

Comparative Study Of Effects Of Dexmedetomidine And Clonidine Premedication In Perioperative Hemodynamic Stability And Postoperative Analgesia In Laparoscopic Cholecystectomy

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Citation

S Kumar, B B Kushwaha, R Prakash, S Jafa, A Malik, R Wahal, J Aggarwal, R Kapoor. *Comparative Study Of Effects Of Dexmedetomidine And Clonidine Premedication In Perioperative Hemodynamic Stability And Postoperative Analgesia In Laparoscopic Cholecystectomy*. The Internet Journal of Anesthesiology. 2014 Volume 33 Number 1.

Abstract

Context: α_2 agonists are used in modern anaesthetic practice due to their various beneficial effects. We compared two currently used α_2 agonists for their effects during pneumoperitoneum.

Aims: To compare the effects of Dexmedetomidine and Clonidine premedication in perioperative hemodynamic stability and postoperative analgesia in laparoscopic cholecystectomy.

Settings and Design: randomised, double blind, prospective, comparative clinical study

Methods and Material: Sixty patients aged ≥ 20 - ≤ 60 years, ASA physical status I or II and planned for elective laparoscopic cholecystectomy under GA were included in this study. Group 1: Received 2 $\mu\text{g/kg}$ of clonidine diluted in normal saline, given slow intravenous infusion over 10 min. before induction of GA. Group 2: Received 1 $\mu\text{g/kg}$ of dexmedetomidine diluted in normal saline, given slow intravenous infusion over 10 min. before induction of GA. Laparoscopic cholecystectomy was performed under general anaesthesia (GA) and data was obtained.

Statistical analysis used: Data were summarized as Mean \pm SD. Groups were compared by independent Student's t test. Groups were also 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 by Tukey's post hoc test. Discrete (categorical) variables were compared by chi-square (χ^2) test. A two-sided ($\alpha=2$) p value less than 0.05 ($p<0.05$) was considered statistically significant. All analyses were performed on STATISTICA software (Windows version 6.0).

Results: Results shows that dexmedetomidine and clonidine are effective in attenuating the hemodynamic response to pneumoperitoneum with equal efficacy and without any significant side effect. They also provide reliable post operative analgesia and dexmedetomidine has longer duration of analgesia than clonidine. Dexmedetomidine provides more sedation than clonidine and patient is more comfortable in postoperative period. So, we can say that dexmedetomidine is better premedication drug for laparoscopic cholecystectomy than clonidine. There was no complication noted in the study except bradycardia in 5 patients in group 1 which was not statistically significant and did not required any intervention. Thus, both the drugs were found to be safe.

Conclusions: The study shows that dexmedetomidine and clonidine are effective in attenuating the hemodynamic response to pneumoperitoneum with equal efficacy and without any significant side effect.

INTRODUCTION

α_2 agonists are used in modern anaesthesia practice due to their various beneficial effects like sedation, analgesia, attenuation of stress response and reduction in anaesthetic

drug requirement. Clonidine and dexmedetomidine is the two currently used drugs with dexmedetomidine having higher selectivity for α_2 receptor. Premedication with clonidine blunts the stress response to surgical stimuli and

requirement of the narcotic and anaesthetic drug are also reduced. In addition, clonidine increases cardiac baroreceptor reflex sensitivity to increase in systolic blood pressure, and thus stabilises, blood pressure. There have been a number of studies on dexmedetomidine and sedation, ventilation and metabolic rate in volunteers, oxygen consumption in dexmedetomidine-premedicated patients and postoperative sympatholytic effects. [1],[2] However, its role in contemporary intraoperative anaesthesia practice has not yet been established. The sedative and anxiolytic properties of dexmedetomidine as well as sympatholytic characteristics make this drug of particular interest for premedication. In our best knowledge, no clinical study has examined the comparative effects of dexmedetomidine and clonidine premedication in perioperative hemodynamic stability and postoperative analgesia in cases of elective laparoscopic cholecystectomy. We therefore, proposed to conduct a prospective, randomised, double blind, controlled study to compare the hemodynamic and analgesic effect of these two α_2 agonist in laparoscopic cholecystectomy.

SUBJECTS AND METHODS

This was a randomised, double blind, prospective, comparative clinical study. After getting approval from institutional ethical committee, an informed consent was taken from the patient and his attendants explaining the purpose, method and risk of the study and the rights of enrolled in the study.

Sixty patients aged ≥ 20 - ≤ 60 years, ASA physical status I or II, planned for elective laparoscopic cholecystectomy were included. Heart block of second degree or above, inability to communicate with the patient due to any reason, patient with neurologic, cardiovascular, renal, hepatic diseases or diabetes mellitus, pregnant or breast-feeding females, duration of procedure lasting for more than 120 minutes, anticipated difficult airway, patient on antihypertensive, antipsychotic, analgesic or sedative medication were excluded from the study.

The patients were randomly allocated into two groups (n=30) using the computer generated random number table.

Group 1: Received 2 $\mu\text{g/kg}$ of clonidine diluted in 20 ml normal saline, given slow intravenous infusion over 10 min. before induction of GA.

Group 2: Received 1 $\mu\text{g/kg}$ of dexmedetomidine diluted in 20 ml normal saline, given slow intravenous infusion over

10 min. before induction of GA.

On arrival of patient in the operating room, standard monitoring including pulse oximetry, non-invasive blood pressure, electrocardiography, temperature and end tidal CO₂ was started and baseline cardio-respiratory parameters were noted.

All patients were pre-medicated with intravenous ondansetron 4 mg, glycopyrrolate 0.2 mg and fentanyl 2 $\mu\text{g/kg}$. In group 1, clonidine in 2 $\mu\text{g/kg}$ was diluted in 20 ml normal saline and infused over 10 min. before induction and in group 2; dexmedetomidine 1 $\mu\text{g/kg}$ was diluted in 20 ml normal saline and infused over 10 min before induction.

After preoxygenation, general anaesthesia was induced with propofol 2 mg/kg by weight and endotracheal intubation was facilitated by vecuronium bromide 0.1 mg/kg intravenously and anaesthesia was maintained with oxygen and nitrous oxide in ratio of 33:66 and with halothane was given at 0.5-1% v/v. Muscle relaxation was maintained by vecuronium bromide 0.02 mg/kg intermittently thereafter. Controlled mechanical ventilation was done to maintain end tidal CO₂ between 30-40 mmHg. Intraabdominal pressure during pneumoperitoneum was maintained between 12-14 mmHg. Patient was placed in supine position with 15° left lateral tilt and 30° head elevation.

Intraoperative monitoring included non invasive arterial blood pressure, electrocardiography, capnography, pulse oximetry and temperature. At the end of surgery residual neuromuscular block was reversed by neostigmine in dose of 0.05mg/kg and glycopyrrolate in dose of 0.2mg per mg of neostigmine intravenously. Trachea was extubated after complete reversal of neuromuscular blockade and restoration of spontaneous respiration and patients were transferred to recovery room. Patient sedation score noted according to Ramsay sedation score at preinduction and during postoperative period.

Pain was assessed on 10 point visual analogue score (VAS) at the end of surgery, 15 min., 30 min., 45 min., 60 min. and 90 min.

Patients were observed in the post operative room till VAS score of 5. Rescue analgesia in the form of injection Diclofenac sodium 75 mg IV first and inj. Tramadol 2mg/kg IV was given as second line of analgesic.

STATISTICAL ANALYSIS

Data were summarized as Mean \pm SD. Groups were compared by independent Student's t test. Groups were also 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 by Tukey's post hoc test. Discrete (categorical) variables were compared by chi-square (χ^2) test. A two-sided ($\alpha=2$) p value less than 0.05 ($p<0.05$) was considered statistically significant. All analyses were performed on STATISTICA software (Windows version 6.0).

RESULTS

The basic characteristics viz. age, sex, weight and ASA grade of two groups at presentation (admission) are summarized in Table/Fig-1. The baseline characteristics of the patients of both the groups were similar. The majority of the patients were females.

The perioperative SBP and DBP (mmHg) of two groups over the periods are summarized in Table/Fig 2. The mean trend of SBP in both groups was similar over the periods with slightly being higher in Group 1 at all periods as compared to Group 2. Further, during the periods, the mean SBP in Group 1 ranged from 123.33 mmHg (11 min) to 132.87 mmHg (90 min) (variation of 9.53 mmHg.); while in Group 2 it ranged from 117.80 mmHg (11 min) to 127.80 mmHg (5 min) (variation of 10.00 mmHg). Comparing the mean SBP of two groups over the periods together (within groups), ANOVA revealed significant effect of both groups ($F=15.53$, $p<0.001$) and periods (time) ($F=1.79$, $p=0.041$) on SBP. However, the interaction (groups x periods) effect of both on SBP was found insignificant ($F=1.00$, $p=0.447$).

Further, comparing the mean SBP at baseline (pre treatment) to other post periods (within groups), Tukey test revealed similar ($p>0.05$) SBP in both groups at all post periods as compared to respective baseline. Similarly, for each period, comparing the mean SBP between the two groups (between groups), Tukey test further revealed similar ($p>0.05$) SBP between the two groups at all periods i.e. not differed statistically.

The mean trend of DBP in both groups was similar over the periods with slightly being higher in Group 1 especially after 60 min to till end (Extubation) as compared to Group 2. Further, during the periods, the mean DBP in Group 1 ranged from 81.27 mmHg (30 min) to 87.30 mmHg (90 min)

(variation of 6.03 mmHg); while in Group 2 it ranged from 79.37 mmHg (75 min) to 84.43 mmHg (45 min) (variation of 5.07 mmHg).

Comparing the mean DBP of two groups over the periods together (within groups), ANOVA revealed insignificant effect of both groups ($F=2.35$, $p=0.131$) and periods (time) ($F=1.07$, $p=0.380$) on DBP. Further, the interaction (groups x periods) effect of both on DBP was also found insignificant ($F=1.19$, $p=0.285$).

Further, comparing the mean DBP at baseline (pre treatment) to other post periods (within groups), Tukey test also revealed similar ($p>0.05$) DBP in both groups at all post periods as compared to respective baseline. Similarly, for each period, comparing the mean DBP between the two groups (between groups), Tukey test further revealed similar ($p>0.05$) DBP between the two groups at all periods i.e. not differed statistically.

The Perioperative MAP (mmHg) of two groups over the periods is summarized in Table/Fig4. The mean MAP trend in both groups was similar over the periods with slightly being higher in Group 1 especially after 60 min to till end (Extubation) as compared to Group 2. Further, during the periods, the mean MAP in Group 1 ranged from 95.16 mmHg (11 min) to 101.84 mmHg (90 min) (variation of 6.69 mmHg); while in Group 2 it ranged from 92.42 mmHg (11 min) to 98.78 mmHg (5 min) (variation of 6.36 mmHg).

Comparing the mean MAP of two groups over the periods together (within groups), ANOVA revealed significant effect of groups ($F=4.95$, $p=0.030$) while insignificant of periods (time) ($F=1.39$, $p=0.160$) on MAP. However, the interaction (groups x periods) effect of both on MAP was found insignificant ($F=1.11$, $p=0.343$).

Further, comparing the mean MAP at baseline (pre treatment) to other post periods (within groups), Tukey test also revealed similar ($p>0.05$) MAP in both groups at all post periods as compared to respective baseline. Similarly, for each period, comparing the mean MAP between the two groups (between groups), Tukey test further revealed similar ($p>0.05$) MAP between the two groups at all periods i.e. not differed statistically.

The Perioperative HR (beats/min) of two groups over the periods is summarized in Table/Fig.5. The mean trend of HR in both groups was almost similar over the periods with slightly being higher in Group 2 at 5-12 min and especially

45 min to till end (Extubation) as compared to Group 1. Further, during the periods, the mean HR in Group 1 ranged from 78.47 beats/min (10 min) to 91.20 beats/min (0 min) (variation of 12.73 beats/min); while in Group 2 it ranged from 81.03 beats/min (11 min) to 89.00 beats/min (0 min) (variation of 7.97 beats/min).

Comparing the mean HR of two groups over the periods together (within groups), ANOVA revealed insignificant effect of groups ($F=0.75$, $p=0.389$) while significant effect of periods (time) ($F=3.95$, $p<0.001$) on HR. However, the interaction (groups x periods) effect of both on HR was found insignificant ($F=1.02$, $p=0.435$).

Further, comparing the mean HR at baseline (pre treatment) to perioperative periods (within groups), Tukey test revealed significantly ($p<0.05$ or $p<0.01$ or $p<0.001$) different and lower HR in Group 1 at 10 and 11 min, 20 min, 45-105 min and 120 min as compared to baseline. However, in Group 2, it remains similar ($p>0.05$) at all post periods as compared to baseline. Moreover, the mean HR also not differed ($p>0.05$) between the two groups at all periods i.e. found to statistically the same.

The mean trend of etCO_2 in both groups was almost similar over the periods. Further, during the periods, the change in mean etCO_2 in Group 1 ranged from 33.13 mmHg (20 min) to 34.77 mmHg (90 min) (variation of 1.67 mmHg); while in Group 2 it ranged from 31.23 mmHg (15 min) to 34.30 mmHg (variation of 3.07 mmHg) (Extubation). Comparing the mean etCO_2 of two groups over the periods together (within groups), ANOVA revealed insignificant effect of groups ($F=2.39$, $p=0.128$) while significant effect of periods (time) ($F=8.30$, $p<0.001$) on etCO_2 . Further, the interaction (groups x periods) effect of both on etCO_2 was found significant ($F=5.19$, $p<0.001$).

Further, comparing the mean etCO_2 at baseline (pre treatment) to other post periods (within groups), Tukey test revealed significantly ($p<0.01$ or $p<0.001$) different and higher etCO_2 in Group 2 at all post periods as compared to at Intubation. However, in Group 1, it remains similar ($p>0.05$) at all post periods as compared to at Intubation. Moreover, at Intubation, the mean etCO_2 differed and lowered significantly ($p<0.001$) in Group D as compared to Group 1 but in rest of the periods it remains ($p>0.05$) similar between the two group i.e. not differed statistically.

At the end of the surgery, the mean VAS of Group 2 differed and lowered significantly as compared to Group 1 ($3.13 \pm$

1.50 vs. 1.33 ± 1.30 , $t=4.97$; $p<0.001$) as shown in Table/Fig. 3 and 7.

At both periods, the mean sedation score of Group 2 (Pre induction: 1.67 ± 0.48 vs. 2.57 ± 0.50 , $t=7.09$; $p<0.001$; At the time of extubation: 1.60 ± 0.50 vs. 2.93 ± 0.50 , $t=10.88$; $p<0.001$) was significantly different and higher as compared to Group 1 as shown in Table/Fig. 3 and 6.

The Frequency of rescue analgesia requirement was significantly different and higher in Group 1 as compared Group 2 (30.0% vs. 0.0%, $\chi^2=10.59$, $p=0.001$).

In majority of the patients no complications was observed in both the groups as shown in Table/Fig. 3.

DISCUSSION

To attenuate these hemodynamic responses during laparoscopic surgeries, a wide variety of agents are being used both during premedication and induction. Research fellows have tried beta blockers, α_2 agonists, magnesium sulphate, opioid, vasodilators, and gasless approach to negate the hemodynamic variations. [3], [4], [5], [6], [7], [8]

We studied the two most commonly used α_2 agonist in the anaesthetic practice and compared their efficacy in reduction of stress response and hemodynamic changes associated with laparoscopy and to postoperative pain relief.

Both groups showed decrease in SBP which was statistically significant as compared to baseline. It was found that the SBP was lower with dexmedetomidine at intubation, during pneumoperitoneum, at extubation and during postoperative period than clonidine, however this difference is statistically insignificant. The fluctuations in SBP were also attenuated in both the group, therefore, we can safely conclude that dexmedetomidine and clonidine stabilise the SBP and reduce the increase in SBP during various phases of anaesthesia and laparoscopy. There was increase in SBP at the time of extubation in clonidine which was not seen with dexmedetomidine, thus it seems that the SBP stabilising effect of dexmedetomidine lasted till extubation while clonidine is less effective in preventing the hemodynamic response to extubation. Similarly, clonidine and dexmedetomidine reduces the DBP and prevents its rise during early periods of procedure but does not suppress increase of DBP during extubation completely.

In initial phase of the procedure, there was no significant difference in the two groups regarding MAP and both drugs

were equally efficacious in preventing the rise in MAP but towards the end of procedure, the efficacy of clonidine declines and it is unable to suppress the increase in MAP in response to surgical stress completely.

The mean heart rate was lower in dexmedetomidine as compared to clonidine throughout the procedure but it was statistically insignificant. However, the heart rate was lower in both groups as compared to baseline and it was statistically significant. In spite of its more pronounced effect on heart rate, none of the patient receiving dexmedetomidine suffered from significant bradycardia and required any form of treatment or dose reduction for bradycardia. The heart rate lowering effect of both study drugs reduces the myocardial oxygen demand of the patient which was very useful in patient suffering from coronary artery disease and dexmedetomidine is more effective in this regard and our finding was consistent with previous study. [9]

Thus, we can see that both study drugs provide hemodynamic stability during laparoscopic cholecystectomy and dexmedetomidine is equally effective as clonidine for this purpose. Study using oral clonidine as premedication has similar result as found in our study. [10] Dexmedetomidine as a preanaesthetic medication and intraoperative infusion significantly attenuates sympathoadrenal response to tracheal intubation compared to clonidine and it was also seen in previous study. [13]

Previous study using clonidine 1 µg/kg intravenous showed attenuated hemodynamic stress response to pneumoperitoneum but not due to intubation and extubation.[11] Clonidine 2 µg/kg prevented hemodynamic stress response to pneumoperitoneum and also to intubation and extubation.[11] In our study, we used 2 µg/kg of clonidine and the response to laryngoscopy and intubation were prevented but the response to extubation was not suppressed completely although this difference was not statistically significant as compared to 1µg/kg dose of dexmedetomidine. So, 1µg/kg dose of dexmedetomidine is more effective than 1µg/kg of clonidine and its effect is comparable to 2 µg/kg of clonidine.

The mean VAS of the patients in clonidine was 3 at the end of procedure and all of the patients required analgesic after 60 minutes of surgery and 9/30 patients require rescue analgesia at extubation, while with dexmedetomidine, the mean VAS at the end of procedure was 1 and most patients

had adequate analgesia up to 90 min. Thus, we can appreciate that dexmedetomidine is far better analgesic as compared to clonidine regarding duration of analgesia. [12]

The mean sedation scores at the end of the procedure were 1.60 and 2.33 respectively in clonidine and dexmedetomidine which was statistically significant. Thus, patients were more sedated in dexmedetomidine as compared to clonidine. The patients in clonidine were less sedated, required less postoperative monitoring and were more cooperative. This reflects the more sedative property of dexmedetomidine than clonidine and it also shows that the sedative property of the α₂ agonists is proportional to their analgesic action as we can see here that dexmedetomidine is better analgesic but with more sedation. But none of the patient in our study had sedation score > 4, so none of the patient requires any type of airway or ventilator support.

There was no complication noted in the study except bradycardia in 5 patients in clonidine which was not statistically significant and did not require any intervention. Thus, both the drugs were found to be safe.

Thus, we can conclude that both α₂ agonists are effective in attenuating the hemodynamic response to pneumoperitoneum during laparoscopic cholecystectomy and provides reliable postoperative analgesia when used as a premedication agent.

TABLES AND FIGURES

Table 1

Basic characteristics of Clonidine and Dexmedetomidine

Characteristics	Clonidine (n=30) (%)	Dexmedetomidine (n=30) (%)	χ ² /t value	p value
Age (yrs):				
Mean ± SD	41.63 ± 8.39	39.03 ± 7.14	1.29	0.201
Sex:				
Females	22 (73.3)	25 (83.3)	0.88	0.347
Males	8 (26.7)	5 (16.7)		
Weight (kg):				
Mean ± SD	57.80 ± 5.35	56.37 ± 4.48	1.13	0.265
ASA grade:				
1	17 (56.7)	14 (46.7)	0.61	0.438
2	13 (43.3)	16 (53.3)		

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Table 2

		SAP					DAP				p-value
Observation periods	Periods	Clonidine		Dexmedetomidine		p value	Clonidine		Dexmedetomidine		
	(min)	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Baseline	0	130.43	10.22	125.80	12.20	0.88	86.80	15.73	83.80	9.47	0.65
Premedication	5	130.00	11.79	127.80	12.61	0.78	84.13	8.26	84.27	10.70	0.57
	10	126.87	16.15	122.30	13.20	0.67	84.03	10.69	81.87	9.28	0.76
Induction	11	123.33	17.12	117.80	14.61	0.45	81.70	13.19	79.73	11.68	0.88
Intubation	15	127.90	17.63	117.93	12.38	0.58	83.07	12.99	81.83	12.60	0.87
	20	128.10	16.26	118.33	14.20	0.59	82.60	11.22	80.83	12.60	0.79
Skin incision	30	127.85	15.02	121.47	17.62	0.996	83.27	11.05	82.43	12.50	0.69
CO ₂ insufflation	45	127.47	16.86	123.37	16.94	0.76	82.53	12.94	84.43	13.85	0.91
	60	129.30	17.40	120.23	14.74	0.780	86.60	13.64	80.20	12.39	0.940
	75	129.10	13.26	119.27	12.67	0.422	85.27	11.38	79.37	11.28	0.937
Extubation	90	132.67	12.93	120.30	15.30	0.131	87.30	8.95	82.87	14.02	0.067
	105	131.10	10.92	119.27	12.70	0.222	86.23	9.19	80.50	10.95	0.984
	120	130.70	13.06	120.37	13.89	0.510	86.37	9.31	80.50	11.78	0.978
	135	131.63	12.28	122.20	13.47	0.708	85.83	8.47	82.27	11.11	0.89

Table 3

Secondary outcome measures of two groups at the end of surgery

Secondary outcome measures	Clonidine (n=30)	Dexmedetomidine (n=30)	t value	p value
Visual Analogue Scale (VAS)	3.33 ± 1.50	1.33 ± 1.30	4.97	<0.001
Sedation				
Pre induction	1.67 ± 0.48	2.57 ± 0.50	7.09	<0.001
At the time of extubation	1.60 ± 0.50	2.93 ± 0.50	10.88	<0.001
Rescue analgesia required just after extubation	9 (30%)	0 (0.0)	$\chi^2=12.30$	0.001
Duration of analgesia (in min.)	138.33	191.33	11.10	p<0.001
No complications	25 (83.3%)	30 (100.0)	χ^2	0.02
			=5.46	

Figure 4

Perioperativemean MAP of two groups over the periods

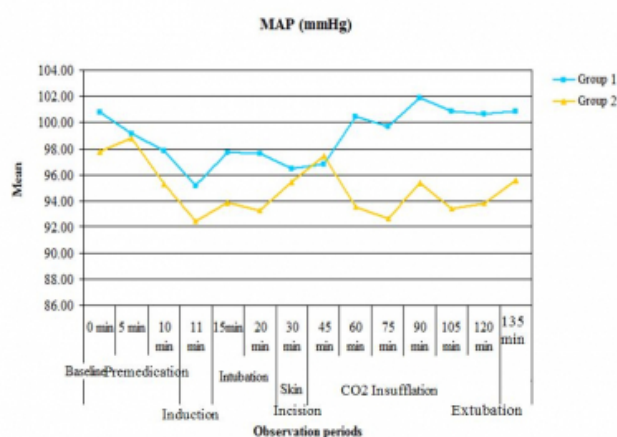


Figure 5

Perioperative mean HR of two groups over the periods.

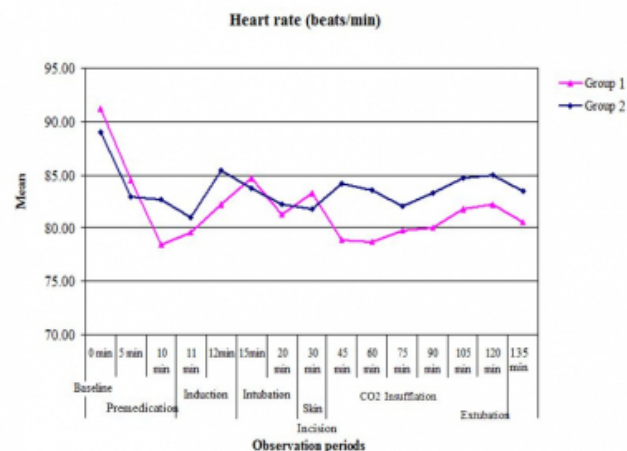


Figure 6

Sedation scores in two groups

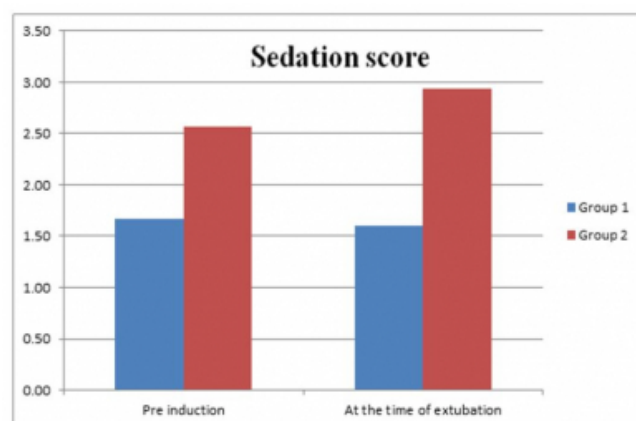
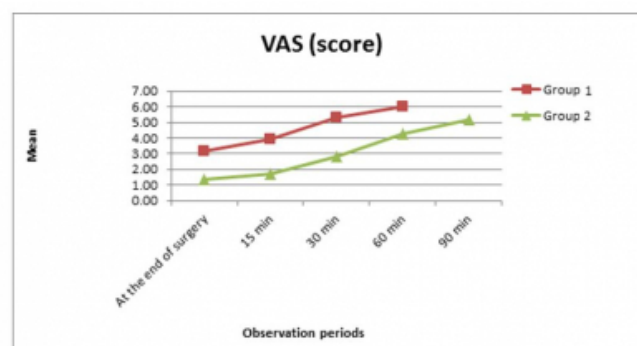


Figure 7

VAS scores in two groups



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