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EFFECTS ON INTRAOPERATIVE HEMODYNAMICS AND POST OPERATIVE PAIN AND SEDATION FOLLOWING LIDOCAINE VERSUS DEXMEDETOMIDINE INFUSION IN LAPAROSCOPIC SURGERY

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ABSTRACT

Background: Laparoscopic surgery has got tremendous popularity due to fast recovery and shortened hospital stay. The hall mark of laparoscopy, pneumoperitoneum is an additive to intubation in stimulating the neuro-humoral responses that create a pathway to hemodynamic instability which is the major hurdle faced by anaesthesiologist during laparoscopic procedure. Among the many drugs that are used to control the effects caused by pneumoperitoneum, we have used infusion of lignocaine and dexmedetomidine and compared their efficacy.

Methods: After obtaining ethical committee approval, a prospective, randomized, double blinded study was conducted on 86 patients at a tertiary care hospital in Eastern India to compare Dexmedetomidine vs Lignocaine, in laparoscopic surgery, to obtund changes in hemodynamic parameters in response to creation of capno-pneumo-peritoneum, their effect on post-operative analgesia and also their effect on recovery from anaesthesia. In Group L, immediately before induction of anaesthesia, patients received a bolus of 1.5 mg/kg lidocaine followed by an intravenous infusion of 1.5 mg/kg/h Lidocaine hydrochloride through an infusion pump. In Group D, immediately before induction of anaesthesia, patients had received a bolus of 0.5 µg/kg followed by intravenous infusion of 0.5µg/kg/hr dexmedetomidine hydrochloride through an infusion pump. In both groups, the infusion had been continued throughout the surgery and terminated after release of pneumoperitoneum. Hemodynamic parameters were recorded at predefined time interval, first at the time of intubaton, then at the time of creation of capno-pneumoperitoneum by insufflation of CO_2, then after 10, 20 and 30 minutes of creation of pneumoperitoneum, then at the time of release

of pneumoperitoneum and finally at the time of extubation. While VAS score as a measurement of post-operative analgesia was recorded at the time of arrival at PACU, then after 1 hour of stay at PACU, then finally at the time of discharge from PACU. Similarly University of Michigan Sedation Score (UMSS), as a measurement of recovery from anaesthesia was measured at the time of arrival at PACU, then after 1 hour of stay at PACU and finally at the time of discharge from PACU.
Results: Demographic data such as age, weight, sex was comparable between the groups. At the time of intubation, there were no significant difference noted in hemodynamic parameters such as SBP, DBP, MAP and HR, when compared between dexmedetomidine and lignocaine. But parameters such as SBP, DBP, MAP and HR were better controlled with dexmedetomidine in comparison to lignocaine with respect to baseline values in subsequent time points with statistically significant p-value<0.05. Pain score which was measured as VAS on arrival at PACU, 1 hour after stay at PACU and at the time of discharge from PACU had better values in dexmedetomidine group. It was noted that, recovery from anaesthesia, which was measured as University of Michigan Sedation Score (UMSS), at the time of arrival at PACU, was delayed with dexmedetomidine in comparison to lignocaine. But 1 hour after stay at PACU was showing no significant statistical difference between lignocaine and dexmedetomidine showing no difference in recovery from anaesthesia with dexmedetomidine in comparison to lignocaine after 1 hour of stay at PACU.
Conclusion: The study has shown that dexmedetomidine infusion can obtund hemodynamic changes associated with pneumo-peritoneum creation, better than lignocaine infusion in laparoscopic surgeries, also providing better post-operative analgesia than lignocaine, but dexmedetomidine shows delayed recovery from anaesthesia at the time of arrival to PACU. Though, recovery from anaesthesia was similar after 1 hour of stay at PACU between both groups.

Keywords: Intraoperative hemodynamics, Lidocaine, Dexmedetomidine, Laparoscopic Surgery

Introduction

Laparoscopic surgery is nowadays a common daily-performed procedure worldwide, replacing many types of open surgeries. It has the benefits of small incision, improved cosmetic aspects, less postoperative pain, and quick recovery time to normal activities [1]. Three types of pain are reported after laparoscopic surgery: parietal (somatic) pain, due to the holes made in the abdominal wall for the trocars; visceral pain, due to surgical handling and diaphragmatic irritation by the dissolved CO_2; and shoulder tip pain, due to rapid distension of the peritoneum (associated with tearing of blood vessels, traumatic traction of the nerves and the release of inflammatory mediators) and excitation of the phrenic nerve. Visceral pain is predominant during the first 24h postoperatively. It is short-lived, unaffected by mobilization and is increased by coughing. Shoulder pain can sometimes last for 3 days. [2]

Creation of pneumoperitoneum is associated with significant hemodynamic changes in the form of abrupt elevations of mean arterial blood pressure (MAP) and heart rate (HR), thus increasing the morbidity of the patient [3].These hemodynamic responses are due to the increased release of catecholamine, vasopressin or both [4], possibly because of an increase in the intraperitoneal pressure and CO_2 stimulation of the peritoneum. Various pharmacological agents like nitro-glycerine [5], β- blockers, opioids, gabapentin, pregabalin, magnesium sulphate, clonidine, and dexmedetomidine are used to provide hemodynamic stability during pneumoperitoneum, with varying success rates. [6]

Dexmedetomidine, the pharmacologically active d-isomer of medetomidine, is a highly selective and specific α_2-adrenoceptor agonist; this might permit its application for sedation and analgesia. These properties render it suitable during the whole perioperative period. Dexmedetomidine provides significant sympatholytic (postsynaptic activation of α_2 adrenoceptors in the central nervous system) and hemodynamic stability. [7] Dexmedetomidine modulates the hemodynamic changes during pneumoperitoneum by inhibiting the release of catecholamines and vasopressin. Dexmedetomidine induces analgesia by action at the locus coeruleus and at the spinal cord, by

inhibiting nociceptive process. It does not have a respiratory depressant effect or addictive potential, when dexmedetomidine is administered as a continuous infusion, but care should be taken when administered to patients who are volume depleted, vasoconstricted or have severe heart block, as dexmedetomidine can cause hypotension and bradycardia. [8]
Lignocaine, a weak base and a systemic local amide, has analgesic, anti-inflammatory, and antihyperalgesic properties [2]. Mechanism of action includes alteration of transmembrane conductance of cations, especially sodium, potassium and calcium, both in the neurons and myocytes. Intravenous lignocaine has a hemodynamic-stabilizing effect during pneumo-peritoneum created during laparoscopic surgery. Lignocaine has a stabilizing effect on the heart and blood pressure, possibly by its direct myocardial depressant effect, peripheral vasodilating effect and through its anti-inflammatory activity [2]. Analgesic action of lignocaine infusion in patients with chronic neuropathic pain is well known but its place in relieving postoperative pain is yet to be established.
In our study we had taken these two drugs and compared their effects with respect to intraoperative hemodynamic stability during laparoscopic surgery, postoperative analgesia, recovery from anaesthesia following laparoscopic surgery.

Materials and Methods
This prospective double-blinded, randomized control study had been conducted among patients in Department of Anaesthesia at a tertiary care facility in Eastern India for a period of 1 year after receiving approval from the institutional ethics committee. The subjects were randomly allocated to either of study groups, using website http//www.randomizer.org. Total sample size taken for study was 86, which was divided into two groups. Both groups (group L and group D) had 43 patients each.
Inclusion Criteria: The study included the patients of either sex, aged 18-60 years, who had an American Society of Anaesthesiologists (ASA) grading of I or II and who were scheduled for elective laparoscopic surgery.
Exclusion criteria: Patients were excluded if they had history of hepatic disease, renal dysfunction, any cardiac dysrhythmias, atrio-ventricular block and hypertension, had history of hypersensitivity to any of the study medication, where laparoscopy was converted to open procedure, where anticipated duration of surgery was more than 3 hours.
Sample size estimation: Although we were studying several different points in our study, the sample size calculation is based on; mean arterial blood pressure (MAP), which was calculated 10 minutes after creation of pneumoperitoneum**.** We could not find in any study, where exact values of MBP were given, but the study done by Sherif G *et al.* had presented value of mean blood pressure in the graphical presentation. [9]
The graph indicated that SD (Standard Deviation) for both groups was 7 mmHg and to detect difference of 3 mmHg with a power of 80% and significance level of 5%, the minimum sample size calculated using the below mentioned formula was 86.

$$\mathbf{n = \frac{(\sigma_1^2 + \sigma_2^2)[Z_{\alpha/2} + Z_\beta]^2}{\delta^2}}$$

$Z\alpha_{/2}$ = the critical value of the Normal distribution at α/2 (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96),
Z_β = the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2).
σ_1 &σ_2 = the expected sample SD of the two groups.

Study Procedure:
Patients who satisfied the criteria for inclusion were told about the anaesthetic technique and the study design, and informed written consent was obtained. Groups were assigned to patients based

on computer-generated random numbers and group allocation was done by sealed envelopes. Pre anaesthetic evaluation (PAC) was done and patients were fasted as per standard protocols. Routine standard non-invasive monitoring was done with recording of BP (SBP, DBP, MAP) with HR, and S_PO_2 (Saturation of O2) in preoperative area. Injection paracetamol 1 gm, intravenous was given to the patients in the preoperative room before shifting to operation theatre. Later patients were shifted to the operation theatre and standard monitors viz ECG, NIBP, $EtCO_2$, SpO_2 and temperature monitoring had been attached. I.V. access was obtained and crystalloid infusion at rate of 4 mL/kg/hr was started and colloids to were used, when needed. Injection Fentanyl 2 µg/kg was given. Anaesthesia had been induced with Injection propofol 2 mg/kg and muscle relaxation obtained with injection atracurium 0.5 mg/kg and patient intubated with appropriate size endotracheal tube. Patients were mechanically ventilated and adjusted to maintain $EtCO_2$ of 30-35 mmHg. Anaesthesia was maintained with Air:O2::1:1 and sevoflurane adjusted to 1-2 MAC and muscle relaxants were given as needed. ECG, NIBP, SPO2, EtCO2, Temperature was monitored throughout the surgery. For rescue analgesia, we had used Injection diclofenac sodium, 75 mg, IV when VAS was more than 3.

Group L: Immediately before induction of anaesthesia, patients received a bolus of 1.5 mg/kg lidocaine followed by an intravenous infusion of 1.5 mg/kg/h lignocaine hydrochloride through an infusion pump.

GROUP D: Immediately before induction of anaesthesia, patients received a bolus of 0.5 µg/kg followed by intravenous infusion of 0.5µg/kg/hr dexmedetomidine hydrochloride through an infusion pump.

In both groups infusion had been continued throughout the surgery and terminated after release of pneumoperitoneum.

The visual analog scale (VAS) is a psychometric response scale which can be used in questionnaires. For analysis, pain severity was categorized as- Absent (VAS=0), Mild (VAS=1–3), Moderate (VAS=4–7), Severe (VAS=7–9), Very Severe (VAS=10).

Post-operative sedation has been assessed with University of Michigan sedation scale (UMSS) which was devised as a simple scale to facilitate the rapid assessment and documentation of the depth of sedation in all patients who receive a sedative agent for a diagnostic or therapeutic procedure where categories are as follows: 0 awake and alert, 1 Minimally Sedated, 2 Moderately Sedated, 3 Deeply sedated, 4 Unarousable.[10]

Outcome Variables:

1) Hemodynamic parameters (mean values of SBP,DBP, MBP and HR) at baseline, before induction of anaesthesia, 5 min after endotracheal intubation, before pneumoperitoneum, throughout intraoperative procedure at 10 min of interval, after release of pneumoperitoneum and post extubation.
2) Postoperative pain score: Intensity of pain was monitored on arrival in the PACU (post anaesthesia care unit), 1 hour after arrival and before shifting to ward using the VAS score.
3) Postoperative sedation score was monitored on arrival in the PACU, 1 hour after arrival and before shifting to ward using the UMSS score.

Statistical Analysis: The statistical analysis was performed using a standard SPSS software package, version 21.0 (SPSS Inc, Chicago, Illinois, USA). Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. The difference in the values of hemodynamic parameters(SBP, DBP, MAP and HR) from these specified observation points to baseline had been compared between the two groups and tested for statistical significance by paired student t test. Comparison of post- operative pain score (VAS) and post-operative sedation (University of Michigan Sedation Score) in the two groups was done by unpaired student t test. p-value of < 0.05 was considered statistically significant.

Observations:

Significant differences across the two study groups did not exist with respect to patient's baseline characteristics like age, sex, height, weight indicating successful randomization and the homogeneity of groups.

Table 1 shows the comparison of differences in the mean Arterial blood Pressure (MAP) from baseline at different time interval of measurement during study period. It was observed that the mean difference between MAP at the time of intubation from the baseline for Group L was -4.46 ± 14.79 and for Group D was -2.79 ± 13.043 with p-value of 0.57, thus showing no statistically significant difference between two groups; while other time points showed statistically significant differences, displaying better hemodynamic control in Group D.

Table 1- Comparison of changes in MAP between group D and Group L at different time of measurement from baseline

Differences between measurement at different Times to baseline	Mean MAP (in mmHg)		Standard Deviation		p-value
	L	D	L	D	
I-B(difference in MAP at the time of intubation from baseline)	-4.4651	-2.79	14.79438	13.04308	0.579
PN-B(difference in MAP at time of pneumo-peritoneum creation to baseline)	1.600	-13.535	17.76050	16.56639	<0.001*
10-B (difference in MAP 10 minute after pneumo-peritoneum creation to baseline)	8.9302	-10.744	19.75251	16.52429	<0.001*
20-B B (difference in MAP 20 minute after pneumo-peritoneum creation to baseline)	3.0233	-12.419	21.08880	15.85985	<0.001*
30-B B (difference in MAP 30 minute after pneumo-peritoneum creation to baseline)	4.000	-12.512	21.14237	15.51247	<0.001*
PR-B(difference in in MAP at the time of pneumo-peritoneum release to baseline)	4.6279	-11.163	21.64544	15.62649	<0.001*
PE-B(difference in MAP post extubation to baseline)	8.1628	-9.2326	21.88164	16.95911	<0.001*

Figure 1 shows mean value of mean arterial blood pressure at different point of observation in both group L and Group D.

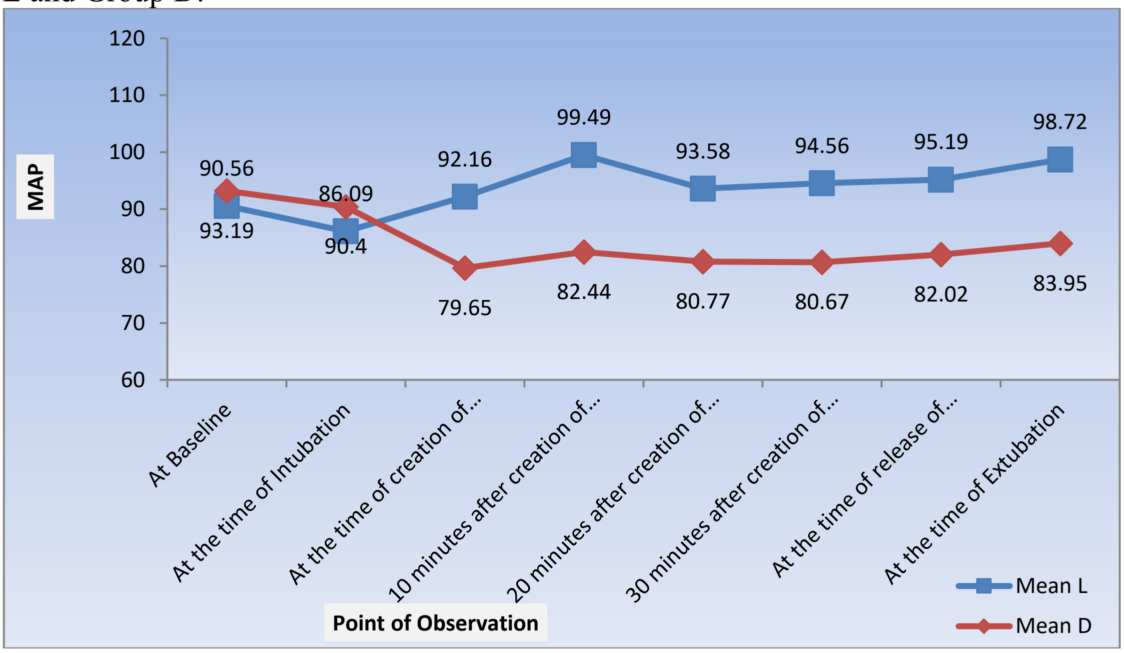

Figure 1- Comparison of MAP between group D and Group L at different times of observations.

Figure 2 shows mean value of heart rate (HR) at different point of observation in both group L and Group D.

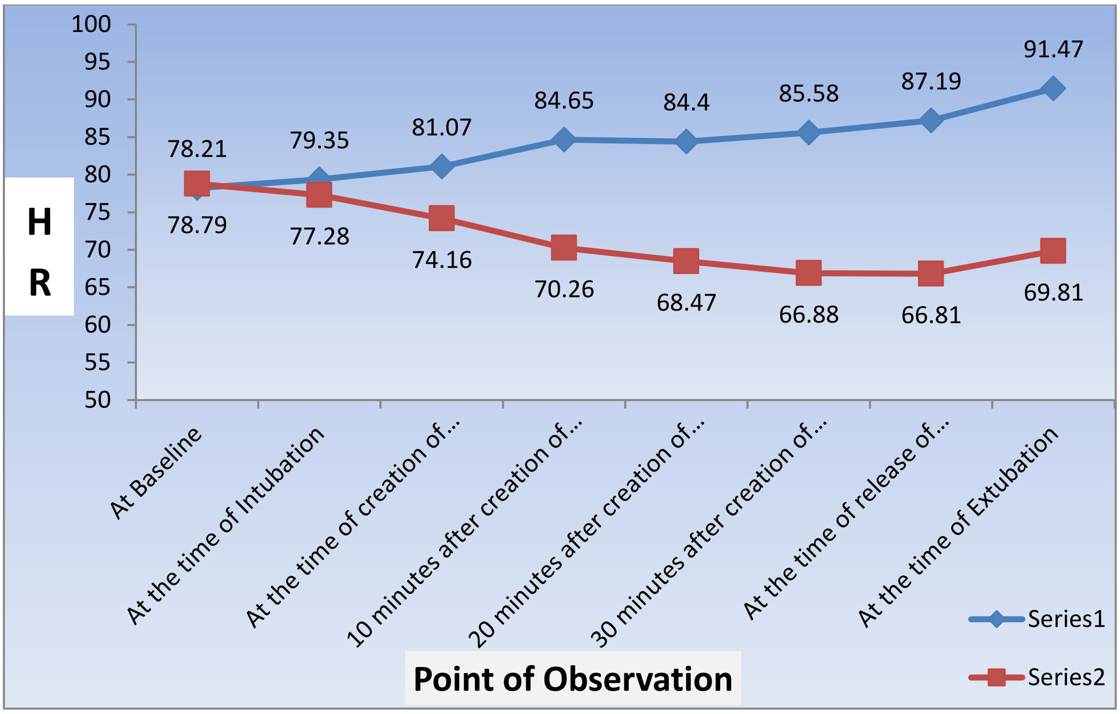

Figure 2- Comparison of HR between group D (Series 2) and Group L (Series 1) at different times of observations.

Table 2 demonstrates Pain score, which was measured on Visual Analogue Scale (VAS), on arrival at PACU had better values in dexmedetomidine with mean value of 0.77 ± 0.75 in comparison to lignocaine, which had mean value of 2.14 ± 0.743 with p-value of <0.01. Later, at the time of discharge from PACU, VAS score was better with Group D with mean value of 0.98 ± 0.152 in comparison to Group L.

Table 2- Comparison of Postoperative Analgesia by VAS (Visual Analogue Scale) between group D and Group L at different time of measurement.

Point of observation	Group	Mean	Std. Deviation	p-value
On arrival at PACU	L	2.14	0.743	<0.01*
	D	0.77	0.751	
After 1 hour of stay in PACU	L	2.00	0.690	<0.01*
	D	0.84	0.433	
At the time of discharge from PACU	L	1.86	0.560	<0.01*
	D	0.98	0.152	

Figure 3 shows the comparison of UMSS, as a measurement of recovery from anaesthesia. It was observed that mean value of UMSS at the time of arrival at PACU (Post Anaesthesia Care Unit) for Group L was 1.86 ± 0.351 and for group D was 1.58 ± 0.626 with p-value of 0.01, which was statistically significant, later after 1 hour of stay in PACU, mean value for UMSS for Group L was 1.07 ± 0.258 and for Group D was 1.21 ± 0.412 with p-value of 0.06 which was statistically not significant. At the time of discharge from PACU, mean value for UMSS for Group L was 1.0 ± 0.00 and for Group D was 1.0 ± 0.00. The P-value cannot be calculated for UMSS at time of discharge as the standard deviations for both groups was zero.

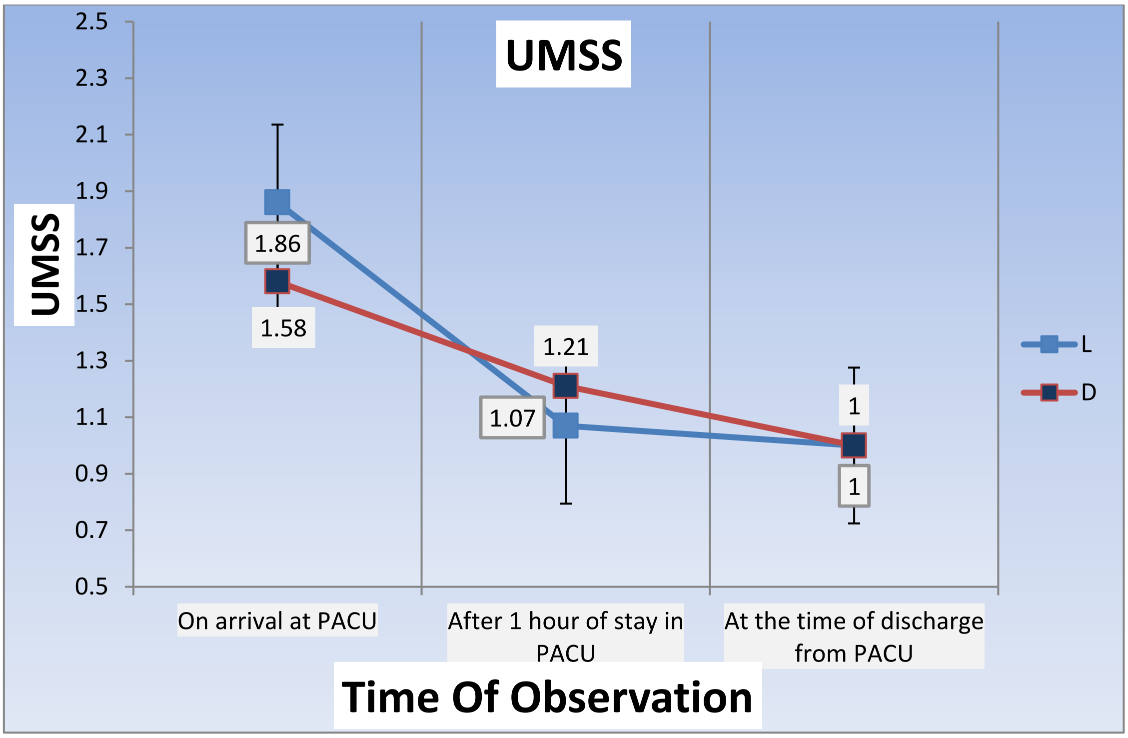

Figure 3- Comparison of UMSS between group D and Group L at different time of measurement

Discussion

This prospective, randomized, double blinded study was conducted on 86 patients at a tertiary care hospital in Eastern India to compare the effects of lignocaine versus dexmedetomidine infusion on hemodynamic parameters, post-operative analgesia and sedation in laparoscopic surgery.

Laparoscopic surgery has been developed to reduce postoperative morbidity, decrease the duration of hospitalization with early patient ambulation and decrease tissue damage, thus accelerating postoperative recovery with reduced analgesic needs [11]. Optimal postoperative pain relief is needed not only for patients's comfort and satisfaction but also to facilitate their early mobilization with enhanced quality of life; with less postoperative cognitive impairment and reduced risk for persistent postoperative pain. This results in better overall outcome and reduced clinical expenses. Also, creation of pneumoperitoneum is associated with significant hemodynamic changes in the form of abrupt elevations of mean blood pressure (MAP) and heart rate (HR), thus increasing the morbidity of the patient [3].

With regards to mean values of the changes in MAP from baseline to different observation point, statistically significant better values have been noted for patients receiving dexmedetomidine in comparison to patients who had received lignocaine at all observation points intra-operatively with p-value less than 0.005, except at I-B, which signified the difference in MAP values at the time of intubation from baseline with p-value of 0.579.

With regards to mean values of the changes in HR from baseline to different observation point, statistically significant better values have been noted for patients receiving dexmedetomidine in comparison to patients who had received lignocaine at all observation points intra-operatively with p-value less than 0.005, except at I-B, which signified the difference in HR values at the time of intubation from baseline with p-value of 0.189. In 2019, Chandrakala KR *et al.* had studied the effect of continuous infusion of dexmedetomidine to attenuate the hemodynamic response during laparoscopic surgery in children that also concluded that continuous infusion of dexmedetomidine as an adjuvant, combined with isoflurane anaesthesia effectively attenuated the hemodynamic responses to noxious stimuli at various stages of the laparoscopic surgeries in children.[12] Similarly in 2018, Krishna Murthy TK *et al.* had evaluated the effect of perioperative intravenous lignocaine

infusion on haemodynamic responses and postoperative analgesia in laparoscopic cholecystectomy surgeries and found that perioperative intravenous infusion of lignocaine attenuated haemodynamic response during the intubation and extubation of the trachea. In addition, it also increased the mean pain free period postoperatively. [13]
VAS had been recorded at three observation points, first on arrival at PACU, after 1 hour of stay at PACU and at the time of discharge from PACU. At time of arrival to PACU, VAS score was better with dexmedetomidine with statistically significant p-value of <0.01. Later, at the time of discharge from PACU, VAS score was still better with dexmedetomidine. Thus showing significantly better analgesia profile with dexmedetomidine in comparison to lignocaine and showing decreased analgesia requirement in patients receiving dexmedetomidine after 1 hour of stay at PACU. It was to be noted that patients who had VAS score of more than or equal to 3 had received supplementary analgesia as Inj. Diclofenac, 75 mg in 100 ml normal saline dilution over 30 minutes. This result was similar to the study by Menshawi *et al.* who in 2019 conducted a study and 90 patients were randomly distributed to one of three equal groups: group L received lignocaine (1.5 mg/kg loading, 2 mg/kg/h infusion), group D received dexmedetomidine (1 μg/kg loading, 0.5 μg/kg/h infusion), and group C received isotonic saline 0.9% in the same volume and pattern as the study drugs and found that dexmedetomidine had a better sparing effect on intraoperative anesthetic consumption and longer time to the first postoperative analgesic demand than that of lignocaine. [14]
Post-operative sedation score was measured by University of Michigan Sedation Scale (UMSS). University of Michigan sedation score, as a measurement of recovery from anaesthesia was measured at three observation point, first on arrival at PACU, after 1 hour of stay at PACU and at the time of discharge from PACU. On arrival at PACU, mean value for University of Michigan sedation score for dexmedetomidine was 1.58 ± 0.626 in comparison to lignocaine which had mean value of 1.86 ± 0.351 with p-value of 0.01, showing delayed recovery in patients receiving dexmedetomidine in comparison to lignocaine, which had shown earlier recovery. 1 hour after stay at PACU, no statistically significant difference in mean values of University of Michigan sedation score was noted; between patients who had received dexmedetomidine and patients who had received lignocaine as p-value was 0.06. In 2016, Sherif GA *et al.* had similar findings regarding the postoperative sedation score. [9] In their study, patients in group D recorded significantly higher median values throughout the study period: after 15 min, 30 min, and 1 h from arrival at the PACU (P=0.003, 0.04, <0.001, respectively).

Limitations: The studies have limitations like the single-center design, and the absence of ASA class III and IV patients, which makes it difficult to apply the investigations to higher-risk populations. These findings need to be validated with additional studies, preferably at the scale of the centers, corroborated by surgery type and comorbidities, and larger studies.

Conclusion

In our study we observe that dexmedetomidine infusion can obtund hemodynamic changes associated with pneumoperitoneum creation, better than lignocaine infusion in laparoscopic surgeries, also providing better post-operative analgesia than lignocaine, but dexmedetomidine shows delayed recovery from anaesthesia at the time of arrival to PACU. Though, recovery from anaesthesia was similar after 1 hour of stay at PACU between both groups.

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