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Effect of Dexmedetomidine Infusion on Perioperative Hemodynamic Stability in Patients Undergoing Laparoscopic Cholecystectomy: A Placebo Controlled, Randomised Blinded Study

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ABSTRACT

Laparoscopic surgery induces significant alterations of hemodynamic characterized by increased arterial pressure and elevation of systemic and pulmonary vascular resistance. Although these changes may be well tolerated in patients without any other comorbidities, however the tolerance is questionable in extremes of age and in cardiac patients. Suppressing the most refractory response, hypertension and tachycardia, to the most profound stimulus, intubation requires more opiod and hypnotic. In recent years α2 agonists have gained wide acceptance in anaesthetic practice due to their sedative, anxiolytic, sympatholytic and analgesic sparing properties. Dexmedetomidine is a selective α2 agonist with 8 times more affinity for α2 receptors than clonidine and possess all the properties of α2 agonist without respiratory depression (41). The primary objective was to evaluate the effect of dexmedetomidine infusion on hemodynamic stability in response to the following events in patients undergoing laparoscopic cholecystectomy: laryngoscopy and endotracheal intubation, creation of pneumoperitoneum and extubation. The secondary objective was to observe the effects on level of analgesia in immediate post operative period, level of sedation at the end of surgery, occurrence of any adverse effects, other relevant findings, if any. A placebo controlled, randomised blinded study was conducted under the Department of Anaesthesiology and Critical Care, Gauhati Medical College and Hospital, Guwahati. 60 patients were divided into two groups of 30 each. Group A received normal saline 0.9% and Group B receiving Dexmedetomidine infusion 0.4 mcg/kg/hr. Infusion of study drug was started 10 minutes prior to induction. The same general anaesthesia technique was used in all cases. Hemodynamic parameters: Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and SpO2 were recorded at 1 minute after intubation, after pneumoperitoneum at 1 min, 15min, 30 min, 45 min and 60 min and at 1 min after extubation. All the patients were observed for one hour postoperatively in the holding area outside of the operating room. The Visual Analogue Scale (VAS) score for post operative pain and Ramsay Sedation Score were noted. The statistical analysis was done using PSW software version 21.0. Chi square test, unpaired t test, Mann Whitney test were used to determine p value. There was no significant difference in the age distribution, sex, ASA physical status, duration of surgery between both the groups. However there was significant difference in the hemodynamic parameters between the two groups. There is better stability of heart rate in the Dexmedetomidine group in the perioperative period in comparison to Normal Saline group.

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Key Words

General anaesthesia, laparoscopic surgery, pneumoperitoneum, laryngoscopy, intubation, α2 agonists, hemodynamic stability, analgesia, sedation

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INTRODUCTION

Endotracheal intubation, as well as laryngoscope and other airway instrumentation provide intense noxious stimulus via vagal and glossopharyngeal afferent, which results in reflex autonomic activation. This usually results in hypertension and tachycardia in adults in adults and adolescents. Similar complications can also occur during extubation of the trachea. Although hypertension and tachycardia are usually of short duration, but they may have consequences in patients with significant cardiac disease[1]. Perioperative myocardial infarction is a leading cause of morbidity and mortality due to hypertension and tachycardia[2]. Hemodynamic changes observed during laparoscopy result from the combined effects of pneumoperitoneum, patient position, anaesthesia and hypercapnia from the absorbed CO_2. Additionally reflex increases of vagal tone and arrhythmia can also develop. These disturbances are characterized by decreases in cardiac output, by increased arterial pressure and elevation of systemic and pulmonary vascular resistance[3]. These hemodynamic changes are further compounded by the reverse Trendelenburg or head up position used in laparoscopic cholecystectomy. This position causes reduction in venous return and thus causing a reduction in cardiac output in addition to that caused by pneumoperitoneum. More severe hemodynamic changes occur in volume depleted patients. Hemodynamic perturbations occur mainly at the beginning of peritoneal in sufflations. Catecholamines, the rennin-angiotensin system and specially vasopressin are all released during the presence of pneumoperitoneum and may contribute to increasing the afterload[4]. Pneumoperitoneum in cardiac patients carries a higher predisposition for development of myocardial ischaemia. Modern anaesthesia practices, therefore, plan to prevent sympathetic discharge and provide hemodynamic stability preoperatively. Various agents in the form of opioid analgesics, benzodiazepines, beta blockers and vasodilator have been used to achieve this objective with variable success. In recent years α2 agonists have gained wide acceptance in anaesthetic practice due to their sedative, anxiolytic, sympatholytic and analgesic sparing properties. Dexmedetomidine is a selective α2 agonist with 8 times more affinity for α2 receptors than clonidine and possess all the properties of α2 agonist without respiratory depression[5]. The aim of this study is to study the effects of dexmedetomidine infusion on perioperative hemodynamic stability in patients undergoing laparoscopic cholecystectomy. The primary objective was to evaluate the effect of dexmedetomidine infusion on hemodynamic stability in response to the following events in patients undergoing laparoscopic cholecystectomy: laryngoscopy and endotracheal intubation, creation of pneumoperitoneum and extubation. The secondary objective was to observe the effects on level of analgesia in immediate post operative period, level of sedation at the end of surgery, occurrence of any adverse effects, other relevant findings, if any.

MATERIALS AND METHODS

A placebo controlled, randomised blinded study was conducted under the Department of Anaesthesiology and Critical Care, Gauhati Medical College and Hospital, Guwahati, with prior permission and approval from the institutional ethics committee after fulfilling the norms (No- MC/190/2007/pt-11/Dec 2019/08) and CTRI registration (No: CTRI/2020/06//026037) and obtaining informed written consent from the patients. The study was done for a period of 1 year from 1st July 2020 to 30th June 2021. Patients with valid consent in the age group 18-60 years, belonging to ASA status I or II, of either sex, undergoing elective laparoscopic cholecystectomy requiring endotracheal intubation were included in the study. Patients who refused, have known allergy either to Dexmedetomidine or any of the drugs to be administered, pregnant or lactating female, with known history of substance abuse, with hypotension, bradycardia or preexisting heart block or with anticipated/ unanticipated difficult airway were excluded from the study. Study by Manne GR *et al.* (2014) reported the mean with standard deviation of heart rate and mean arterial pressure (MAP) for different points of time. Based on this study[5], the pooled variance at each point in time was calculated. To detect a decrease in heart rate by 10 bpm and MAP by 10mmHg in patients receiving dexmedetomidine infusion during laparoscopic cholecystectomy, the sample size required was 25 to achieve a power of 90% at confidence interval of 95%. Considering possible dropouts as 20%, sample size was calculated as total of 60 with 30 in each group. The patients were visited in the pre-operative day in the ward and a thorough pre anaesthetic assessment was done. Baseline parameters like heart rate and blood pressure were noted. Relevant laboratory investigations were done. Patients were explained and written consent was obtained. Sixty patients meeting the inclusion criteria and consenting to participate in the study were divided into two groups A and B by a computer-generated random selection using block randomization with blocks of variable size. The study drugs were prepared by a post graduate resident on the morning of surgery who was not involved in any other aspect of the study. Details of group and drug to be given were sealed within envelopes, which were randomly picked up and the drug was administered according to randomization

sequence. The patients were also blinded to the group they belong. Group A-patients receiving normal saline 0.9%. Group B-patients receiving Dexmedetomidine infusion 0.4 mcg/kg/hr The study drugs were administered as intravenous infusion started approximately 10 minutes prior to induction of anaesthesia and was continued throughout the operation till the end of surgery. All patients were explained regarding the procedure of the study during the preanesthetic checkup. The patients were also educated regarding the ten-point Visual Analogue Scale (VAS) score the day prior to scheduled surgery. A score of zero indicated “no pain" while a score of ten indicated “worst imaginable pain". All vital parameters like Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Pressure, SpO2 were recorded pre operatively. After measuring baseline parameters, the sealed envelope with patient allocation was opened and the study drugs will be infused as per allocation. Thus, the investigator performing intubation and taking care of anaesthetic technique was blinded to the drug administered. Thereby, double blinding was achieved as both the patient as well as investigator were unaware of the group. Following this, infusion of study drug was started 10 minutes prior to induction. After 10mins, the readings were taken once more just prior to induction. The same general anaesthesia technique was used in all cases. Tracheal intubation was done under direct laryngoscopic vision with appropriately sized cuffed endotracheal tube. hemodynamic parameters: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and SpO2 were recorded thereafter at 1 minute after intubation. Patients were put on controlled mechanical ventilator. Intra operatively, readings were taken at following intervals: after pneumoperitoneum at 1 min, 15min, 30 min, 45 min and 60 min and at 1 min after extubation. Other parameters recorded were ECG, EtCO2 hemodynamic management: hemodynamic end point of anaesthetic management was maintenance of heart rate and blood pressure within 20% of baseline values. If heart rate rises >20% beats/min (tachycardia) or MAP increased by >20%mmHg (hypertension) over baseline values or if HR falls below 50 beats/min (bradycardia) or MAP decreased by >20%mm Hg (hypotension) of baseline, then the following interventions were given. Bradycardia was treated by administration of injection Atropine 0.6mg. Hypotension was treated by administration of 6mp ephedrine. In case of tachycardia and hypertension, attempts were made to attenuate it by increasing sevoflurane concentration by 0.2% every 3mins up to 2%. If persisting, fentanyl (1mcg/kg) was repeated once. Injection Nitroglycerin was used in titrated dose if hypertension persisted despite other measures. Injection Esmolol 5mg in incremental doses every 5mins was given if tachycardia persisted despite other measures. Neuromuscular block was reversed and the patients were extubated when awake or able to protect the airway. The time from discontinuation of sevoflurane and extubation and the time from discontinuation of trial drug infusion to extubation were noted in both groups. All the patients were observed for one hour postoperatively in the holding area outside of the operating room. The Visual Analogue Scale (VAS) score for post operative pain and Ramsay Sedation Score were noted at 1min, 15min, 30min and 60mins after extubation. Any complications such as postoperative nausea and vomiting, dryness of mouth, seizure, sedation, hypotension, allergic reaction, respiratory depression was noted. Rescue analgesia: injection ketorolac 0.5mg/kg intravenously if VAS >4 was noted or at patient’s request. The data was entered into MS Excel spreadsheets and analysis was carried out. Chi square test, unpaired t test, Mann Whitney test and Fisher’s exact test were used to determine p value.

RESULTS AND DISCUSSIONS

Out of 60 patients enrolled in the study, 55 patients completed the study. 5 patients (8.3%) were excluded from the study due to being converted to open cholecystectomy. There was no significant difference in the age distribution, weight distribution, sex, ASA physical status, duration of surgery between both the groups (p value> o.o5). The baseline hemodynamic parameters of HR, SBP, DBP, MAP were comparable in both the groups with p value>0.05. The intergroup differences in HR was significant(p<0.05) at 1min after laryngoscope, 1 min and 45 min after pneumoperitoneum and 1 min after extubation with the increase in HR more in Group A than in Group B. After start of trial drug, mean heart rate decreased in comparison to baseline in both the groups at 10mins after start of infusion (before induction). In both these groups, the decrease in heart rate was statistically not significant (p>0.05).

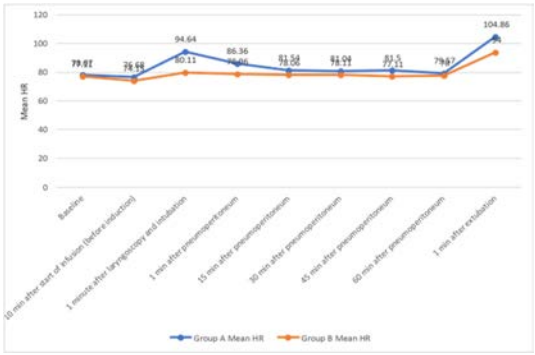

Fig. 1: Intergroup Comparison of Mean Heart Rates (bpm) at Different Points of Time

After the start of trial drug infusion, mean systolic blood pressure and mean diastolic blood pressure was seen to decrease in both the groups at 10mins after start of infusion (before induction). Intergroup comparison between Groups A and B shows a significant reduction in SBP ($p<0.05$), but no significant reduction in Group B as compared to Group A at 10mins after start of infusion (before induction). Intergroup comparison shows the rise in SBP at 1 min after laryngoscopy and intubation, at 1 min after pneumoperitoneum to be significantly high in Group A in comparison to Group B ($p<0.001$). At 15mins, 30mins, 45mins and 60mins after pneumoperitoneum, the SBP remained elevated in both Group A and B with regard to respective baseline SBP. However, on intergroup comparison, the SBP is significantly high ($p<0.05$) in Group A compared to Group B at 15mins, 30mins and 45mins after pneumoperitoneum and 1 min after extubation. The mean DBP was significantly more in Group A as compared to Group B (p value <0.001) at 1 min after laryngoscopy and intubation, at 1min after pneumoperitoneum and 1min after extubation. After start of trial drug infusion, mean MAP decreased in both the groups at 10mins after start of infusion. Intergroup comparison at 10mins after start of infusion shows a significant reduction in MAP in Group B as compared to Group A ($p<0.001$). At 1 min after laryngoscopy and intubation, MAP increased significantly by 22.4mmHg (23.9%) in Group A as compared to baseline ($p<0.001$). In Group B, the MAP increased by 8.18mmHg (8.70%) with regard to baseline which is also significant ($p<0.001$). Although the MAP increased in both the groups, intergroup comparison shows a significantly greater increase in MAP in Group A as compared to Group B at 1 minute after laryngoscopy and intubation ($p<0.001$). Intergroup comparison shows the rise in MAP to be significantly more ($p<0.001$) in Group A than in Group B at 1 min after pneumoperitoneum. At 15min, 30 min and 45 min after creation of pneumoperitoneum, the MAPA increased significantly in Group A ($p<0.05$) at all 3 intervals while at 60 min after pneumoperitoneum no significant increase occurred ($p>0.05$). In Group B, the MAP remained elevated throughout the period of pneumoperitoneum at all intervals, i.e., at 15mins, 30mins, 45mins and 60 mins but the increase in MAP was not significant ($p>0.05$) at all the 4 intervals. Intergroup comparison at 15min, 30 min and 45 min after pneumoperitoneum showed a significantly higher MAP in Group A than in Group B ($p<0.05$) at all 3 intervals while no significant difference was seen at 60mins after pneumoperitoneum between the two groups. Although the MAP remained elevated in both the groups at 1 min after extubation, but intergroup comparison shows a significantly greater increase in MAP occurred in Group A as compared to Group B ($p<0.001$).

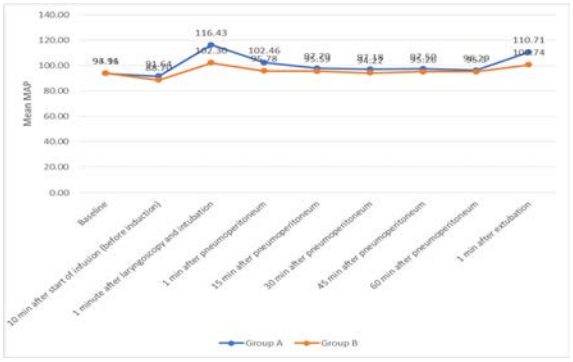

Fig. 2: Intergroup Comparison of Mean MAP Between the Two Groups-A and B

From the start of trial drug infusion, throughout the period of pneumoperitoneum up to 1 minute after extubation, no significant difference was observed in mean SpO2 between the two groups ($p>0.05$) at all intervals. The ETCO2 increased at 15min after pneumoperitoneum in both the groups and remained elevated for all the intervals throughout the surgery, however there was no significant difference between the groups in the intergroup comparison. At 1 min after extubation, the mean VAS in Group B (1.44± 0.751) is significantly lower ($p<0.001$) than the mean VAS in Group A (3.43±0.504) . At 15mins after extubation, no significant difference was seen in the VAS score between Group A (2.29±1.049) and Group B (1.96±0.706). At 30 and 60mins after extubation, the VAS score remained significantly lower in Group B (mean VAS at 30mins was 2.63±0.884 and at 60mins was 3.41±0.747) than in Group A (mean VAS at 30mins was 3.68±0.612 and at 60mins was 4.25±0.701) with $p<0.001$ at both the intervals. At 1 min and 15 min after extubation, the RSS remained significantly higher ($p<0.001$) in Group B (3.3±0.542) than in Group A (2.14±0.891). Dry mouth was a common side effect in Group B.

In our study, the demographic variables in both the study groups were comparable in terms of age, sex, weight and ASA physical status. Further, the mean duration of surgery was also comparable in both the groups. The baseline hemodynamic parameters in terms of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were comparable between Group A and Group B. Thus, from the above discussion, it may be observed that the comparison of the trial drugs on hemodynamic parameters in the present study is justified. Furthermore, the type of surgery, anaesthetic

technique and equipment used were same for both the groups. Also, any confounding factors like patients with cardiovascular or respiratory diseases or patients on any drugs affecting the cardiovascular functions were excluded from the study. The two groups differed only with respect to the study drugs that were used. In our study we have used 0.4mcg/kg/hour of dexmedetomidine as i.v. infusion and normal saline starting from 10 minutes before induction till the end of surgery. Many other studies have used a similar dose[5,6]. In our study, it was observed that after 10mins of starting infusion of the trial drug, the SBP, DBP and MAP decreased with respect to the baseline in both the groups. A significant difference was noted between the two groups with a greater reduction in the dexmedetomidine group compared to normal saline group. An insignificant reduction in heart rate from baseline was also noted in both the groups 10mins after the start of trial drug infusion. Although the reduction of HR was more in Dexmedetomidine group in comparison to Normal Saline group, however, this difference was not significant. This initial reduction in blood pressure and heart rate in the dexmedetomidine group could be due to its central sympatholytic and anxiolytic effects[7]. Similar reduction in blood pressure and heart rate in dexmedetomidine group in the pre laryngoscopic period was noted in a study by **Aantaa**[8] and **Manne**[5]. In our study, it can be seen that the maximum increase in SBP, DBP and MAP occurred at laryngoscopy and intubation in both the groups. Other studies have a similar finding and support that dexmedetomidine can blunt the hemodynamic response to laryngoscopy and intubation[9]. In our study, at 1 min after creation of pneumoperitoneum, on inter group comparison, increase in HR, SBP, DBP and MAP was significantly more in Normal Saline group than in Dexmedetomidine group at 1min, 15min, 30min and 45mins following the establishment of pneumoperitoneum. Therefore, from our study it can be observed that Dexmedetomidine infusion at the rate of 0.4mcg/kg/hour can provide hemodynamic stability after creation of pneumoperitoneum. The results observed by certain other studies[10,11] were comparable to the results in our study. In our study, at 1min after extubation we found an increase in HR, SBP, DBP and MAP in both the groups, with a significantly greater increase in Group A (Normal Saline) than in Group B (Dexmedetomidine). Therefore, from our study, it can be observed that dexmedetomidine attenuates hemodynamic response to extubation. In our study, it was observed that at 1 min after extubation, the mean VAS score in Group B was significantly lower than the mean VAS score in Group A. At 15mins after extubation, the VAS score remained lower in Group B but no significant difference was seen between the two groups which could be due to the requirement of rescue analgesia in Group A. Further, the VAS score remained significantly lower at 30 and 60min in Group B than in Group A. Therefore, it can be observed from our study that infusion Dexmedetomidine reduces post operative pain after laparoscopic cholecystectomy as seen by lower VAS scores than Normal Saline group. These results of our study correlate well with that of **Meena**[12]. In our study it was observed that the RSS remained significantly higher till 30mins after extubation, but no significant difference was observed between the two groups at 60mins after extubation. Therefore, from our study we observed that sedation score was initially higher in Dexmedetomidine group as compared to Normal Saline group but decreased gradually over a period of one hour. There was no significant change in Spo2, mean EtCO2 in both the groups during the perioperative period. There was no remarkable change in ECG of the patients of either group during the perioperative period. The trial drugs were well tolerated by patients and no serious complications were noted during the study period. No incidence of hypotension or bradycardia (HR<50) was seen in either group. Dryness of mouth is a common side effect of dexmedetomidine. Our study had several limitations as only ASA I and II patients were included, plasma catecholamine levels were not estimated for comparison between the two groups which would have given a better idea of sympathy-adrenal response, the VAS is limited by ceiling effects that often leaves patients with no ability to quantify worsening of pain. There was no conflict of interest.

CONCLUSION

Intravenous infusion of Dexmedetomidine at a rate of 0.4mcg/kg/hour from before induction till the end of surgery helps to attenuate the stress response associated with laryngoscopy and intubation, pneumoperitoneum and extubation by maintaining better hemodynamic stability in comparison to Normal Saline. It also provides added benefits of post operative analgesia. Though it causes sedation in the immediate post operative period but does not cause respiratory depression.

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