Original Article

Evaluation of postoperative analgesic efficacy and perioperative hemodynamic changes with low dose intravenous dexmedetomidine infusion in patients undergoing laparoscopic cholecystectomy – A randomised, double-blinded, placebo-controlled trial

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Abstract

Background and Aim: Dexmedetomidine is a α2-agonist with sedative, sympatholytic and analgesic properties and hence, it can be a very useful adjuvant in anesthesia as stress response buster, sedative and analgesic. We aimed to evaluate the effects of low dose dexmedetomidine infusion (0.5 mcg/kg/h) on postoperative analgesic efficacy along with the perioperative hemodynamic changes in patients undergoing laparoscopic cholecystectomy.

Material and Methods: Eighty patients of American Society of Anesthesiologists (ASA) physical grades I and II undergoing laparoscopic cholecystectomy were randomly allocated into two groups of 40 patients each. Group I (Normal Saline group) patients received normal saline and group II (Dexmedetomidine group) patients received dexmedetomidine infusion at 0.5 mcg/kg/h respectively, starting 15 min before induction and continued till the end of surgery. Parameters noted were heart rate, mean arterial pressure, oxygen saturation, post-operative pain was evaluated using VAS and analgesic requirement. Statistical tests such as ANOVA test for continuous variables, *post-hoc* test for intergroup comparison, and Chi-square test for discrete values were applied.

Results: Post-operative efficacy was found to be limited in the dexmedetomidine group in terms of VAS score. The analgesic requirement in 24-hour was observed to be reduced in dexmedetomidine group when compared to the NS group; however, not statistically significant. In group NS, significant hemodynamic stress response was seen following laryngoscopy, tracheal intubation, creation of pneumoperitoneum and extubation. On intergroup comparison, the hemodynamic response was significantly attenuated in the dexmedetomidine group when compared to the NS group. No significant side effects were noted.

Conclusion: Dexmedetomidine IV in an infusion dose of 0.5 μg/kg/hr is effective in providing postoperative analgesia in terms of significant reduction in analgesic consumption in 24 hours and in addition to the effective obtundation of the pneumoperitoneum-induced hemodynamic changes.

Keywords: Laparoscopic cholecystectomy, low dose dexmedetomidine, postoperative analgesia

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Introduction

Laparoscopic cholecystectomy has become the standard technique of choice for symptomatic gall bladder diseases. Although pain after laparoscopic cholecystectomy is less intense, but many patients experience considerable pain or discomfort during first 24 hours in post-operative period. Multimodal analgesia is now recommended to prevent and treat post-laparoscopy pain.[1-3]

Dexmedetomidine is a highly selective alpha-2 receptor agonist with sympatholytic, sedative, analgesic, amnestic and opioid-sparing properties.[4] In the past few years, intravenous (IV) dexmedetomidine has been widely evaluated for its efficacy in improving perioperative hemodynamic stability and postoperative analgesia in patients undergoing laparoscopic cholecystectomy.[5-9] Most of the clinical studies evaluated the role of IV Dexmedetomidine in patients undergoing laparoscopic cholecystectomy had used a bolus dose of 1 μg/kg over a period of 10 min before induction of anaesthesia, followed by infusion of 0.5 μg/kg/hr till the removal of gall bladder.[6-9] The dose of 1 μg/kg bolus is known to produce a 'Biphasic response' i.e., initial rise in blood pressure which is followed by hypotension and a reflex fall in HR.[10,11] This initial rise in BP can be attenuated by a slow infusion or by avoiding the bolus administration of drugs.[11] Bhattacharjee *et al.*,[12] Park *et al.*[13] and Manne *et al.*[14] have evaluated the effects of various low infusions doses of IV dexmedetomidine i.e. 0.2 μg/kg/hr, 0.3 μg/kg/hr, and 0.4 μg/kg/hr, respectively, on hemodynamics and anesthetic requirements in patients undergoing laparoscopic cholecystectomy. In the first two studies, the infusion doses evaluated were very low and the post-operative analgesic efficacy was not evaluated; however, Manne *et al.* have evaluated the analgesic efficacy as the secondary outcome and concluded this dose to be efficacious in terms of postoperative pain management.

To reconfirm the findings, the present randomized, double-blinded prospective study was undertaken to evaluate the analgesic efficacy along with the hemodynamic stability of IV dexmedetomidine in a dose of 0.5 μg/kg/hr in patient undergoing laparoscopic cholecystectomy.

Material and Methods

The present randomized, double-blinded, placebo-controlled, prospective study was undertaken following approval from the institutional ethical committee- Human (IEC-H) and written informed consent from each patient. The duration of the study was 18 months. All patients aged 18–50 years with American Society of Anesthesiologists (ASA) physical status class I or II undergoing laparoscopic cholecystectomy under general anesthesia (GA) were included in the study. Patients were excluded from the study if they had BMI >30 kg/m^2, renal or hepatic insufficiency, neurologic, psychiatric disease, preoperative HR <45/min or on antihypertensive medication with any α_2 adrenergic agonists e.g., clonidine.

Alprazolam 0.25 mg orally on the night prior and on the morning of surgery was administered as premedication. Patients were randomly allocated into two groups by using a computer-generated random numbers tables. The consultant in-charge enrolled the participants and assigned the intervention and did not participate in data collection. Patients in Group I received normal saline (NS) @30 ml/hr and patients in Group-II received 0.5 μg/kg/hr dexmedetomidine infusion in NS (30 ml/hr), 10 min before induction of anesthesia till the removal of gall bladder. Standard anesthetic technique for GA was followed in all the patients. The investigator, the patient as well as the outcome assessors were blind to the group allocation. Baseline hemodynamic parameters were recorded. Patients was monitored by using continuous electrocardiogram (ECG), heart rate (HR), non-invasive blood pressure (NIBP at 5-min interval) and oxygen saturation (SpO_2) after starting the IV infusion of study drug through a separate IV line.

Anesthesia was induced with propofol 2 mg/kg and morphine 0.1 mg/kg. Tracheal intubation was facilitated by vecuronium 0.1 mg/kg. Anesthesia was maintained with 66% nitrous oxide in oxygen in combination with 0.8–1.5% of isoflurane maintaining a MAC of around 1- 1.2. The HR, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were measured at baseline, before induction, 3 min after endotracheal intubation, before pneumoperitoneum (P0); at an interval of 10 min thereafter till the release of pneumoperitoneum {(P10), 20 (P20), (P30)}, 10 min after release of pneumoperitoneum, and 10 min after extubation. Hypotension (<20% of baseline SBP) was treated with Ringer's lactate bolus or mephentermine 3-6 mg bolus IV, if required. Bradycardia of ≤45 bpm was treated with atropine 0.5 mg IV.

During laparoscopy, intra-abdominal pressure (IAP) was maintained at 10–12 mmHg and CO_2 was carefully evacuated at the end of surgery. All patients received IV ondansetron 0.1 mg/kg to prevent the postoperative nausea and vomiting and IV diclofenac 1.5 mg/kg before the completion of surgery and was continued every 12 hourly for the first 2 days. At the end of surgery, residual neuromuscular block was reversed and tracheal extubation was performed. Patients' vitals were monitored using continuous ECG, SpO2 and intermittent SBP, DBP, and MBP recorded at 5 min,

15 min, 30 min, 1 hr and 2 hrs. Pain was assessed using VAS and sedation was assessed using four-point sedation scale (0- awake, 1- drowsy but responding to commands, 2- sleepy but easy to arouse by loud command or glabellar tap, 3- deep sleep and difficult to arouse) at the following times intervals immediately after arrival in post-anaesthesia care unit (PACU), and then after 15 min, 30 min and at the end of 1st, 2nd, 4th, 8th, 12th and 24th hours after operation. Rescue analgesia was in boluses of tramadol 1 mg/kg IV, whenever VAS pain score was ≥3. This dose was repeated if pain relief was found to be inadequate to the maximum dose of 200 mg.The number of patients requiring rescue analgesia and the total consumption of tramadol in 24 hours was recorded in each patient. Any side effects such as hypotension, bradycardia, sedation, nausea, vomiting, dizziness was recorded. The primary outcome of the study was mean VAS pain score and secondary outcomes were total tramadol consumption in 24 hours, mean MBP and HR between the two groups.

Sample size and statistical analysis

Sample size calculation was based on the previous study involving IV dexmedetomidine with multimodal analgesia in patients undergoing laparoscopic cholecystectomy.[6] We had considered the reduction in VAS of 1.5 as clinically significant when taken at the time of arrival in post-operative anesthesia care unit (PACU) taking standard deviation of 2.2. A priori, 38 patients were required for each group assuming an α-value of 0.05 and power of 80%. So, 40 patients in each group and a total of 80 patients were included.

Data was summarized as mean ± SD. Baseline parameters like age, sex, weight and duration of surgery were compared by independent Student's *t*-test.Groups were compared by two factor repeated measure analysis of variance (ANOVA) using general linear models (GLM) and the significance of mean difference within and between the groups was done using Tukey's *post hoc* test. Scores like VAS pain score and sedation score were compared by Mann-Whitney U test for in-between the groups. ASA physical status, sex ratio and need for rescue analgesia were analysed using Chi-square. $P < 0.05$ was considered statistically significant.

Results

A total of 89 patients were enrolled in the study. Following randomisation, nine were excluded in view of the change of the laparoscopic procedure to open cholecystectomy and finally a total of 80 patients were included with 40 patients in each group. The demographic profile of the participants is shown in Table 1.

The analgesic efficacy was evaluated in terms of post-operative mean VAS pain scores and mean total tramadol consumption in 24 hours. A statistically significant reduction in the mean VAS pain score in Dexmedetomidine group was observed when compared to group NS in the initial 15 min following shifting of the patient to the postoperative area. Thereafter, no significant difference in mean VAS pain score was observed between the two groups [Table 2]. The mean tramadol consumption in 24 hours was found to be significantly higher in the NS group i.e., 131.25 ± 33.37 when compared to the Dexmedetomidine group i.e., 112.50 ± 31.52 (P=0.012).

On comparison between the two groups, the mean HR at baseline, pre-induction and 3 min after intubation were comparable in between the two groups. There was statistically significant difference in the mean HR in between the two groups soon after pneumoperitoneum till 10 min after the release of pneumoperitoneum. The mean HR at 10 min following tracheal extubation was not different in the two groups [Figure 1]. On intergroup analysis of intra-operative mean arterial pressure (MAP) in between the two groups, there was statistically significant difference in the mean MAP values at pre-induction, 3 min after intubation, throughout the pneumoperitoneum till 10 min after the release of pneumoperitoneum and also at 10 min after the extubation of trachea. A significant reduction in the mean MAP in group II was observed before induction and 3 min after intubation the reason for this is also could be due to the fact that till this point of time patients had already received dexmedetomidine infusion for 10 min and around 15 min, respectively [Figure 2].

Table 1: Demographic profile

	Group -I	Group-II
Age (years)	35.7±6.9	32.8±8.5
Weight (kg)	58±7.7	58±9.8
Sex M/F	1/39	1/39
ASA I/II	33/7	35/2

Group- I - NS group, Group-II - Dexmedetomidine group

Table 2: Post-operative VAS score

Time interval	Group I (NS) (*n*=40)	Group II (Dexmedetomidine) (*n*=40)	*P*
0 min	2.6±2.5	0.6±1.2	0.000*
15 min	3.7±2.2	2.6±2.3	0.021*
30 min	2.6±1.4	3.0±2.4	0.395
60 min	2.8±1.4	3.1±2.0	0.563
2 h	3.4±1.7	2.8±1.9	0.145
4 h	2.6±1.6	3.3±1.8	0.073
8 h	2.6±1.7	3.0±1.8	0.370
12 h	1.8±1.6	1.8±1.5	0.828
24 h	1.2±0.8	1.5±0.7	0.145

*Group- I - NS group, Group-II - Dexmedetomidine group. *P<0.05*

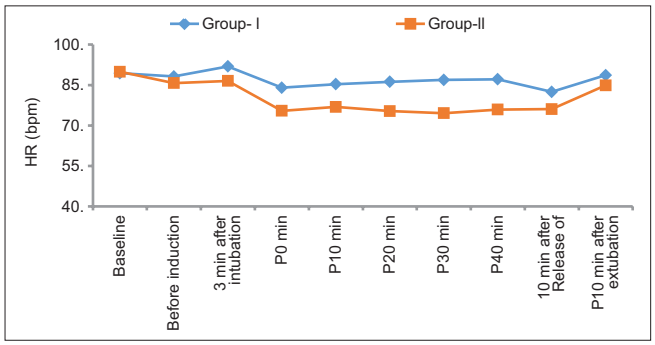

Figure 1: Trends showing changes in intraoperative HR. Group- I – NS group, Group-II – Dexmedetomidine group

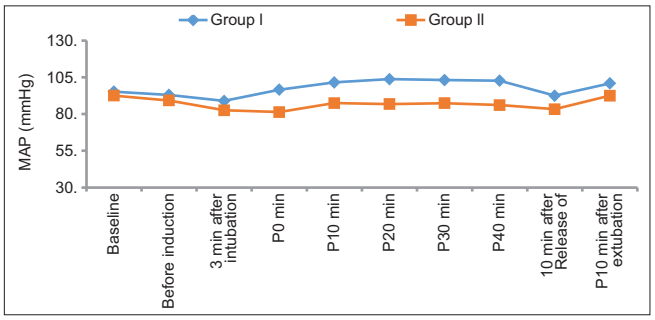

Figure 2: Trends showing changes in intraoperative MAP. Group- I – NS group, Group-II – Dexmedetomidine group

The mean HR in the postoperative period at various designated intervals was not significantly different between the two groups; however, the mean MBP in the postoperative period at various designated intervals were found to be significantly reduced in the Dexmedetomidine group when compared to the normal saline group at all points of time.

On inter-group analysis, the mean sedation score in the postoperative period was found to be significantly higher in the Dexmedetomidine group in the initial 15 min only. Thereafter, it was observed to be consistently higher in the Normal saline group at all time points; however, the difference was statistically significant only at the 2nd and 4th hours [Table 3]. Nausea and shivering were observed in 2 (5%) and 5 patients (12.5%) respectively, in the control group only. In the intra-operative period, hypotension was observed in 15% of patients ($n = 6$) in the Dexmedetomidine group only; whereas, none of the patients had bradycardia in any group. Out of six patients who had hypotension in Dexmedetomidine group, three developed hypotension soon after intubation of trachea and rest three developed it during pneumoperitoneum. It was managed with IV fluids and none of the patient required vasopressor.

Discussion

The present study results show that the postoperative analgesic efficacy of IV Dexmedetomidine in an infusion dose of 0.5 μg/kg/hr is observed to be limited; however, it was found to be effective in obtunding the pneumoperitoneum-induced hemodynamic changes.

Dexmedetomidine, an alpha-adrenoceptor agonist has been widely studied in patients undergoing laparoscopic cholecystectomy for premedication,[7] anesthetic adjuvant,[15] prevention of PONV,[16] attenuation of pneumoperitoneum-induced hemodynamic changes[17] and for postoperative pain management.[6] Till date, we could retrieve only three prospective, double-blinded study which have studied the effect of IV dexmedetomidine in a low dose of 0.2 μg/kg/hr, 0.3 μg/kg/hr and 0.4 μg/kg/hr on hemodynamics in patients undergoing laparoscopic cholecystectomy.[12,13,14] Out of the three, the postoperative analgesia was evaluated only by Manne *et al.* for the dose of 0.4 μg/kg/hr and was found to be efficacious in terms of postoperative analgesia and hemodynamics.

Dexmedetomidine has anti-nociception action which has been studied by various authors for postoperative pain management in laparoscopic cholecystectomy. Few studies have evaluated intravenous dexmdetomidine for its postoperative analgesic effect in patients undergoing laparoscopic cholecystectomy in terms of VAS pain score and total analgesic requirement in 24 hours.[6,8,12,13,14] Park *et al.* evaluated dexmedetomidine 1 μg/kg bolus followed by 0.5 μg/kg/hr with multi-modal analgesia in patients undergoing laparoscopic cholecystectomy and observed a significant reduction in VAS pain scores for only I hour in the post-operative period.[6] Bakri *et al.* evaluated dexmedetomidine in bolus dose of 1 μg/kg for premedication and observed that the VAS pain score was significantly lower in the Dexmedetomidine group during the first 4 hours in the post-operative period when compared to the dexamethasone group.[18] In the present study, there was statistically significant reduction in the VAS scores in Dexmedetomidine group when compared to the NS group only in the initial 15 min of shifting the patient to the post-operative area following which, no significant difference in the VAS pain score was observed in-between the two groups. The reason for this finding could be due to the greater use of rescue analgesic i.e. tramadol in the control group when compared to the dexmedetomidine group at different time points beyond 15 min and/or the low dose of dexmedetomidine i.e. 0.5 μg/kg/hr in comparison to the aforementioned studies using the standard dose of 1 μg/kg bolus followed by 0.2-0.5 μg/kg/hr.

The total tramadol consumption in 24 hr was found to be significantly higher in the control group when compared to the Dexmedetomidine group. Our finding is in concordance to Park *et al.* in which they had used dexmedetomidine in a dose of 1 μg/kg bolus followed by 0.5 μg/kg/hr and observed that

Table 3: Post-operative Sedation score

Time interval	Group I (NS)	Group II (Dexmedetomidine)	*P*
0 min	1.6±0.7	2.4±0.5	0.000
15 min	1.5±0.7	1.9±0.7	0.013
30 min	1.8±0.5	1.7±0.6	0.400
60 min	1.7±0.5	1.6±0.6	0.416
2 hr	1.4±0.7	1.8±0.6	0.022
4 hr	1.8±0.4	1.6±0.6	0.037
8 hr	1.7±0.6	1.5±0.6	0.363
12 hr	2.0±0.5	2.0±0.6	0.837
24 hr	1.7±0.6	1.7±0.7	0.714

Group- I - NS group, Group-II - Dexmedetomidine group

the amount of ketorolac/tramadol requirements during 24 hr after laparoscopic cholecystectomy were significantly less in dexmedetomidine group when compared to the Normal saline group [6]. Despite the use of low dose of dexmedetomidine in the present study, the reduction in the rescue analgesic consumption in 24 hr was found to be significant.

Dexmedetomidine has also been found to obtund the pneumoperitoneum-induced hemodynamic response in laparoscopic cholecystectomy. In the present study, on comparing the HR in between the two groups, there was significant reduction in HR in the Dexmedetomidine group throughout the pneumoperitoneum at all time points when compared to the Normal saline group. Anjum *et al.*[18] and Srivastava *et al.*[17] evaluated dexmedetomidine in the conventional dose of 1 μg/kg bolus followed by 0.5 μg/kg/hr in laparoscopic cholecystectomy and observed significant reduction in HR in the dexmedetomidine group. Two patients had bradycardia during insufflation in the study by Anjum *et al*. In our study, none of the patients had bradycardia and this could be attributed to the omission of the bolus dose of dexmedetomidine.

In the present study, on intergroup comparison, there was a significant reduction in MBP at various time intervals throughout the pneumoperitoneum extending till the end of the surgery in the dexmedetomidine group when compared to the NS group. Hypotension was noted in 6 patients (15%) in the dexmedetomidine group but all responded to IV fluid boluses and no pharmacological intervention was required. Our finding is consistent with Srivastava *et al.*[17] where significant reduction in SBP, DBP and MBP were observed throughout the surgery in patients receiving dexmedetomidine infusion. The intra-operative hemodynamic trends observed in our study is also in concordance to the studies evaluating the low-dose of IV dexmedetomidine in laparoscopic cholecystectomy i.e., Park *et al.*[12] and Bhattacharjee *et al.*[13]

The sedative and analgesic-sparing effects of dexmedetomidine are through α2- adrenoceptor in locus coeruleus. It does not cause respiratory depression. In the present study, the mean sedation score in the postoperative period was found to be significantly higher in the Dexmedetomidine group in the initial 15 min only. Thereafter, it was observed to be consistently higher in the Normal saline group at all time points; however, the difference was statistically significant at 2nd and 4th hour. The higher sedation scores in the aforementioned designated intervals in the first 15 min could be attributed to the effect of IV dexmedetomidine infusion which was continued till the removal of gall bladder. Our result is in contrast with Swaika *et al.* in which sedation score was observed to be more in the Dexmedetomidine group (1 μg/kg bolus followed by 0.5 μg/kg/hr for 24 hr) when compared to paracetamol (1 g over 10 min pre-operatively and 6 hourly thereafter for 24 hr) in patients undergoing laparoscopic cholecystectomy. Various studies have assessed the anti-emetic effect of dexmedetomidine in laparoscopic cholecystectomy.[16,18-20] In the present study, the incidence of PONV was 12.5% in the normal saline group; however, none of the patients had nausea or vomiting in the Dexmedetomidine group. Intravenous dexmedetomidine have been evaluated for prevention of PONV in both single loading doses i.e., 1 μg/kg bolus[17] and 0.2–0.5 μg/kg/hr[21] in patients undergoing laparoscopic cholecystectomy. In our study, we had used low dose dexmedetomidine and the anti-emetic effect obtained was found to be satisfactory. Dexmedetomidine has a proven role in the prevention of post-anaesthesia shivering.[15] In the present study, none of the patient in dexmedetomidine group had shivering; whereas, it was observed in 5% of patients ($n = 2$) in the Normal saline group.

The limitation of the study is that the sedative effect of the low dose dexmedetomidine could not be evaluated; on the contrary since higher sedation scores were observed in the control group at 2nd and 4th hours. The possible reason for the higher sedation scores could be attributed to the sedative potential of tramadol which was used more frequently in the normal saline group for rescue analgesia.

To conclude, IV Dexmedetomidine in an infusion dose of 0.5 μg/kg/hr is effective in providing postoperative analgesia in terms of significant reduction in analgesic consumption in 24 hr in addition to the effective obtundation of the pneumoperitoneum-induced hemodynamic changes. The side effects like hypotension and bradycardia are observed to be mild; not requiring any active intervention.

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Conflicts of interest
There are no conflicts of interest.

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