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Effect of Intraoperative Dexmedetomidine Infusion on Postoperative Nausea and Vomiting After Laparoscopic Cholecystectomy under General Anaesthesia

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Abstract: ***Background: Post-operative nausea and vomiting (PONV) is the most frequently encountered complication after laparoscopic cholecystectomy.The evidence regarding the effect of dexmedetomidine in decreasing PONV is insufficient. The aim of this study was to evaluate the effect of dexmedetomidine infusion as an adjuvant to general anaesthesia on PONV after laparoscopic cholecystectomy. Methods: One hundred twenty ASA grade 1&2 adult patients scheduled for elective laparoscopic cholecystectomy were randomly allocated to receive either dexmedetomidine infusion 0.5 mcg/kg/hr(groupA-n=60) or normal saline infusion(groupB-n=60).The incidence and severity of PONV were assessed during first 24 hours postoperatively. The need for postoperative rescue antiemetic was also recorded. Results: The demographic profile of patients were comparable in both groups.VRS score of nausea (1.2±0.9) was significantly less in group A, as compared to group B (6.7±1.7),(3.1±1.2).Moreover the number of episodes of vomiting and retching were significantly reduced in group A as compared to group B ,p value (0.0096),(0.0033) respectively.Twenty one percent of patients in group A and fifty eight percent patients in group B required rescue antiemetic in postoperative period .Conclusion: Dexmedetomidine infusion when used as an adjuvant to general anaesthesia reduces the incidence and severity of PONV during first 24 hours after laparoscopic cholecystectomy***

Keywords: Dexmedetomidine, Postoperative Nausea and Vomiting, Laparoscopic Cholecystectomy

1. Introduction

Laparoscopic surgery has become a gold standard for the treatment of gall bladder diseases.The increasing success of this procedure can be attributed to the multiple benefits compared with open procedures[1][2]. Post-operative nausea and vomiting (PONV) is the most frequently encountered complication of laparoscopic cholecystectomy. The incidence of PONV after laparoscopic cholecystectomy has been reported upto 25-70%.[3]

PONV is an unpleasant, distressing and exhausting experience for the patient and can lead to sweating, tachycardia, abdominal pain, prolonged recovery duration, increased risk of aspiration, expanded nursing care and potential hospital admission. The etiology of PONV after laparoscopic cholecystectomy is still not very clear but it appears to be a multifactorial phenomenon.[4]

Dexmedetomidineis a potent highly – selective α_2 - adrenergic agonist, and is being used widely in clinical practice due to it's hypnotic, sedative, anxiolytic, sympatholytic, and analgesic properties. Its sympatholytic effect decreases mean arterial blood pressure and heart rate by reducing norepinephrine release[5][6]. In addition when used as an adjuvant to general anaesthesia it has the ability to reduce both analgesic and anaesthetic requirement during perioperative period[7][8][9]

The dexmedetomidine when used as an adjuvant to general anaesthesia has shown a significant reduction in the requirement of opioids and inhalational anaesthetics ,reduced postoperative pain and a better recovery profile without producing any adverse haemodynamic effects[10].Gurbet A et al demonstrated that continuous infusion of dexmedetomidine during abdominal surgeries significantly reduced PONV as well as perioperative analgesic requirement[9].Therefore we aimed to study the effect of intraoperative dexmedetomidine infusion as an adjuvant to general anaesthesia on postoperative nausea and vomiting in first 24 hours after laparoscopic cholecystectomy.

2. Literature Survey

PONV is the most frequently encountered complication in laparoscopic cholecystectomy .Dexmedetomdine a highly - selective and potent α_2 - adrenergic agonist since its approval by FDA in 1999 has attracted many researchers for its usage because of its multiple effects on physiology . Gurbet A et al[9] studied the effect of Intraoperative infusion of Dexmedetomidine during abdominal surgeries on postoperative analgesia , Tufanogullari B et al[11] compared the effect of different doses of Dexmedetomidine infusion

during laparoscopic bariatric surgery on the severity of pain, analgesic requirements, patient satisfaction, quality of recovery, resumption of dietary intake and recovery of bowel function . IslamM. Massad et al[12] studied the effect of adding Dexmedetomidine to balanced anaesthesia on postoperative nausea and vomiting after laparoscopic gynecological surgery while H. Okawa et al[13] studied it's effect on PONV in patients undergoing coronary artery bypass surgery . Here we aimed to study the effect of intraoperative dexmedetomidine infusion as an adjuvant to general anaesthesia on postoperative nausea and vomiting in first 24 hours after laparoscopic cholecystectomy.

3. Materials and Methods

This randomized controlled double blind study was conducted after approval by Institutional ethical committee and Research Review Board. Sample size was calculated 56 subjects for each of the group at α (alpha) error 0.05 and power 80% assuming proportion of nausea, vomiting in placebo, dexmedetomidine group 59% and 31% respectively. Informed written consent was obtained from each patient. One hundred twenty,American society of anesthesiologists (ASA) physical status 1 and 2 patients scheduled for elective laparoscopic cholecystectomy under general anesthesia between December 2015 and March 2016 were enrolled in the study. Patients were randomly allocated to receive either dexmedetomidine infusion 0.5 mcg/kg/hr(groupA,n=60) or normal saline infusion at the same rate(group B,n=60). Randomization was done by computer generated numbers. Patients with history of PONV or motion sickness, smoking, major systemic disease, who received antiemetic or cortisone within 48 hrs before surgery were excluded from the study. Pregnant or breast feeding females, patients with mental, or psychiatric illness were also excluded from the study.

Anaesthetic technique was standardised for all patients. Patients were premedicated with glycopyrrolate(0.2 mg) i.v. and midazolam(1mg) i.v. Standard monitoring included electrocardiogram, arterial oxygen saturation (SpO2) measured by pulse oximeter, non invasive blood pressure(NIBP), end tidal CO2(etCO2) and bispectral index(BIS). Test drug infusion was prepared by adding 200µg/2mL dexmedetomidine ampoule in 48mL 0.9 % of Normal saline (NS) infused at the rate of 0.5 mcg/kg/min in group A and saline in group B with the same rate. No antiemetic was given to any patient. Injection fentanyl 1.5 µg/kg was also given.

Induction was done 5 minutes after start of test drug infusion with Inj. Propofol 2 mg/kg, followed by Inj. Atracurium 0.5 mg/kg. Patients were ventilated with face mask with 100% oxygen and intubation was done with endotracheal tube of appropriate size after direct laryngoscopy.

Maintenance was done with Isoflurane titrated to maintain BIS value 40-60 throughout the surgery and ventilation was done with 50% O_2 + 50% N_2O. Muscle relaxation was provided by subsequent doses of inj. Atracurium 0.1 mg/kg s.o.s. Intraoperative Monitoring heart rate (H.R.), non-invasive blood pressure (N.I.B.P.), peripheral oxygen saturation (SpO_2), capnography (E_tCO_2),end tidal isoflurane (Et iso) and bispectral index (BIS) were monitored continuously. Data of H.R., systolic blood pressure (S.B.P.) ,diastolic blood pressure (D.B.P.), mean arterial pressure (M.A.P.),SpO_2, $EtCO_2$, and BIS were collected at every 5 min. for initial 15 min. and every 15 mins., thereafter till the extubation of the patient. Endtidal isoflurane was also recorded at 10 min,15 min. and at 30 min.

M.A.P. was maintained within ±25% of baseline value. Hypotension (defined as MAP value <25% of baseline value on two consecutive recordings within 2-3 minutes) not responding to a decrease in the inspired Isoflurane concentration and a 200 ml fluid bolus, was treated with inj.Ephedrine 3 mg i.v.The test drug infusion was discontinued if hypotension persists > 2 min after these interventions.

Hypertension (defined as M.A.P. value > 25% of baseline value on two consecutive readings within 2-3 min.) despite an increase in inspired isoflurane concentration. Any patient not responding to above measure was given hypotensive agents accordingly to maintain M.A.P. within ± 25% of baseline value. Bradycardia (H.R. <45/min.) was managed by inj.Atropine. Any patient developing intraoperative hypotension/hypertension or bradycardia requiring drugs other than our standard anaesthesia protocol (as described above) was excluded from the study.

Reversal was done with i.v. Inj. Neostigmine (0.05 mg/kg) and Inj. Glycopyrrolate (0.01 mg/kg) only after onset of spontaneous respiration. Extubation was done when fully satisfied with patient recovery (BIS >80, ability to open the eyes, ability to obey anaesthesiologist's verbal commands and ability to maintain a regular breathing pattern).

Ringer Lactate was infused to all patients intraoperatively @ of 15ml/kg/hr. Inj. Diclofenac 75 mg i.v. was given to all patients intraoperatively. Duration of anaesthesia was calculated from the start of test drug infusion to the extubation of patient.

Inj.Diclofenac 75 m.g. i.m. 8 hourly was given for postoperative analgesia, pain scale above 3 according to the VRS was treated initially with 1 g.m. I.V. Paracetamol, if VRS persisted above 3 after 30 min, a bolus of 50 m.g. inj. Tramadol i.v.was administered and the patient was excluded from the study. In post-operative period patients were assessed for nausea and vomiting at 0,4,8, 12& 24 hrs(Zero hour is considered from 10 minutes after extubation). The pain intensity was assessed at 0,4,8,12, and 24 hrs, using 11 point VRS scale[11]. Nausea and vomiting were assessed by direct questioning of patient at 0,4,8,12,24 hrs after recovery from anaesthesia. In post-operative period blood pressure, heart rate, respiratory rate, VRS were recorded at 0,4,8,12,24 hrs.

Nausea was assessed according to a verbal rating scale (VRS – 0 represents - no Nausea, 10 worst nausea) and retching and vomiting was assessed by simply questioning for yes or no, no retching or vomiting was scored 0 and yes was scored 1.

Nausea was defined as a subjective, unpleasant sensation associated with awareness of the urge to vomit. Retching was

defined as laboured, spasmodic, rhythmic contractions of the respiratory muscles without expulsion of gastric contents.Vomiting was defined as forceful expulsion of gastric contents from the mouth.

Inj. Ondansetron 4 mg was permitted as a rescue antiemetic when episode of retching or vomiting was there or a Nausea VRS> 6 and if the patient requests treatment. No use of rescue medication was scored 0 and if used was scored as 1. The primary outcome measure of this study was the occurrence of nausea & vomiting during the first 24 hrs postoperatively. Need for rescue antiemetic,VRS score for pain in first 24 hours and adverse effect if any were also recorded.

For Statistical Analysis all the data were entered on Excel sheet and analyzed statistically using Primer software and XL- Stat. All the quantitative data were summarized in the form of Mean ± SD. The difference between mean value of both groups was analyzed using Student t test. All the qualitative data were summarized in the form of number and percentage. The differences between proportions were analyzed using Chi square test. The levels of significance and α - error were kept 95% and 5% respectively, for all statistical analyses. P value<0.05 was considered as Significant (S) and > 0.05 as Non Significant (NS).

4. Results

All one hundred twenty patients completed the study and data were analysed. There were no statistically significant differences regarding age, weight, gender distribution, ASA grading and duration of surgery between the two study groups (table 1)

Table 1: Demographic Variables

	Group A (dexmedetomidine)	Group B (saline)	P value
Age (yrs)	37.5 ± 12.3	40.1 ± 9.6	0.1889
Weight (kgs)	55.6 ± 8.8	57.8 ± 7.9	0.1538
Duration of surgery (min)	47.4 ± 5.8	47.1 ± 6.1	0.8060
ASA 1 : ASA 2	51 : 9	49 : 11	0.6242
Female : Male	44 : 16	49 : 11	0.2744

The overall VRS score of nausea shown in table 2 depicts that the score in group A is significantly less as compared to group B in first eight hours postoperatively (p=<0.05). Though the severity of nausea was less in group A(dexem) than group B(saline) between 8-24 hours but it did not reach statistical significance(p=> 0.05).

Table 2: Comparison of VRS Score For Nausea In Both Groups

	Group A		Group B		P value
	Mean	SD	Mean	SD	
0-4 hrs	1.2	0.9	6.7	1.7	0.0000
4-8 hrs	3.1	1.8	4.1	1.4	0.0005
8-12 hrs	3.2	1.7	3.7	1.2	0.0678
12-24 hrs	3.1	0.9	3.3	0.6	0.0530

The incidence of retching was 6.7% (4 patients) in dexmedetomidine group compared to 26.7%(16 patients) in the saline group(p value-0.003)table no 3 The number of patients who suffered from vomiting were 8(13.3%) and 20 (33.3%) in group A and B respectively (p value-0.009).Total number of patients who required antiemetic were 13(21.7%) in group A and 35(58.3%) in group B and the difference was statistically significant(p value 0.000).(Table no 3)

Table 3: Comparison of Patients Suffered from Episodes of Vomiting and Vomiting and Requirement of Antiemetic in Postoperative Period

Parameters	Group A		Group B		P Value
	0	1	0	1	
Retching	56	4	44	16	0.0033
Vomiting	52	8	40	20	0.0096
Requirement of antiemetic	47	13	25	35	0.0000

It was also observed that end tidal isoflurane concentration was significantly less in dexmedetomidine group (p value-0.000). (Table no 4)

Table 4: Comparison of End Tidal Isoflurane Concentration in Both Groups

	Group A		Group B		P-Value
	Mean	SD	Mean	SD	
Intraop10 Min	0.5	0.1	0.8	0.1	0.0000
Intra op 15 Min	0.4	0.1	0.8	0.1	0.0000
Intraop30	0.4	0.1	0.8	0.1	0.0000

Postoperative pain was assessed by VRS score and the severity of pain was significantly less in dexmedetomidine during first 4 hours postoperatively, in rest of the period the difference was statistically insignificant.(Table no. 5)

Table 5: Comparison of VRS Score For Pain In Both Groups

	Group A		Group B		P-Value
	Mean	SD	Mean	SD	
0 hrs	0.9	0.8	3.1	1.2	0.0000
4 hrs	1.4	1.2	2.0	0.7	0.0009
8 hrs	1.4	1.0	1.7	0.6	0.0871
12 hrs	1.0	0.8	1.3	0.6	0.0535
24 hrs	0.9	0.5	1.1	0.6	0.1063

None of the patient had any complication such as hypotension or bradycardia.

5. Discussion

Postoperative nausea and vomiting (PONV) is the common complication following laparoscopic surgeries. Incidence of PONV after laparoscopic cholecystectomy has been reported upto 25-70 %[3]. In addition to patient dissatisfaction, PONV may have other adverse consequences such as delayed recovery, unexpected extended hospital stay and delayed return to work.

PONV after laparoscopic cholecystectomy is considered to be a multifactorial phenomenon. The factors which may contribute to PONV after laparoscopic cholecystectomy are the peritoneal distention, increased intraabdominal pressure, diaphragmatic stimulation and intra-abdominal manipulation.[4]

Earlier studies by Gubert et al during abdominal surgeries[9], Mohamed H. Bakri et al in laparoscopy choecystectomy[10], Tufanogullari et al in bariatric surgery[12], Islam M et al in laparoscopic gynaecological surgery[13], H.okawa et al in coronary artery bypass surgeries[14] demonstrated that the continuous infusion of dexmedetomidine reduces incidences of PONV. Our study was aimed to compare the effect of intraoperative dexmedetomidine infusion with matched control in patients undergoing laparoscopic cholecystectomy in terms of occurrence of post operative nausea and vomiting in first 24 hours postoperatively and need for rescue antiemetic in first 24 hours postoperatively.

The present study showed that dexmedetomidine infusion when given as an adjuvant to general anaesthesia reduces the incidence and severity of PONV. Our results are consistent with Mohmed H Bakri et al[10] and Islam A et al[13].They attributed this effect to overall reduction in the requirement of opioids and inhalational anaesthetic agent. Goksu et al used dexmedetomidine as a sedative during functional endoscopic sinus surgery performed under local anaesthesia and found a significantly less incidence of PONV in dexmedetomidine group.[14]

Jalonen J et al[15]demonstrated the propensity of dexmedetomidine to produce hypotension and bradycardia when it is administered to volunteers or patients, it was important to determine an infusion rate that would maximize the anesthetic and analgesic sparing effect while minimizing the occurrence of adverse cardiovascular side effects requiring therapeutic interventions. In several reports dexmedetomidine infusion rate ranging from 0.4 to 10 mcg/kg/hr have been used, in some other reports high dose (>1 mcg/kg/hr) of dexmedetomidine was administered as the primary drug in a total i.v.anaesthetic technique. In study done by Tufanogullari et al[12] dexmedetomidine was used as an adjuvant to volatile anaesthetic desflurane, they evaluated dexmedetomidine infusion rate of 0.2, 0.4, and 0.8 mcg/kg/hr their results suggested that the selected infusion rate of dexmedetomidine(0.2-0.8 mcg/kg/hr) were in the appropriate therapeutic range when it is used as part of a balanced anaesthetic technique. Moreover they did a pilot study with a loading bolus dose of dexmedetomidine (0.5 mcg/kg i.v.) that resulted in a higher incidences of hypotension immediately after tracheal intubation, this was the reason we used the lower doses.

Assessment of intraoperative Et isoflurane in both groups at 10 min, 15 min, 30 min showed that the mean of Et isoflurane was more in group B(0.8,0.8,0.8) as compared to group A(0.5,0.4,0.4) respectively. These results are supported by the study done by Martina Aho et al[8] who studied the effect of intravenously administered dexmedetomidine on perioperative isoflurane requirements in patients undergoing abdominal hysterectomy and concluded that there was diminished requirement of isoflurane along with dexmedetomdine as compared to saline group. Our results are also supported by one more study done by Tufanogullari et al[12] in laparoscopic bariatric surgery using dexmedetomidine infusion .They found that End tidal concentrations of desflurane during the operation were significantly lower in (dex) group as compared to control group.

Apfel et al[16] showed that the volatile anaesthetics (Isoflurane, Enflurane, Sevoflurane) are the leading cause of early postoperative vomiting so reduced concentration of emetogenic isoflurane might result in reduced incidences of PONV. Islam M et al[13] also recorded the significant drop in the requirement of each component of the balanced anaesthetic mixture when used with dexmedetomidine infusion. The findings in present study demonstrated that the isoflurane end tidal concentration was reduced in group who received dexmedetomidine this is in accordance of the study done by Yildiz et al[17] who found that preoperative administration of dexmedetomidine reduced the requirements of sevoflurane and fentanyl both of which are emetogenic.This could be the possible explanation for the reduced incidence of PONV in our study.

Dexmedetomdine binds to alpha-2 presynaptic inhibitory adrenereceptors present in locus coeruleus, a major nor adrenergic cell group located in the pontine brain stem and decreases noradrenergic activity which may contribute to it's antiemetic effect[18]. Antiemetic effect of dexmedetomidine may also be related to the decrease in overall sympathetic outflow and release of catecholamines.[19]

In postoperative period VRS score for pain was of mild degree in both groups but there was statistically significant difference in VRS score of two groups only during first four postoperative hours, in rest period there was insignificant difference, our results are similar to earlier studies done by Mohamed H.Bakri et al.[10]Gurbt et al[11] found that the intraoperative infusion of dexmedetomidine significantly reduced the PONV as well as the perioperative analgesic requirements in patients undergoing total abdominal hysterectomy surgery. No explanation of this finding were discussed. The possible explanation for reduced pain in early postoperative period could be explained by the activation of alpha 2 receptor by dexmedetomidine in the dorsal horn of spinal cord and thus inhibiting the release of substance P which modulates the nociceptive signal transmission in the central nervous system resulting in decreased nociceptive inputs during acute postoperative pain.[10]

None of the patients from both of the groups had any adverse effects (hypotension, bradycardia, respiratory depression, sedation), this is in accordance to the study done by Riker RR et al[20]who demonstrated that the incidence of hypotension and bradycardia are related to administration of the loading dose, omitting the loading dose or giving upto 0.4 µg/kg reduces the incidences of hypotension.

The limitation of our study was that we could not study the opioid sparing effect of dexmedetomidine as mean duration of surgery in our study was 47.4 min. in group A, 47.1 min in group B and we did not use any additional doses of fentanyl intraoperatively. In this study we did not follow the patients beyond 24 hours so we could not study the effect of dexmedetomidine on quality of late recovery period and duration of hospital stay.

6. Conclusion

The use of dexmedetomidine infusion as a part of balanced anaesthesia technique reduces the incidence and severity of post-operative nausea, vomiting and requirement of antiemetics in postoperative period after laparoscopic cholecystectomy under general anaesthesia.

7. Future Scope

Our study established the fact that dexmedetomidine when used as a part of balanced anaesthesia reduces incidence of PONV and can be considered as an agent of choice during surgeries associated with high risk of PONV but further studies of longer duration follow up (more than 24 hours) are required.

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