

Original Research Article

Prospective Comparative Study of Clonidine, Magnesium Sulphate and Dexmedetomidine on Hemodynamic Changes During Laparoscopic Surgeries

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ABSTRACT

Background: Hemodynamic changes following pneumoperitoneum are common during laparoscopic surgeries. Various measures and drugs have been tried but none has proved ideal.

Aim: To evaluate the attenuation of hemodynamic changes during laparoscopic surgeries using intravenous clonidine, magnesium sulphate and dexmedetomidine in adult patients.

Methods: A randomised prospective study was conducted over 10 months after Institutional Ethical Committee clearance. Ninety-two patients were randomly allocated into four groups of 23 each including a control group: Group I (clonidine 1 µg/kg), Group II (magnesium sulphate 30 mg/kg), Group III (dexmedetomidine 1 µg/kg) and Group IV (normal saline). Heart Rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and rate pressure product (RPP) were compared before induction, after induction, before and after intubation, before pneumoperitoneum (BP) and 5 min (P5), 10 min (P10), 15 min (P15), 30 min (P30) & 45 min (P45) after pneumoperitoneum.

Result: A significant fall in HR, SBP, DBP, MAP and RPP was seen with time in all the groups ($p < 0.001$ for all). Dexmedetomidine significantly attenuated HR compared with control at 5, 10 and 15 minutes after pneumoperitoneum creation. A significant time×group interaction was seen with SBP ($p < 0.001$, partial $\eta^2 = 0.101$), DBP ($p = 0.002$, partial $\eta^2 = 0.085$) and MAP ($p < 0.001$, partial $\eta^2 = 0.122$), but not for RPP ($p = 0.16$). Bonferroni-adjusted comparisons showed dexmedetomidine had significantly lower HR than clonidine at 5 minutes and lower HR than control at 5, 10 and 15 minutes; lower SBP than control at 10 and 15 minutes; and lower MAP than control at 10 and 15 minutes. Clonidine had significantly lower SBP than control at 15 minutes and lower MAP than control at 15 minutes. Magnesium sulphate did not differ significantly from control at any time point, but had significantly higher SBP than dexmedetomidine at 15 minutes and higher MAP than dexmedetomidine at 10 and 15 minutes. RPP showed no significant time×group interaction or overall between-group difference.

Conclusion: Dexmedetomidine produced the most consistent attenuation of HR, SBP and MAP at specific early time points after pneumoperitoneum creation. Clonidine showed isolated attenuation of SBP and MAP, whereas magnesium sulphate did not differ significantly from control in adjusted comparisons. RPP changed significantly with time but showed neither a significant time×group interaction nor an overall between-group difference.

Keywords: Clonidine, Dexmedetomidine, Magnesium Sulphate, Hemodynamics, Pneumoperitoneum, Laparoscopic Surgery.

INTRODUCTION

Pneumoperitoneum created during laparoscopic surgeries is challenging for

anesthesiologists because of positioning, altered physiology and the stress response to hypercarbia, which can cause severe

hypertension or tachycardia. Although it may be self-limiting, this stress response can result in potentially dangerous complications such as left heart failure, pulmonary edema, myocardial ischemia or stroke in vulnerable populations.^[1,2] A number of strategies have been used to blunt these adverse hemodynamic changes including drugs like opioids, vasodilators, beta blockers, calcium channel blocker, alpha2 agonists and magnesium sulphate.^[3,4] Alpha-2 agonists, especially clonidine and dexmedetomidine, have been routinely employed to blunt the sympathetic response during surgery; they act through G-protein-coupled transmembrane receptors present in the pre- and post-synaptic autonomic ganglia.^[5,6] Magnesium sulphate is a more recent addition that acts by blocking the release of catecholamines from adrenergic nerve terminals and adrenal glands. It decreases the sensitivity of receptors to catecholamines in addition to directly acting on blood vessels to cause vasodilatation.^[5,7,8] This study was designed to compare the effects of intravenous clonidine, magnesium sulphate and dexmedetomidine with a normal-saline control on hemodynamic changes during laparoscopic surgery.

MATERIALS AND METHODS

This prospective randomised controlled study was conducted from June 2022 to March 2023 after obtaining approval from the Institution Ethics Committee.

Inclusion Criteria

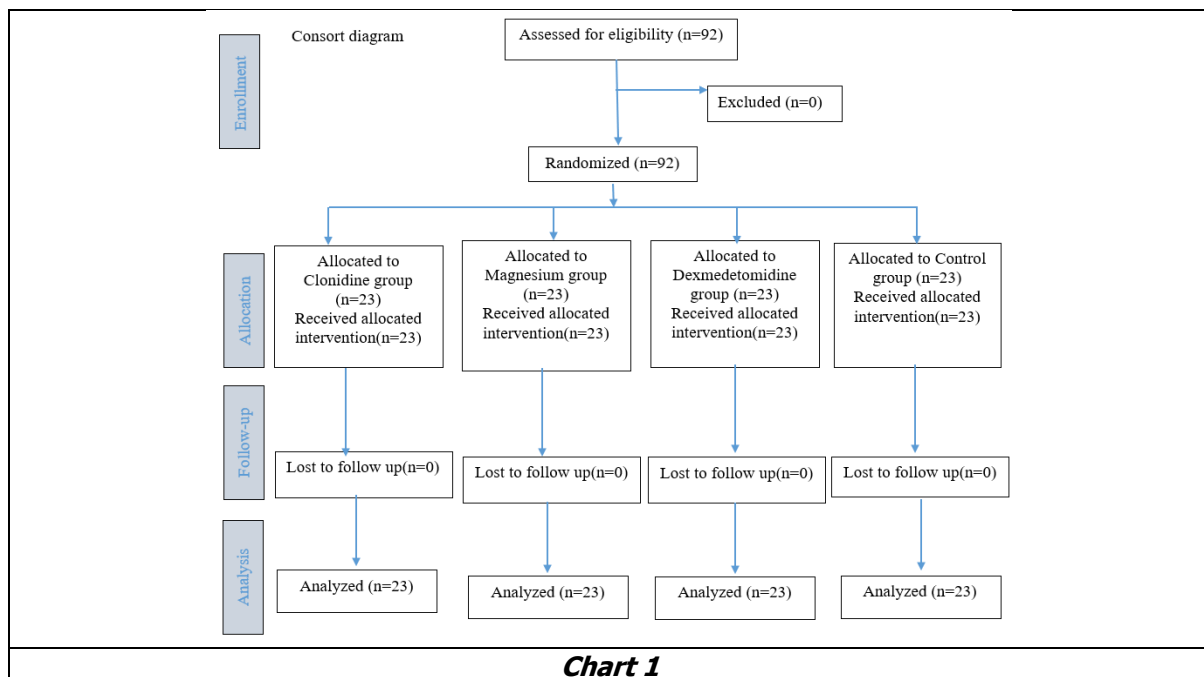
All the adult patients between the age group of 18-64 years of either sex of ASA-1 and 2 risk undergoing elective laparoscopic procedures under general anaesthesia were included.

Exclusion Criteria

1. Age below 18 years or 65 years and above.
2. Patients with ASA 3 and ASA 4 risk as per ASA risk stratification.
3. Patients in whom the procedures were converted to open surgery.
4. Emergency surgeries

Statistical Analysis

All data collected were entered in MS. Excel sheets and analysed using SPSS for Windows, Version 16.0. Chicago, SPSS Inc. All the qualitative factors like Sex, Operative Procedure and All the quantitative parameters like HR, SBP, DBP, MAP, RPP at different time points were represented with means and standard deviation. For each haemodynamic parameter, a mixed-design repeated-measures ANOVA was performed across all the time points with treatment group (clonidine, magnesium sulphate, dexmedetomidine, control) as the between-subjects factor. Mauchly's test was used to assess the assumption of sphericity for each parameter; when this assumption was violated, Greenhouse–Geisser-corrected results were used for the within-subject (time and time × group) effects. For inter-group comparisons at individual time points, Bonferroni-adjusted pairwise comparisons of estimated marginal means were used, and effect sizes were expressed as partial eta-squared (partial η^2). A p-value <0.05 was considered statistically significant. Patients with a missing value at any of the seven analysed time points when surgery would have got over earlier were excluded from the corresponding repeated-measures model for that parameter.



All the patients who fulfilled inclusion criteria were assessed by the anaesthesiologist a day prior to surgery premedicated with Tab. Alprazolam 0.5mg and Tab. Ranitidine 150mg on the night before surgery and Inj. pantoprazole 40mg and ondansetron 4mg iv on the morning 1 h before surgery.

A closed envelope technique was used to assign patients into four groups of 23 each. Group I received injection clonidine, Group II received injection magnesium sulphate, Group III received injection dexmedetomidine and Group IV received 50 ml normal saline as control. Anaesthesia was administered by a specialist anaesthesiologist with at least 2 years' experience. After application of all standard ASA monitoring devices and preoxygenation, all patients were premedicated with Inj. Midazolam 0.1mg/kg, Inj. Glycopyrrolate 0.005mg/kg and Inj. Fentanyl 2 µg/kg IV) before induction.

Induction was done with injection propofol 2 mg/kg and injection succinylcholine 2mg/kg. Intubated with appropriate sized cuffed endotracheal tube and anaesthesia maintained with closed circuit IPPV with oxygen: nitrous oxide 1:1 with isoflurane (0.6%). Injection atracurium 0.5mg/kg IV bolus and 0.1mg/kg every 20 minutes was used for muscle relaxation. Injection Fentanyl 0.5mcg/kg IV was repeated after 30 minutes of initial dose.

Group I patients received injection clonidine 1.0µg/kg in 50 ml of normal saline

RESULTS

over 10 min, prior to creation of pneumoperitoneum. Group II patients received injection magnesium sulphate 30 mg/kg, Group III received injection Dexmedetomidine 1 mcg/kg, and Group IV (control) received 50 ml normal saline; all infusions were given over 10 min in 50 ml of normal saline before pneumoperitoneum. Systolic blood pressure (SBP), diastolic blood pressure (DBP), Mean arterial pressure (MAP), Heart Rate (HR) and Rate pressure product (RPP) were recorded before induction (baseline values), after induction, before pneumoperitoneum (BP), after pneumoperitoneum creation (AP), 5 min after pneumoperitoneum creation (P5), 10 min after pneumoperitoneum creation (P10), 15 min (P15), 30 min (P30), 45 min (P45), 60 min (P60) and at extubation. Pneumoperitoneum inflation pressures were maintained at 14 mm Hg.

During surgery, IV fluid ringer lactate was infused for maintenance volume requirements. Intra operative hypertension (BP >160/100) was managed by infusion of nitroglycerine 0.5 to 1 mcg/kg/min. Hypotension as defined as fall in MAP <20% from baseline was managed with fluid bolus of 250ml or Mephentermine 6 mg intravenous. Atropine 0.6 mg intravenous was given if HR < 52/min.

Patient was reversed with Injection Neostigmine 0.05 mg/kg and Injection Glycopyrrolate 0.01 mg/kg at the end of the surgery and extubation was done.

Variable	Group I (Clonidine)	Group II (Magnesium)	Group III (Dexmed)	Group IV (Control)
Age, mean (years)	38	35	42	40
Male, n	5	1	8	4
Female, n	18	22	15	19
Average duration of surgery	45 minutes	40 minutes	45 minutes	50 minutes
Average weight	55 kg	62 kg	58 kg	60 kg
Total laparoscopic hysterectomy	7	8	6	8
Laparoscopic cholecystectomy,	5	9	6	7
Laparoscopic appendicectomy,	4	3	6	5
Other surgeries,	7	3	5	3

Table 1. Profile of participants

As shown in Table 1, there was a mean age (35–42 years) and the distribution of female preponderance in all four groups, and procedures were broadly similar across groups.

Hemodynamic Profile

Heart Rate	Clonidine	Magnesium	Dexmed	Control	P Value
BI	90.3 ± 17.749	88.74 ± 15.609	95.22 ± 20.545	87.7 ± 19.3	0.523
AI	99.13 ± 15.098	96.83 ± 16.921	102.26 ± 23.663	93.17 ± 14.345	0.373
BP	85.04 ± 13.404	83.61 ± 10.858	79.35 ± 16.87	87.83 ± 13.674	0.221
AP	88.65 ± 12.209	84.26 ± 12.764	83.39 ± 15.026	91 ± 16.404	0.224
5 Mins	90.17 ± 13.753	82.13 ± 13.071	78.87 ± 13.036	89.57 ± 12.169	0.008
10 Mins	84.41 ± 10.742	82.48 ± 12.365	78.65 ± 16.126	90.35 ± 13.523	0.032
15 Mins	82.68 ± 10.513	83.83 ± 11.831	79.22 ± 16.73	90.95 ± 13.974	0.036
30 Mins	82.46 ± 14.604	80.5 ± 11.325	79.75 ± 15.667	87.57 ± 14.5	0.405
45 Mins	80.22 ± 14.584	86.08 ± 9.81	76.45 ± 15.339	80.63 ± 9.899	0.327
60 Mins	88 ± 0	91.4 ± 7.57	76.9 ± 16.468	76 ± 19.519	0.339
Extubation	87.65 ± 8.515	94.17 ± 14.865	87.57 ± 16.384	91.43 ± 14.119	0.301

Table 2: Heart rate (mean ± SD). BI, before induction; AI, after induction; BP, before pneumoperitoneum; AP, after pneumoperitoneum

Time point	Comparison	Mean difference	SE	Adjusted p	95% CI
5 min	Clonidine vs Magnesium	7.46	3.86	0.34	–2.97 to 17.89
5 min	Clonidine vs Dexmedetomidine	10.72	3.86	0.04	0.29 to 21.15
5 min	Clonidine vs Control	–0.77	3.90	1.00	–11.32 to 9.77
5 min	Magnesium vs Dexmedetomidine	3.26	3.82	1.00	–7.05 to 13.57
5 min	Magnesium vs Control	–8.23	3.86	0.22	–18.66 to 2.20
5 min	Dexmedetomidine vs Control	–11.49	3.86	0.02	–21.92 to –1.07
10 min	Clonidine vs Magnesium	1.93	3.96	1.00	–8.77 to 12.63
10 min	Clonidine vs Dexmedetomidine	5.76	3.96	0.90	–4.94 to 16.46
10 min	Clonidine vs Control	–6.77	4.01	0.57	–17.59 to 4.05
10 min	Magnesium vs Dexmedetomidine	3.83	3.92	1.00	–6.75 to 14.41
10 min	Magnesium vs Control	–8.70	3.96	0.18	–19.40 to 2.00
10 min	Dexmedetomidine vs Control	–12.53	3.96	0.01	–23.23 to –1.83
15 min	Clonidine vs Magnesium	–1.14	4.02	1.00	–12.01 to 9.72
15 min	Clonidine vs Dexmedetomidine	3.46	4.02	1.00	–7.40 to 14.33
15 min	Clonidine vs Control	–8.27	4.07	0.27	–19.26 to 2.72
15 min	Magnesium vs Dexmedetomidine	4.61	3.98	1.00	–6.14 to 15.36
15 min	Magnesium vs Control	–7.13	4.02	0.48	–18.00 to 3.74
15 min	Dexmedetomidine vs Control	–11.74	4.02	0.03	–22.61 to –0.87

Table 3: Bonferroni-adjusted pairwise comparisons of heart rate

- As seen from Tables 2 and 3, mean HR changed significantly over time in all four groups (time effect, $p < 0.001$): it rose after induction and intubation and then declined

- at later time points.
- Between-group differences in HR were significant at 5 minutes ($P = 0.008$), 10 minutes ($P = 0.032$) and 15 minutes ($P = 0.036$) after pneumoperitoneum creation. On Bonferroni-adjusted comparison (Table

3), these differences were attributable to the dexmedetomidine group, which had significantly lower HR than control at all three time points and lower HR than clonidine at 5 minutes; magnesium did not differ significantly from control or from the other groups.

Systolic Blood Pressure	Clonidine	Magnesium	Dexmed	Control	P Value
BI	148.7 ± 22.042	140.09 ± 20.42	146.78 ± 15.696	132.61 ± 23.013	0.039
AI	124.3 ± 25.503	125.35 ± 22.205	131.87 ± 24.106	117.91 ± 17.63	0.227
BP	99.3 ± 11.348	100.7 ± 11.255	106 ± 22.161	107 ± 14.774	0.251
AP	123.35 ± 28.064	119.17 ± 19.595	113.52 ± 19.707	122.26 ± 20.585	0.444
5 Mins	136 ± 25.136	126.83 ± 22.329	124.78 ± 29.315	135.39 ± 26.104	0.334
10 Mins	122.78 ± 20.54	124.22 ± 14.349	112.26 ± 16.688	131.52 ± 23.189	0.01
15 Mins	114.3 ± 12.223	123.39 ± 12.157	108.57 ± 14.884	129.09 ± 15.808	<0.001
30 Mins	115.23 ± 16.167	119.32 ± 15.948	107.9 ± 15.204	129.36 ± 18.084	0.004
45 Mins	110.11 ± 13.411	124.31 ± 13.256	110.45 ± 10.444	135.63 ± 22.809	0.002
60 Mins	117 ± 0	130 ± 10.677	116.7 ± 3.917	138 ± 14.177	0.004
Extubation	130.52 ± 22.468	142.83 ± 19.439	123.61 ± 18.438	135.3 ± 25.414	0.027

Table 4: Systolic blood pressure

Time point	Comparison	Mean difference (mmHg)	95% CI	Adjusted p
10 min	Dexmedetomidine vs Control	-19.26	-34.38 to -4.14	0.005
15 min	Clonidine vs Control	-14.79	-25.82 to -3.76	0.003
15 min	Magnesium vs Dexmedetomidine	14.82	3.79 to 25.85	0.003
15 min	Dexmedetomidine vs Control	-20.52	-31.55 to -9.49	<0.001

Table 5: Bonferroni-adjusted pairwise comparisons of systolic blood pressure

- As seen from Tables 4 and 5, SBP changed significantly over time in all groups (time effect, $p < 0.001$): it fell after induction, rose after intubation and was significantly lower than baseline in the three drug groups after pneumoperitoneum creation.
- Between-group differences in SBP were significant at 10 minutes ($P = 0.010$), 15 minutes ($P < 0.001$), 30 minutes ($P =$

0.004), 45 minutes ($P = 0.002$) and 60 minutes ($P = 0.004$); the 30–60 minute values are unadjusted univariate comparisons. In the Bonferroni-adjusted analysis (Table 5), dexmedetomidine had significantly lower SBP than control at 10 and 15 minutes and lower SBP than magnesium at 15 minutes and clonidine had significantly lower SBP than control at 15 minutes

Diastolic Blood Pressure	Clonidine	Magnesium	Dexmed	Control	P Value
BI	87.04 ± 11.424	79.78 ± 9.959	83.48 ± 11.504	76.61 ± 10.067	0.009
AI	72.43 ± 16.714	70.39 ± 15.814	79.91 ± 15.991	71.22 ± 13.122	0.147
BP	58.04 ± 10.164	59.74 ± 10.235	64.43 ± 17.686	65.13 ± 10.459	0.159
AP	78.09 ± 18.171	76.09 ± 15.803	74.39 ± 17.665	79 ± 13.708	0.78
5 Mins	86 ± 17.088	79.13 ± 14.922	76.78 ± 19.002	83.17 ± 14.218	0.236
10 Mins	74.7 ± 12.687	76.17 ± 8.643	70.83 ± 14.25	78.91 ± 12.856	0.166
15 Mins	71.43 ± 6.795	74.96 ± 9.537	67.26 ± 12.256	78.64 ± 11.03	0.002
30 Mins	70.77 ± 14.675	72.2 ± 12.159	64.9 ± 9.941	77.43 ± 11.036	0.029
45 Mins	68.78 ± 11.344	72.38 ± 10.211	65.45 ± 10.26	77.88 ± 12.403	0.105
60 Mins	79 ± 0	72 ± 12.124	67.5 ± 11.759	80 ± 2	0.352
Extubation	78.04 ± 12.122	81.78 ± 11.326	73.52 ± 12.866	80.83 ± 13.234	0.113

Table 6: Diastolic blood pressure

Time point	Comparison	Mean difference (mmHg)	95% CI	Adjusted p
Before induction	Clonidine vs Control	10.498	1.78 to 19.21	0.01
15 min	Dexmedetomidine vs Control	-11.375	-19.51 to -3.24	0.002

Table 7: Bonferroni-adjusted pairwise comparisons of diastolic blood pressure

- As seen from Tables 6 and 7, DBP changed significantly over time in all groups (time effect, $p < 0.001$): it fell after induction, rose after intubation and declined thereafter. Baseline DBP differed significantly among groups ($P = 0.009$), with the clonidine group higher than control (Table 7).
- Between-group differences in DBP were significant at 15 minutes ($P = 0.002$) and 30 minutes ($P = 0.029$), but not at the other time points after pneumoperitoneum creation ($P > 0.05$). In the adjusted analysis (Table 7), only dexmedetomidine at 15 minutes differed significantly from control (mean difference -11.4 mmHg; 95% CI -19.5 to -3.2).

MAP	Clonidine	Magnesium	Dexmed	Control	P Value
BI	111.36 ± 13.422	102.73 ± 13.786	107.88 ± 11.704	97.52 ± 14.311	0.006
AI	92.35 ± 20.117	91.3 ± 18.465	99.64 ± 20.174	88.7 ± 13.769	0.23
BP	73.74 ± 9.517	76.13 ± 10.164	79.39 ± 15.839	80.52 ± 10.595	0.2
AP	95.43 ± 22.103	92.35 ± 17.552	89.3 ± 17.729	94.91 ± 14.918	0.653
5 Mins	105.83 ± 20.404	97.83 ± 18.047	95.83 ± 22.53	102.39 ± 17.725	0.316
10 Mins	92.87 ± 15.256	94.96 ± 11.113	85.45 ± 14.275	99.48 ± 16.256	0.014
15 Mins	87.3 ± 8.493	93.78 ± 10.322	82.73 ± 13.505	97.91 ± 10.748	<0.001
30 Mins	86.85 ± 13.165	89.17 ± 12.917	81.05 ± 11.803	98.14 ± 13.766	0.004
45 Mins	83.56 ± 12.551	94.23 ± 11.497	82.36 ± 10.24	99.75 ± 14.16	0.007
60 Mins	95 ± 0	93.2 ± 10.521	87.9 ± 6.42	101.67 ± 3.786	0.079
Extubation	97.74 ± 14.445	106.3 ± 14.037	93.32 ± 14.83	100.91 ± 16.415	0.034

Table 8: Mean arterial pressure

Time point	Comparison	Mean difference (mmHg)	95% CI	Adjusted p
Before induction	Clonidine vs Control	13.84	3.22 to 24.46	0.004
10 min	Dexmedetomidine vs Control	-14.03	-25.46 to -2.60	0.008
15 min	Clonidine vs Control	-10.61	-19.30 to -1.92	0.008
15 min	Magnesium vs Dexmedetomidine	11.05	2.36 to 19.74	0.005
15 min	Dexmedetomidine vs Control	-15.18	-23.87 to -6.49	<0.001

Table 9: Bonferroni-adjusted pairwise comparisons of mean arterial pressure. Mean differences are differences between the group means in Table 8 (pooled within-group variance, six comparisons per time point); only comparisons that remained significant after adjustment are shown

- As seen from Tables 8 and 9, MAP changed significantly over time in all groups (time effect, $p < 0.001$), following the same pattern as SBP and DBP. Baseline MAP differed significantly among groups ($P = 0.006$), with the clonidine group higher than control (Table 9).
- Between-group differences in MAP were significant at 10 minutes ($P = 0.014$), 15 minutes ($P < 0.001$), 30 minutes ($P = 0.004$), 45 minutes ($P = 0.007$) and extubation ($P = 0.034$); the 30-minute, 45-minute and extubation values are unadjusted univariate comparisons. In the adjusted analysis (Table 9), dexmedetomidine had significantly lower MAP than control at 10 and 15 minutes and than magnesium at 15 minutes, and clonidine had significantly lower MAP than control at 15 minutes. Magnesium did not differ significantly from control

RPP	Clonidine	Magnesium	Dexmed	Control	P Value
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BI	13509.74±3751.151	12585.91±3279.343	14021.48±3832.975	11836.83±4100.244	0.21
AI	12673 ± 3168.905	12272.74±3809.689	13560.17±4257.333	11075.57±2798.029	0.129
BP	8617.91 ± 2106.537	8472.22 ± 1503.048	8626.91 ± 2812.344	9453.22±2295.649	0.434
AP	10651.96±2554.277	10030.74±2409.865	9502.61 ± 2387.276	11307.57±3429.412	0.139
5 Mins	12354.39±3450.675	10512 ± 2829.916	9914.7 ± 3026.372	12265.39±3384.161	0.02
10 Mins	10499.61±2473.349	10285.04±2308.763	8787±2452.014	11957.52±2932.949	0.001
15 Mins	9450.32±1896.291	10377.3 ± 1970.53	8703.26±2528.129	11771.14 ± 2387.2	<0.001
30 Mins	9613.92± 2645.17	9663.65 ± 2219.83	8809.8 ± 2232.267	11409.21±2728.404	0.029
45 Mins	8895.56 ± 2234.927	10723 ± 1847.176	8602.82±2147.714	10982.63±2609.71	0.034
60 Mins	10296 ± 0	11575.8 ± 1435.789	8845.8 ± 1785.663	10457 ± 2851.753	0.102
Extubation	11527.96±2399.325	13560.74±3198.081	10825.57±2938.853	12475.3±2857.238	0.011

Table 10: Rate Pressure Product (RPP)

Effect	F	df	p-value	Partial η^2
Time	9.803	1,749, 152.183	<0.001	0.101
Time × Group	1.602	5,248, 152.183	0.16	0.052
Group	1.472	3, 87	0.228	0.048

Table 11: Repeated-measures ANOVA for rate-pressure product

- As seen from Tables 10 and 11, RPP changed significantly over time (time effect, $p < 0.001$; partial $\eta^2 = 0.101$), with no significant between-group difference at baseline ($P = 0.21$).
- There was no significant time × group interaction ($P = 0.16$) and no significant overall group effect ($P = 0.228$) for RPP (Table 11). The unadjusted per-time-point comparisons in Table 10 were significant at 5 minutes ($P = 0.020$), 10 minutes ($P = 0.001$), 15 minutes ($P < 0.001$), 30 minutes ($P = 0.029$), 45 minutes ($P = 0.034$) and extubation ($P = 0.011$), with the lowest mean RPP in the dexmedetomidine group at each of these time points; because the interaction was not significant and no adjusted pairwise comparison is available, these differences should be regarded as exploratory.

DISCUSSION

Hemodynamic surges following pneumoperitoneum creation have long been recognised; however, interest in newer and more effective drugs to control them has recently renewed because of the increasing number of patients with cardiovascular and coronary artery disease presenting for laparoscopic surgery.^[9] Dexmedetomidine, a highly selective α -2 agonist, has become the most popular of these agents.^[4,10] Most published data compare either intravenous clonidine or dexmedetomidine with control; subsequent studies have compared the two drugs, a few using varying doses of clonidine. Very few studies have compared magnesium with placebo, or with clonidine or

dexmedetomidine.^[10-12] In this study, we compared clonidine, dexmedetomidine and magnesium sulphate against a normal-saline control using a repeated-measures analytical framework that accounts for the correlated, within-subject nature of the serial hemodynamic measurements, an approach that also allowed us to separate the overall (omnibus) between-group effect from the time-specific pattern of group differences captured by the time×group interaction.

Mean age, surgical duration and the distribution of procedures were broadly similar across groups but sex distribution and mean weight varied. Similarly, baseline heart rate and blood pressures differed significantly and varied. These imbalances were borne in mind and Mauchly's test was used to assess the assumption of sphericity for each parameter; when this assumption was violated, Greenhouse–Geisser-corrected results were used for the within-subject (time and time × group) effects when interpreting the time-specific comparisons. Total laparoscopic hysterectomy was the most common procedure, followed by laparoscopic cholecystectomy and appendectomy, consistent with earlier reports on laparoscopic surgical case-mix.^[5,8]

Dexmedetomidine produced a significantly lower heart rate than control at 5, 10 and 15 minutes after pneumoperitoneum creation and a significantly lower heart rate than clonidine at 5 minutes. Clonidine and magnesium did not differ significantly from control at any time point and no significant between-group differences were seen from 30 minutes onwards. This is broadly consistent

with earlier reports of dexmedetomidine producing a more pronounced heart-rate attenuation than clonidine or magnesium,^[13,14] although, notably, several previous studies used higher clonidine doses (1.5–3 µg/kg) than the 1 µg/kg used here,^[15] and some used a higher magnesium dose (50 mg/kg) than the 30 mg/kg used in this study.^[9]

In our study, SBP was significantly lower than control with dexmedetomidine at 10 and 15 minutes and with clonidine at 15 minutes; unadjusted between-group differences persisted up to 60 minutes. This is in agreement with earlier published literature.^[16-18] In contrast to SBP, DBP differed significantly between groups only at 15 and 30 minutes (P15 and P30) and in the adjusted analysis only dexmedetomidine at 15 minutes differed significantly from control. Few earlier researchers had similar findings where the fall in DBP was not consistent across the time frames following pneumoperitoneum creation.^[19] In contrast, magnesium sulphate 30 mg/kg did not differ significantly from control for any variable in the adjusted analysis, and gave significantly higher SBP than dexmedetomidine at 15 minutes and higher MAP at 15 minutes. In our study, MAP was significantly lower than control with dexmedetomidine at 10 and 15 minutes and with clonidine at 15 minutes, whereas magnesium did not differ significantly from control. Dexmedetomidine also had the lowest unadjusted mean MAP from 10 to 45 minutes. A similar attenuation of MAP has been reported consistently by earlier researchers, although most have compared dexmedetomidine with only one of clonidine or magnesium.^[20]

There have been very few studies that have examined RPP as an index of hemodynamic response, although its clinical importance especially in patients with CAD and hypertension is well known.^[20,21] Dar et al.^[20] comparing clonidine with placebo, found that RPP was significantly lower in the clonidine group up to 30 minutes after pneumoperitoneum creation, although they used a higher clonidine dose.

In our study, neither the time × group interaction ($P = 0.16$) nor the overall group effect ($P = 0.228$) for RPP was significant. Although unadjusted mean RPP was lowest with dexmedetomidine at every time point from 5 minutes to extubation (Table 10), these per-time-point differences are without adjusted pairwise comparisons and may not establish a drug effect on myocardial workload.

Overall, our findings suggest that

dexmedetomidine attenuated HR, SBP and MAP most consistently during the earliest time frames after pneumoperitoneum creation. Clonidine attenuated SBP and MAP at isolated time points, whereas magnesium sulphate did not differ significantly from control and was inferior to dexmedetomidine for SBP and MAP at 15 minutes. HR attenuation with clonidine and magnesium was similar and did not differ significantly from control.

Limitations

The surgical team was not uniform and changed according to patient need; hence, varying degrees of tissue damage and nociceptive stimulation cannot be ruled out. The repeated-measures re-analysis was restricted to the first seven perioperative time points because of lack of comparable values at the later time points (45 and 60 minutes, and extubation) in a subset of patients where surgery would have got over earlier which also accounts for the modest variation in the denominator degrees of freedom between parameters.

CONCLUSION

Pneumoperitoneum-related hemodynamic responses are clinically important. In this study, dexmedetomidine 1 µg/kg most consistently attenuated heart rate, systolic and mean arterial pressure during and after pneumoperitoneum creation. Clonidine 1 µg/kg lowered SBP and MAP relative to control at isolated time points, whereas magnesium sulphate 30 mg/kg did not differ significantly from control in adjusted comparisons. RPP showed no significant time × group interaction. Magnesium sulphate is less expensive than dexmedetomidine, but our study did not establish equivalence; Larger, adequately powered trials may be required to confirm our time-specific findings.

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