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Original Research Article

The Effect of Intraoperative Dexmedetomidine Infusion on Analgesia in Laparoscopic Cholecystectomy

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Abstract

Background and Aims: Laparoscopic cholecystectomy requires creation of pneumoperitoneum following direct laryngoscopy and tracheal intubation, all of which may lead to several deleterious haemodynamic alterations. Dexmedetomidine has been found to blunt these haemodynamic responses effectively along with providing sedation without respiratory depression and also decrease postoperative analgesic requirements.

Objectives: The current study was thus planned with an aim to evaluate the overall efficacy of intra-operative dexmedetomidine infusion during laparoscopic cholecystectomy.

Materials and Methods: 80 patients posted for laparoscopic cholecystectomy were divided in two equal groups. After giving general anaesthesia, patients in Group D received Dexmedetomidine infusion at a rate of 1µ/kg bolus followed by a continuous infusion set at 0.5µ/kg/hr whereas those in group C received Normal Saline in the same dose. Haemodynamic profiles were recorded every 15 minutes, total intraoperative analgesic consumption was calculated at the end of surgery. Any adverse effects, Pain and sedation scores were assessed postoperatively.

Results: Heart rate and Mean arterial pressures were better maintained, with significantly lower values from 15 and 30 minutes respectively in Group D. The total analgesic consumption was significantly low in Group D (142.50 ± 38.48 µg in Group D versus 240 ± 30.38 µg in Group C). The mean pain and sedation scores as also incidences of adverse events were also significantly less in Group D subjects than in patients of Group C.

Conclusion: Dexmedetomidine infusion serves as an efficacious analgesic adjuvant for laparoscopic cholecystectomy.

Keywords: Dexmedetomidine, Laparoscopic cholecystectomy, Normal Saline

Introduction

Laparoscopic cholecystectomy is presently, the recommended operation for the management of symptomatic cholelithiasis [1], owing to its superior outcome to the conventional open procedure in terms of recovery time, post -operative pain, hospital stay [2]. However, the pneumoperitoneum and carbon dioxide insufflations, required in laparoscopic surgeries lead to increase in plasma catecholamine levels and plasma renin activity [3], which ultimately results in increase in heart rate, blood pressure, systemic and pulmonary vascular resistance, and reduced cardiac output. In addition, anaesthetic manoeuvres like direct laryngoscopy, tracheal intubation and extubation involve severe sympathetic stimulation. All these haemodynamic changes predispose the myocardium to ischemia that may be life threatening in a vulnerable patient. Modern anaesthesia practices, therefore, plan to prevent sympathetic discharge and provide haemodynamic stability perioperatively.

Opioids have traditionally been the first choice regarding perioperative analgesia. However, their use has been associated with several post-operative complications like sedation, nausea, vomiting, respiratory depression and paralytic ileus [4], which ultimately, can delay recovery, resulting in unanticipated hospital stay. Intraoperative opioids could even induce hyperalgesia, which increases the pain intensity and ultimately, opioid consumption. It is therefore required to minimize these side effects by restricting the use of opioid and by using multimodal analgesic approach or adjuvant therapies.

In last few years, a great enthusiasm has been shown toward the use of α2 agonists in anaesthesia practice because of their anxiolytic, sedative, sympatholytic and analgesic sparing properties [5]. Dexmedetomidine, introduced in 1999 for human use, is a selective α2 agonist with 8 times more affinity for α2 adrenergic receptors compared to clonidine and possesses all the properties of α2 agonist without respiratory depression [6]. Intravenous use of dexmedetomidine in the perioperative period had been found to decrease serum catecholamine levels by 90% [7] to blunt the haemodynamic response to laryngoscopy, tracheal intubation, pneumoperitoneum and extubation [8], to provide sedation without respiratory depression [9] and to decrease postoperative analgesic requirements. It has also been found to be effective for preventing opioid induced hyperalgesia [10].

It's use in patients undergoing Laparoscopic Cholecystectomy has also shown to reduce anaesthetic requirements, inflammatory response, shivering, perioperative opioid requirement [11] and provide better haemodynamic response to pneumoperitoneum [12-15].

There has, however, been scarcity of data or knowledge regarding the effect of intravenous Dexmedetomidine in laparoscopic cholecystectomy in this part of the world. In the current context, the present study was planned to determine the efficacy of intravenous Dexmedetomidine for providing perioperative analgesia during laparoscopic cholecystectomy.

Materials and Methods

The present comparative, analytical study was conducted over a period of one and half year at a tertiary medical college after getting approval from the Institutional Ethics Committee (IEC). 80 patients, aged 18-60 years of either sex with ASA physical status I & II, scheduled for laparoscopic cholecystectomy were included in this study. Patients with allergy to dexmedetomidine, having uncontrolled endocrine, metabolic, hepatic, cardiac or neuro-muscular diseases, history of seizures, chronic use of steroids or analgesics were excluded from the present study. Pregnant women or those requiring emergency cholecystectomy were not

included as well. After taking written informed consent from the patients included, they were randomly divided into two equal groups, Group D and Group C having 40 patients each.

A thorough pre-anaesthetic evaluation of all the patients were done a day prior to surgery and all the necessary investigations were carried out including specific investigations if required. On arrival to the operation theatre after overnight fasting, each patient was attached to multichannel monitor to display heart rate, SpO_2, NIBP and continuous ECG tracings. Intravenous line was secured with an 18G cannula and an infusion of Lactated Ringer's solution was started. Each patient was pre medicated with Inj. Glycopyrrolate (0.02 mg/kg) and Inj. Fentanyl (2µ/kg) and anaesthesia was induced with Propofol (2mg/kg) and Atracurium (0.5mg/kg). After achieving endotracheal intubation with an adequately sized tube, the selected patients were randomly assigned into two groups as mentioned earlier. Group D patients received Dexmedetomidine infusion at a rate of 1µ/kg bolus followed by a continuous infusion set at 0.5µ/kg/hr through an infusion set and was continued till skin closure. Group C, on the other hand was the control group, which received Normal Saline (0.9% NS) infusion at the same fashion as Dexmedetomidine in the previous group. Additional Fentanyl was given when heart rate and Mean Arterial Pressure (MAP) increased more than 20% of preoperative baseline values. Haemodynamic profiles were recorded every 15 minutes till the end of surgery. Total intraoperative analgesic (Fentanyl) consumption was calculated at the end of surgery. Any adverse effects such as sedation, pain, nausea, vomiting, or respiratory distress were recorded at 0, 2, 4, 6 post-operative hours. Pain and sedation assessment was carried out using Visual Analog Scale (VAS) and Ramsay Sedation Scale respectively at the same intervals as was the adverse events noted.

For statistical analysis, collected data were entered into MS Excel and analysed using the SPSS version 20. Descriptive analysis was done in the form of proportion for categorical variables, mean or median for continuous variables. Data were checked for normal distribution using tests for normality and non-parametric test was performed accordingly. The difference between proportions was analysed using Chi square test; p value of less than 0.05 was considered statistically significant.

Results

The present study was done on 80 patients divided into two equal groups, Group D in which patients received Dexmedetomidine infusion, while Group C (control group) received normal saline infusion.

As evident from Table 1, the two groups were comparable demographically.

Table 1: Demographic profile of the two groups

		Group D (n = 40)	Group C (n = 40)	p value
Age (in years)	19 - 34	12	20	0.187
	35 - 50	19	14	
	> 50	09	06	
Sex	Male	08	09	0.785
	Female	32	31	
ASA	I	27	24	0.485
	II	13	16	

Table 2 shows the distribution of baseline and intraoperative heart rate (mean ± SD) among the study subjects. The table shows that heart rate was better maintained among the group D subjects

and the mean intraoperative heart rate was comparatively lower among group D than that group C. This difference of heart rate was statistically significant from 15 minutes onward.

Table 2: Distribution of heart rate among the study subjects

Time	Group D (Mean ± SD)	Group C (Mean ± SD)	p value
Baseline	87.45 ± 13.81	89.50 ± 11.17	0.349
15 minutes	85.83 ± 17.09	97.95 ± 19.90	0.006
30 minutes	88.85 ± 18.31	109.40 ± 17.27	<0.001
45 minutes	80.78 ± 12.98	100.20 ± 15.77	<0.001
60 minutes	77.43 ± 12	104.53 ± 15.57	<0.001

Table 3 shows the distribution of baseline and intraoperative MAP (mean ± SD) among the study subjects. The mean intraoperative arterial pressure was also better preserved among group D than group C, and the association was statistically significant at 45 and 60 minutes.

Table 3: Distribution of Mean Arterial Pressure (MAP) among the study subjects

Time	Group D (Mean ± SD)	Group C (Mean ± SD)	p value
Baseline	94.48 ± 5.71	95.28 ± 7.78	0.692
15 minutes	101.33 ± 7.97	102.38 ± 8.02	0.446
30 minutes	102.83 ± 10.80	107.20 ± 8.57	0.165
45 minutes	97.05 ± 6.42	107.10 ± 10.14	<0.001
60 minutes	95.55 ± 4.80	101.70 ± 7.87	<0.001

Figure 1 shows that the amount of total analgesic consumed [mean (SD) and median (Inter quartile range)] among Group C was 240 (30.38) and 250 (200, 250) whereas that among group D was 142.50 (38.48) and 150 (100, 150) respectively. The difference of total intraoperative analgesic (Fentanyl) consumed was lesser in Group D than in Group C, which was also statistically significant.

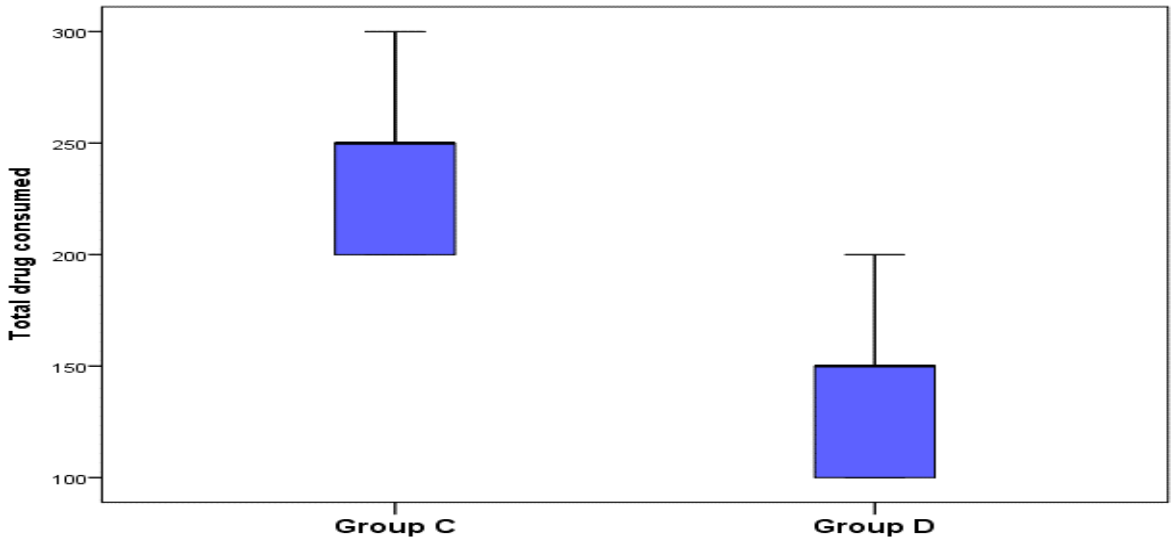

Figure 1: Box whisker plot showing the distribution of total intraoperative analgesic (Fentanyl in µg) consumption among the study subjects

The mean pain score and mean sedation score was less in Group D subjects than in patients of Group C, which was also statistically significant, as evident from Table 4.

Table 4: Distribution of study subjects according to pain score (VAS) and sedation score (RAMSEY SEDATION SCALE)

		Group D (Mean ± SD)	Group C (Mean ± SD)	p value
Pain score (VAS)	0 hrs	1.23 ± 0.57	2.75 ± 0.67	<0.001
	2 hrs	0.30 ± 0.60	1.50 ± 0.84	<0.001
	4 hrs	0.08 ± 0.26	0.43 ± 0.74	0.005
	6 hrs	--	0.05 ± 0.22	0.155
Sedation Score (RAMSEY SEDATION SCALE)	0 hrs	2.55 ± 0.50	2.95 ± 0.22	<0.001
	2 hrs	--	2.23 ± 0.42	0.002
	4 hrs	--	--	--
	6 hrs	--	--	--

Table 5 shows that the incidences of adverse effects were significantly less among the subject of Group D than that of Group C, which were statistically significant.

Table 5: Distribution of study subjects according to adverse effects

Adverse Effects		Group D (n = 40)		Group C (n = 40)		p value
		Absent	Present	Absent	Present	
Nausea	0 hrs	40	-	07	33	<0.001
	2 hrs	40	-	35	05	0.021
	4 hrs	40	-	38	02	0.152
	6 hrs	-	-	-	-	-
Vomiting	0 hrs	40	-	34	06	0.011
	2 hrs	40	-	37	03	0.077
	4 hrs	40	-	37	03	0.077
	6 hrs	40	-	37	03	0.077
Respiratory depression	0 hrs	40	-	34	06	0.011
	2 hrs	40	-	37	03	0.077
	4 hrs	-	-	-	-	-
	6 hrs	-	-	-	-	-
Pain	0 hrs	34	06	03	37	<0.001
	2 hrs	37	03	24	16	0.001
	4 hrs	40	-	38	02	0.152
	6 hrs	-	-	-	-	-
Sedation	0 hrs	17	23	02	38	<0.001
	2 hrs	40	-	28	12	<0.001
	4 hrs	-	-	-	-	-
	6 hrs	-	-	-	-	-

Discussion

Laparoscopic cholecystectomy has presently become the procedure of choice for variable range of gall bladder problems, owing to its better postoperative outcomes. Although pain after laparoscopic cholecystectomy is less intense than that after open cholecystectomy,

some patients still experience considerable discomfort, specially during the first 24 hours postoperatively. Pain after laparoscopy is multifactorial and different treatments have been proposed to provide adequate pain relief [16-18]. Among them, opioids has been traditionally used as the preferred agent for analgesia, however, owing to their significant side effect profile, focus has now been diverted towards non-opioid based multimodal analgesia.

Dexmedetomidine, a highly selective α2 adrenergic receptor agonist has been found to decrease serum catecholamine levels by 90%7, thereby blunting the haemodynamic response to both pneumoperitoneum as also laryngoscopy and tracheal intubation, thus resulting in decreased postoperative analgesic requirements.

The present study was formulated with a view to determine the efficacy of intravenous Dexmedetomidine to decrease intraoperative pain intensity during laparoscopic cholecystectomy and to also determine the safety of intravenous Dexmedetomidine at the dose used. 80 patients with comparable demography, posted for laparoscopic cholecystectomy, divided into two equal groups, Group D and Group C received Dexmedetomidine and Normal Saline infusions respectively. The findings show that patients in Dexmedetomidine group maintained a haemodynamic profile which was significantly superior to those in Group C. Heart Rate was significantly well maintained from 15 minutes onwards and Mean Arterial Pressure was also more stable and significantly low from 30 minutes onwards in Group D (Table 2 & 3). The total fentanyl consumed was significantly less in Group D (Figure 1), although both pain score and sedation score were also less in the same group (Table 4).

Study of Volkov *et al.* reported that dexmedetomidine led to a decreased requirement for opioid analgesics, inhaled anesthetics, and the incidence of severe circulation problems during traumatic phases of surgeries [19].

Premedication with a single intravenous dose of 0.5 μg/kg dexmedetomidine was found to decrease the intraoperative propofol and postoperative analgesic requirements, and increase the postoperative satisfaction and sedation level considerably in patients undergoing laryngoscopic biopsy under total intravenous anaesthesia in the study by Mizrak A *et al* [20].

Another randomized, double-blind, multicenter study conducted by Candiotti KA *et al*. reported that dexmedetomidine is an effective anaesthetic adjuvant for patients undergoing local anaesthesia for a broad range of surgical procedures, providing better patient satisfaction, lower opioid requirements, and less respiratory depression than placebo [21].

In another study done by Bielka *et al*. they had similar results, in patients undergoing elective Laparoscopic Cholecystectomy. Dexmedetomidine infusion in their study, was associated with a marked decrease in postoperative morphine consumption, lower incidence of severe postoperative pain, and significantly longer time to first use of rescue analgesia. However, the median pain intensity measured with a VRS did not differ between the groups 3, 6, 12 or 24 h after surgery [22].

Other studies also showed synergic action of intraoperative dexmedetomidine with local anaesthetics on postoperative acute pain after craniotomy [23], morphine-sparing effect and significantly lower pain intensity after hysterectomy [24]. Meta-analysis also showed that opioid-PCA strategies decrease postoperative pain intensity and opioid consumption [25].

All of these findings are similar with the statistically significant finding of the present study which also reveals that the pain score was less among the group D subjects

receiving dexmedetomidine than group C (Table 4).

Regarding adverse events, in the study done by Bielka *et al*. there was no inter-group difference in the incidence of postoperative sedation (p = 0.7) [22]. Some studies showed a higher incidence of sedation in the dexmedetomidine group, with a mean difference on the Ramsay Sedation Scale of 1.60 units (95% CI 1.49–1.71 units) [26,27]. These findings are, however contrary to the finding of the present study (Table 4) which reveals that mean sedation score was less among the group D subjects than group C, which was also statistically significant.

Incidence of postoperative nausea and vomiting was reduced in Group D (Table 5), which is similar with what was observed in another study done by Tufanogullari B *et al*. [28] and metaanalysis [29]. These findings are similar with the findings of the present study (Table 5) which also reveals that adverse effects were significantly less among the subject of group D than group C, which were statistically significant.

Concerning the incidences of hypotension and bradycardia, no differences were found in the study done by Bielka *et al* [22]. This finding is contrary to the findings of the present study (Table 3) which reveals that mean arterial pressure was also better preserved among group D than group C, and the association was statistically significant at 45 and 60 minutes. The incidence of hypertension was significantly higher in Group C (OR 13.8, 95%CI 4–48, p < 0.0001) in the study done by Bielka *et al* [22]. Similar results were reported by other authors [23,30] with tachycardia and hypertension being registered in seven (35%) and six patients (30%) in the control group, compared with one (5%) and two (10%) patients in the dexmedetomidine group.

So, from this study we can see that Dexmedetomidine can effectively reduce opioid consumption with stable intraoperative hemodynamic parameters, less pain score and significantly less adverse effects during laparoscopic cholecystectomy. From this, we may thus conclude that low dose infusion of dexmedetomidine is an efficacious analgesic adjuvant, thereby serving as a very useful alternative to control haemodynamic stress response to intubation, pneumoperitoneum and extubation as also postoperative analgesia in patients undergoing laparoscopic cholecystectomy.

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