1ug/kg. Each syringe contained a fixed volume of 20cc. Intraoperative maintenance infusion drugs were prepared in 20cc syringe with only normal saline in group M and Dextmedetomidine in group D Dexmedetomidine infusion was prepared in normal saline in the concentration of 0.4µg/cc. Maintenance drip rate was adjusted as per Dexmedetomidine 0.4µg/kg/hr. Two syringes were handed over to the investigator as loading dose and maintenance infusion. Decoding was done at end of study for statistical analysis A complete history obtained from the patient. Basic routine and specific investigation as per history and clinical finding were carried out. Patients ASA physical classification was determined. As per Inclusion and exclusion criteria patients enrolled in study and written valid informed consent taken from each patient posted for surgery B) Patient preparation: Baseline monitor like electrocardiogram (ECG), Pulse oximetry, Non invasive blood pressure (NIBP) were attached. Baseline value of systolic, diastolic and mean blood pressure, Heart rate, Respiratory rate by inspection. Two intravenous lines were secured one for routine fluid and other exclusively for Dexmedetomidine using 20 gauge cannulas. Every 5 min pulse, BP, SpO_2, RR noted. Degree of sedation monitored using the six point scale described by Ramsay andcolleagues. Ramsay Sedation score noted as baseline, 5min after loading dose of study drug postoperative every 15 mins for period of 2 hrs. In group D patients given Dexmedetomidine 1µg/kg iv over 10 min using a infusion pump. In group Midazolam, patient received normal saline with Midazolam 0.03mg/kg. Over 10 mins. After loading dose, then infusion was changed to maintenance infusion. After noting the sedation score after loading dose of study drug patients in both the group were given Fentanyl citrate 1µg/kg. Pulse, BP, SpO_2, RR recorded for every 5 min before induction. 3 mins after giving Fentanyl citrate Patient preoxygenated with 100% O_2 for 3 min. Induction was done with Inj Thiopentone sodium (3-5mg/kg) in graded doses till loss of eyelash reflexes and Inj Succinylcholine1.5mg/kg was given to facilitate endotracheal intubation. After intubation pulse, BP, SPO_2 monitored for every 10 minute. Patient maintained on O_2+N_2O+Isoflurane (0.3%) inspired concentration using closed circuit. $ETCO_2$ attached and monitored and maintained below 35-40 mmhg by adjusting tidal volume and respiratory rate. Intraoperative anaesthetic requirement was decided on basis of haemodynamics. Increase in HR, increase in SBP 20% from the baseline patient were given Fentanyl

in dose of 0.5µg/kg increment once dose of Fentanyl exceeded 2µg/kg, Propofol top up of 10 mg given when needed. In addition to hemodynamic sign of anaesthetic depth we look for other signs of lightness such as sweating lacrimation, swallowing or movement. HR, BP noted down at the time of induction, intubation, during pneumoperitonium, the time of extubation and in PACU. Time from creation of pneumoperitonium to release of pneumoperitonium taken as duration of pneumoperitonium. All patients received intravenous Ringer lactate solution at the rate of 5 ml/kg/hr as maintenance fluid. NM block was maintained Vecuronium bromide 0.02mg/kg. CO_2 was insufflated to create pneumoperitonium + abdominal pressure (IAP) monitored intraoperatively and kept below 15 mmhg Adversehaemodynamics monitored perioperativly Hypotension (systolic BP <90 treated with rapid infusion of 250ml of glucose salt solution followed by Ephedrine 2.5mg in repeated doses if systolic BP did not increase above 90 mmhg within 2 min. Bradycardia treated with inj atropine 0.01mg/kg if pulse rate less than 50.Maintainance infusion was decided to stop if hypotension, bradycardia persisted inspite of above. Maintenance drip of study drug was stopped when trocar was removed also Isoflurane and Propofol stopped at the same time. Then time of awakening and responding to verbal command from the end of drip was noted. Diclofenac sodium 75mg added to iv fluid for postoperative analgesia. Requirement of additional Fentanyl and Propofol noted down. Patients were reversed and extubated when they fulfilled criteria for extubation like sustained head lift and then patient were transferred to PACU. In recovery patient observed for Ramsay sedation score and vitals including blood pressure, heart rate, and respiratory rate for a minimum of 2hrs duration. No of patient requiring analgesia (inj. Tramadol 50mg) and amount of analgesia needed noted. Haemodynamics parameters monitored during perioperatively are Blood pressure and heart rate baseline,at the time of induction, at the time of Laryngoscopy, mean value during pneumoperitonium, at the time of Extubation, Mean value in PACU.

Results

Study reveals that mean duration of surgery was **70.52 mins** in Group D group which was comparable to 70.20mins in Group M

Table 1:

Groups	Mean Dose of Induction Thiopentone (mg) ($\overline{X} \pm SD$)
Group D	262.40 ± 32.68
Group M	334.36 ± 39.51
p value	*0.001

By Student't' test *Significant

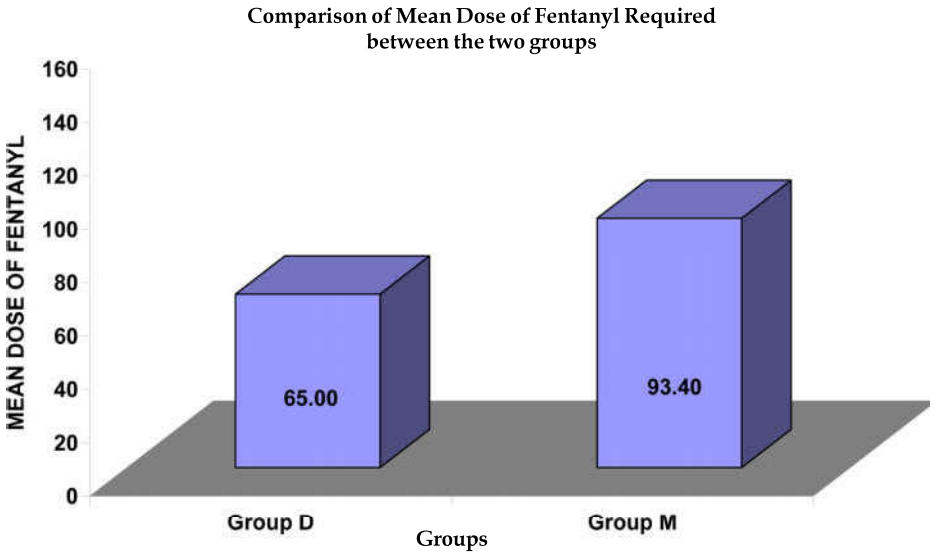

Fig. 1: Comparison of mean degree of sedation

Mean anesthesia recovery time for Group D group was 8.78 mins which was comparable to 8.65 mins in Group M.Data revealed that Mean PACU discharge time for Group D group was 100.76 mins which was more as compared to 93.0 mins in Group M.

- As per this data, at baseline Mean Degree of sedation wassame i.e. 1.00 for Group D group and Group M group 5mins after loading study drug and postoperative Mean Degree of sedation was significantly more as compared to M group. Mean Heart rate at baseline was 73.84 beats/min in Group D group which was comparable to 74.52 beats/min Group M. Same observed intraoperative period and in PACU.

Data reveals mean SBP at baseline was 134.56mmHg in Group D group which was comparable with 132.96mmHg for Group M.At 5mins after 122.96mmHg for Group D which significantly less as compared 133.60mmHg for Group M. Same trend observed intraoperative period and Mean value in PACU.

Mean DBP at base line was 84.96mmHg in Group D which was 87.36mmHg for Group M, mean MBP at baseline was 100.84mm Hg in Group D which was comparable with 102.56mm Hg for Group M. At 5mins after infusion, that was 91.92mmHg for Group D which was significantly less as compare 103.47mmHg.

Comparison of Mean Heart Rate between the Two Groups

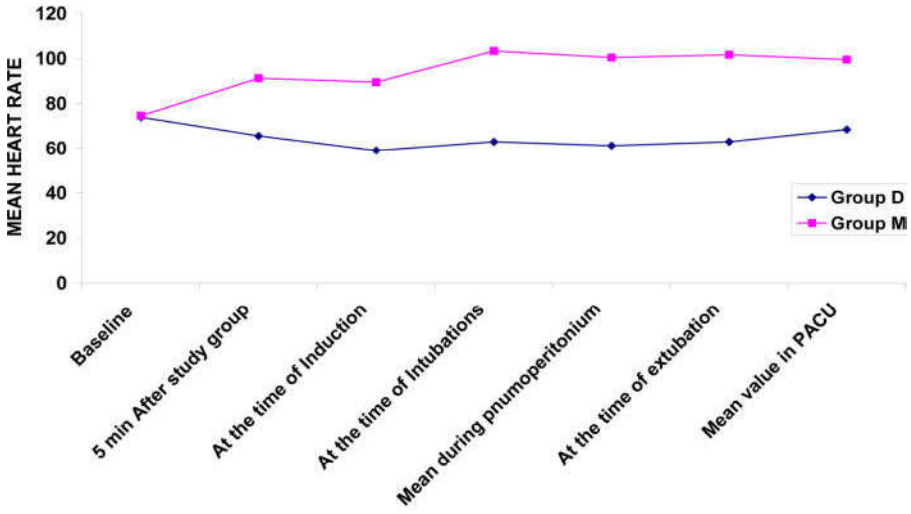

Fig. 2:

Comparison of Average Mean Blood Pressure between the Two Groups

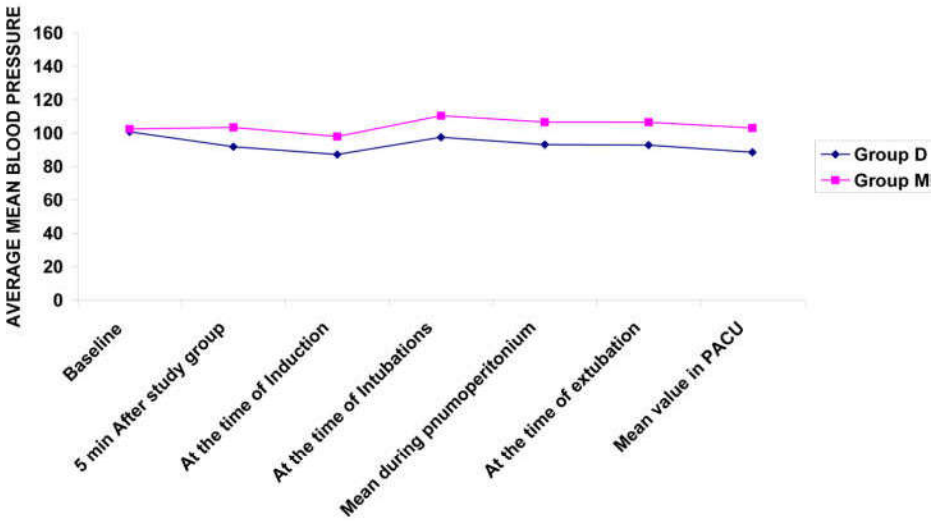

Fig. 3:

Table 2: Between the two groups

Duration	Mean Degree of sedation ($\bar{X} \pm SD$)		P value
	Group D (N=25)	Group M (N=25)	
Baseline	1.00±0.00	1.00±0.00	1.000(NS)
5mins after loading Study drug	2.00±0.00	1.32±0.48	*0.001
Postoperative	1.16±0.37	1.08±0.28	0.3929(NS)

By Student't' test *Significant NS = Not Significant

Discussion

Dexmedetomidine is gaining popularity for its sedative, hypnotic, anxiolytic and sympatholytic properties without significant respiratory depression. In recent studies, Dexmedetomidine has been shown to have clinically significant effects on anaesthetic requirements, haemodynamics responses induced by anaesthesia and surgery in patients [4]. It also produces sedation and diminishes the intraoperative requirement of analgesics. The major sedative and antinociceptive effects of Dexmedetomidine are attributable to its stimulation of α2 A subtype located in locus ceruleus [5].

Dexmedetomidine potentiate anaesthetic effect of all intraoperative anaesthetic, regardless of method of administration. The profound decrease in anaesthetic requirement shown to be mediated through central α adrenergic receptor. Laparoscopic surgery offers intraoperative stress during pneumoperitonium by increasing systemic vascular resistance and BP and at same time producing nociception [3].

Carbon dioxide (CO_2) is usually used to produce pneumoperitonium during laparoscopic surgical procedures [6,7]. Both CO_2 and pneumoperitonium causes adverse cardiovascular and renal effects [8]. Some of these effects are related to CO_2 and some to elevated intra abdominal pressure. Immediately after creation of pneumoperitonium, plasma level of Norepinephrine, Epinephrine and plasma Renin activity increases [9]. Increased catecholamine level activates the renin–angiotensin–aldosterone–system. All these changes together contribute to elevated arterial pressure, increased systemic and pulmonary vascular resistance and reduced cardiac output [10].

Dexmedetomidine significantly reduces release of catecholamine and almost completely reduces norepinephrine release and attenuate the increase in systemic vascular resistance.

This unique property of Dexmedetomidine renders it suitable as anaesthetic adjuvant for analgesia during the perioperative period in especially in laparoscopic surgery [11]. General anaesthesia with Midazolam as sedative and Fenatanyl as analgesic Opioids is standard practice of anaesthesia for laparoscopic surgeries in our institution. There are very few studies comparing Dexmedetomidine with Midazolam as perioperative sedation in general anaesthesia. Therefore we conducted this study.

In the study of Gulay [12], et al for comparison of Dextmedetomidine in dose of 1μg/kg with 3 different doses of Midazolam is 0.02 and 0.04 and 0.06mg/kg in preoperative sedation. Dexmedetomidine and Midazolam in dosage 0.04 and 0.06 mg/kg cause statistically significant difference in Ramsay sedation score and VAS as compared to baseline values.

Though Dexmedetomidine and 0.06 mg/kg Midazolam were equally sedative. The decrease in SpO2 levels was more evident and resultant hypoxemia was more frequent in 0.06 mg/kg Midazolam group. He also concluded that though Dexmedetomidine leads to depressant effect on haemodynamics parameters at dose of 1 μg/kg but it did not reach level of severe impairment and its effect on respiration was definitely lower as compared to Midazolam

Thus in our study we have taken Midazolam as 0.03 mg/kg because Fentanyl (1μg/kg) added in the study as Midazolam has no analgesic properties and this combination is conventionally used for premedication in our institution.

Hypotension and bradycardia has been observed with Dexmedetomidine in studies done earlier [4,13,14]. These effects are known to be related to dose, route of administration and infusion rate. In intravenous Dexmedetomidine administration report of its use state that α2 agonist effect is observed but not α1 effect on administration of low and moderate dosage and slow rate infusion consequently peripheral vasoconstriction and hypertension would not be expected in these instances [15,16].

Taking these data into account we elected to use Dexmedetomidine in dosage of 1 μg/kg and gave it in infusion over 10 min so as to avoid side effect associated with high dose and infusion rate Tanskanen [17], *et al*. in their study showed that intraoperative infusion of Dexmedetomidine at a rate of 0.4 μg/kg/hr maintains heart rate and blood pressure in acceptable range for a longer duration as compared to placebo group. .We thus kept intraoperative maintenance drip rate of Dexmedetomidine 0.4 μg/kg/hr and kept it constant to avoid many intraoperative variable.

It has also shown that Dexmedetomidine potentiate analgesia caused by Fentanyl and reduces its dose requirement in human during surgery while Midazolam does not have analgesic properties. Therefore we gave both groups Fentanyl as analgesic but in dose of 1μg/kg [18]. We gave both the group fixed concentration 0.3% inspired Isofluraneformaintenance of anaesthesia with O_2:N_2O as 50:50.We would have preferred giving end tidal Isoflurane for more accuracy but we do not have this facility in our institution.

Following pneumoperitonium with carbon dioxide, ventilation was adjusted to maintain normocapnia. Still Pneumoperitonium produces significant hemodynamic derangements which may be detrimental and needs to be prevented. In our study we considered both these factors altering hemomodynamics and were controlled in both groups.

Then we compared efficacy and safety of the drug on the following parameter.

Degree of sedation was observed 5 mins after end of loading dose of drug. As this time corresponds approximately to peak effect of Midazolam and Dexmedetomidine. Sleepiness appears within 5 mins after intravenous administration of Dexmedetomidine and reaches its maximum within 15 min [4].

In our study,5 min after receiving loading dose of drug, patient in Dexmedetomidine group were oriented and tranquil with mean sedation score of 2 as compared to Midazolam group where mean sedation score was 1.32. Few patients in both group there was fall of saturation to 95-96% which returned to normal on asking them to take deep breath. Similar sedation without any adverse event of hypoxia obtained with similar dose of Dexmedetomidine in study by keniya [19] et al and Bajwa [20] et al.

In the study by Gulay Eren [12] et al shown that sedative effect of Midazolam at the dose of 0.02 mg/kg was not adequate, started later, and lasted shorter. They also noted that prevalence of hypoxia SpO_2 <90% was significantly higher with Midazolam 0.06mg/kg than in other group and two patient in that group needed O_2 support with mask. This suggests Dexmedetomidine causes better sedation without respiratory depression.In our study mean dose of induction agent Thiopentone required was 262.40 mg for Dexmedetomidine group which was less as compared to 334.36 mg in Midazolam group and the difference was statistically significant.

Similar were finding of study by V. Keniya [19] et al who observed 30% decrease in dose requirement of Thiopentone for induction in Dexmedetomidine group as compared to control group when same dose of Dexmedetomidine as ours was used. In our study dose of Propofol required intra-operatively in Dexmedetomidine group was (32mg) much less as compared to Midazolam(194 mg) group. Our results were comparable to that of Ghodki [6] et al .

Intra-operative requirement of Fentanyl (65±15.21μg) was significantly reduced as compared (93.4±30.98μg) to Midazolam group. Similar results were observed in study by Bajwa [20] et al in whom mean Fentanyl dose required was 1.2 μg/kg in Dexmedetomidine as against 2.6±1.2 in control group. This suggested that opioid sparing property of Dexmedetomidine in perioperative period.

On comparing hemodynamic parameter in Midazolam group HR, SBP, DBP, MAP increased from baseline with loading dose and persisted after induction, intubation and during entire period of pneumoperitonium, at extubation and even in PACU while in Dextmedetomidine group heart rate systolic, diastolic, and mean BP fell from baseline with loading dose and after that minimal change was observed at induction, intubation, during entire perioperative period of pneumoperitonium, at extubation and even in PACU.

The similar result obtained with Chiragpatel [22] et al Dexmedomidine as compared to Midazolam group effectively controlled vasopressor response during laryngoscopy intubation and sympathoadrenal response occurring with pneumoperitonium. This hemodynamic stability shown by Dexmedetomidine is due to decreased central sympathetic outflow and thereby attenuating increase in serum epinephrine and norepinephrine from baseline [23].

Only one patient in Dexmedetomidine group developed hypotension which responded to fluid therapy similar result were obtained by Feld [24] et

al, Ghodkiet al, M Aho et al. Various studies have used Dexmedetomidine in various dosage and shown that significant incidence of bradycardia and hypotension are definitely associated with rapid bolus or higher dosage.

Mean Ramsay sedation score in our patient was 1.16 in Dexmedetomidine group while 1.08 in Midazolam group. Bajwa et al observed significantly better sedation score in group Dexmedetomidine, attributed it to lower requirement of inhalational agent and other anaesthetic drug and analgesia as compared to control group but Chirag Patel [22] et al observed higher sedation score in Dexmedeto-midine group may be due to higher infusion rate and attributed it to sedative property of Dexmedetomidine however they found no difference in both group at end of 2 hour. PACU discharge time was slightly longer in Dexmedetomidine group as compared to Midazolam group similar finding was noted by Chirag Patel [22] et al Because lack of reliable and easily monitored clinical indices to determine anaesthesia depth we used haemodynamic end point because unavailability of EEG dependant indices in our institution Other limitation was we also carried out study in surgical procedure of short duration (<2 hrs) and in small no of patients, studied in ASA I/II, so larger study, long duration of surgery. Studies focusing its effect on more debilitated patients are needed.

In conclusion this randomised, double blind study demonstrated that when compared to Midazolam Dexmedetomidine is more effective anaesthetic adjuvant that causes adequate sedation without respiratory depression, decreases requirement of anaesthetic and opioid , attenuate sympathoadrenal response, maintains stable haemodynamicsperioperatively at the same time provide excellent recovery profile without any adverse events but continuous monitoring for hypotension and bradycardia is essential during first two hours of postoperative period if higher infusion rate are used.

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