



## COMPARISON OF DEXMEDETOMIDINE VERSUS MAGNESIUM SULPHATE IN LAPAROSCOPIC CHOLECYSTECTOMY - A BIS AND ANI GUIDED STUDY

Dr. Komal Paswan<sup>1</sup>, Dr. Badri Prasad Das<sup>2\*</sup>, Dr. Anup Kumar Harichandan<sup>3</sup>, Dr. Sudhansu Sekhar Nayak<sup>4</sup>, Dr. Gyanendra Kumar Sinha<sup>5</sup>

<sup>1</sup>Senior Resident, Department of Anaesthesiology and Critical Care, IMS, Banaras Hindu University, Varanasi, Uttar Pradesh, India.

<sup>2\*</sup>Associate Professor, Department of Anaesthesiology and Critical Care, IMS, Banaras Hindu University, Varanasi, Uttar Pradesh, India.

<sup>3</sup>Assistant Professor, Department of Anaesthesiology and Critical Care, M.K.C.G. Medical College, Berhampur, Odisha, India.

<sup>4</sup>Assistant Professor, Department of Anesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences (AIIMS), New Delhi, India.

<sup>5</sup>Senior Professor, Department of Anaesthesiology and Critical Care, IMS, Banaras Hindu University, Varanasi, Uttar Pradesh, India.

**\*Corresponding Author:** Dr. Badri Prasad Das

\*Associate Professor, Department of Anaesthesiology and Critical Care, IMS, Banaras Hindu University, Varanasi, Uttar Pradesh, India.

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### ABSTRACT

**BACKGROUND:** Laparoscopic cholecystectomy is a routinely performed surgery always demanding a stable intraoperative hemodynamic status. The pneumoperitoneum and the patient positions required for laparoscopy induce pathophysiologic changes that complicate anaesthetic management. And search for an ideal anaesthetic adjuvant for attenuating such changes is still on. The present study was conducted to compare the effects of dexmedetomidine and magnesium sulfate as adjuvant in maintaining perioperative cardiovascular stability, with propofol consumption as a part of total intravenous anaesthesia (TIVA) and postoperative analgesia in laparoscopic cholecystectomy, with Bispectral index (BIS), and Analgesia and Nociception Index (ANI) as a guidance.

**MATERIAL AND METHODS:** After thorough pre-anaesthetic check-up, 60 adult patients aged 20-60yrs with ASA physical status of I and II, belonging to either sex and scheduled for undergoing laparoscopic cholecystectomy, were randomly allocated into two groups of 30 each, using computer generated random table, to receive blinded study drugs:

**Group 1:** received magnesium sulfate 30mg/kg bolus (made to 20ml saline) infused over 20min, 20min before induction, followed by 15mg/kg/hr.

**Group 2:** received dexmedetomidine at a bolus dose of 1 mcg/kg (made to 20ml saline) infused over 20min, 20 min before induction, followed by 0.5 mcg/kg/hr.

This study was carried over a period of 15 month.

Statistical analysis was done using SPSS version 20.0. Sample size was calculated using previous similar studies, and keeping  $\alpha < 5\%$  and  $\beta = 20\%$ , power of study = 80%. Mean  $\pm$  SD and Student's t-

test was used for statistical analysis and comparison of age, weight, haemodynamic parameters, dose of study drugs used, dose of propofol, time to extubation, and the use of rescue analgesia between the two groups, with a p-value of <0.05 considered significant.

**RESULTS:** In our study we found that the mean requirement of propofol in group 1 at the time of induction in mg was  $57.00 \pm 9.52$  and in group 2 it was  $58.33 \pm 9.85$  with no significant difference ( $p=0.596$ ). With maintenance infusion of magnesium and dexmedetomidine in the recommended mean dose ( $15\text{mg/kg/hr}$  and  $0.5\text{mcg/kg/hr}$  respectively), the mean requirement of propofol infusion for maintenance of depth of anaesthesia (to maintain BIS and ANI 40-60) was  $133.33 \pm 41.91$  mg (in group 1) and  $183.33 \pm 51.107$  mg (in group 2) with a statistical significant difference ( $p= 0.03$ ). Thus, there was a significant propofol sparing effect of around 56 mg, with magnesium use. With 1 ampule of magnesium sulfate being Rs 8.50 and 1 ampule of dexmedetomidine being Rs. 759, the mean cost was  $152.4 \pm 22.2$  and  $909.4 \pm 22.2$  respectively. Hence we got a significant cost effectiveness for patients with magnesium use. Therefore as per this study the sedative property is almost equal in both drugs and less propofol required to maintain adequate depth of anaesthesia in magnesium sulfate.

**CONCLUSION:** Hence, this study concludes that magnesium sulfate shows a promising role as an adjunct to total intravenous anesthesia (TIVA) for patients undergoing laparoscopic cholecystectomy. It offers comparable intraoperative hemodynamics, a higher propofol-sparing effect for maintaining general anesthesia, better postoperative analgesia, with cost-effectiveness, as compared to dexmedetomidine.

**KEYWORDS:** Laparoscopic Cholecystectomy, TIVA, Dexmedetomidine, Magnesium Sulfate, BIS, ANI.

## INTRODUCTION

Elective laparoscopic cholecystectomy has revolutionized gallbladder surgeries and is now the gold standard for treating cholelithiasis. It's a commonly performed surgical day-care procedure which often requires high quality anaesthesia and a good multimodal postoperative pain management, with minimal side effects<sup>[1]</sup>.

The main disadvantage of conventional laparoscopic procedures involves the insufflation of carbon dioxide (CO<sub>2</sub>) and elevation in intraabdominal pressure, which can lead to serious changes in the haemodynamic parameters of patients. Out of different anaesthetic adjuvants available in our armamentarium for supplementing general anaesthesia, searching for an ideal one for attenuating such hemodynamic changes in laparoscopic surgeries, is still a matter of debate, warranting multiple modalities<sup>[1]</sup>. We have Bispectral index (BIS), and Analgesia and Nociception Index (ANI) as advanced patient monitoring devices which ensures the best possible depth of anaesthesia and a good quality analgesia.

Propofol as an IV agent is being widely used in anaesthesia for induction and maintenance as a part of total intravenous anaesthesia (TIVA). The kinetics of propofol allow for adequate maintenance and rapid recovery of consciousness. The exceptionally high clearance rate probably contributes to relatively rapid recovery after a continuous infusion.

Although the pain following a laparoscopic cholecystectomy is less intense than open surgery, patients often suffer visceral pain with coughing, respiratory movements and mobilisation during the first hours and shoulder pain secondary to peritoneal insufflations after the eighth postoperative hour during the night after surgery. This can delay the patients' autonomy, lengthen the hospital stay and increase morbidity and costs. Multimodal analgesic techniques are therefore necessary to provide effective postoperative analgesia for several components of pain. Many methods have been used to reduce postoperative pain including non-steroidal inflammatory drugs (NSAID), local anaesthetics and opioids with varying doses. Administration of intraperitoneal LA either during or after surgery is used by many surgeons as a method of reducing postoperative pain.

Dexmedetomidine, a highly selective  $\alpha_2$  receptor agonist compared to  $\alpha_1$  receptor (1620:1) having sedative and analgesic properties seems to be apt enough to control this sympathetic response as well as provide a stable haemodynamics during extubation and in the postoperative period. Activation of  $\alpha_2$  receptors in the locus coeruleus of the brain stem reduces the central sympathetic output and increases the firing of the inhibitory neurons. It does this by inhibiting the release of catecholamine and vasopressin.<sup>[2-3]</sup> Thereby, producing its anxiolytic sedative and analgesic effect. Gourishankar Reddy Manne et al. found that low dose dexmedetomidine infusion in the dose of 0.4 mcg/kg/h effectively attenuates haemodynamic stress response during laparoscopic surgery with reduction in postoperative analgesic requirements. Now, magnesium is a noncompetitive blocker of N-methyl-D-aspartate (NMDA) receptor with antinociceptive effects. It is also a physiological calcium antagonist at different voltage gated channels which may be important in the mechanism of antinociception.<sup>[4-6]</sup> It provides good postoperative pain relief and obtunds hypertensive response to intubation. According to Montes et al. (2008) evaluated the analgesic efficiency of perioperative magnesium sulphate infusion in patients undergoing laparoscopic cholecystectomy and concluded that per-operative 50 mg/kg magnesium sulphate infusion is effective in reducing post-operative pain in such patients. With this background this study aimed to compare the effectiveness of dexmedetomidine versus magnesium as adjuvant in attenuating the haemodynamic response to pneumoperitoneum in patients scheduled for laparoscopic cholecystectomy under TIVA, with BIS and ANI as guidance.

## MATERIAL AND METHODS

The present study was conducted in the department of Anaesthesiology, Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi.

After ethics clearance from Institutional ethics committee, written informed consent from the patients, and a thorough pre-anaesthetic check-up, 60 adult patients aged 20-60yrs with ASA physical status of I and II, belonging to either sex and scheduled for undergoing laparoscopic cholecystectomy, were randomly allocated into two groups of 30 each, using computer generated random table, to receive blinded study drugs:

**Group 1:** received magnesium sulfate 30mg/kg bolus (made to 20ml saline) infused over 20 min, 20 min before induction, followed by 15mg/kg/hr.

**Group 2:** received dexmedetomidine at a bolus dose of 1 mcg/kg (made to 20 ml saline) infused over 20min, 20 min before induction, followed by 0.5 mcg/kg/hr.

This study was carried over a period of 15 month.

## Technique Used

Patients with history of allergy to study drugs, uncontrolled diabetes and hypertension, history of MI, Atrioventricular conductance disturbance, any neurological disorders, opioid or analgesic abuse, or pregnant females and those with deranged liver or renal function test were not included in the study. Surgical procedure lasting more than 90 min due to technical difficulty were also excluded from the study as drop outs.

In the pre-op room, a 18 G intravenous line was secured. After applying standard monitoring device (noninvasive blood pressure, electro cardio gram, percent saturation of arterial oxygen, end tidal carbon dioxide monitors), sensors for special monitoring BIS (Bispectral index) and ANI (Analgesia and nociception index) were attached. The loading doses of blinded study drugs were given over 20min.

Then the patient were taken into OT and GA was given according to standard protocol (preoxygenation for at least 3 min with 100% oxygen). Premedication was done with inj. Glycopyrrolate 0.01 mg/kg to reduce airway secretions and fentanyl was given @2 mcg /kg.

GA was induced with titrated doses of 2- 2.5 mg/ kg body weight of propofol and after injection vecuronium 0.1 mg/kg given and airway secured with appropriate sized endotracheal tube. Intubation was done at BIS 40. The infusion doses of the study drugs were started, as per above description, immediately after intubation and well before pneumoperitonium starts. Anaesthesia maintained with a mixture of oxygen and nitrous oxide in 50:50 ratio and propofol infusion 50-200mcg/kg/min.

Propofol infusion was titrated to target BIS at 40-60 for maintenance of depth of anaesthesia. Further maintenance dose of vecuronium was guided by curare notch in EtCO<sub>2</sub> graph. Minute ventilation was titrated to keep EtCO<sub>2</sub> in the range of 30-35. The study drugs were titrated to ensure heart rate and systolic blood pressure within 30% of the pre- pneumoperitonium value. Titration was done by starting the drug at the midpoint of the dose range and titrated upwards or downwards depending on the increase or decrease of haemodynamic parameters respectively. The intraabdominal pressure of pneumoperitonium was kept constant at 12 mmHg.

The infusion of both the study drugs were stopped at end of pneumoperitonium. Nitrous oxide was stopped 20min before last stitch and propofol was stopped at the last stitch. Haemodynamic parameters were noted just before establishing the pneumoperitonium and every three minutes after establishing the pneumoperitonium for the first 10 minutes and subsequently every 10 minutes till the end of pneumoperitonium using an automated multi-channel monitor. Similarly BIS and ANI were monitored.

The 30% increase in systolic blood pressure (SBP) or Heart rate(HR) to that of the pre pneumoperitonium value were rescued with bolus dose of inj. Labetalol 20mg slow iv over 2 minutes. Hypotension was treated with bolus dose of injection Mephentermine 6 mg while bradycardia was described as fall in heart rate below 50bpm and treated with injection atropine 0.6 mg in divided dose. Injection paracetamol 20mg/kg over 20min, and inj.Ondansatrom 0.1mg/kg were given 20 min before closure.

After the establishment of spontaneous respiration and reversal of residual effect of muscle relaxant by inj.neostigmine 0.04mg/kg and glycopyrrolate 0.01mg/kg, patients were extubated once they start responding. Rescue analgesia in form of tramadol 2 mg/kg was given when required in postoperative period.

Data recordings are done for changes in haemodynamic parameters before and after establishment of pneumoperitonium, total duration of pneumoperitonium (TDOP), Mean dose of study drugs used (MDOD), mean dose of propofol (MDOP), number of rescue doses of inj. Fentanyl and inj. Labetalol needed during procedure, time to extubation after stopping the study drug (TTE), haemodynamic parameters on extubation, post extubation VAS score.

### Statistical Analysis

Statistical analysis is done using SPSS version 20.0. Sample size was calculated using previous similar studies, and keeping  $\alpha < 5\%$  and  $\beta = 20\%$ , power of study=80%. Mean±SD and Student's t-test was used for statistical analysis and comparison of age, weight, haemodynamic parameters, TDOP, MDOD, TTE, PERS and TTRS2 between the two groups with a p-value of <0.05 considered significant. Chisquare test will be used for qualitative data comparison (sex, ASA grading).

### RESULTS

	Group	Mean±SD	t-value p-value
EtCO <sub>2</sub> _baseline	Group 1 (n=30)	29.83±2.60	t=-0.401 p=0.690
	Group 2 (n=30)	30.10±2.55	
EtCO <sub>2</sub> _Postinduction	Group 1 (n=30)	30.00±2.51	t=-0.200 p=0.842
	Group 2 (n=30)	30.13±2.63	
EtCO <sub>2</sub> _after_1 min	Group 1 (n=30)	30.27±2.44	t=-0.306 p=0.761
	Group 2 (n=30)	30.47±2.60	

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EtCO2_5min	Group 1 (n=30)	31.00±2.56	t=-0.221 p=0.826
	Group 2 (n=30)	31.13±2.08	
EtCO2_10min	Group 1 (n=30)	31.70±2.50	t=-0.112 p=0.911
	Group 2 (n=30)	31.77±2.09	
EtCO2_15min	Group 1 (n=30)	31.87±2.51	t=-0.860 p=0.393
	Group 2 (n=30)	32.40±2.28	
EtCO2_20min	Group 1 (n=30)	32.27±2.70	t=-0.312 p=0.756
	Group 2 (n=29)	32.45±1.61	
EtCO2_25min	Group 1 (n=30)	32.63±2.81	t=-0.607 p=0.546
	Group 2 (n=30)	33.00±1.74	
EtCO2_30min	Group 1 (n=29)	33.31±2.59	t=-0.039 p=0.969
	Group 2 (n=30)	33.33±1.82	
EtCO2_45min	Group 1 (n=22)	32.86±2.33	t=-0.487 p=0.629
	Group 2 (n=19)	33.21±2.20	
EtCO2_60min	Group 1 (n=13)	32.62±2.43	t=-1.380 p=0.183
	Group 2 (n=9)	34.00±2.12	
EtCO2_75min	Group 1 (n=6)	31.50±2.88	
	Group 2 (n=0)		
EtCO2_90min	Group 1 (n=2)	29.00±1.41	
	Group 2 (n=0)		
EtCO2_120min	Group 1 (n=0)		
	Group 2 (n=0)		
EtCO2_at_end_of_surgery	Group 1 (n=29)	33.55±2.44	t=-0.085 p=0.933
	Group 2 (n=30)	33.60±1.90	

Table 1: EtCO2

	Group	Mean±SD	t-value p-value
BIS .baseline	Group 1 (n=30)	90.13±9.96	t=-0.574 p=0.568
	Group 2 (n=30)	91.20±2.04	
BIS_Postinduction	Group 1 (n=30)	40.83±2.69	t=-0.122 p=0.903
	Group 2 (n=30)	40.77±1.30	
BIS_after_1min	Group 1 (n=30)	43.20±4.49	t=0.205 p=0.838
	Group 2 (n=30)	42.97±4.32	
BIS_5min	Group 1 (n=30)	46.07±5.55	t=1.160 p=0.251
	Group 2 (n=30)	44.47±5.12	
BIS_10min	Group 1 (n=30)	47.30±4.56	t=0.684 p=0.497
	Group 2 (n=30)	46.43±5.22	
BIS_15min	Group 1 (n=30)	49.23±3.57	t=0.854 p=0.397
	Group 2 (n=30)	48.27±5.06	
BIS_20min	Group 1 (n=30)	51.27±3.97	t=1.743 p=0.087
	Group 2 (n=30)	49.07±5.65	
BIS_25min	Group 1 (n=30)	51.77±3.98	t=0.517 p=0.607
	Group 2 (n=30)	51.10±5.83	
BIS_30min	Group 1 (n=29)	52.17±4.48	t=-1.685 p=0.098
	Group 2 (n=30)	54.30±5.17	
BIS_45min	Group 1 (n=20)	51.20±4.83	t=-2.046 p=0.048 (S)
	Group 2 (n=17)	54.76±5.77	
BIS_60min	Group 1 (n=11)	52.00±6.01	t=-0.872 p=0.395
	Group 2 (n=08)	54.38±5.63	
BIS_75min	Group 1 (n=6)	55.00±7.45	
	Group 2 (n=0)		
BIS_90min	Group 1 (n=1)	55.00	
	Group 2 (n=0)		

BIS_120min	Group 1 (n=0)		t=-1.424 p=0.160
	Group 2 (n=0)		
BIS_at_end_of_surgery	Group 1 (n=29)	53.97±5.05	
	Group 2 (n=30)	55.73±4.47	

**Table 2: Bispectral Index (BIS)**

	Group	Mean±SD	t-value p-value
VAS_30min	Group 1 (n=30)	0.07±0.36	t=-29.00 p=0.000 (HS)
	Group 2 (n=30)	2.00±0.00	
VAS_1hr	Group 1 (n=30)	0.07±0.36	t=-29.00 p=0.000 (HS)
	Group 2 (n=30)	2.00±0.00	
VAS_2hr	Group 1 (n=30)	0.07±0.36	t=-29.00 p=0.000 (HS)
	Group 2 (n=30)	2.00±0.00	
VAS_3hr	Group 1 (n=30)	0.07±0.36	t=-29.00 p=0.000 (HS)
	Group 2 (n=30)	2.00±0.00	
VAS_4hr	Group 1 (n=30)	0.07±0.36	t=-29.00 p=0.000 (HS)
	Group 2 (n=30)	2.00±0.00	
VAS_5hr	Group 1 (n=30)	0.07±0.36	t=-21.612 p=0.000 (HS)
	Group 2 (n=30)	2.53±0.50	
VAS_6hr	Group 1 (n=30)	0.07±0.36	t=-23.629 p=0.000 (HS)
	Group 2 (n=30)	2.67±0.47	
VAS_7hr	Group 1 (n=30)	0.10±0.54	t=-19.067 p=0.000 (HS)
	Group 2 (n=30)	2.97±0.61	
VAS_8hr	Group 1 (n=30)	0.10±0.54	t=-24.365 p=0.000 (HS)
	Group 2 (n=29)	3.45±0.50	

**Table 3: Visual Analogue Score (VAS)**

Rescue analgesic 30 min				
		Group 1 (n=30)	Group 2 (n=30)	Total
	N	1	0	1
	%	3.3%	.0%	1.7%
NR	N	29	30	59
	%	96.7%	100.0%	98.3%
Total	N	30	30	60
	%	100.0%	100.0%	100.0%
Rescue analgesic 1 hr				
		Group 1 (n=30)	Group 2 (n=30)	Total
NR	N	30	30	60
	%	100.0%	100.0%	100.0%
Total	N	30	30	60
	%	100.0%	100.0%	100.0%
Rescue analgesic 2 hr				
		Group 1 (n=30)	Group 2 (n=30)	Total
NR	N	30	30	60
	%	100.0%	100.0%	100.0%
Total	N	30	30	60
	%	100.0%	100.0%	100.0%
Rescue analgesic 3 hr				
		Group 1 (n=30)	Group 2 (n=30)	Total
NR	N	30	30	60
	%	100.0%	100.0%	100.0%
Total	N	30	30	60
	%	100.0%	100.0%	100.0%

Rescue analgesic 4 hr				
		Group 1 (n=30)	Group 2 (n=30)	Total
NR	N	30	30	60
	%	100.0%	100.0%	100.0%
Total	N	30	30	60
	%	100.0%	100.0%	100.0%
Rescue analgesic 5 hr				
		Group 1 (n=30)	Group 2 (n=30)	Total
NR	N	30	30	60
	%	100.0%	100.0%	100.0%
Total	N	30	30	60
	%	100.0%	100.0%	100.0%
Rescue analgesic 6 hr				
		Group 1 (n=30)	Group 2 (n=30)	Total
NR	N	30	30	60
	%	100.0%	100.0%	100.0%
Total	N	30	30	60
	%	100.0%	100.0%	100.0%

**Table 4: Rescue analgesic Details**

		Group 1 (n=30)	Group 2 (n=30)	Total
NR	N	30	25	55
	%	100.0%	83.3%	91.7 %
R	N	0	5	5
	%	0.0%	16.7%	8.3%
Total	N	30	30	60
	%	100.0%	100.0%	100.0%

**Table 5: Rescue analgesic 7 hr**  
 $\chi^2=5.455, P=0.020 (S)$

		Group 1 (n=30)	Group 2 (n=30)	Total
NR	N	30	18	48
	%	100.0%	60.0%	80.0%
R	N	0	12	12
	%	0.0%	40.0%	20.0%
Total	N	30	30	60
	%	100.0%	100.0%	100.0%

**Table 6: Rescue analgesic 8 hr**  
 $\chi^2=15.000, P=0.000 (HS)Ta$

	Group 1 (n=30)	Group 2 (n=30)	t-value p-value
Induction propofol	57.00±9.52	58.33±9.85	t=-0.533 p=0.596
Infusion propofol	133.33±41.91	183.33±51.107	t=-4.143 p=0.000 (HS)

**Table 7 : Induction propofol and Infusion propofol**

Table 1 shows comparison of End tidal CO<sub>2</sub> which was comparable at all-time intervals. It was kept between 25-35 in both the groups. Table 2 shows comparison of BIS which shows on significant difference and our target to keep BIS 40-60 was fulfilled at all-time intervals of surgery. Table 3 shows comparison of mean VAS score of group 1 and group 2 which was not comparable in both the groups with higher value in group 2, (showing on average of 2.00±0.00 in group 2 and 0.07±0.36 in group 1 with p value =0.00, till 6hr) and mean VAS score at 7<sup>th</sup> hour was 0.10±0.54 in

group 1 and  $2.97 \pm 0.61$  in group 2 with  $p$  value = 0.00 and at 8<sup>th</sup> hour it was  $0.10 \pm 0.54$  in group 1 and  $3.45 \pm 0.50$  in group 2 with  $p$  value = 0.00. This shows that the pain was bearable and required no analgesia till 6hr in both the group although it was better controlled in group 1 (magnesium) but VAS score gradually increased in group 2 at 7hr onwards.

Table 4 shows comparison of requirement of analgesia in group 1 and 2 at 30<sup>th</sup> min, 1 hr, 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup> and 6<sup>th</sup> hour of postoperative period where it showed that there was no requirement of analgesia in any of the groups.

Table 5 shows the comparison of mean of requirement of analgesia in group 1 and 2 where it showed that in group 2, 5 patients required the analgesia (tramadol/diclofenac). And there was no requirement of analgesia in group 1. And it significant with  $p$  value = 0.020

Table 6 shows the comparison of mean of requirement of analgesia in patients of group 1 and group 2 and it showed that 12 patients in group 2 required rescue analgesia at 7<sup>th</sup> and 8<sup>th</sup> hour onwards with  $p$  value = 0.000, which shown a significant difference in group 1 and group 2 where group no patients of group 1 required rescue analgesia, hence showing magnesium a better drug for control over analgesia.

Table 7 shows comparison of mean induction dose of propofol required in group 1 and 2 ( $57.00 \pm 9.52$  and  $58.33 \pm 9.85$  respectively with  $p$  value = 0.596) which was comparable in both the groups. Table also shows comparison of of mean infusion dose of propofol in group 1 ( $133.33 \pm 41.91$ mg) and group 2 ( $183.33 \pm 51.107$ ) with  $p$  value = 0.03, which showed the significant difference of requirement of propofol with greater requirement in group 2.

## DISCUSSION

The 60 patients were allocated into both groups, with 30 in each of the 2 groups, according to computer generated randomization chart. These patients belonged to ASA I and ASA II grades, between age group of 20-60 years who were scheduled for laparoscopic cholecystectomy. We evaluated the effect of magnesium sulfate and dexmedetomidine in attenuating haemodynamic stress response associated with pneumoperitonium, and the requirement of propofol and analgesics, to maintain a target of BIS 40-60 and ANI 40-60. Also, postoperative analgesia requirements were compared.

In this study we have found that both drugs are effective in attenuating the haemodynamic response during pneumoperitonium.

The result of this study about effect of magnesium sulfate on haemodynamics intraoperative correlate well with Lee and Kwon,<sup>[7]</sup> who found that preoperative intravenous magnesium sulfate attenuated arterial pressure increases during general anaesthesia for Caesarean section to avoid perioperative press or response resulting from inadequate anaesthesia, analgesia or both of them. Jee et al.<sup>[8]</sup> also found that intravenous magnesium sulfate before pneumoperitonium attenuates arterial pressure increases during laparoscopic cholecystectomy and this attenuation is apparently related to reductions in the release of catecholamine, vasopressin or both of them.

The effect of magnesium on haemodynamics due to interact in the activation of membrane Ca-ATPase and Na-K-ATPase is involved in transmembrane ion exchanges during depolarisation and repolarisation phases, thus acting as a cell membrane stabiliser and also as an intracytoplasmic organelles stabiliser. This calcium inhibitory effect of Mg causes central arteriolar vasodilatation and acts against vasospasm. Another mechanism could involve the reduction of catecholamine release with sympathetic stimulation, thereby decreasing the stress response to surgery. The analgesic effect of magnesium is due to it blocks N- methylD- aspartate (NMDA) receptor which plays significant role in the mechanisms underlying central sensitisation in spinal cord and is crucial for the establishment of several pain states.

Similarly for dexmedetomidine, Jaakola et al<sup>[9]</sup> found decrease in BP and heart rate during intubations following the administration of 0.6 mcg/kg bolus of dexmedetomidine preoperatively. Lawrence et al<sup>[10]</sup> found decreased hemodynamic response to tracheal intubation or extubation following a single high dose of dexmedetomidine (2mcg/kg). Ghodki et al<sup>[11]</sup> used dexmedetomidine



1 mcg/kg intravenously over 15 min before induction followed by maintenance infusion of 0.2 mcg/kg/hr and observed favourable vasopressor response during laryngoscopes, with minimal change in BP with pneumoperitoneum which is similar to the result of our study.

Dexmedetomidine is a highly selective  $\alpha_2$  adrenergic agonist. It acts through three types of  $\alpha_2$  receptors  $\alpha_2$  A,  $\alpha_2$  B and  $\alpha_2$  C situated in brain and spinal cord. The resultant action is sedation, anxiolysis, analgesia and sympatholysis, the latter leading to hypotension and bradycardia. Activation of  $\alpha_2$  A receptors in brain stem vasomotor centre results in suppression of norepinephrine release, hypotension and bradycardia. Stimulation of  $\alpha_2$  A and  $\alpha_2$  C in locus ceruleus causes sedation. In the spinal cord, activation of both  $\alpha_2$  A and  $\alpha_2$  C receptors directly reduce pain transmission by reducing release of substance P.<sup>[12]</sup>

Above explanation is the mechanism of dexmedetomidine for control of haemodynamic response. In our study there was no episode of hypotension or bradycardia.

In this study we have used BIS and ANI to maintain depth of anaesthesia and adequate analgesia to prevent haemodynamic instability and to maintain depth of anaesthesia we have used propofol as an agent to give total intravenous anaesthesia with dose in the range of 50-200 mcg/kg/min and its dose was modified intraoperatively as per requirements to keep BIS between 40 and 60. The doses of dexmedetomidine and magnesium sulfate were kept constant.

In order to keep ANI 40-60, none of the patients required fentanyl as rescue analgesia intraoperatively at a dose of 2mcg/kg I.V. Though there was a difference of VAS score at 7 hr onwards in postoperative period requiring rescue analgesia in group 2.

In our study we found that the mean requirement of propofol in group 1 at the time of induction in mg is  $57.00 \pm 9.52$  and in group 2 it was  $58.33 \pm 9.85$  with no significant difference ( $p=0.596$ ).

With maintenance infusion of magnesium and dexmedetomidine in the recommended mean dose (15mg/kg/hr and 0.5mcg/kg/hr respectively), the mean requirement of propofol infusion for maintenance of depth of anaesthesia (to maintain BIS 40-60) was  $133.33 \pm 41.91$  mg (in group 1) and  $183.33 \pm 51.107$  mg (in group 2) with statistical significant difference ( $p=0.03$ ).

Thus there was a significant propofol sparing effect of around 56 mg, with magnesium use. With 1 ampule of magnesium sulfate being Rs 8.50 and 1 ampule of dexmedetomidine being Rs. 759, the mean cost was  $152.4 \pm 22.2$  and  $909.4 \pm 22.2$  respectively. Hence we got a significant cost effectiveness for patients with magnesium use.

Therefore as per our study the sedative property is almost equal in both drugs and less propofol required to maintain adequate depth of anaesthesia in magnesium sulfate.

In previous studies Choi and colleagues<sup>[13]</sup> demonstrated that the usage of propofol reduced from 167 to 81 mg/kg/min after administering bolus dose of  $MgSO_4$  (50mg/kg) followed by continuous  $MgSO_4$  infusion (8mg/kg/min) in gynaecological surgeries.

In other study conducted by Seyhan and colleagues<sup>[14]</sup> infusion of  $MgSO_4$  in patients significantly reduced the amount of intraoperative propofol and neuromuscular blocking agent. Postoperative pain and opioid analgesics consumption was also reduced.

In other study done by Chiteswar and colleagues<sup>[15]</sup> on propofol sparing effect of dexmedetomidine and magnesium sulfate during BIS targeted anaesthesia, a prospective randomised placebo controlled trial in which result shows that propofol required in group D for induction was significantly lower  $101.3 \pm 16.5$  than group M and N (placebo) with dose of  $114 \pm 15.5$  and  $160.50 \pm 25.08$  respectively ( $p < 0.001$ ), this is contradictory to our study where propofol requirement was similar for induction. In their study they did not compare infusion requirement for TIVA. In our study, we did a BIS guided comparison for propofol sparing effect and found out that it was significantly less in group 1 (magnesium) in comparison to group 2 (dexmedetomidine) to maintain targeted BIS of 40-60.

To maintain haemodynamic response it is important to maintain depth of anaesthesia and also analgesia for which we used analgesia noiception index (ANI) and target to keep that between 40-60, and to target this we need not to repeat fentanyl intraoperatively in both group.

In postoperative period we used visual analogue score to assess pain and requirement of analgesia. VAS score at 30min, 1,2,3,4,5 hr shows significant difference with VAS score of group 2 was  $2.00 \pm 0.00$  and group 1 was  $0.07 \pm 0.36$  with p value  $< 0.000$ , mean VAS score at 8<sup>th</sup> hour was  $3.45 \pm 0.5$  and group 1 was  $0.10 \pm 0.54$  which shows significant difference ( $p < 0.00$ ). Though there was statistical significant difference in VAS score, group 1 having vas score of 0 at all points of time ( $p < 0.001$ ), there was no clinical significant difference in quality of postoperative analgesia. The group 2 had VAS score of around 2 at most of the time points, and a vas score of around 4 at 8<sup>th</sup> hour ( $p < 0.001$ ). None of the patients required rescue analgesia in postoperative period, except in group 2 where 5 patients at 7<sup>th</sup> hour (16.7%) and 12 patients at 8<sup>th</sup> hour (40%) required rescue analgesia ( $p = 0.02$  and  $p < 0.001$ , respectively).

In previous study done by Rania et al<sup>[16]</sup> on effect of intraperitoneal magnesium sulfate on hemodynamic changes and its analgesic effect in laparoscopic cholecystectomy the result shows that hemodynamic parameters were significantly higher in group C compared with group M at 10, 20 and 30 min after pneumoperitonium, and at the time of extubation. Recovery characteristics in terms of extubation time, emergence time, and time to reach full aldrete score were significantly longer in group M compared with group C. Mean pain scores (visual analog scale) were significantly lower in group M compared with group C during the first 6 postoperative hours, and time to first analgesic requirement was longer in group M ( $9.2 \pm 3h$ ) compared to group C ( $2.4 \pm 1.3h$ ) which supports the result of our study.

## SUMMARY AND CONCLUSION

Laparoscopic cholecystectomy is routinely performed surgery and it is desirable to have a stable intraoperative hemodynamic status by avoiding hypertension, hypotension and tachycardia. Dexmedetomidine and magnesium sulfate have generated interest in this regard. There were studies which evaluated these agents exclusively. To our best of knowledge none of the earlier studies compared these two agents for evaluating haemodynamics and propofol sparing effect for the whole perioperative period. the present study was conducted to establish and compare the effects of dexmedetomidine and magnesium sulfate in maintaining perioperative cardiovascular stability, propofol consumption as a part of TIVA and postoperative analgesia in laparoscopic cholecystectomy, with BIS and ANI as a guidance.

### Our study indicated that

1. Both the drugs were effective and comparable in attenuating the haemodynamic response to laryngoscopy, surgical stress and pneumoperitonium. The mean heart rate was lower at few points of time (10<sup>th</sup>, 15<sup>th</sup> and 20<sup>th</sup> min) with dexmedetomidine, though there was no episode of symptomatic bradycardia requiring treatment. SBP and DBP were lower at few points of time (post induction, 1 min, 5 min and 10<sup>th</sup> min) with magnesium use but none of the patients required any vasopressor treatment
2. There was a significant propofol sparing effect (of around 56 mg) with magnesium use for maintenance of GA but not during induction.
3. Intraoperative Opioid sparing effect was similar for both the groups, though few patients required rescue analgesia in late postoperative period (beyond 7<sup>th</sup> hour) with dexmedetomidine use. None of the patients in magnesium group required rescue analgesia (VAS was zero for 8 postoperative hours).
4. In view of the propofol sparing effect and cost per ampule of magnesium sulfate, this drug proved to be more cost effective (mean difference in expenditure was around Rs. 757).

Based on our study, we concluded that magnesium sulfate shows a promising role as an adjunct to total intravenous anesthesia (TIVA) for patients undergoing laparoscopic cholecystectomy. It offers comparable intraoperative hemodynamics, a greater propofol-sparing effect for maintaining general anesthesia, better postoperative analgesia, and cost-effectiveness compared to dexmedetomidine.

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