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Use of remifentanil or dexmedetomidine with ketamine for upper gastrointestinal endoscopy

Ersin Koksal[a*], Yasemin Burcu Ustun[a], Cengiz Kaya[a], Aysun Caglar Torun[b], Mehmet Ziya Yılmaz[b], Yunus Oktay Atalay[a], Fatih Ozkan[a]

[a] *Department of Anesthesiology and Reanimation, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey*
[b] *Department of Anesthesiology, Faculty of Dentistry, Ondokuz Mayıs University, Samsun, Turkey*

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*** Correspondence to:**
Ersin Koksal
Department of Anesthesiology and Reanimation,
Faculty of Medicine,
Ondokuz Mayıs University, Samsun, Turkey
e-mail: ersin.koksal@omu.edu.tr

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ABSTRACT

We compared the effects of adding remifentanil or dexmedetomidine infusions to ketamine on the quality of anaesthesia, haemodynamics and recovery in upper gastrointestinal endoscopy (UGE). The study included 80 patients. The patients were randomised into two groups. Group R received a remifentanil infusion at a loading dose of 0.5 μg/kg/10 min, followed by 0.1 μg/kg/min of remifentanil plus 1 mg/kg of ketamine. Group D received a dexmedetomidine infusion at a loading dose of 0.5 μg/kg/10 min, followed by 0.2 μg/kg/min of dexmedetomidine plus 1 mg/kg of ketamine. In both groups, propofol (0.5-1 mg/kg) was added to the anaesthesia regimen if adequate sedation could not be achieved. The procedure commenced when a Ramsay sedation score (RSS) of 4 was achieved. After termination of anaesthesia, the modified Aldrete score (MAS) was used as the criterion for the discharge of patients from the postanaesthesia care unit. After a MAS of 9 was reached, the patient was discharged from the postanaesthesia care unit. Demographic and haemodynamic data were similar in both groups. The requirement for propofol was significantly higher in group D (p=0.002). In group R, the RSS was relatively higher in the first minute of UGE but lower at 15 min. The time to reach an RSS of 4 was significantly shorter in group R (p<0.001). Post procedural MAS values were similar in both groups (p=0.716). The time to achieve an MAS score of 9 was significantly prolonged in group D. (p=0.030). The procedural times were comparable in both groups. In conclusion; remifentanil infusion added to ketamine provides faster, more efficient sedoanalgesia and relatively more rapid recovery when compared with a dexmedetomidine infusion.

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1. Introduction

During procedures performed outside the operating room, benzodiazepines, opioids and ketamine are often used to achieve an appropriate level of anaesthesia (Melloni, 2007; Lichtenstein et al., 2008). In recent years, propofol and dexmedetomidine have also been frequently employed (Melloni, 2007; Lichtenstein et al., 2008). Due to serious adverse effects (respiratory depression, nausea, vomiting and prolonged sedation), recurrent use of benzodiazepines and opioids are a source of concern (Gan, 2006). Propofol is preferred because of its rapid onset and shorter duration of activity. However, dose titration is needed because of its depressive cardiac and respiratory effects (Fabbri et al., 2012). Ketamine is preferred as anaesthetic agent due to its lack of suppressive effects on cardiac and respiratory systems. However, it has cholinergic side effects, including agitation, hallucinations and nightmares. To prevent these side effects, ketamine must be used in combination with other agents (Smally et al., 2011).

As remifentanil is a short-acting agent, it is frequently used for anaesthesia in procedures performed outside the operating room. Easier and faster titration of the level of sedation and a lower incidence of nausea and vomiting when compared with other opioids have popularized its use in anaesthesia procedures performed outside the operating room (Esen et al., 2005; Jung et al., 2011).

Table 1. Ramsay sedation scale

Patient is anxious and agitated or restless, or both	1
Patient is cooperative, oriented and tranquil	2
Patient responds to commands only	3
Patient exhibits brisk response to light glabellar tap or loud auditory stimulus	4
Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus	5
No response	6

Dexmedetomidine was first used in the intensive care unit for conscious sedation, but it is now increasingly administred during procedures performed outside the operating room (McMorrow and Abramo, 2012). Unlike other hypnotic agents, dexmedetomidine results in stable haemodynamics and effective analgesia (Demiraran et al., 2007; Takimo et al., 2011).

In this study, we aimed to compare the effect of remifentanil or dexmedetomidine infusions added to ketamine outside the operating room on quality of life, haemodynamics and recovery from anaesthesia in patients undergoing upper gastrointestinal endoscopy (UGE).

2. Material and method

Approval for the study was obtained from ethics committee of the Ondokuz Mayıs University Research and Education hospital (29.11.2012-112) and informed written consent was obtained from all the patients. Eighty patients aged between 18 and 65 years scheduled to undergo UGE were enrolled in the study. The patients had ASA I-II physical status according to the criteria of the American Society of Anesthesiologists (American Society of Anesthesiologists Task Force on Preanesthesia Evaluation, 2002). Patients with cardiovascular, respiratory, neuromuscular, renal or hepatic diseases, and pregnant women were excluded from the study. The patients underwent electrocardiogram, and blood pressure, and peripheral oxygen saturation (SpO_2) were monitored noninvasively.

The patients were randomly separated into two groups (group R and group D) using a double-blind design. Group R (n=40) received remifentanil at a loading dose of 0.5 μg/kg/10 min, followed by an infusion dose of 0.1 μg/kg/min plus 1 mg/kg of ketamine. Group D (n=40) received dexmedetomidine at a loading dose of 0.5 μg/kg/10 min, followed by an infusion dose of 0.2 μg/kg/min plus 1 mg/kg of ketamine. The randomisation was done using codes in a random number list. These codes were enclosed in opaque, sealed envelopes. An independent assistant blinded to the study opened the envelopes, prepared suitable medications and administered them.

In both groups, achievement of a Ramsay sedation score (RSS) (Ramsay et al., 1974) (Table 1) of 4 was accepted as an adequate level of sedation and propofol (0.5-1 mg/kg) was added when adequate sedation could not be accomplished. The RSSs and time to achievement of an RSS of 4 were recorded. After termination of anaesthesia, the modified Aldrete score (MAS) was used as the criterion for the discharge of patients from the postanaesthesia care unit (Aldrete, 1995) (Table 2). The MAS, time to achievement of a MAS of 9 and procedural times were recorded. After a MAS of 9 was reached, the patient was discharged from the postanaesthesia care unit.

Table 2. Modified Aldrete score

Activity	Able to move four extremities consciously	2
	Able to move two extremities consciously	1
	There is no movement	0
Respiration	Able to breathe deep and cough freely	2
	Dyspnea or limited breathing	1
	Apneic	0
Circulation	Systolic blood pressure ±20% of preanesthetic level	2
	Systolic blood pressure ±20-49% of preanesthetic level	1
	Systolic blood pressure ±50% of preanesthetic level	0
Consciousness	Fully awake and oriented	2
	Arousable on calling	1
	Not responding	0
O_2 Saturation	Able to maintain SpO_2>92% on room air	2
	Needs O_2 support to maintain SpO_2>90%	1
	SpO_2<90% even with O_2 supplementation	0

In both groups, heart rate (HR), mean arterial pressure (MAP), SpO_2, need for additional propofol (none, once, ≥2) and side effects were recorded. Respiratory depression was defined as SpO_2 less than 90% and treated with the jaw-thrust manoeuvre or bag-mask ventilation. Bradycardia was defined as a HR of <50/min and treated with 0.5 mg of atropine.

Statistical analysis

The data were analysed with the IBM SPSS 21.0 package program. In both groups, a Mann-Whitney U test was used for comparison of data without a normal distribution, and a T-test was used for data with a normal distribution. The correlation between qualitative variables was analysed with a Spearman rank correlation. $p<0.05$ was considered statistically significant.

3. Results

No statistically significant intergroup difference was detected with respect to age, gender, body weight and ASA data (Table 3).

There were also no statistically significant intergroup differences in HR, MAP and SpO_2 values ($p>0.05$). Bradycardia occurred in two patients in group R and was treated with 0.5 mg of atropine. Desaturation was observed in two patients in groups R and one in group D and was treated with the jaw-thrust manoeuvre. There was no statistically significant difference in side effects between the two groups (p=0.338).

Table 3. Demographic data

	Group R	Group D	P
Age (mean±SD)	44.30±13.78	47.88±17.93	0.320
Gender (n %)			
Female	27 (67.5%)	24 (60%)	0.642
Male	13 (32.5%)	16 (40.0%)	
Body weight (kg) (mean±SD)	78.65±13.14	72.53±14.64	0.053
ASA (n %)			
1	17 (42.5%)	17 (42.5%)	
2	21 (52.5%)	19 (47.5%)	0.682
3	2 (5.0%)	4 (10.0%)	

Table 4. Clinical data of groups

	Group R (n:40)	Group D (n:40)	p
Procedural time (min) (Mean ± SD)	16.73±7.79	19.43±9.19	0,161
Post-procedural MAS (Mean ± SD)	7.43 ±1.412	7.18±1.89	0.716
Time to achieving a MAS of 9 (min) (Mean ± SD)	12.13±11.75	17.38±11.35	0.030

MAS: Modified aldrete score

The need for additional propofol was significantly highThe need for additional propofol was significantly higher in group D (44.10±23.16 mg) than in group R (16.12±23.16 mg) (p=0.001). The RSS was significantly higher at 1. min in group R (2.98±0.15) than in group D (2.18±0.44) (p<0.001), whereas it was relatively lower at 15. min in both groups (group R: 3.63±0.77; group D: 4.35±0.48) (p<0.001). The time to achievement of an RSS of 4 was significantly shorter in group R than in group D (2.53±0.71 vs. 4.30±0.68) (p<0.001).

The post-procedural MAS values and procedural times were comparable (p=0.716 and p=0.161, respectively). The time to achievement of an MAS of 9 was statistically significantly longer in group D (P=0.030) (Table 4).

4. Discussion

Many anaesthetic agents have been used singly or in combination to achieve appropriate sedoanalgesia in UGE (Melloni, 2007). Ketamine can provide an adequate level of anaesthesia during procedures performed outside the operating room, and it aids bronchodilation and preservation of airway reflexes (Nejati et al., 2011; Smally et al., 2011; Khajavi et al., 2013). However, it is generally used in combination with other anaesthetic agents to decrease associated side effects (agitation, hallucination and hypersecretion) (Smally et al., 2011). In the present study, we used ketamine in combination with remifentanil or dexmedetomidine infusions.

Remifentanil is a specific μ opioid receptor agonist, which is rapidly broken down by plasma esterases (Triantafillidis et al., 2013). As a result, it is a short-acting agent, with rapid onset of action, and faster recovery times (Triantafillidis et al., 2013). In addition to sedoanalgesic efficacy, remifentanil provides haemodynamic stability (Kramer et al., 2012; Nooh et al., 2013). Manolaraki et al. (2008) compared analgesia, haemodynamic stability, respiratory depression, and recovery following IV infusions of remifentanil and midazolam-pethidine in patients undergoing colonoscopy. They reported sufficient analgesia, less respiratory depression, better haemodynamic stability, and faster recovery with remifentanil. In a similar study, Fanti et al. (2009) administered remifentanil using patient-controlled analgesia or meperidine at bolus doses. They reported comparable levels of sedoanalgesia and haemodynamic stability in both groups but faster recovery in the remifentanil group.

Owing to its selective α_2 adrenoceptor agonistic activity, dexmedetomidine inhibits sympathetic activity and demonstrates sedative, analgesic, and antisialagogue effects (Venn et al., 2002). Dexmedetomidine, which is used in intensive care units for the sedation of patients connected to mechanical ventilators, has been increasingly used in settings outside the operating room because it does not depress respiration and the sedation it induces can be reversed with a verbal stimulus (Hoy and Keating, 2011). Dexmedetomidine exerts sedative and analgesic effects by decreasing the release of endogenous noradrenaline in the brain and the spinal cord. It is also a short-acting drug with a relatively short half-life (Kamibayashi and Maze, 2000; McMorrow and Abramo, 2012). Vazquez-Reta et al. (2011) compared midazolam versus dexmedetomidine for sedation in patients undergoing UGE. They found that the drugs seemed to produce comparable levels of sedation, with a similar side effect profile. However, the recovery times were shorter with dexmedetomidine. In another study that compared dexmedetomidine, midazolam and propofol, the authors reported more efficient sedation and higher patient satisfaction with dexmedetomidine (Takimoto et al., 2011). They also found that patients under dexmedetomidine sedation showed fewer reactive movements during endoscopic submucosal dissection of gastric cancer.

Similar to the literature in our study, ketamin-remifentanil combination provided rapid onset of sedation when compared with ketamin-dexmedetomidine combination (Kamibayashi and Maze, 2000; Venn et al., 2002; Demiraran et al., 2007; Devabhakthuni, 2013). In the remifentanil group, additional propofol administration was required less frequently. This was likely due to the increased analgesic effectiveness of remifentanil when compared with dexmedetomidine. In addition, patients in the remifentanil group recovered more rapidly. This may be due to the lower amnesic effect of remifentanil and the longer elimination half-life of dexmedetomidine (Kamibayashi and Maze, 2000; Demiraran et al., 2007; Chen et al., 2014).

Failure to evaluate post-procedural pain levels is a limitation of the present study. An additional limitation is the failure to compare satisfaction levels of the patients and physicians.

In conclusion, the combination of ketamine with remifentanil or dexmedetomidine provided effective and successful sedoanalgesia in UGE. However, remifentanil ensured faster and more efficient sedoanalgesia, in addition to faster recovery, than dexmedetomidine.

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