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COMPARATIVE STUDY OF INFUSION DEXMEDETOMIDINE AND MAGNESIUM SULPHATE ON HEMODYNAMIC RESPONSE AND POST-OPERATIVE ANALGESIA IN LAPAROSCOPIC ABDOMINAL SURGERY UNDER GENERAL ANAESTHESIA.

Anaesthesiology

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ABSTRACT

Background: Maintaining the circulatory responses during laparoscopy is a challenging task for an anesthesiologist. The aim of this study was to compare the efficacy of Dexmedetomidine and Magnesium sulphate in attenuating the hemodynamic stress responses during laparoscopic surgery under general anaesthesia and their effect on post-operative analgesia.

Method: A cross- sectional, randomized, comparative study was conducted in 100 patients with American Society of Anesthesiologists (ASA) physical status Grade I and Grade II of 18-60 years age group, undergoing elective laparoscopic surgery were scheduled to receive general anaesthesia with endotracheal intubation. Patients were randomly allocated into two groups. Before premedication, study drug was administered as Dexmedetomidine to one group named Group D and Magnesium sulphate to another Group named Group M. General anaesthesia was administered in the same manner to all the patients. Hemodynamic parameters were noted in frequent intervals, the data collected were analysed and compared to see which drug is more effective in controlling the hemodynamic variations.

Results: Heart rate, systolic blood pressure, diastolic blood pressure is significantly lower with Dexmedetomidine group than Magnesium sulphate group. The Ramsay sedation score (RSS) of patients showed significant difference(p value is less than 0.05) with late recovery time and time of onset of post-operative pain being longer of the Group D patients from general anaesthesia after extubation between as compared to Group M.

Conclusion: Dexmedetomidine, being highly selective and specific alpha-2 agonist, is superior to Magnesium sulphate in attenuating the hemodynamic stress responses of pneumoperitoneum during laparoscopic surgeries under general anaesthesia and in reducing the requirement of analgesic in the post-operative period.

KEYWORDS

Dexmedetomidine, Magnesium sulphate, Postoperative analgesia, Laparoscopic surgery.

INTRODUCTION

In order to reduce the patient trauma, morbidity, mortality and hospital stay, with consequent reductions in health care cost, laparoscopic procedures are the preferred choice of surgical approach in the developing as well as the developed countries. Hemodynamic changes in laparoscopic surgery are a major concern for an anesthesiologist. The hemodynamic consequences of pneumoperitoneum are increase in mean arterial pressure, rise in systemic venous resistance[1,2,3], myocardial oxygen demand, leading to myocardial ischemia, cerebral haemorrhage.

Both mechanical and neuroendocrine factors contribute to the hemodynamic changes induced by CO_2 pneumoperitoneum. An increase in intra-abdominal pressure more than 10 mmHg and patient positioning inflicts significant changes including decreased thoracopulmonary compliance (30% to 50%), increased systemic and pulmonary vascular resistance (SVR, PVR), severely increased arterial pressure and IVC compression leading to decreased venous return, consequently, decreased cardiac output (10% to 30%). These factors can precipitate an adverse cardiac event in patients with pre-existing cardiovascular diseases.

Maintaining the hemodynamic parameters during laparoscopic procedures is of paramount importance because of the significant hemodynamic variations observed, even in healthy individuals. The two main factors responsible for the hemodynamic variations are raised PaCO2 and intra-abdominal pressure. Various pharmacological agents are being used to attenuate the hemodynamic response to pneumoperitoneum. These include Beta-blockers like Atenolol, Esmolol[4];calciumchanel blocker[5], α2-adrenergic receptors agonists – clonidine[6], dexmedetomidine;[7]Opioids like– Fentanyl, Remifentanyl; Vasodilators – Nitroglycerine, Nicardipin.

In this study aim was to compare the two drugs Dexmedetomidine and Magnesium sulphate and observe the variations in heart rate, blood pressure, mean arterial pressure, SPO2, ETCO2 and post-operative analgesia following intravenous administration of Magnesium sulphate and Dexmedetomidine as premedication during Laparoscopic surgery under general anaesthesia.

METHODS

After getting approval from institutional ethical committee and informed consent, 100 patients of ASA physical status I & II, age between 18yrs to 60yrs undergoing elective laparoscopic surgery under general anaesthesia were divided into two equal groups randomly, Group-D patients received intravenous Dexmedetomidine at a dose of 1mcg/kg body weight over 10 minutes, 15 min before induction of pneumoperitoneum, followed by 0.5mcg/kg/hour infusion. (200mcg of Dexmedetomidine was dissolved in 0.9% NS up to 50 ml, each ml constitute of 4mcg Dexmedetomidine.) Group-M patients received infusion of magnesium sulphate 30mg/kg over 10 minutes, 15 mins before induction of pneumoperitoneum, followed by10mg/kg/hour infusion. (12 ml 50% magnesium sulphate was dissolved in 0.9% NS up to 50 ml, each ml constitutes of 120mg magnesium sulphate.)

Inclusion Criteria were patient willing to give consent for the study with ASA physical status I & II of either sex with age between 18-60 years. Exclusion Criteria were patient refusal, patients undergoing emergency surgery, allergy to trial drugs, history of drug and alcohol abuse, patients on cardio active drugs like alfa-2 agonist, methyldopa, beta blockers, calcium channel blocker, ACE inhibitors, anticipated difficult intubation, ASA Grade III & IV, Pregnancy and age < 18 years and > 60 years.

Patient's pulse, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), SpO_2, $ETCO_2$were monitored at baseline, at the time of start of infusion, at the time of premedication, at induction time, 1 min. before pneumoperitoneum, post - pneumoperitoneum at 5min, 10min, 15min,30 min ,45min, 60 min. & 90min, at the time of desufflation, at the time of reversal and at shifting

time.

Routine hematological investigations like Hemoglobin%, Total leukocyte count, Differential count, platelet count, Blood sugar (Fasting and Post Prandial), BUN, Serum urea and creatinine, bilirubin, BT, CT, PT – INR, SGOT/SGPT, Chest X-ray (PA view), ECG-all 12 leads were advised.

Procedure

Patients undergoing elective laparoscopic surgery under general anaesthesia were screened for the eligibility. Patients fulfilling selection criteria were selected for the study and briefed about the nature of study and explained about anaesthetic procedure. A written informed consent (in Hindi or English) was obtained from all patients. A thorough pre-anaesthetic evaluation was performed. Eight hour preoperative fasting guideline was followed.

Then the patients were transferred to the operation theatre. After arrival of the patient in operation theatre, fasting status, PAC and consent was checked monitors (ECG leads, blood pressure cuff and pulse oxymeter probe) were attached.

Anaesthesia machine, airway equipment, Suction apparatus, drugs for resuscitation and general anaesthesia were being kept ready in hand before starting the procedure. IV line was secured and IV fluid was started (RL 500 ml.). The patients were being monitored by NIBP, HR, continuous ECG, pulse oximetry, MAP and $EtCO_2$ throughout the surgery. Patients were made to lie in supine position and study drug started 15 mins before induction using infusion pump @ 1mcg/kg/hr.
Group-D (dexmeditomidine of 1mcg/kg body weight over 10 minutes, 15 min before induction of pneumoperitoneum, followed by 0.5mcg/kg/hour). These drugs were prepared in volumetric infusion set and infusions were given 15 minutes before induction and infused over 15 minutes through infusion pumps.

Group M (magnesium sulphate 30mg/kg over 10 minutes, 15 mins before induction of pneumoperitoneum, followed by10mg/kg/hour.) premedication given with .004mg/kg glycopyrolate and fentanyl 1.5µg/kg iv, patient was preoxygenated with 100% O_2 for 3 minutes, general anaesthesia was induced with iv propofol 2mg/kg followed by atracurium 0.5mg/kg iv to facilitate endotracheal intubation which was done with proper sized Macintosh laryngoscope and appropriate size ET in less than 15 seconds and tube position was confirmed by bilateral chest auscultation and $EtCo_2$monitoring.

Anaesthesia was maintained with nitrous oxide and oxygen (40:60) and isoflurane 0.2 volume %. Muscle relaxation was maintained by intermittent dose of atracurium 0.1mg/kg IV. Heart rate, systolic blood pressure(SBP), diastolic blood pressure (DBP) mean arterial pressure(MAP), respiratory rate, Spo2 ,ETCO2 values were recorded. Controlled ventilation with closed circuit system used to maintain $EtCo_2$level between 35-40 mm of Hg.

Any hypotension (mean arterial pressure lower than 20% of baseline) or bradycardia (heart rate < 50/min) incidents were treated with phenylephrine. 50-100 microgram or atropine 0.6 mg incremental dose. A decrease in SPO_2 to less than 90% is being defined as hypoxia and is treated accordingly.

Study drug infusion discontinued at the end of the pneumoperitoneum and vitals were recorded. After completion of surgery, neuromuscular block was reversed with neostigmine 0.05mg/kg and glycopyrolate 0.004mg/kg. Patients were then extubated. Vitals were noted and transferred to recovery room.

Time to recovery was noted as well as intra-op and post- op complications were recorded. Sedation was recorded by Ramsay Sedation Scale. Time of onset of post – operative pain was recorded and inj. Fentanyl sulphate was given for post- op analgesia.

STATISTICAL METHODS

Continuous variables like SBP, DBP, Post-op variation were expressed as Mean ± Standard Deviation and compared between two groups. Softwares used for the study were Statistica version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001], SPSS Statistics version 17 [Illinois, Chicago: SPSS Inc., 2008], GraphPad Prism version 5 [San Diego, California: GraphPad Software Inc., 2007]

All numerical variable are normally distributed by Kolmogorov-Smirnoff goodness-of-fit test. Categorical variables like sex, outcomes are expressed as number of patients and percentage of patients and compared between 2 groups using Pearson's ChiSquare test for Independence of Attributes. Comparison of numerical variables between Groups D and M – by unpaired t-test. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant.

RESULTS

Comparison of mean heart rate between the groups (Figure 1)

On applying **Unpaired t test**, no statistically significant difference in HR was found among the groups at baseline and up to HR6 i.e. HR 5 min post pneumoperitoneum. Then after 10 mins, 15 min, 30 min., and up to HR 15 (reading at the time of shifting) H.R. was found to be significantly lower in Dexmedetomidine than magnesium sulphate.

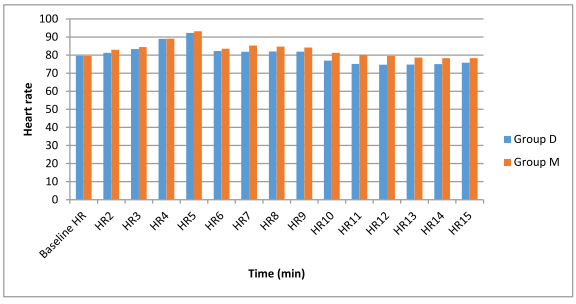

Figure-1. Mean Heart Rate Column Chart Of Group D &M.

Comparison of systolic blood pressure between the groups (Figure 2)

Applying the **unpaired t test,** no statistically significant difference ($p > 0.05$) among the groups were found at baseline systolic blood pressure ($p=0.835$).Then after starting of infusion and up to the shifting time, SBP was insignificantly lower with Dexmedetomidine than with magnesium sulphate.

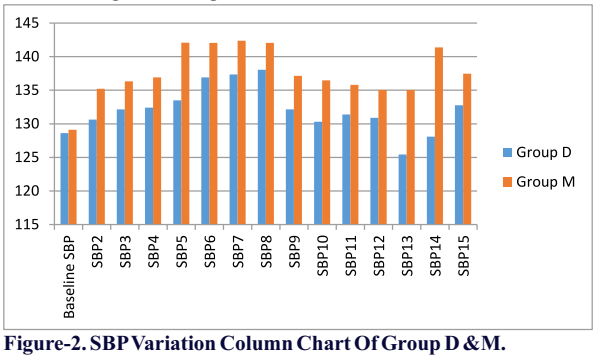

Figure-2. SBP Variation Column Chart Of Group D &M.

Comparison Of Diastolic Blood Pressure Between The Groups. (figure 3)

Applying the **Unpaired t test**, no statistically significant difference ($p > 0.05$) was found among the groups at baseline diastolic blood pressure ($p=0.832$).Then after starting of infusion and upto the time of shifting, DBP was significantly lower with Dexmedetomidine than with magnesium sulphate and control groups ($p < 0.05$) .

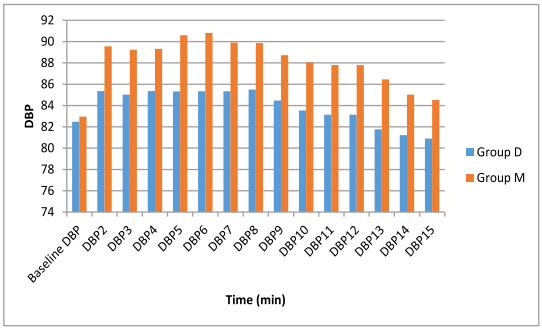

Figure-3, DBP Variation Column Chart Of Group D &M

MAP VARIATION BETWEEN THE GROUPS. (Figure 4)

Applying the **Unpaired t-test**, no statistically significant difference ($p > 0.05$) was found among the groups at baseline MAP. p value is 0.824 but after the start of infusion until the time of shifting the patient , there is significant difference in the MAP of patients of group D and group M.

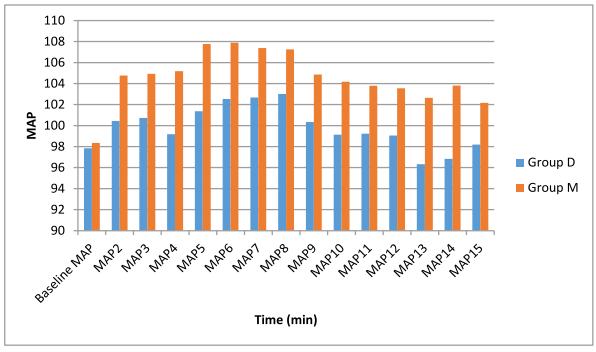

Figure-4. MAP Variation Column Chart Of Group D &M.

SPO2 VARIATION BETWEEN THE GROUPS.(Figure 5)

Applying the **Unpaired test,** no statistically significant difference ($p > 0.05$) was found between the groups at baseline and until the time of shifting the patient, there was no significant difference in the SpO2 of the patients of group D and group M.

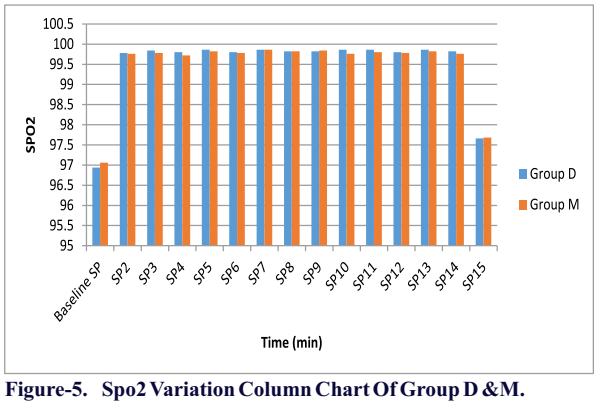

Figure-5. Spo2 Variation Column Chart Of Group D &M.

ETCO2 VARIATION BETWEEN THE GROUPS. (Figure 6)

Applying the **Unpaired test,** no statistically significant difference ($p > 0.05$) was found between the groups at baseline and until the time of shifting the patient, there was no significant difference in the ETCO2 of the patients of group D and group M.

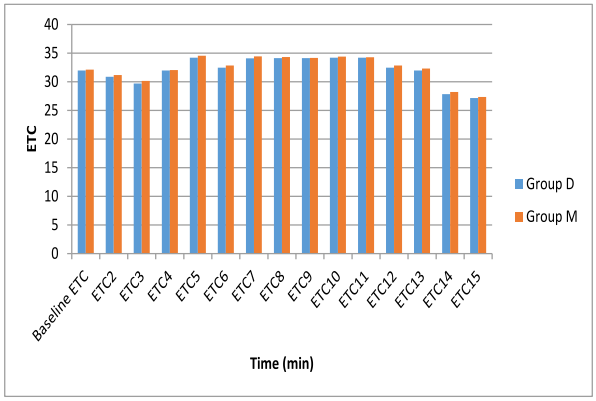

Figure-6. EtCO2 Variation Column Chart Of Group D &M.

RSS VARIATION BETWEEN THE GROUPS. (Figure 7)

Applying the **Chi square test,** statistically significant difference ($p > 0.05$) was found between the groups at the time of recovery, of the patients of group D and group M.

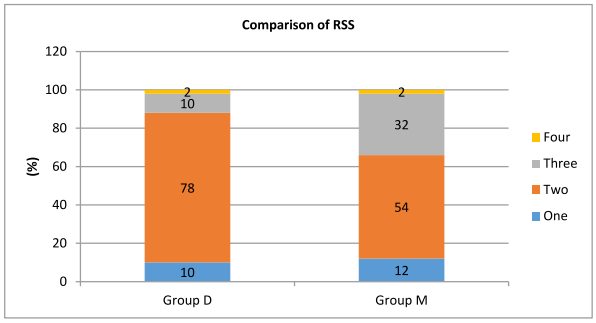

Figure 7.column Chart Showing Rss In Groups D&M.

POST-OP VARIATION BETWEEN THE GROUPS. (Figure 8)

Applying the **Chi square test,** statistically significant difference (p value > 0.05) was found between the groups in the onset of post-operative pain of the patients of group D and group M.

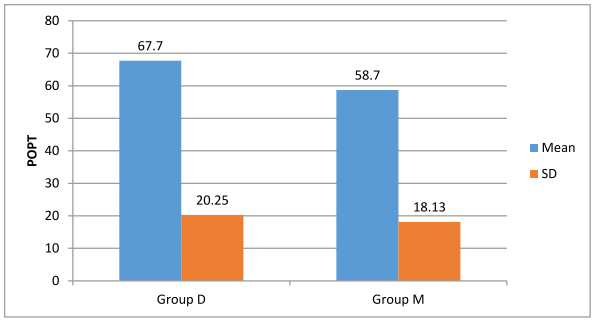

Figure 8. Column Chart Showing Post-op Pain Onset Time In Groups D & M.

DISCUSSION

The baseline heart rate are comparable in both the groups. A statistically insignificant difference in HR was found between the groups ($p > 0.05$) at baseline ($p=0.935$), at the time of start of infusion ($p=0.378$), and up to 5 minutes post pneumoperitoneum ($p = 0.49$). Thereafter upto the time of shifting the patient in post-operative room, H.R. was significantly lower in Dexmedetomidine than magnesium sulphate group ($p < 0.05$). In the present study, Dexmedetomidine and magnesium sulphate are administered as a bolus dose followed by maintenance doses as infusion. The lack of significant difference after premedication and up to 5 min post pneumoperitoneum is probably due to predominant effect of anaesthetic agents administered at the time of induction.

The baseline systolic blood pressures are comparable between the groups. Statistically insignificant difference ($p > 0.05$) was found between the groups at baseline; ($p =0.835$). Thereafter up to the time of shifting the patient to post-operative room, SBP was found to be significantly lower with Dexmedetomidine than with magnesium sulphate ($p < 0.05$) .

The baseline diastolic blood pressure are comparable between the groups. Statistically insignificant difference ($p > 0.05$) was found between the groups at baseline diastolic blood pressure; ($p = 0.842$). Thereafter up to time of shifting the patient to post-operative room DBP was found to be significantly lower with Dexmedetomidine than with magnesium sulphate ($p < 0.05$). Post-hoc comparisons (following Unpaired t- test), it is found that there is significant difference ($p < 0.05$) of DBP at 30 min. of pneumoperitonium.

The baseline mean arterial pressure is comparable between the groups. Statistically insignificant difference ($p > 0.05$) was found between the groups at baseline mean arterial pressure; ($p = 0.824$).Thereafter up to time of shifting the patient to post-operative room, MAP was found to be significantly lower with Dexmedetomidine than with magnesium sulphate and control groups ($p < 0.05$) .

The oxygen saturation of blood values (SPO2) are comparable between the groups. Statistically insignificant difference ($p > 0.05$) was found between the groups at baseline; ($p = 0.698$) and up to the time of shifting the patient to post-operative room.

The End tidal volume of CO2 values (ETCO2) are comparable between the groups. Statistically insignificant difference ($p > 0.05$) was found between the groups at baseline; ($p = 0.801$) and up to the time of shifting the patient to post-operative room.

The Ramsay sedation score of patients was noted with both the drugs and significant difference ($p < 0.05$) was found in the recovery time of the patients from general anaesthesia after extubation between both the group of drugs with mean RSS of 2.00 in Group D patients and mean RSS 2.28 in Group M patients ;($p = 0.023$). Patients having RSS 2 were 41 (84%) in Group D and 25 (50%) in Group M.

The onset of post-operative pain time was noted in both the group of patients and there was significant difference($p < 0.05$) in the POPT between both the group of patients with mean POPT 67.7 mins.in Group D and 58.7 mins. in Group M; ($p = 0.021$).

Therefore, this study shows that Dexmedetomidine is superior to Magnesium sulphate in diminishing the circulatory responses of pneumoperitoneum and in providing effective post-operative analgesia.

The study correlates with the study done by Kalra et al.[8] in which administration of magnesium sulphate and clonidine was done for attenuation of hemodynamic responses to pneumoperitoneum. The authors conducted that Clonidine (1.5mcg/kg) blunts hemodynamic responses to pneumoperitoneum more effectively than magnesium sulphate (50mg/Kg) used 15min before pneumoperitoneum. In this study Dexmedetomidine 1mcg/kg body weight over 10 minutes, was given before induction of pneumoperitoneum, followed by 0.5mcg/kg/hour. And infusion of magnesium sulphate 30mg/kg over 10 minutes, 15 mins before induction of pneumoperitoneum, followed by 10mg/kg/hour and it was observed that Dexmedetomidine group was more effective in the attenuation of haemodynamic surge than magnesium sulphate group. A significant difference (p value is less than 0.05) was observed in this value. Out of 50 cases in 5 cases of Group-M slightly delayed neuromuscular recovery was noted.

Kalra et al.[8] assessed which of magnesium or clonidine attenuates hemodynamic stress response to pneumoperitoneum better and found that systolic blood pressure was significantly higher in control group as compared to study groups during pneumoperitoneum with no significant difference between magnesium and clonidine groups given in dose of 1 µg/kg. However, the attenuation of the surge was observed to be better in patients receiving clonidine in dose of 1.5 µg/kg.

Another study correlates with us, Godhki et all, Dexmedetomidine (1 mcg\kg) over 10 min, 15min before induction and infusion 0.2mcg/kg/hour in laparoscopic surgery. They found that Dexmedetomidine can be safely used in laparoscopic surgery without fear of awareness.[9]

Concerning laparoscopic surgery, the obtained results supported what was previously reported by Smania et al. who found that Dexmedetomidine efficiently blocks the hemodynamic responses to nociceptive stimuli when combined with inhaled isoflurane for anesthesia of children submitted to laparoscopic video appendectomy.[10]

The effect of dexmedetomidine on hemodynamics is due to decrease of sympathetic outflow from the locus ceruleus. Its sympatholytic effect leads to decrease of mean arterial blood pressure (MAP) and heart rate (HR) by reducing norepinephrine release. Its analgesic actions are mediated by releasing of substance P from the dorsal horn of the spinal cord.

Gourishankar Reddy Manneet al[11], Reported that low dose dexmedetomidine infusion (0.2 mcg/Kg/h and 0.4mcg/Kg/h started 15 minutes before induction) in the dose of 0.4 mcg/kg/h showed lower values of heart rate and mean arterial pressure than other groups, and also it effectively attenuates haemodynamic stress response during laparoscopic surgery with reduction in post-operative analgesic requirements. In this study dexmedetomidine 1mcg/kg body weight over 10 minutes was used followed by 15 min before induction of pneumoperitoneum, followed by 0.5mcg/kg/hour. In our study also similar effects with Dexmedetomidine were observed. No cases of delayed arousal in group-D was noted and recovery time was lesser in Group D as compared to Group M.

Limitations of the present study were as follows.

1. The study is conducted on a small size of population. Including a larger population would give better results and more clarification.
2. The study involved ASA physical status Class I and II patients only. Therefore, we cannot emphasize the results from our study on ASA physical status Class III and IV patients, e.g. patients with uncontrolled hypertension and/or uncontrolled diabetes mellitus.
3. The study does not include the patients below 16 years and above 60 years of age; therefore effect of the study drugs in pediatric population or geriatric population cannot be analyzed.

CONCLUSION

From this study we conclude that intravenous premedication with Dexmedetomidine infusion for laparoscopic surgery under general anaesthesia is more beneficial than Magnesium sulphate infusion in attenuating the hemodyanamic stress responses during laparoscopic surgery under general anaesthesia and in reducing the requirement of analgesia post operatively.

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