Research Article **Biochemistry**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

EFFECTS OF DEXMEDETOMIDINE ON HAEMODYNAMICS IN PATIENTS UNDERGOING INTRA-ABDOMINAL LAPAROSCOPIC SURGERIES: A COMPARATIVE STUDY

VISHWANATH[1], BALARAJU.T.C[2], SWATHI RAJASHEKAR[3] AND SREEKANTHA*[4]

1- ASSISTANT PROFESSOR, Department of Anesthesiology and critical care, Navodaya Medical College Hospital and Research centre,Raichur,Karnataka.
2-Associate Professor, department of Anaesthesiology and critical care,Navodaya Medical College Hospital and Researchcentre,Raichur,Karnataka.
3-Tutor, department of Anatomy,Navodaya Medical College, Raichur,Karnataka.
4-Professor of Biochemistry,RIMS,Raichur,Karnataka.

ABSTRACT

Laparoscopic surgeries are advantageous over conventional laparotomy. Pneumoperitoneum and intraoperative positional changes cause significant haemodynamic changes for which various drugs have been used to attenuate these changes. We performed a prospective, randomised, double blind study to evaluate the effect of dexmedetomidine. Sixty American society of anaesthesiologist's physical status I and II patients undergoing intra-abdominal laparoscopic surgeries, were randomly allocated to receive either dexmedetomidine 1mcg/kg intravenously over 10minutes before induction of anaesthesia and 0.4mcg/kg/hrintraoperatively till the end of pneumoperitoneum (group D, n=30) or 0.9% saline at the same rate as dexmedetomidine (group S, n=30). Intraoperative heart rate and mean arterial pressures were monitored continuously and charted after bolus drug administration, 1min after induction, 1min after intubation, and after pneumoperitoneum at 15min interval till end of pneumoperitoneum and postoperative period. Time of response to verbal commands, tracheal extubation and time to become fully awake is noted. Patients were observed for any adverse events like bradycardia, tachycardia, hypotension, hypertension and postoperative nausea and vomiting. Heart rate and mean arterial pressure variation in dexmedetomidine group were less after pneumoperitoneum when compared to control group with p value <0.001 which is statistically significant. No significant differences in the parameters of recovery were observed between both the groups. Dexmedetomidine provides intra and postoperative haemodynamic stability during the laparoscopic surgery without affecting the recovery. It causes bradycardia and hypotension which is clinically insignificant.

KEY WORDS: **laparoscopic surgeries, pneumoperitoneum, heamodynamics, dexmedetomidine**

***Corresponding author**

SREEKANTHA
Professor of Biochemistry, RIMS, Raichur, Karnataka.

INTRODUCTION

Laparoscopy is a minimally invasive procedure used, as a diagnostic and therapeutic tool for abdominal and pelvic pathologies.Advantages of laparoscopy include shorter hospital stay, rapid return to normal activities, less pain and smaller incisions.[1]During laparoscopic procedures, abdominal organs are visualized by intra-abdominal insufflation of carbon dioxide (CO_2). The use of pneumoperitoneum in combination with positional changes may cause significant haemodynamic and respiratory changes.[2]The creation of pneumoperitoneum with CO_2 insufflation induces cardiovascular response characterized by sudden tachycardia, hypertension and increased myocardial oxygen requirement. CO_2 is readily absorbed from the peritoneal cavity into the circulation resulting in hypercarbia and acidosis. Apart from that, laparoscopic cholecystectomy is performed in reverse Trendelenburg position.[3]This position leads to diminished venous return and thereby further reduction in cardiac output. These changes are considered to be mediated by mechanical and neurohumoral factors. Catecholamine, renin-angiotensin system and vasopressin are released during pneumoperitoneum.[2] To overcome these haemodynamic effects of insufflation various methods have been used like combined epidural with general anaesthesia, propofol infusions, high doses of opioids, beta-blockers, nicardipine, clonidine etc.[4,5,6,7]Dexmedetomidine has eight fold greater affinity for α_2 adrenergic receptors than clonidine and much less α_1 effects. Dexmedetomidine possesses hypnotic, sedative, anxiolytic, sympatholytic and analgesic properties without producing significant respiratory depression.[8] The intravenous administration of dexmedetomidine before induction of anaesthesia attenuates sympathoadrenal responses to laryngoscopy and endotracheal intubation.[9] It also provides improved haemodynamic stability during laparoscopic intra-abdominal surgeries.[10] It also diminishes intraoperative requirement of anaesthetic agents and analgesics.[11,12,13]This placebo controlled, double blind prospective study is designed to evaluate the efficacy of dexmedetomidine to provide haemodynamic stability in patients undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODS

The permission from the Institute's ethical committee was sought. Thereafter, 60patients of both sex**,** aged18 to 65 years, of ASA grade I and II, scheduled for elective laparoscopic surgery were included in the study. Patients with morbid obesity (BMI>40), uncontrolled hypertension, heart block greater than grade I, cardiac dysfunction, severe hepatic, renal and endocrine disease were excluded from the study. A written informed consent was obtained from the patients. A thorough preanaesthetic evaluation was carried out and all patients were premedicated with tablet diazepam 5mg and tablet ranitidine 150mg a night before surgery and 1hr before on the morning of surgery.Patients were assigned to one of the two groups, dexmedetomidine group (D) and saline group (S), comprising 30 patients each using a computerised randomisation. Group D received dexmedetomidine 1mcg/kg iv over 10min before induction of anaesthesia and 0.4mcg/kg/hrintraoperatively. Group S received 0.9%saline. The study medication was prepared by an anaesthesiologist blinded to the study in identical 50ml syringes. Dexmedetomidine 200mcg (2ml) added to 38ml 0.9%saline making a total volume of 40ml (resulting concentration 5mcg/ml).Anaesthesia machine check drill was performed. Necessary drugs (routine & emergency) were loaded into labelled syringes. Airway equipments checked and kept ready for use.On receiving the patient in operating room, pre-induction monitors: Pulse-Oximeter, ECG and Non-invasive blood pressure (NIBP) were connected. Post-induction temperature and $EtCO_2$ were monitored. Baseline recording of heart rate, SBP, DBP and MAP were noted down. Study drug infused at 0.2ml/kg over 10min and maintenance at 0.08ml/kg/hr. Patients were induced after 10min of infusion of study drug with fentanyl 1.5-2mcg/kg iv and propofol 1.5-

2mg/kg iv. Endotracheal intubation facilitated by muscle relaxant vecuronium 0.1mg/kg. Anaesthesia maintained with oxygen (1L/min) in air (1L/min), isoflurane in concentration between 1-2%, intermittent doses of fentanyl 0.5mcg/kg and vecuronium 0.01mg/kg. Inj. Diclofenac sodium 75mg administered intramuscularly after induction.Peritoneal cavity was insufflated with CO_2 at 2L/min to create pneumoperitoneum with IAP of 14mmHg throughout the laparoscopic procedure. Patients were mechanically ventilated to keep $EtCO_2$ between 35-40mmHg. Ondansetron 4mg iv was given for prevention of PONV when laparoscope was withdrawn. At the start of wound closure the study medication was stopped and isoflurane was stopped after wound closure. Residual neuromuscular blockade reversed with appropriate dose of neostigmine and glycopyrolate and tracheal extubation was performed. Fentanyl 1mcg/kg is used as rescue analgesia based on VAS score. HR, MAP were charted after bolus drug administration, 1min after induction, 1min after intubation, and after pneumoperitoneum at 15min interval till end of pneumoperitoneum and postoperative period. Timing of following events were recorded: time from stopping isoflurane in response to verbal commands, time from stopping isoflurane to tracheal extubation, time from stopping isoflurane to become fully alert and duration of surgery. Patients were observed for any adverse events like bradycardia, tachycardia, hypotension, hypertension and PONV. MAP was maintained within ± 25% of baseline. Hypotension (MAP<25% of baseline on two consecutive readings within 2-3min) treated with fluid bolus and ephedrine 3mg iv boluses. Infusion of study medication discontinued if hypotension persisted for >2min. Upon return of MAP to ± 25% of baseline, the study medication was resumed at 50% of initial infusion rate. Hypertension (MAP >25% of baseline on 2 consecutive readings within 2-3min) and/or tachycardia (HR >25% of baseline for >2min) treated with metoprolol 1mg iv boluses. Bradycardia (HR<45 for more than 2min) treated with atropine 0.5mg intravenous boluses.Statistical Methods[15,16,17,18] : Descriptive statistical analysis has been carried out in the present study. Results of continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. Student "t" test (two tailed, independent) has been used to find the significance of study parameters on a continuous scale between two groups, inter group analysis and on metric parameters. Chi-square test has been used to find the significance of study parameters on a categorical scale between two or more groups. Values of P<0.05 were considered significant and P<0.001 as highly significant. The Statistical software, namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

Demographic profile(table 1) were compared among the two groups of the patients and no significant difference was found.

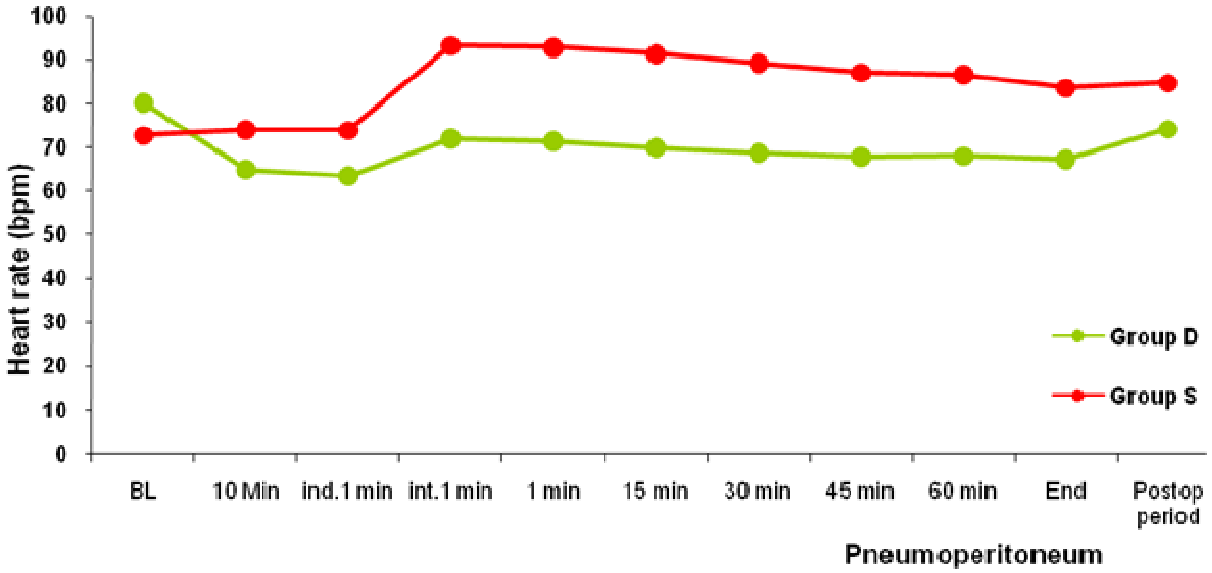
Table 1
demographic profile of the patients who underwent laparoscopic surgeries

Demographic characteristics	Group D (n=30)	Group S (n=30)
Age in years (mean±SD)	44.67±9.56	47.93±5.56
Gender M/F	19/11	22/8
Weight in kg (mean±SD)	63.37±13.38	61.67±10.13
Duration of surgery in minutes (mean±SD)	52.77±13.14	56.83±10.37
ASA grade I/II	12/18	10/20

At specific times (intubation and 1, 15, 30, 45, 60 min after creation of pneumoperitoneum, end of pneumoperitoneum and postoperative period) as mentioned in the table 2 and graph 1, the heart rate variation in dexmedetomidine group were less when compared to saline group with p value <0.001 which is statistically significant, showing that dexmedetomidine group has less haemodynamic responses to pneumoperitoneum.

Table 2
Comparison of heart rate in two groups of patients studied

HR (bpm)	Group D	Group S	P value
Baseline	80.20±15.76	72.73±9.13	0.029
Bolus 10 minutes	64.97±11.67	73.93±9.42	0.002
Induction 1 minute	63.43±10.85	73.90±8.81	<0.001
Intubation 1 minute	71.93±13.07	93.27±13.64	<0.001
After pneumoperitoneum			
1 minute	71.43±12.6	92.93±14.85	<0.001
15 minutes	69.93±10.15	91.47±9.40	<0.001
30 minutes	68.70±12.95	89.30±9.40	<0.001
45 minutes	67.83±12.01	87.21±8.11	<0.001
60 minutes	68.00±9.71	86.63±9.07	<0.001
End of pneumoperitoneum	67.33±8.61	83.63±10.24	<0.001
Postoperative period	74.17±13.18	84.70±10.04	<0.001

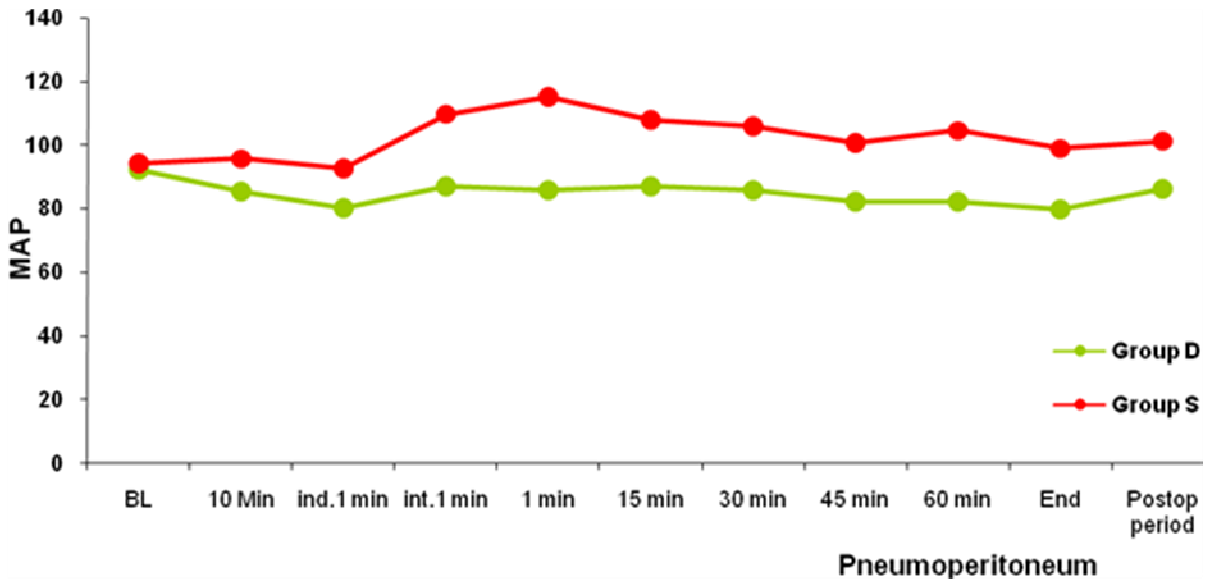


Graph 1
Comparison of heart rate in two groups of patients studied

At specific times (intubation and 1, 15, 30, 45, 60min after creation of pneumoperitoneum, end of pneumoperitoneum and postoperative period) as mentioned in the table 3 and graph 2, the MAP variation in dexmedetomidine group was less when compared to saline group with p value <0.001 which is statistically significant, showing that dexmedetomidine group has less haemodynamic responses to pneumoperitoneum.

Table 3
Comparison of MAP (mmHg) in two groups of patients studied

MAP	Group D	Group S	P value
Baseline	92.27±9.01	94.13±9.27	0.432
Bolus 10 minutes	85.50±12.18	95.57±8.09	<0.001
Induction 1 minute	80.30±13.67	92.47±7.07	<0.001
Intubation 1 minute	87.17±14.50	109.63±15.46	<0.001
After pneumoperitoneum			
1 minute	85.80±9.49	115.20±15.63	<0.001
15 minutes	86.97±9.29	107.83±15.61	<0.001
30 minutes	85.90±9.40	105.87±10.00	<0.001
45 minutes	82.26±8.26	100.64±5.86	<0.001
60 minutes	82.17±8.71	104.50±10.26	<0.001
End of pneumoperitoneum	79.80±7.97	98.77±9.80	<0.001
Postoperative period	86.17±7.30	101.13±9.04	<0.001



Graph 2
Comparison of MAP (mmHg) in two groups of patients studied

As shown in table 4, dexmedetomidine does not prolong the time in response to verbal commands, extubation and to become fully alert which is indicated by the p value which is not significant and at the same time in dexmedetomidine group the time to requirement of rescue analgesia is delayed as the p value is <0.001 which is highly significant. Intensity of pain was less in Group D as compared to Group S (VAS 2.2±1.04 Vs 5.8±2.62) during immediate postoperative period.

Table 4
Comparison of Time to response to oral commands, Time to extubation, Time to fully alert, Time of rescue analgesia in two groups of patients studied

		Group D	Group S	P value
a.	Time to response to oral commands (min)	8.60±3.46	7.63±2.43	0.215
b.	Time to extubation (min)	10.07±3.17	10.00±3.07	0.934
c.	Time to fully alert (min)	13.10±4.11	14.23±4.35	0.304
d.	Time of rescue analgesia (min)	97.80±36.81	29.47±10.19	<0.001

As shown in table 5, the amount of isoflurane, propofol and fentanyl used to maintain adequate analgesia and anaesthesia is less in dexmedetomidine group as p values are <0.001 which is statistically significant.

Table 5
Comparison of requirement intraoperative anaesthetic agents

		Group D	Group S	P value
a.	Required isoflurane (%)	0.62±0.12	1.26±0.12	<0.001
b.	Required Fentanyl (mcg)	121.67±28.42	202.5±23.99	<0.001
c.	Required Propofol (mg)	64.33±11.94	97.00±5.96	<0.001

Dexmedetomidine group has absolutely no risk of hypertension or tachycardia and at the same time has statistically insignificant hypotension, bradycardia and PONV (table 6).

Table 6
Comparison of side effects

Side effects	Group D (n=30)	Group D (n=30)	p value
Hypotension	4(13.3%)	0	0.112
Hypertension	0	12(40.0%)	<0.001
Bradycardia	1(3.3%)	0	1.000
Tachycardia	0	17(56.7%)	<0.001
PONV	1(3.3%)	2(6.6%)	0.55

DISCUSSION

Anaesthetic management of the patients undergoing laparoscopic surgery is complicated by the major physiologic effects of pneumoperitoneum and patient positioning. Cardiovascular changes are characterized by an increase in arterial pressure and systemic and pulmonary vascular resistances, with a slight increase in heart rate. Various pharmacological agents have been used to overcome these haemodynamic responses to pneumoperitoneum. This double blind prospective study was carried out in 60 adult patients, to evaluate the effect of dexmedetomidine in attenuating haemodynamic stress response associated with pneumoperitoneum. In the present study (table 2 and 3), decreases in HR and MAP were noticed in the dexmedetomidine group. Inspite of maintaining normocapnia and keeping intra-abdominal pressure below 14mmHg, significant rises in HR and MAP were noticed in the control group. Our findings were similar to study conducted by,Bhattacharjee DP et al.[10] In their study, they have shown that HR and MAP values were significantly lower ($p<0.05$) after pneumoperitoneum and remained lower throughout the pneumoperitoneum in dexmedetomidine group when compared to control group. In a similar study by Tufanogullari B et al[14], a significant increase in MAP in the

control group throughout the intraoperative period from the baseline was seen. In the dexmedetomidine group they found that the patients remained haemodynamically stable. This shows that dexmedetomidine provides perioperative haemodynamic stability. In the present study (table 4), we noticed that difference in the time to response to verbal commands, time to extubation and time to become fully alert was statistically insignificant between two groups. These findings indicate that dexmedetomidine does not interfere with recovery from anaesthesia. Our findings were similar to the study conducted by Bhattacharjee DPet al.[10] In their study, they showed that there is no significant difference in the parameters of recovery between the two groups ($p>0.05$). In the present study (table 4), time of requirement of rescue analgesia was prolonged in dexmedetomidine group compared to control group, which is statistically highly significant ($p<0.001$). In a similar study conducted by Tufanogullari B et al[14], amount of fentanyl administered in the PACU after emergence from anaesthesia was significantly reduced in the Dex 0.2, 0.4, and 0.8 groups compared with the control group (113±85, 108±67, 120±78 v/s 187±99 mcg, respectively, $p<0.05$).In the present study (table 5), the mean requirement of fentanyl, propofol and isoflurane were reduced in the dexmedetomidine group comared to control group. Dexmedetomidine reduced the requirement of fentanyl by 39.9%, propofol by 33.68% and isoflurane by 50.79%, which is highly significant ($p<0.01$). Our findings were similar to study conducted by Hassan S Bakhameeset al.[12]In their study they have shown that dexmedetomidine infusion reduced the requirement of propofol by 33% and intraoperative fentanyl by 45% compared with placebo group. In a similar study conducted by Hofer et al[11], the intraoperative requirement of isoflurane was lower in dexmedetomidine group when compared to narcotic group. The reduced requirement of isoflurane intraoperatively can be explained by the fact that α_2 agonist drugs reduce the MAC of inhalational agents.[13]In the present study (table 6), 1 patient out of 30(3.3%) in dexmedetomidine group had bradycardia (HR less than 25% of baseline value) whereas no patients had bradycardia in saline group, which is not significant statistically ($p=1.000$). 4 patients out of 30(13.3%) in dexmedetomidine group had hypotension (MAP<25% of baseline value) whereas none of the patients in saline group had hypotension, which was statistically insignificant ($p= 0.112$). 17 patients out of 30(56.7%) in saline group had tachycardia (HR>25% of baseline value) whereas none of the patients in dexmedetomidine group had tachycardia, which is statistically significant ($p<0.001$). 12 out of 30(40%) patients had hypertension (MAP>25% of baseline value) whereas none of the patients in dexmedetomidine had hypertension, which is statistically significant ($p<0.001$). In the postoperative period, we also observed for the occurrence of PONV. 1 patient out of 30 (3.3%) in dexmedetomidine group had PONV whereas 2 patients out of 30 (6.6%) in saline group had PONV, which is statistically insignificant ($p=0.55$). In a similar study conducted by Hassan S Bakhameeset al[12], there was no difference in the incidence of PONV between both groups (group D- 5% and group S- 7.5%).

CONCLUSION

In the present study, we concluded that dexmedetomidine attenuates the haemodynamic response to pneumoperitoneum with CO_2 effectively than saline but can cause bradycardia and hypotension which is not statistically significant. Anaesthesiologist should be aware and vigilant to diagnose these side effects and prepare to treat them. Side effects are dose dependent and easily treatable by intravenous atropine for bradycardia and fluid boluses and vasopressor for hypotension. Dexmedetomidine is relatively safe and effective to blunt the haemodynamic response to pneumoperitoneum with CO_2 if given in appropriate dosage. It also reduces the requirement of anaesthetic agents and analgesics. At the same time it does not interfere with the recovery from anaesthesia. Difference in the risk of PONV between dexmedetomidine and saline group is statistically insignificant.

REFERENCES

1. Jean L. Jaris. Chapter 68, In: Ronald D Miller, Lars I. Eriksson, Lee A. Fleisher, Jeanine P. Wienener-Kronish, William L. Young. Miller's Anaesthesia. 7th edition, Churchill Livingstone: Volume II: 2185-2202. (2010)
2. Jonis J, Noirot D, Legnand M, et al. Haemodynamic changes during laparoscopic cholecystectomy. AnesthAnalg; 76: 1067-72. (1993)
3. Wilcox S, Vandar LD. Trendelenburg and his position. AnesthAnalg 67: 574-78. (1988);
4. Koivusalo AM, Scheinin M, Tikkanen I, Yli-Suomu T, Ristkari S, Laakso K, Lindgren L. Effects of Esmolol on Haemodynamic response to carbon dioxide pneumoperitoneum for laparoscopic surgery. ActaAnaesthesiolScand May; 42(5): 510-517.(1998)
5. Laisalmi M, Koivusalo AM, Valta P, Tikkanen I, Lindgren L. Clonidine provides opioid sparing effect, stable haemodynamics and renal integrity during laparoscopic surgery. SurgEndosc ; 15: 1331-1335.(2001)
6. Hea JO Yoon, Young Suck JE. Haemodynamic effects of intravenous bolus dosing of nicardipine on pneumoperitoneum during laparoscopically assisted vaginal hysterectomy. Korean J Anaesthesiol; 50(6): 43-47.(2006)
7. Elisabetta Marana, StefaniaColicci, Francesco Meo, Ricardo MR. Poeirotti. Neuroendocrine stress response in gynaecological laparoscopy: TIVA with propofol versus sevoflurane anaesthesia. J ClinAnaesth ; 22(4): 250-255.(2007)
8. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic and analgesic properties of small dose Dex infusions. AnesthAnalg; 90: 699-705. (2000)
9. Scheinin B et al. Dex attenuates sympathoadrenal response to tracheal intubation. BJA ; 68: 126-131.(1992)
10. Bhattacharjee DP et al. Effects of Dex in patients undergoing laparoscopic cholecystectomy. J AnaesthClinPharmacol; 26(1): 45-48.(2010)
11. Hofer RE, Sprung J, Sarr MG and Wedel DJ. Anaesthesia for a patient with morbid obesity using dexmedetomidine without narcotics. Can J Anesth ; 52: 176-180.(2005)
12. Hassan S Bakhamees et al. Effects of Dex in morbidly obese patients undergoing laparoscopic gastric bypass. M. E. J. Anaesth ; 19(3): 537-551.(2001)
13. Thomas J. Ebert. Chapter 15, In: Paul G. Barash, Bruce F. Cullen, Robert K. Stoelting. Clinical anaesthesia, 5th edition, Lippincott Williams and Wilkins , 397-398.(2006)
14. Tufanogullari B, White P, Peixoto M, Kiampour D, Lacour T, Griffin J, Skrivanek G, Macaluso A, Shsh M, Provest DA. Dexmedetomidine infusion during laparoscopic bariatric surgery: the effect on recovery outcome variables. AnesthAnalg ; 106: 1741-8(2008)
15. Bernard Rosner. Fundamentals of Biostatistics, 5th Edition, Duxbury, page 80-240. (2000)
16. Robert H Riffenburg. Statistics in Medicine, 2nd edition, Academic press, page 85-125. (2005)
17. Sunder Rao PSS, Richard J. An Introduction to Biostatistics, A manual for students in health sciences, New Delhi. Prentice Hall of India, page 86-160. (2008)
18. John Eng. Sample size estimation: How many Individuals Should be Studied? Radiology 227: 309-313. (2003).