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Original Article

Anaesthesia Section

Dexmedetomidine in Attenuation of Haemodynamic Response and Dose Sparing Effect on Opioid and Anaesthetic Agents in Patients undergoing Laparoscopic Cholecystectomy- A Randomized Study

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ABSTRACT

Introduction: Perioperative procedures are stressful and lead to haemodynamic instability with potentially devastating consequences. Dexmedetomidine is found to have many of the desired characteristics that are required in perioperative period.

Aim: To evaluate the ability of pre and intraoperative dexmedetomidine to attenuate stress induced haemodynamic responses, quantifying the anaesthetic agents sparing as well as its cost-effectiveness in patients undergoing laparoscopic cholecystectomy.

Materials and Methods: The present single blind randomized study was conducted with 120 ASA I and II consented patients who underwent laparoscopic cholecystectomy. Patients were randomly divided into 2 groups (i.e., group D and group N). Prior to induction, group D received 1 µg/kg of Dexmedetomidine and group N received Normal saline infusion over 20 minutes. Group D also received maintenance Dexmedetomidine intraoperatively. Bispectral index and minimum alveolar concentration monitoring was done in both the groups. Haemodynamic parameters were noted till 100 minutes post laryngoscopy. Opioid and anaesthetic agent consumptions were also noted and cost analysis was done. Medcalc–Version 12.5.0.0 software was used for statistics and $p < 0.05$ was considered significant.

Results: Dexmedetomidine attenuated the stress induced haemodynamics responses and produced stable, relatively non fluctuating haemodynamics throughout. The Minimum Alveolar Concentration (MAC) requirement and the consumptions of Fentanyl and Isoflurane were significantly less in the Dexmedetomidine group ($p<0.0001$). However, despite anaesthetic dose sparing effect the anaesthetic technique was not cost-effective.

Conclusion: Dexmedetomidine is effective in attenuating haemodynamic responses in laparoscopic surgery and having dose sparing effect on Fentanyl, Propofol and Isoflurane. However, overall this technique is not cost-effective.

Keywords: Anaesthetic dose sparing, Cost-effective health care, Laryngoscopy, Stress response

INTRODUCTION

Stress response, arising from various stimuli in perioperative period is a well known factor for haemodynamic changes. Attenuation of these haemodynamic responses during laryngoscopy and surgery has been one of the most desired goals in conducting smooth anaesthesia. Clonidine, an α-2 agonist has been extensively described for this purpose [1,2]. However, the basic need for the desired availability of a drug that effectively suppresses all the hazardous responses to obnoxious stimuli within a maximum margin of safety is being continuously felt among the anaesthesiologist fraternity. Dexmedetomidine is having eight times more affinity for α-2 adrenoceptors as compared to Clonidine. It is also known to decrease the plasma catecholamine levels and catecholamines release [2-4]. Opioids are also effective in attenuating the stress response; however, the dose required for effective attenuation of stress response is fairly high. Numerous drugs have been used as adjuncts in decreasing the dose of opioids with varied level of success, but are not absolutely free from side effects [5,6]. On the other hand, pneumoperitoneum during laparoscopic surgeries poses an additional risk for haemodynamic instability [7,8]. Based on these findings, the present study hypothesized that the pre and intraoperative Dexmedetomidine will not only attenuate the haemodynamic response to laryngoscopy and intubation but also during pneumoperitoneum and surgery; and will lead to cost-effective dose sparing effect of opioids and anaesthetic agents.

MATERIALS AND METHODS

After Institute Ethical Committee approval and informed consent from the participants the present single blinded, randomized control study was conducted in a tertiary care teaching institute during the period of May 2013 to January 2015. One hundred twenty ASA-I and II (American Society of Anaesthesiologist) patients, aged 18–60 years, undergoing laparoscopic cholecystectomy under general anaesthesia with endotracheal intubation were included. The patients were divided into 2 groups of 60 patients each {group D (Dexmedetomidine) and group N Normal Saline (NS)} by computer generated randomized numbers packed and sealed in an opaque envelope. Patients with cardiovascular disease, epilepsy, hypertension, chronic obstructive pulmonary disease, taking any antipsychotic medications or having a history of allergy to any of the drugs which were used during study and in whom the intubation attempts lasted longer than 30 seconds were excluded from the study.

Premedication was kept uniform in both the groups. Baseline haemodynamic parameters were recorded in the pre-op room. Ringer's lactate was used for fluid therapy as per body weight, fluid abstinence period and loss. Group D received 1 µg/kg of Dexmedetomidine (Themis Medicare Ltd., India) loading dose in 50 ml of NS while group N received only 50ml NS infusion 20 minutes prior to induction. Dexmedetomidine 0.5mg/kg/min in group D and volume matched NS in group N was continued throughout the surgery. Intravenous Fentanyl citrate (Verve Health Care Ltd., India) 1.5µg/kg was given in both the groups before induction. Injection Propofol (Neon Laboratories Ltd., India) in a dose sufficient to abolish the verbal response was used for induction. Injection Vecuronium bromide (Neon Laboratories Ltd., India) 0.1 mg/kg was used to facilitate tracheal intubation.

Bispectral Index (BIS) (BIS quarto from Aspect Medical System, Norwood) was used for the evaluation of depth of anaesthesia in both the groups over and above monitoring of anaesthetic gas fraction and MAC using anaesthetic gas concentration monitoring system incorporated in the Mindray Beneview T8 monitoring system and Penlon Prima SP_2 workstation. Laryngoscopy was performed with a Macintosh laryngoscope blade and trachea intubated with a cuffed endotracheal tube of appropriate size after 3 minutes of bag mask ventilation with 100% oxygen and isoflurane. Monitoring of haemodynamic parameters at the time of induction, laryngoscopy, post intubation 1 minute, 5 minutes and 10 minutes and thereafter at 10 minutes intervals till 100 minutes of post laryngoscopy were done.

Anaesthesia was maintained with Isoflurane (Baxter Healthcare of Puerto Rico), oxygen and intermittent positive pressure ventilation sufficient to keep $EtCO_2$ between 26 to 34 mmHg. Intraoperatively, additional dose of vecuronium and extubation timing was guided by neuromuscular monitoring (TOF watch from Organon). The adjustment in the inspiratory concentration of Isoflurane was carried out in increment or decrement values of 0.2% to keep BIS within target value of 40-60. If the Heart Rate (HR) or Mean Arterial Pressure (MAP) increased by 20% above baseline while BIS within target and TOF score zero, an additional 0.5 µg/kg dose of Fentanyl was repeated. Even after that, if HR and MAP remained above 20% from the baseline values, Isoflurane was increased by fraction of 0.2%.

Fresh Gas Flow (FGF) was set at 6L/minute during induction, 4L/minute post induction for 5 minutes than 2L/minute for 5 minutes and then 0.5L/minute throughout the procedure for both the groups. The average inspiratory concentration of Isoflurane was calculated by the sum of the products of inspiratory concentration and duration of anaesthesia according to Dion's method [9]. The cost of the anaesthetic agent was calculated by using Dion's formula [9] from the concentration (%) of gas delivered, FGF (L/min), duration of inhaled anaesthetic delivery (min), molecular weight (MW in g), cost per mL (Indian rupees), a factor 2412 to account for the molar volume at 21°C (24.12 L), and density (D in g/mL) the Cost of 250 ml of Isoflurane was Rs 2816.62 at the time of study.

Cost (Rs) = {(Concentration) (FGF) (Duration) (MW) (Cost/mL)}/{(2412)(D)}.

STATISTICAL ANALYSIS

Statistical analysis of data was carried using Medcalc–Version 12.5.0.0 software with appropriate statistical test and p-value of <0.05 was considered significant.

RESULTS

All the 120 patients completed the study and were included for analysis. There were 8 men and 112 women. The total number of female patients was higher i.e., 112 (93.33%) however, sex wise distribution among the two groups were not different statistically (p>0.05). The differences between the participants of both the groups with respect to demographic parameters and ASA physical status were also not significant (p>0.05) [Table/Fig-1].

The mean (SD) value of highest and lowest BIS, $EtCO_2$ and temperature during the surgery were also not statistically different [Table/Fig-2]. All cases were performed by 4 port techniques. The mean (SD) surgery duration was higher in group D (Dexmedetomidine) than group N (Normal saline) (99.83(±10.88) versus 89.33(±9.81 minutes) and the difference is however, statistically extremely significant (p<0.0001). Heart rate in group D was significantly lower than the group N throughout the intraoperative period [Table/Fig-3]. Heart rate decreased intraoperatively by 5.7% from the base line in group D while it increased in group N by 16% from base line (p<0.0001). Although the mean blood pressure increased in both the groups from baseline, the fluctuation was less in group D as compared to Group N (2.1% versus 8.4%) [Table/Fig-4].

Parameters	Group N n (%) # or Mean (SD)	Group D n (%) or Mean (SD)	p-value (two tailed)
Male#	6 (10)	2 (3.33)	0.2719
Female#	54 (90)	58 (66.67)	0.2719
Age (years)	39.65 (12.32)	37.95 (12.34)	0.451
Weight (kg)	58.92 (11.32)	58.1 (10.45)	0.680
Height (cm)	152.5 (5.45)	152.68 (5.52)	0.857
BMI (kg/m2)	25.08 (3.85)	24.84 (3.79)	0.731
ASA Class	1.02 (0.13)	1.02 (0.13)	1
ASA I#	47 (78.33%)	44 (73.33%)	
ASA II#	13 (21.67%)	16 (26.67%)	

[Table/Fig-1]: Result of demographic parameters of the cohort expressed in number and percentage scale (marked as #) and analysed by unpaired t-test.
BMI-Body Mass Index, ASA-American Society of Anaesthesiologists, SD-Standard Deviation

Intraoperative Parameters	Group N	Group D	p-value	95% CI of Diff b/w means
	Mean (SD)	Mean (SD)		
Lowest $EtCO_2$ (mm Hg)	24.77 (6.34)	23.02 (5.16)	0.09994	-0.65 – 4.15
Highest $EtCO_2$ (mm Hg)	35.12 (1.98)	34.82 (1.69)	0.37301	-0.46 – 1.06
Highest BIS (at start)	96.97 (0.91)	97.07 (0.89)	0.54493	-0.47 – 0.27
Highest BIS (maintenance)	54.89 (0.41)	46.07 (0.49)	0.0001	-0.45 – 3.14
Lowest BIS (maintenance)	36.48 (4.39)	37.6 (5.29)	0.21078	-3.13 – 0.9
Surgery duration (minutes)	89.33 (9.81)	99.83 (10.88)	<0.0001	-14.79 – 6.21
Lowest temperature (in °C)	36.67 (0.26)	36.01 (0.14)	0.42193	- 0.44 – 3.12
Highest temperature (in °C)	37.19 (0.18)	37.04 (0.23)	0.32134	- 0.34 – 1.26
Dial settings in maintenance (%)	1.8 (0.13)	1.0 (0.11)	<0.0001	-16.79 – 14.21
MAC requirement	1.12 (0.07)	0.76 (0.24)	<0.0001	-12.79 – 11.21

[Table/Fig-2]: Intraoperative parameters analysed using unpaired t-test.
Group N-Normal Saline, Group D-Dexmedetomidine, $EtCO_2$-end tidal carbon dioxide, MAC-Minimum Alveolar Concentration, BIS-Bispectral Index, SD- Standard Deviation, CI-Confidence Interval

Heart rat (Beat in per minute)	Group N	Group D	95% CI of difference between means	p-value (two tailed)
	Mean (SD)	Mean (SD)		
Preoperative Base line	80.3 (7.68)	78.75 (10.14)	-2.18 to 5.28	0.347
At Induction	82.7 (8.28)	70.7 (12.02)	7.72 to 16.28	<0.0001
At laryngoscopy	97.58 (13.27)	74.65 (12.25)	17.64 to 28.23	<0.0001
1 minute after laryngoscopy	90.12 (13.24)	74.9 (12.25)	9.93 to 20.5	<0.0001
5 minute after laryngoscopy	92.25 15.11	72.87 10.37	14.01 to 24.75	<0.0001
10 minute after laryngoscopy	98.4 (15.69)	71.93 (10.66)	20.91 to 32.03	<0.0001
20 minute after laryngoscopy	93.37 (14.79)	74.38 (9.78)	13.79 to 24.18	<0.0001
30 minute after laryngoscopy	92.75 (16.5)	74.13 (8.99)	13.11 to 24.12	<0.0001
40 minute after laryngoscopy	92.87 (15.68)	73.22 (9.47)	14.28 to 25.02	<0.0001
50 minute after laryngoscopy	95.77 (10.9)	74.9 (10.41)	16.45 to 25.28	<0.0001
60 minute after laryngoscopy	95.76 (11.23)	74.85 (11.4)	16.22 to 25.6	<0.0001
70 minute after laryngoscopy	93.47 (15.06)	73.97 (9.83)	14.23 to 24.77	<0.0001
80 minute after laryngoscopy	90.4 (10.81)	75.98 (9.22)	10.25 to 18.58	<0.0001
90 minute after laryngoscopy	89.1 (7.41)	75.22 (9.25)	10.4 to 17.35	<0.0001
100 minute after laryngoscopy	90.17 (9.0)	74.67 (8.78)	11.81 to 19.18	<0.0001

[Table/Fig-3]: Trend of heart rate at different times analysed using unpaired t-test.
Group N-Normal Saline, Group D-Dexmedetomidine, SD-standard deviation, CI-confidence interval

Blood Pressure (mm Hg)	Group N	Group D	95% CI of difference between means	p-value (two tailed)
	Mean (SD)	Mean (SD)		
Preoperative Base line	80.3 (7.68)	87.8 (6.16)	-10.39 to -4.61	<0.0001
At Induction	87.43 (8.66)	91.05 (9.93)	-7.48 to 0.25	0.03556
At laryngoscopy	83 (11.72)	89.92 (10.52)	-11.53 to -2.3	0.00092
1 minute after laryngoscopy	84.88 (12.49)	89.47 (12.76)	-9.82 to 0.65	0.04913
5 minute after laryngoscopy	89.68 (12.6)	89.08 (13.11)	-4.73 to 5.93	0.79876
10 minute after laryngoscopy	92.48 (13.57)	91.75 (5.81)	-3.59 to 5.06	0.70103
20 minute after laryngoscopy	92.05 (13.06)	87.88 (13.03)	-1.24 to 9.58	0.08265
30 minute after laryngoscopy	91.48 (10.07)	91.67 (12.04)	-4.78 to 4.42	0.92807
40 minute after laryngoscopy	91.02 (11.81)	93.5 (11.99)	-7.41 to 2.45	0.25525
50 minute after laryngoscopy	91.82 (11.65)	92.22 (12.3)	-5.37 to 4.57	0.85519
60 minute after laryngoscopy	90.07 (11.28)	94.73 (10.5)	-9.18 to -0.15	0.02066
70 minute after laryngoscopy	91.3 (9.82)	92.67 (9.98)	-5.47 to 2.74	0.45099
80 minute after laryngoscopy	88.16 (6.41)	91.4 (8.1)	-6.26 to -0.21	0.01682
90 minute after laryngoscopy	90.26 (8.37)	91.04 (5.9)	-3.78 to 2.23	0.55878
100 minute after laryngoscopy	94 (11.6)	90.39 (7.42)	-0.43 to 7.64	0.04457

[Table/Fig-4]: Trend of mean arterial pressure at different times analysed using unpaired t-test.
Group N-Normal Saline, Group D-Dexmedetomidine, SD-standard deviation, CI-confidence interval

MAC	Group N	Group D	95% CI of difference between means	p-value (two tailed)
	Mean (SD)	Mean (SD)		
At Induction	0.55 (0.14)	0.45 (0.09)	0.05 to 0.15	<0.0001
At laryngoscopy	0.66 (0.15)	0.63 (0.15)	-0.03 to 0.09	0.28992
1 minute after laryngoscopy	0.78 (0.18)	0.72 (0.14)	-0.01 to 0.13	0.04652
5 minute after laryngoscopy	0.84 (0.14)	0.74 (0.12)	0.05 to 0.16	<0.0001
10 minute after laryngoscopy	0.92 (0.15)	0.73 (0.13)	0.13 to 0.24	<0.0001
20 minute after laryngoscopy	0.95 (0.16)	0.68 (0.14)	0.2 to 0.33	<0.0001
30 minute after laryngoscopy	1.0 (0.11)	0.68 (0.14)	0.27 to 0.38	<0.0001
40 minute after laryngoscopy	1.02 (0.12)	0.67 (0.15)	0.3 to 0.41	<0.0001
50 minute after laryngoscopy	1.04 (0.1)	0.67 (0.14)	0.32 to 0.42	<0.0001
60 minute after laryngoscopy	1.06 (0.11)	0.66 (0.15)	0.34 to 0.46	<0.0001
70 minute after laryngoscopy	1.06 (0.12)	0.65 (0.15)	0.35 to 0.46	<0.0001
80 minute after laryngoscopy	1.05 (0.13)	0.64 (0.16)	0.34 to 0.47	<0.0001
90 minute after laryngoscopy	1.33 (1.8)	0.62 (0.13)	0.18 to 1.24	<0.0028
100 minute after laryngoscopy	1.04 (0.13)	0.63 (0.14)	0.35 to 0.46	<0.0001

[Table/Fig-5]: Trend of MAC requirement at different times analysed using unpaired t-test.
MAC-Minimum Alveolar concentration, Group N-Normal Saline, Group D-Dexmedetomidine, SD-standard deviation, CI-confidence interval

Drug requirement	Mean		Cost (INR)		p-value (two tailed)
	Group N	Group D	Group N	Group D	
Propofol induction	124 mg	86 mg	177.32	122.98	<0.0001
Total Fentanyl	114 mcg	96 mcg	25.65	21.60	<0.0001
Isoflurane	12.39 ml	6.91 ml	139.62	77.89	<0.0001
Propofol+ Isoflurane + Fentanyl (+ Dexmedetomidine * in Group D)	---	---	342.59	563.39*	

[Table/Fig-6]: Cost analysis of Fentanyl, Propofol and Isoflurane dose sparing effect of Dexmedetomidine.
Group N-Normal Saline, Group D-Dexmedetomidine, INR-Indian Rupees

In order to maintain BIS within 40-60, group N required higher dial settings of Isoflurane [Table/Fig-2] as compared to Group D {1.8 (+ 0.13) versus 1.0 (+ 0.11)}. The MAC requirement was very high in group N just after laryngoscopy and remained persistently high throughout as compared to group D, where it was uniform and low [Table/Fig-5]. The MAC requirement in the group D was less as compared to group N (36% reduction) to keep BIS value within the target.

The consumption of each of Propofol, Isoflurane and Fentanyl was significantly lower in group D (p<0.0001). Additional dose (0.5mg/kg) of Fentanyl was required mostly in group N [Table/Fig-6].

DISCUSSION

Dexmedetomidine has proven analgesic, sedative, anxiolytic and sympatholytic activity [10-13]. The added advantage of dexmedetomidine is that it provides conscious sedation and analgesia without respiratory depression leading to a cooperative patient [14]. Therefore, dexmedetomidine has been a recent target for attenuation of these adverse haemodynamic responses while planning a smooth anaesthesia.

Laparoscopic surgery poses an added stress of pneumoperitoneum during surgery and is well known for increasing heart rate, mean arterial pressure and decrease in cardiac index [7,8]. All these stress inducing circumstances increases haemodynamic instability. This in turn can lead to cardiac demand supply mismatch and has the potential to cause myocardial ischemia. A meta analysis has shown that α 2-adrenoreceptor agonists have the ability to reduce the number of ischemic episodes and a reduced risk of myocardial infarction during cardiac and vascular surgery [1]. Therefore, it has been the recent drug of interest for the researchers as well as perioperative physicians for the purpose of stress response reduction.

Opioid like fentanyl has also shown to reduce stress response induced by laryngoscopy and intubation in dose dependant manner [15]. As, high dose of opioid produces heavy sedation as well as respiratory depression, perioperative practices in context to dose sparing of opioid has also been one of the goal in modern anaesthesia. Single dose preoperative Dexmedetomidine 1 mg/kg has also shown to be better than injection Fentanyl 2 mg/kg in attenuating haemodynamic response to laryngoscopy [16]. Bradycardia has been a well known side effect of Dexmedetomidine as well as Fentanyl. However, literature suggests that Dexmedetomidine can be combined with Fentanyl even in patients receiving beta blockers [17]. Therefore, combined Dexmedetomidine and Fentanyl have also been used for this purpose. Preoperative single dose Dexmedetomidine has proved to be effective in blunting the haemodynamic responses during laryngoscopy, and reduced anaesthetic requirements in patients undergoing major surgeries. However, it has not been able to fully blunt the stress response induced haemodynamics [18].

Alhough there is a significant amount of work done in various types of sugeries, most of the work is done with single dose preinduction Dexmeditomedine and study has been mostly limited to laryngoscopy and intubation and dose sparing effect of mostly inducing agents. There is dearth of data on the effect during the surgery, dose sparing effect on opioid, intravenous as well as inhalational agents jointly and its impact on cost-effectiveness. This present single blind, single centre, randomized study was designed to answer these issues.

In the present study, the anaesthetic management was standardized to reduce performance bias and depth of anaesthesia as measured objectively by BIS. Comparable age, temperature and $EtCO_2$ in the both groups indicate that the impact of these factors on anaesthetic agent consuption is equally prevalent in both the groups and is not a significant confounding factor on the result.

In current study Dexmedetomidine attenuated and obtunded the haemodynamic responses to laryngoscopy, tracheal intubation, surgery as well as pneumoperitoneum. Injection Fentanyl 1.5 mg/kg alone used in the group N was not sufficient to attenuate the stress responses to laryngoscopy and tracheal intubation adequately as indicated by significant increase in HR from baseline (21.5%). The dosage of general anaesthetic agents for the induction of anaesthesia decreased significantly, as was evident from the decreased requirement of Propofol in group D till loss of verbal response. Even the requirement of Isoflurane for maintenance of anaesthesia was reduced markedly (i.e., 43.99% reduction) during the surgical procedure (p<0.0001). There was also approximately 40% less MAC requirement as well as less opioid requirement in the Dexmedetomidine group. Single dose preinduction Dexmedetomidine has shown to reduce anaesthetic requirements in patients undergoing major surgeries [18]. In an observational study using entropy monitoring, it is also found that Dexmedetomidine as an anaesthetic adjuvant in laparoscopic surgery decreased the requirement of Propofol and end tidal Isoflurane while maintaining depth of anaesthesia [19].

The present study also has shown significant reduction of consumption and cost of Fentanyl, Propofol and Isoflurane which indicates the dose sparing effect of Dexmedetomidine. The less requirement of additional Fentanyl dose in group D also indicates the analgesic activity of Dexmedetomidine. However, when the cost of Dexmedetomidine (brand, company and price) was taken in to account against the cost saved; it did not appear to be cost-effective in laparoscopic cholecystectomy.

Dexmedetomidine has sympatholytic effect while it preserves the baro-reflex mechanisms [20]. It is associated with hypotension and bradycardia [21]. Both of these problems usually resolve without intervention [22]. Significant bradycardia was noted in 5 (8.33%) patients of Dexmedetomidine group requiring injection Atropine in the present study. Bradycardia appeared mostly in the first 30 minutes of Dexmedetomidine infusion especially during loading dose administration. Atropine was required in the present study probably due to the usage of a relatively higher dose of Dexmedetomidine. Current study also observed a slight reduction in the MAP from the baseline values during loading dose.

It was also observed that Dexmedetomidine group experienced smoother extubation compared to control group and was more comfortable in post operative period. However, extubation time, sedation score, postoperative pain score was not monitored and compared objectively in the present study as it was outside the objectives of the present study.

LIMITATION

The present study is also limited due to the fact that, it is a single centre and single blind study and direct measurements of catecholamine levels were not done. Future studies can be done in this field with different categories of patients to build data bank and strong evidence.

CONCLUSION

Dexmedetomidine is effective in attenuating haemodynamic response to laryngoscopy, intubation, surgery and pneumoperitoneum. It is also effective in sparing the dose of opioid and Isoflurane. The dose sparing effect is not cost-effective; however, prevention of significant change in haemodynamics and smooth emergence are good effects to advocate its use.

Authors' contribution: First author has contribution in experimental studies, data collection, and statistical analysis and draft preparation. Second and third author has contribution in conception, design, result analysis and interpretation, write up and revision. Fourth author has contribution in experimental studies and manuscript revision. Fifth and sixth author has contribution in concept, manuscript editing and review.

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