Original Research Paper

Volume : 5 | Issue : 7 | July 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Comparative Study Between Dexmedetomidine Versus Propofol-Ketamine Versus Propofol-Fentanyl When Used for Sedation During Gastrointestinal Endoscopies

Medical Science

KEYWORDS : Dexmedietonidine, Propofol, Ketamin, Fentanyl

P SATEESH KUMAR	Assistant Professor, Department of Anaesthesia, Andhra Medical College, Visakhapatnam, Ap
DR A PADMAJA*	Associate Professor,Department of Anaesthesia, Andhra Medical College, Visakhapatnam, Ap *Corresponding Author
DR A SATYANNARAYANA	Professor & HOD, Department of Anaesthesia, Andhra Medical College, Visakhapatnam, Ap
DR KHASIM	Junior Resident, Department of Anaesthesia, Andhra Medical College, Visakhapatnam, Ap

ABSTRACT

OBJECTIVE ; The aim of this study is to compare Dexmedetomidine,propofol- ketamine and propofol- fentanyl for the sedation of patients undergoing upper gastrointestinal endoscopic procedures in terms of induction and recovery profiles, sedation and adverse effects ,patient and endoscopist satisfaction. MATERIALS AND METHODS; After approval from hospital ethics committee a randomized comparative study was conducted in 9patients who were undergoing upper gastrointerstinal endoscopies in the Department of Gasteroenterology. Patients were randomized into 3 groups of 30 each by computer generated random numbers. Group 1(n=30), patients received loading dose of inj.Dexmedetomidine 1.5 µg/kgi.v infused over 10 min followed by maintainance infusion at a rate of 0.5µg/kg/hr.Group 2(n=30),patients received inj ketamine 0.5mg/kg i.v and inj.Propofol 1-2 mg/kgi.v followed by infusion of inj.propofol 50µg/kg/min i.v as maintainance.Group 3(n=30),patients received inj. fentanyl 1µg/kg i.v and inj.Propofol 1-2 mg/kgi.v followed by infusion of inj.propofol 50µg/kg/min i.v as maintainance. All procedures were performed after achieving a sedation level of 4-5 Ramsay sedation score RESULTS;.Results were analysed by Analysis of variance [ANOVA] tests. P value<0.05 was considered to be significant. There was a statistically significant difference between groups with respect to the induction time and recovery time. Induction time was shorter in ketamine propofol group than propofol fentanyl group and dexmedetomidine group. However recovery was faster in propofol fentanyl group when compared to other groups. CONCLUSION :Patients in Propofol Fentanyl group have early induction and faster recovery profiles with lower incidence of side effects compared to Dexmedetomidine and Ketamine Propofol groups. There by Propofol Fentanyl combination can be used as a safe sedative regimen in upper Gastrointestinal endoscopies.

INTRODUCTION

Sedation is defined as a drug-induced depression of the level of consciousness. Sedation and analgesia are integral parts of each GI endoscopy procedure. Majority of GI endoscopies are typically performed under moderate sedation1 with benzodiazepines alone or in combination with an opioid. The main purposes of sedation and analgesia during gastrointestinal endoscopy are to relieve patient's discomfort, pain and anxiety, to reduce memory of the unpleasant event and to facilitate the procedure. Benzodiazepines are the most often used as sedation agents by endoscopists2. Benzodiazepines do not provide analgesia and for this reason they are commonly co-administered with opioids3.Fentanyl, alfentanil and remifentanil have appeared as good alternatives for GI sedation4.

Propofol has rapid onset and short duration of action which makes it suitable for sedation in gastrointestinal endoscopy 5.It provides higher patient satisfaction6.In spite of its favourable profile, due to lack of analgesic properties, large doses may be needed for maintenance of anaesthetic depth especially in prolonged procedures which can cause cardio respiratory adverse effects7,8. Propofol requirement can be reduced with addition of adjuvants like ketamine and fentanyl .

Ketamine is N-Methyl-D-aspartate receptor antagonist, alone or in combination with other sedatives has been evaluated for sedation mainly in pediatric patients for procedural sedation and analgesia9. Its use results in better quality and depth of sedation with shorter recovery times than patients sedated using benzodiazepines and opioids alone. Because pharyngeal and laryngeal reflexes are usually active, ketamine should not be used alone in diagnostic procedures of the pharynx, larynx or bronchial tree. The potential advantages of ketamine-propofol combination over ketamine alone for procedural sedation include shorter recovery time and a lower incidence of ketamine associated emesis and recovery agitation

Dexmedetomidine, a highly selective α-2adrenoreceptor agonist with sedative and analgesic properties has the unique feature of lacking respiratory depression even with accidental over dosage giving it the advantage over other sedatives as benzodiazepines, opioids and propofol as all of them cause dose dependent respiratory depression10,11.Its use for upper GI endoscopies showed good result12,13 .

Considering the complications of propofol ,ketamine ,fentanyl when used alone the present study was designed to evaluate the efficacy of various sedation combinations like Propofol Ketamine ,Propofol Fentanyl aiming to reach adequate sedation with advantage of lesser side effects of individual drugs when used at optimal doses. Also these drug combinations were compared to dexmedetomidine to evaluate its efficacy. The drug combinations are compared in terms of time to induction, time to recovery, efficacy, and safety, as well as patient and endoscopist satisfaction.

AIMS AND OBJECTIVES

The aim of this study is to compare

Dexmedetomidine,propofol- ketamine and propofol- fentanyl for the sedation of patients undergoing upper gastrointestinal endoscopic procedures in terms of induction and recovery profiles, sedation and adverse effects ,pa-

tient and endoscopist satisfaction.The parameters compared are 'Induction and recovery time,Haemodynamic variables(HR,MAP),Respiratory parameters(RR,SP02) ,Effectiveness of sedation(RSS Score), Patient satisfaction (1-10),Endoscopist satisfaction(1-10),and sedation related side effects.

MATERIALS AND METHODS

After approval from hospital ethics committee a randomized comparative study was conducted in 90 patients who were undergoing upper gastrointerstinal endoscopies in the Department of Gasteroenterology, King George Hospital, Andhra Medical College November 2013 to August 2015.

Inclusion criteria includes: Age 18-50years .Patients belonging to ASA grade I and grade II, Patients who gave informed consent. Exclusion criteria are Age<18 years ASA III,IV,V classification ,Unregulated hypertension, Allergic reaction to planned medication in patients medical history, Asthmatic history, hypovolemia,severe bradycardia (HR<50/min) or related bradyarrythmias. Impaired liver and renal function .

After placement of intravenous cannula infusion of Ringer lactate was started .All patients received inj.glycopyrrolate 0.2 mg, inj. midazolam 0.02 mg/kg and Lidocaine 10% was sprayed into the pharynx to achieve pharyngeal anesthesia. Supplemental oxygen was administered to all patients at rate 4 l/min .All procedures were performed after achieving a sedation level of 4-5 Ramsay sedation score14.Patients were randomized into 3 groups of 30 each by computer generated random numbers.

Group 1(n=30), patients received loading dose of inj. Dexmedetomidine 1.5 µg/kgi.v infused over 10 min followed by maintainance infusion at a rate of 0.5µg/kg/hr.

Group 2(n=30),patients received inj ketamine 0.5mg/kg i.v and inj.Propofol1-2 mg/kgi.v followed by infusion of inj.propofol50µg/kg/min i.vas maintainance.

Group 3(n=30),patients received inj. fentanyl 1µg/kg i.v and inj.Propofol1-2 mg/kgi.vfollowed by infusion of inj. propofol 50µg/kg/min i.v as maintainance.

Failure to reach the acceptable level of sedation (Ramsay sedation score of 4-5) to perform the endoscopy was treated with increase in the rate of maintainance infusion of the study drug.Intravenous fentanyl 0.5-1µg/kg was given in divided doses as rescue analgesia for unwanted movements hindering endoscopic procedure which could not be achieved with increasing the infusion rate of maintainance drug.

Monitoring include :Heart rate, Mean arterial pressure, Respiratory rate,Spo2 and Ramsay sedation score were continuously monitored and at recovery after the patient achieved 9-10 points on Aldrete Recovery Scale Score(T4). 15

Patient satisfaction was recorded (where 1=worst medical experience he ever had,while 10=best medical experience he had).Endoscopist satisfaction (where 1=worst method of sedation,while 10=best method of sedation and he would like to have it as regular method of sedation in his practice.The incidence of post operative nausea and vomiting(PONV) , agitation ,movement were recorded and managed accordingly

STATISTICAL ANALYSIS: Statistical analysis of present study was conducted, using the Mean, standard error, Chi-square, Linear Correlation Coefficient and Analysis of variance [ANOVA] tests.

OBSERVATIONS AND RESULTS

Ninety patients were included in this study.

Table 1: Age in years, weight in kilograms ,sex distribution and endoscopy time in the three groups.

Parameter	Group 1	Group 2	Group 3	pvalue
Age in yrs	35.7±10.7	41.3±10.9	37.9±10.5	0.1
Weight in kgs	56.3±6.1	54.5±6.1	56.4±6.7	0.4
Sex M/ Fratio	18/12	17/13	17/13	0.9
Endoscopy time	13.3±3.7	13.1±4.0	13.8±4.2	0.7

p>0.05

Their demographic data showed nostatistical differences(p>0.05) between the groups with respect to age, sex, and weight The duration of endoscopy was comparable in all the groups with no statistically significant difference (p >0.05)(Table 1,Figure 1)

Table 2:Induction and recovery time in minutes.

	Group 1	Group 2	Group 3	p-value
Induction time	10.5±2.4	2.1±0.7	2.8±1.0	0.001
Recovery time	14.0±4.0	12±3.3	7.6±2.2	0.001

p<0.05

There was a highly statistically significant difference(p<0.001) between groups with respect to the induction time and recovery time.Induction time was shorter in group 2 (2.1±0.7) than group3 (2.8±1.0) and group1 (10.5±2.4).Recovery was faster with group3(7.6±2.2) when compared to group 2 (12±3.3)and group 1 (14.0±4.0)(Table 2,Figure 2).

Table 3:Heart rate in beats per min.

	Group 1	Group 2	Group 3	p-value
T0	72.1±6.7	70.8±6.9	72.0±7.0	0.7
T1	59.8±5.6	74.5±6.7	69.2±5.1	0.001
T2	66.9±4.6	69.2±5.1	67.1±4.2	0.11
T3	67.1±4.2	69.2±5.1	66.9±4.6	0.11
T4	68.0±5.0	69.4±6.9	70.8±6.8	0.2

p>0.05

There was a highly statistically significant difference (p<0.001) in heart rate between the groups, during T1(at induction) .Heart rate was higher in group 2 (74.5±6.7 bpm) when compared to group 3 (69.2±5.1 bpm) and group 1(59.8±5.6 bpm) . No statistically significant difference was seen among the groups during T2,T3 intervals.(Table 3)

Table 4: sedation score(score 1 to 6).

	Group 1	Group 2	Group 3	p-value
T1	4.03±0.6	4.1±0.8	4.0±0.6	0.8
T2	3.8±0.6	3.7±0.5	3.7±0.6	0.8
T3	3.7±0.6	3.7±0.6	3.7±0.5	0.8

p>0.05

There was no statistically significant difference among the 3 groups at T1,T2 and T3 interval . All the patients in the three groups were satisfactorily sedated (RSS score 4-5) with mean of 4.03±0.6 in group 1,4.1±0.8 in group 2 and 4.0±0.6 in group 3.(Table 4,)

Volume : 5 | Issue : 7 | July 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

Table 5:Patient and endoscopist satisfaction (Score from 1 to 10).

	Group 1	Group 2	Group 3	p-value
Patient satisfaction	7.4±0.8	7.7±0.8	8.1±0.8	0.004
Endoscopist satisfaction	7.1±0.6	7.4±0.9	8.0±0.7	0.001

p<0.05

In regard to patient satisfaction,the patients in group 3 were more satisfied compared to those in groups 1 and 2 . The p value is 0.001 showing highly significant patient satisfaction score in group 3 with mean and standard deviation 8.1±0.8compared to that in group 1 (7.4±0.8) and group 2 (7.7±0.8). From the endoscopist's perspective the satisfaction score was higher with p value <0.001 in group 3with mean and standard deviation of 8.0±0.7compared to group 1 (7.1±0.6) and group 2 (7.4±0.9) (Table5).

Table 6:Rescue analgesia (n=30).

	Group 1	Group 2	Group 3
Rescue analgesia	12 (40%)	6(20%)	6(20%)

In this study ,rescue analgesic doses of inj .fentanyl 0.5-1µg/kg iv was given in 6 cases (20%) each in group 2 and group 3 compared to 12 cases(40%)in group 1.(Table 6)

Table 7:Sedation related side effects.

Variables	Group 1	Group 2	Group 3
Movement	6(20%)	2(7%)	3(10%)
PONV	2(7%)	3(10%)	2(7%)
Agitation	0	3(10%)	0

In this study,the incidence of movement of patients during procedure was 6 cases (20%) in group 1, 3 cases (10%) in group 3 and 2 cases (7%)in group 2.Post operative nausea and vomiting occurred in two patients (7%) each in group 1 and 3 and in three patients (10%) in group 2.Agitation occurred only in three patients (10%) in group 2.(Table 7)

DISCUSSION:

The present study was done to compare Dexmedetomidine,propofol- ketamine and propofol- fentanyl for the sedation of patients undergoing upper gastrointestinal endoscopic procedures in terms of induction and recovery profiles, sedation and adverse effects ,patient and endoscopist satisfaction.

The combination of ketamine and propofol more properly known as ketofol has many advantages in outpatient procedures like gastrointestinal endoscopies.The opposing physiological effects of these drugs suggest a potential for synergy.[16]

Considering the complications of propofol, ketamine,fentanyl when used solely the present study was designed to evaluate the efficacy of various sedation combinations aiming to reach a state of sedation which meets the patient and endoscopists satisfaction together with the least cardiopulmonary affection and adverse effects of individual drugs..Also these combinations were compared to dexmedetomidine to evaluate its efficacy.

Goal of this study was to provide an adequate level of sedation while minimizing pain and anxiety, minimizing unwanted patient movement during procedurethe adverse drug-related events, and maintaining a stable cardiovascular and respiratory status. Continuous infusion technique was used in this study to maintain a steady state sedation level.

Their demographic data showed nostatistical differences(p>0.05) between the groups with respect to age, sex, and weight.The duration of endoscopy was comparable in all the groups with no statistically significant difference (p >0.05).

Induction of sedation was calculated as time to achieve ramsay sedation score 4-5 that is adequate to perform endoscopy.The induction of sedation was faster in patients receiving ketamine –propofol (2.1±0.7 min) compared to dexmedetomidine (10.5±2.4 min)and propofol-fentanyl(2.8±1.0min).In a study done by Ashraf S.Hasanin17and his colleagues in 2014 comparing dexmedetomidine and propofol for sedation during gastrointestinal endoscopies they found higher induction time with dexmedetomidine (10.51 ±1.75min) than with propofol (3.17 ± 0.72 min)that is similar to the present study.Lera dos santos ME et al18performed a study with propofol-fentanyl for gastrointestinal endoscopy, they observed mean induction time value 2.63±1.62 min which is similar to the present study.

Recovery time was calculated as time to achieve aldrete score of >9 after completion of endoscopy procedure. Recovery was faster with propofol-fentanyl (7.6±2.2 min) when compared to ketamine propofol(12±3.3 min)and dexmedetomidine (14.0±4.0 min).20 RihamHasanein19 and his colleagues also observed shorter recovery time in patients who received propofol fentanyl(9.43±2.3 min) compared to those who received ketamine propofol (11.59±2.59 min).In a study by Ramakiranet al20comparing propofol,dexmedetomidine and ketamine in outpatient ERCP observed that time for attaining modified aldrette score>9 was 16.6±3.18 min with dexmedetomidine ,7.5±3.2 min with propofol and 10±4.17 min for ketamine . The recovery time of the dexmedetomidine group was significantly prolonged which could be attributed to the pharmacological profile of dexmedetomidine, that is similar to the present study.

The heart rate was calculated at induction,5 min after insertion of endoscope and recovery.The heart rate during T1(at induction) was higher in patients receiving ketamine-propofol (74.5±6.7bpm) compared to propofolfentanyl (69.2±5.1bpm) and dexmedetomidine(59.8±5.6 bpm),No statistically significant difference was seen among the groups during T2,T3 intervals.Ketamine causes central sympathetic stimulation and suppression of baroreceptors causing increasing in heart rate and mean arterial pressures. This explains the higher heart rate in the ketamine propofol group.20

The mean arterial pressure in all the groups was stable throughout the procedure.Addition of propofol to ketamine in ketamine propofol group might have blunted the sympathomimetic response of ketamine which would increase the mean arterial pressure.16

There was no statistically significant difference observed with respect to respiratory rate and Oxygen saturation percentage in all the groups (p>0.05).21

In regard to patient satisfaction,the patients who received propofol fentanyl were more satisfied with score8.1±0.8 compared to those who received dexmedetomidine7.4±0.8 and ketamine 7.7±0.8.19 From the endoscopist's perspective the satisfaction score was higher patients receiving propofol fentanyl (8.0±0.7) compared to dexmedetomidine(7.1±0.6) and ketamine propofol(7.4±0.9).18 Higher incidence of unwanted movement was observed in pa-

tients receiving dexmedetomidine(20%), compared to patients receiving propofol fentanyl(10%)and ketamine propofol(7%).21

Post operative nausea and vomiting was higher in patients receiving ketamine propofol (10%)compared to 7% each in dexmedetomidine and propofol fentanyl group. Agitation occurred only in three patients (10%) in ketamine propofol group. 19,22

In this study,rescue analgesic doses of inj .fentanyl 0.5-1µg/kg iv was given in 6 cases (20%) each in ketamine propofol group and propofol fentanyl group compared to 12 cases(40%)in dexmedetomidine group.Rescue analgesia with fentanyl was needed in 30% patients of Group Dexmedetomidinecompared to 17.63% patients of group propofol as observed by Tomar GS and singhF et al21.

SUMMARY

A comparative study was conducted in 90 patients of age 18-50 years,of ASA 1 and 2 scheduled to undergo gastrointestinal endoscopies.The patients were assigned into three groups of 30 each. Group 1(n=30), patients received loading dose of inj.Dexmedetomidine 1.5 µg/kg i.v infused over 10 min followed by maintainance infusion at a rate of 0.5µg/kg/hr.Group 2(n=30),patients received inj ketamine 0.5mg/kg i.v and inj.Propofol1-2 mg/kgi.v followed by infusion of inj.propofol 50µg/kg/min i.v as maintainance.Group 3(n=30),patients received inj fentanyl 1µg/kg i.v and inj.Propofol1-2 mg/kgi.v followed by infusion of inj.propofol 50µg/kg/min i.v as maintainance.

There was a statistically significant difference between groups with respect to the induction time and recovery time. Induction time was shorter in ketamine propofol group than propofol fentanyl group and dexmedetomidine group.However recovery was faster in propofol fentanyl group when compared to other groups.

The heart rate was comparable at all intervals in the three groups except at T1 interval where the heart rate was significantly higher in ketamine propofol group.

The mean arterial pressure,respiratory rate and Oxygen saturation percentage were comparable in all the three groups.RSS score of 4-5 was maintained at the time of insertion of endoscope(T1 interval).

Patient satisfaction and endoscopist satisfaction was more in the patients who received propofol fentanyl than those who are given ketamine propofol and dexmedetomidine.

The incidence of movement during procedure and rescue analgesia requirement was higher in dexmedetomidine group.Post operative nausea and vomiting occurred in two patients (7%) each in dexmedetomidine group and propofol-fentanyl group and in three patients (10%) in ketamine –propofol group .Agitation occurred in three patients (10%) in ketamine-propofol group only.

CONCLUSION :

Patients in Propofol Fentanyl group have early induction and faster recovery profiles with lower incidence of side effects compared to Dexmedetomidine and Ketamine Propofol groups. There by Propofol Fentanyl combination can be used as a safe sedative regimen in upper Gastrointestinal endoscopies.

REFERENCES

1. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists: Practice guidelines for sedation and analgesia by non anesthesiologists. Anesthesiology 2002; 96: 1004-17.
2. Fanti L, Agostoni M, Gemma M, Radaelli F, Conigliaro R, Beretta L, Rossi G, Guslandi M, Testoni PA, Italian Society of Digestive Endoscopy Sedation Commission: Sedation and monitoring for gastrointestinal endoscopy: A nationwide web survey in Italy. Dig Liver Dis 2011; 43: 726-30.
3. Riphaus A, Rabofski M, Wehrmann T: Endoscopic sedation and monitoring practice in Germany: results from the first nationwide survey. Z Gastroenterol 2010; 48: 392-7.
4. Fanti L, Agostoni M, Gemma M, Rossi G, Azzolini ML, Viale E, Guslandi M, Beretta L, Testoni PA: Two dosages of remifentanil for patient-controlled analgesia vs. meperidine during colonoscopy: A prospective randomized controlled trial. Dig Liver Dis 2013; 45: 310-5.
5. Faga E, De Cento M, Giordanino C, Barletti C, Bruno M, Carucci P, De Angelis C, Venon WD, Musso A, Reggio D, Fagoonee S, Pellicano R, Ceretto S, Ciccone G, Rizzetto M, Saracco G: Safety of propofol in cirrhotic patients undergoing colonoscopy and endoscopic retrograde cholangiography: results of a prospective controlled study. Eur J GastroenterolHepatol 2012; 24: 70-6.
6. McQuaid KR, Laine L: A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. GastrointestEndosc 2008; 67: 910-23
7. Smith I, White PF, Nathanson M, Gouldson R: Propofol. An update on its clinical use. Anesthesiology 1994; 81: 1005-43.
8. Kongkam P, Rerknimitr R, Punyathavorn S, Sitthi-Amorn C, Ponauthai Y, Prempracha N, Kullavanijaya P: Propofol infusion versus intermittent meperidine and midazolam injection for conscious sedation in ERCP. J Gastrointestin Liver Dis 2008; 17: 291-7.
9. Varadarajulu S, Eloubeidi MA, Tamhane A, Wilcox CM: Prospective randomized trial evaluating ketamine for advanced endoscopic procedures in difficult to sedate patients. Aliment PharmacolTher 2007; 25: 987-97.
10. Shah A, Mosdossy G, McLeod S, et al. A blinded, randomized controlled trial to evaluate ketamine-propofol versus ketamine alone for procedural sedation in children. Ann Emerg Med. 2011; 57:425-433.
11. Langston WT, Wathen JE, Roback MG, et al. Effect of ondansetron on the incidence of vomiting associated with ketamine sedation in children: a double-blind, randomized,placebo-controlled trial. Ann Emerg Med. 2008;52:30-34.
12. Hogue CW,Jr, Talke P, Stein PK, Richardson C, Domitrovich PP, Sessler DI: Autonomic nervous system responses during sedative infusions of dexmedetomidine. Anesthesiology 2002; 97: 592-8.
13. McMorrow SP, Abramo TJ. Dexmedetomidine sedation, uses in pediatric procedural sedation outside the operating room. PediatrEmer Care 2012;28:292–6.
14. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone–alphadolone. Br Med J 1974;22:656–9.
15. AldreteJA.The post anesthesia recovery score revisited.JClinAnesth 1995;7:89–91.
16. Takimoto K, Ueda T, Shimamoto F, Kojima Y, Fujinaga Y, Kashiwa A, Yamauchi H, Matsuyama K, Toyonaga T, Yoshikawa T: Sedation with dexmedetomidine hydrochloride during endoscopic submucosal dissection of gastric cancer. Dig Endosc 2011; 23: 176-81.
17. Martin E, Ramsay G, Mantz J, Sum-Ping ST: The role of the alpha 2 adrenoceptoragonistdexmedetomidine in postsurgical sedation in the intensive care unit. J IntensiveCare Med 2003; 18: 29–41
18. De Wolf AM, Fragen RJ, Avram MJ et al. The pharmacokinetics of Dexmedetomidine in volunteers with severe renal impairment. AnesthAnalg 2001; 93: 1205-9
19. Dyck JB, Maze M, Haack C et al. Computer-controlled infusion of intravenous Dexmedetomidine hydrochloride in adult human volunteers. Anesthesiology 1993; 78: 821-8.
20. Venn RM, Grounds RN. Comparison between dexmedetomidine and propofolfor sedation in the intensive care unit: Patient and clinician perceptions. Br J Anaesth 2001; 87: 684–90
21. Tryba M, Gehling M. Clonidine-a potent analgesic adjuvant. CurrOpin Anaesthesiology 2002; 15: 511-7.
22. Engelhardt W, Stahl K, Marouche A, Hartung E. Recovery time after (S)- ketamine or ketamine racemate. Recovery time after short anesthesia in volunteers. Anaesthesist1998;47(3):184-192.