



Research article

Effect of low dose ketamine versus dexmedetomidine on gag reflex during propofol based sedation during upper gastrointestinal endoscopy. A randomized controlled study



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ABSTRACT

Objective: The aim of this study is to evaluate the effect of dexmedetomidine versus low dose ketamine on incidence of gag reflex and the total amount of propofol consumed during (UGIE) in patient sedated with propofol.

Methods: This randomized, prospective, double blind study was approved by institutional ethics committee of El-Minia university hospital and carried out in the period ranged from March 2015 to January 2016. 75 male and female patients aged from 18 to 70 years old, ASA class I–II. The patients were randomly (by computer generated table) allocated into 3 equal groups: Group(I) (propofol group), Group(II): (propofol + ketamine group), Group(III): (propofol + dexmedetomidine group). Parameters assessed was - Gag reflex, depth of sedation, total dose of propofol, oxygen saturation (spo₂), hemodynamic data, time to recovery, any side effects as:- emergence delirium, and ny need for airway assistance.

Results: Gag reflex In group(I) was 32% (8 patients) versus 20% (5 patients) in group(II) and 8% (2 patients) in group(III). Patients in group(I) were significantly required higher doses of propofol when compared to group(III) and group(II), while patients in group(II) were required higher doses of propofol than group(III) with significant statistically difference. The changes of HR were comparable between the studied groups except after 2 min of induction, there were significant reduction in mean values of HR in group(I) in comparison to group(II) and group(III). As regard MAP, there were significant elevation in group(II) when compared to group(I) (at 2, 4, 6 min) and group(III) (at 2, 4, 6, 8 min, otherwise there were no significant difference. Oxygen saturation was comparable in the studied groups at all set time and there was no significant difference in their values, only 8% of patients in group(II) versus 12% in group(III) and 20% in group(I) needed jaw thrust as airway assistance. Time to recovery in group(I) was (4.84 ± 0.89 min) which was significantly longer than both group(II) (4.16 ± 1.06 min) and group(III) (4.2 ± 1.04 min).

Conclusion: Dexmedetomidine with propofol in patients undergoing UGIE was safe and effectively, can reduce the incidence of gag reflex better than ketamine when added to propofol, with less propofol consumption and better in recovery time.

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1. Introduction

Upper gastrointestinal endoscopy (UGIE) is increasingly being performed under propofol sedation. Even under propofol sedation, UGIE is associated with gag reflex and retching in approximately 29% of patients [1]. Any further deepening of sedation to minimize gagging may cause respiratory depression and compromise hemodynamics, while continued gag reflex could affect the safety of the

procedure. In a laboratory study, N-methyl-D-aspartate (NMDA) receptor antagonism has been shown to prevent gag reflex [2]. Ketamine, a phencyclidine derivative and NMDA receptor antagonist, is commonly used in sub-anesthetic doses as an adjunct for anesthesia technique. In a laboratory study, N-methyl-D-aspartate (NMDA) receptor antagonism has been shown to prevent gag reflex by abolish the coupling between loss of consciousness and upper airway dilator muscle dysfunction in a wide dose range [3] it is commonly used in sub-anesthetic doses as an adjunct for anesthesia technique [5]. Propofol is a preferred drug for sedation during UGIE [4]. Dexmedetomidine, a short-acting selective alpha-2 agonist, possesses anxiolytic, hypnotic, and analgesic properties

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[6]. It is approximately eightfold more selective for the alpha-2 adrenergic receptor than clonidine and is 1620-fold more potent as an alpha-2 adrenergic receptor agonist than as an alpha-1 adrenergic receptor agonist [7], it provide unique sedative activity not found in conventional sedatives and is thus unlikely to cause the restlessness or respiratory suppression seen with GABA receptor agonists such as propofol alone that minimize physical and emotional discomfort, and facilitate successful completion of the procedure without significant gag reflex [11]. Several randomized controlled trials (RCT) have evaluated the efficacy of dexmedetomidine in comparison with midazolam for gastrointestinal endoscopy [8]. Unfortunately, none of these trials enrolled a sufficient number of patients to produce an adequate power in order to detect meaningful differences. Many authors proposed that systematic pooling of all data from available studies might provide a better understanding the effects of dexmedetomidine [9].

The aim of this study is to evaluate the effect of dexmedetomidine versus low dose ketamine on incidence of gag reflex (primary outcome) and the total amount of propofol used during (UGIE) in patient sedated with propofol.

2. Patients and methods

This randomized, prospective, controlled, double blind study was approved by institutional ethics committee of El-Minia university hospital and carried out in the period ranged from March 2015 to January 2016. A written consent was obtained from 75 male and female patients aged from 18 to 70 years old from ASA class I – II patients, including patients with compensated hepatic cirrhosis undergoing upper GIT endoscopy. We excluded from our study Patients with major organ dysfunction specially patient with decompensated liver disease, also Closed angle glaucoma, any type of analgesics as opioids or corticosteroids preoperative or allergy to any type of studied drugs. A careful medical history was taken, general and local examination including chest, heart, abdomen, and neurological examination. Routine investigations including, liver function tests, complete blood picture, renal function tests, blood sugar, abdominal ultrasound to exclude any hepatic decomposition and electrocardiogram (ECG). The patients were randomly divided into three equal groups (25 of each) using a computer-generated sequence of random numbers and a sealed envelope technique. Study drugs were prepared by an anesthetist who did not participate in the procedure; this study was conducted in a double-blind manner (neither the administrator of the drug nor the patient know the nature of drugs given. Group(I): (propofol group), Patients receive 2 syringes one containing 5 ml normal saline followed by the second containing 50 mg propofol (deprivan, AstraZeneca, Egypt). Group(II): (propofol + ketamine group) 5 ml of normal saline containing 0.20 mg/kg ketamine (ketamine, liorad, Egypt) in the first syringe followed by the second syringe containing 50 mg propofol. Group: (III): (propofol + dexmedetomidine group) 5 ml volume of normal saline containing 0.5 mcg/kg dexmedetomidine (precede, hospira, Egypt) in the first syringe followed by the second syringe containing 50 mg propofol as bolus. Standard monitoring (i.e. ECG, heart rate (HR), pulse oximetry (SpO2), non-invasive arterial pressure measurement, and baseline parameters recorded using (Datex-omedah. GE healthcare co. U.S. A). 20F I.V cannula was inserted for administration of drugs and all patients were premedicated only with intravenous 50 mg ranitidine before start of sedation, Two ml of 2% lignocaine was slowly injected intravenously to prevent propofol induced pain, followed by the administration of content of the test syringes (either saline, ketamine or dexmedetomidine). Immediately after this injection a bolus of propofol (10 mg/ml) was given slowly over 1 min following which sedation was assessed and if needed further top up

Table 1
Ramsay sedation scale [10].

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

doses of propofol were given in 10 mg increments. Sedation was always maintained at Ramsay score of more than 4, Sedation levels were checked every 2–3 min by a light glabellar tap or loud noise according to Ramsay sedation score as shown at Table 1 [10]. Supplemental oxygen was given to all patients using nasal canula the sedation done by anesthesiologist who didn't know the contents the test syringes prepared by the senior author, also, data measured by assistant anesthesiologist who did not know the administered study drugs. **Measured data:** 1 – *Gag reflex:* Was recorded as “present or not” when a vomiting like response was elicited upon insertion of the endoscope. 2 – *Depth of sedation:* Assessed by Ramsay sedation score (Table 1), after 1 min of induction of sedation and all over the time of the procedure every 2 or 3 min. 3 – *Total dose of propofol* administered in each patient. 4 – *Oxygen saturation* (spo2). 5 – *Hemodynamic data:* HR and non invasive mean arterial blood pressure. Bradycardia (heart rate less than 50) and hypotension were defined as 20% decrease below base line values or mean arterial blood pressure less than 60 and if recorded treated by atropine 0.02 mg/kg or bolus dose of ephedrine 6 mg respective 6 – *Time to recovery:* From end of the procedure to Ramsay sedation score 2 (awake, cooperative, accepting ventilation, oriented and tranquil). 7 – *Any side effects* as:- emergence delirium: Patient talking irrelevant or disoriented upon recovery was labeled as having “emergence delirium”. Any recall of the procedure, they were asked “do you remember anything about the endoscopy procedure performed on you. 8 – Any need for airway assistance. Also, other side effects of drugs used in the study if present as (nausea, vomiting, respiratory depression or hypersensitivity to any drug used.)

2.1. Statistical analysis

Based on prior study, the sample size was calculated to detect difference in incidence of gag reflex between the studied groups at power of 0.80, confidence interval of 95% and significance level of 0.05. Calculating for a 20% dropout rate, 25 patients in each group was appropriate to detect this difference. Data was analyzed using Statistical Package of Social Sciences (SPSS) software and expressed as mean ± standard deviation and median (minimum-maximum) for numerical data or as number and percent (%) for categorical data. Intergroup comparisons of continuous numerical variables were done using ANOVA test for parametric data or kruskal-willis one way test for non-parametric data. Intragroup comparisons to baseline values were done using paired *t*-test for parametric data or Wilcoxon test for non-parametric data. The level of significance was fixed at a minimum of 0.05%.

3. Results

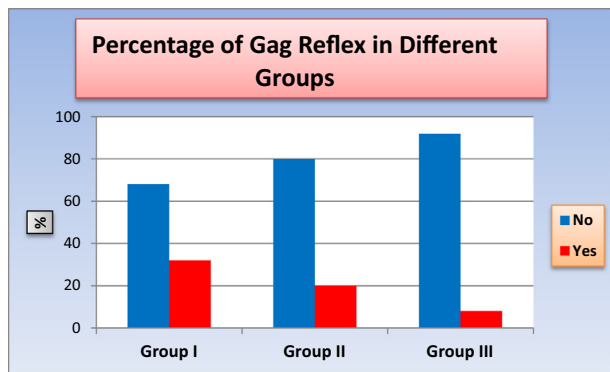
There were no significant differences in age, weight, sex distribution, ASA classification or duration of the procedure among the 3 groups (Table 2).

Gag reflex was recorded as present or not in all groups, there was significant reduction in the incidence of gage reflex in group (III) (8%) when compared with group(I) (32%) (p value: 0.034), also

Table 2
Patient characteristics and operative time in different groups.

Variables	Group I (n = 25)	Group II (n = 25)	Group III (n = 25)	P value		
Age in years				0.419		
Range	(26–60)	(27–60)	(26–60)	I vs II	I vs III	II vs III
Mean ± SD	43.4 ± 8.83	46.72 ± 10.42	43.4 ± 11.22	0.487	1	0.487
Sex				0.492		
Male	12(48%)	16(64%)	15(60%)	I vs II	I vs III	II vs III
Female	13(52%)	9(36%)	10(40%)	0.254	0.395	0.771
Weight in kg.				0.845		
Range	(74–100)	(66–102)	(69–980)	I vs II	I vs III	II vs III
Mean ± SD	85.92 ± 7.94	84.92 ± 11.07	84.44 ± 8.21	0.922	0.837	0.981
ASA				0.820		
Class I (n)	8(32%)	7(28%)	6(24%)	I vs II	I vs III	II vs III
Class II (n)	17(68%)	18(72%)	19(76%)	0.758	0.529	0.747
Operative time in minutes				0.382		
Range	(5–12)	(5–15)	(5–12)	I vs II	I vs III	II vs III
Mean ± SD	7.12 ± 1.83	7.68 ± 2.24	7.88 ± 1.87	0.584	0.374	0.933

Data are expressed as numbers and Mean ± SD for age, sex, weight, and operative time and percentage for ASA class. (n): Number of patients – (SD): Standard Deviation. **Group I:** propofol group. **Group II:** propofol + ketamine. **Group III:** propofol + dexmedetomidine.

**Fig. 1.** Percentage of Gag reflex in the study groups. Group I: propofol group. Group II: propofol + ketamine. Group III: propofol + dexmedetomidine.

gag reflex in group(II) (20%) was less than in group(I) and more than group(III) but without significant differences (p value: 0.333 and 0.221 respectively) (Fig. 1). Oxygen saturation was comparable in the three groups at all set times with no significant difference in their values throughout the studied time. There were significant reduction in mean values of HR in group(I) in comparison to group(III) only after 2 min (p value: 0.042), otherwise changes in mean values of HR were statistically insignificant between the studied groups (Table 3). Regarding MAP in different groups, there were significant reduction in mean values of MAP in group(I) at 2, 4, 6 min when compared with group(II) (p value: 0.046, 0.006, 0.002 respectively), also, in comparison between group(II) and group(III), MAP were lower significantly in group(III) than group (II) at 2, 4, 6, 8 min (p value: 0.029, 0.001, 0.001, 0.007 respectively), in comparison between group(I) and group(III) in mean values of MAP there was no statistically significant difference throughout the study (see Table 4).

Table 3
Heart rate (beat/min) in different groups.

Time	Group I (n = 25)	Group II (n = 25)	Group III (n = 25)	P value		
(1) Base				0.716		
Range	(66–105)	(65–110)	(69–115)	I vs II	I vs III	II vs III
Mean ± SD	87.84 ± 8.77	85.16 ± 13.21	86.52 ± 12.22	0.692	0.914	0.909
(1) 2 min				0.009 [†]		
Range	(63–81)	(64–90)	(65–90)	I vs II	I vs III	II vs III
Mean ± SD	72.56 ± 6.46	79.12 ± 9.08	78 ± 7.63	0.11	0.042 [†]	0.868
(1) 4 min				0.226		
Range	(65–82)	(63–89)	(60–89)	I vs II	I vs III	II vs III
Mean ± SD	74.04 ± 4.97	77.52 ± 9.42	76.96 ± 7.67	0.243	0.367	0.963
(1) 6 min				0.756		
Range	(68–81)	(65–89)	(59–89)	I vs II	I vs III	II vs III
Mean ± SD	74.95 ± 3.96	76.23 ± 9.65	74.63 ± 7.68	0.848	0.990	0.766
(1) 8 min				0.562		
Range	(70–79)	(64–89)	(59–87)	I vs II	I vs III	II vs III
Mean ± SD	74.22 ± 3.19	75.69 ± 9.37	72.66 ± 7.14	0.891	0.872	0.532
(2) 10 min				0.184		
Range	(75–77)	(68–68)	(68–80)	I vs II	I vs III	II vs III
Mean ± SD	75.66 ± 1.15	68 ± 0	73.25 ± 5.73	0.068	0.721	0.140
(2) 12 min				0.259		
Range	(73–105)	(67–110)	(75–115)	I vs II	I vs III	II vs III
Mean ± SD	73 ± 8.77	68 ± 1.41	75 ± 13.21	0.221	0.317	0.221

Data are expressed as numbers, range and Mean ± SD. Value <0.05. (n): Number of patients. (SD): Standard Deviation. **Group I:** propofol group. **Group II:** propofol + ketamine. **Group III:** propofol + dexmedetomidine.

[†] Significant difference at p.

Table 4
Mean Arterial blood pressure (mmhg) in different groups.

Time	Group I (n = 25)	Group II (n = 25)	Group III (n = 25)	P value		
(1) Base				0.162		
Range	(76–106)	(68–110)	(75–108)	I vs II	I vs III	II vs III
Mean ± SD	92.72 ± 8.83	87.76 ± 11.71	88.28 ± 9.11	0.191	0.263	0.981
(1) 2 min				0.018*		
Range	(65–90)	(70–100)	(60–90)	I vs II	I vs III	II vs III
Mean ± SD	79.48 ± 7.26	84.92 ± 7.63	79.08 ± 8.75	0.046*	0.983	0.029*
(1) 4 min				0.001*		
Range	(68–87)	(71–100)	(63–89)	I vs II	I vs III	II vs III
Mean ± SD	79.24 ± 6.15	85.64 ± 6.84	78.4 ± 8.01	0.006*	0.907	0.001*
(1) 6 min				<0.001*		
Range	(65–86)	(70–100)	(65–89)	I vs II	I vs III	II vs III
Mean ± SD	78.63 ± 5.75	86.47 ± 6.93	77.31 ± 7.84	0.002*	0.819	<0.001*
(1) 8 min				0.008*		
Range	(69–85)	(72–100)	(65–90)	I vs II	I vs III	II vs III
Mean ± SD	79 ± 5.61	87 ± 8.87	77.2 ± 7.95	0.066	0.848	0.007*
(2) 10 min				0.172		
Range	(75–88)	(79–97)	(66–80)	I vs II	I vs III	II vs III
Mean ± SD	81 ± 6.55	88 ± 12.72	72.5 ± 5.97	0.564	0.108	0.165
(2) 12 min				0.407		
Range	(80–105)	(78–110)	(74–108)	I vs II	I vs III	II vs III
Mean ± SD	80 ± 8.83	84 ± 8.48	74 ± 9.11	1	0.317	0.221

Data are expressed as numbers, range and Mean ± SD. Value <0.05. (n): Number of patients. (SD): Standard Deviation. **Group I:** propofol group. **Group II:** propofol + ketamine. **Group III:** propofol + dexmedetomidine.

* Significant difference at p.

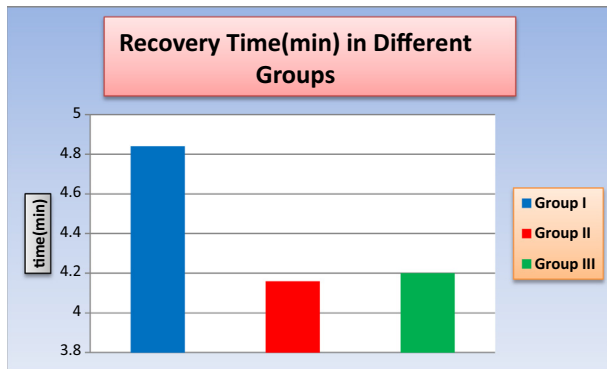


Fig. 2. Recovery time in different groups. Group I: propofol group. Group II: propofol + ketamine. Group III: propofol + dexmedetomidine.

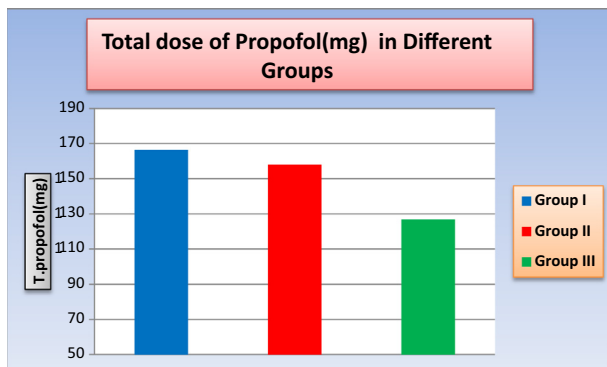


Fig. 3. Total propofol consumption in mg. in different groups. Group I: propofol group. Group II: propofol + ketamine. Group III: propofol + dexmedetomidine.

Time to recovery in group(I) was (4.84 ± 0.89 min) which was significantly longer than group(II) (4.16 ± 1.06 min) and group(III) (4.2 ± 1.04 min) with insignificant difference in comparison

between group(II) and group(III) (Fig. 2). Patients in group(I) were significantly required higher doses of propofol (166.4 ± 19.76 mg) when compared to group(III) (126.8 ± 16.51 mg) (p value < 0.001) with no significant difference when compared to group(II) (158 ± 26.77 mg) (p value: 0.354) while patients in group(II) were required higher doses of propofol than group(III) with statistical significant difference (p value < 0.001) (Fig. 3). Incidence of airway assistance and post-operative delirium in different groups were comparable between the studied groups with no significant statistically difference (see Table 5).

4. Discussion

Our study was Prospective, randomized, double-blind study aimed to evaluate the effect and safety of low doses of ketamine and dexmedetomidine as adjuvants to propofol based sedation in UGIE and their effect on gag reflex and propofol consumption during the procedure. 75 patients were randomly divided into 3 equal groups of 25 patients Group(I): receive 5 ml normal saline only +50 mg propofol as bolus, Group(II): receive 5 ml volume of normal saline containing 0.20 mg/kg ketamine +50 mg propofol as bolus, Group(III): receive 5 ml volume of normal saline containing 0.5 ug/kg dexmedetomidine +50 mg. propofol as bolus, all syringes were injected over 1 min. The results of our study revealed that the incidence of gag reflex In group(I) was 32% (8 patients) versus 20% (5 patients) in group(II) while it was 8% (2 patients) in group (III). The lowest incidence of gag reflex was noted in group(III). As regarding total doses of propofol, Patients in group(I) were significantly required higher doses of propofol when compared to group(II), while patients in group(II) were required higher doses of propofol than group(III) with significant statistically difference, that was explained by both ketamine and dexmedetomidine have additive sedative-hypnotic, analgesic and anxiolytic effects when used with propofol reducing its consumption. The changes of mean values of HR were comparable between the studied groups except after 2 min of induction, there were significant reduction in mean

Table 5
Delirium and airway assistance in different groups.

	Group I (n = 25)	Group II (n = 25)	Group III (n = 25)	P value		
Delirium				0.685		
Yes	3(12%)	2(8%)	4(16%)	I vs II	I vs III	II vs III
No	22(88%)	23(92%)	21(84%)	0.637	0.684	0.384
Airway assistance				0.446		
Yes	5(20%)	2(8%)	3(12%)	I vs II	I vs III	II vs III
No	20(80%)	23(92%)	22(88%)	0.221	0.440	0.637

Data expressed as percentage. (*): Significant difference at p value < 0.05. (n): Number of patients. **Group I:** propofol group. **Group II:** propofol + ketamine. **Group III:** propofol + dexmedetomidine.

values of HR in group(I) in comparison to group(II) and group(III) that may be due to need of more supplemental doses of propofol with its suppressant effect. As regard MAP, there were significant elevation in group(II) when compared to group(I) (at 2, 4, 6 min) and group(III) (at 2, 4, 6, 8 min), that can be explained by sympathomimetic activity of ketamine, otherwise there were no significant difference. Oxygen saturation was comparable in the studied groups at all set time and there was no significant difference in their values, only 8% of patients in group(II) versus 12% in group (III) and 20% in group(I) needed jaw thrust as airway assistance. Time to recovery in group(I) was (4.84 ± 0.89 min) which was significantly longer than both group(II) (4.16 ± 1.06 min) and group (III) (4.2 ± 1.04 min), that can be explained by increase total propofol consumption in group(I). In our study We found decreased incidence of emergence delirium in group(II) (8%) compared with group(I) (12%) and group(III) (16%).

In agreement with our study, Tandon et al., evaluated the effect of sub-anesthetic dose of ketamine (0.15 mg/kg) on propofol based sedation for UGIE and its effect on gag reflex, a total of 270 patients undergoing UGIE, were allocated into tow groups: propofol (P) group (n = 135) and propofol plus 0.15 mg/kg ketamine (PK) group (n = 135), all patients received propofol boluses titrated to Ramsay sedation score of not <4. Patients in PK group in addition received ketamine, gage reflex occurred in 23 patient in propofol group (GroupP) and 3 patients were from the ketamine group (PK), also there were 48% reduction in the incidence of hypotension in group (PK) compared to group (P), that mean ketamine provide more hemodynamic stability during propofol based sedation in UGIE. The incidence of emergence delirium in (PK) group was less than in (P) group with no significant statistically difference [12].

Similar study by Aydogan et al., compared propofol vs. propofol-ketamine combination for upper GIE sedation, the results showed Heart rate, mean arterial pressure, peripheral oxygen saturation were similar between groups in all time intervals, Side effects including respiratory depression, bradycardia, hypotension, nausea, vomiting and secretion increase were found to be similar in both groups. They reported shorter recovery time in their study (7.26 ± 6.8 min) in patients received ketamine-propofol versus (10.30 ± 3.6 min) in patients received fentanyl-propofol [13]. The difference between recovery time reported in Aydogan et al. and that recorded in group(II) in our study might be due to higher doses of ketamine were used. Another study performed by Sethi et al., who studied dexmedetomidine versus midazolam for conscious sedation in Endoscopic retrograde cholangiopancreatography (ERCP). Patients between 18 and 60 years of age with ASA Grade I-II requiring ERCP were enrolled in two groups (30 each). Both groups received fentanyl 1 µg/kg IV at the beginning of ERCP. Group M received IV midazolam (0.04 mg/kg) and additional 0.5 mg doses until Ramsay Sedation Scale (RSS) score reached 3–4. Group D received dexmedetomidine at loading dose of 1 µg/kg over 10 min followed by 0.5 µg/kg/h infusion. There was no significant difference in BP and respiratory rate. The procedure elicited a gag response in 29 (97%) and 7 (23%) subjects in Group M and

Group D respectively. Dexmedetomidine showed higher patient and surgeon satisfaction scores. Also, they reported shorter recovery time for dexmedetomidine group [14]. Kang et al., studied dexmedetomidine versus placebo in remifentanyl-based anesthesia. They reported significant difference in total propofol consumption by the end of their procedure (63.9 ± 16.2 Imic/kg/h) in dexmedetomidine, versus (96.4 ± 10.0 Imic/kg/h) in placebo with this lower values of propofol consumption in their study than values of the current study could be explained by the differences in dexmedetomidine maintenance dose and the addition of remifentanyl infusion to anesthetic technique might play a synergistic role [15]. In disagreement with our study, propofol consumption in a study performed by Saric et al.: In this prospective, double blind study of 40 patients (>65 years) undergoing ERCP, propofol consumption was (352.65 ± 109.44 mg) in ketamine-propofol group versus (380 ± 135.4 mg) in propofol alone, This was more than the propofol consumption reported in our study; this might be due to the longer duration of ERCP procedure [16]. Another study by Muller et al., reported intra-procedural hemodynamic instability of dexmedetomidine as they studied dexmedetomidine alone against propofol-fentanyl for conscious sedation during ERCP. The result was that Dexmedetomidine alone was not as effective as propofol combined with fentanyl for providing conscious sedation during ERCP. Furthermore, dexmedetomidine was associated with greater hemodynamic instability and a prolonged recovery. This might be explained by the lighter level of sedation in dexmedetomidine group; they administered dexmedetomidine in loading dose 1 µg/kg infused over 10 min then maintained by 0.2 µg/kg/h that requiring additional sedatives [17].

In conclusion, using dexmedetomidine in addition to propofol in patients undergoing UGIE was safe and effectively reducing the incidence of gage reflex also addition of dexmedetomidine to propofol was better than ketamine in reducing gag reflex, require less doses of propofol and better in recovery time.

Left to point out, there were several limitations to our study, first the enrolled sample population all consists of ASA class. I or II only second was small sample size of patients in our study and finally we use a single dose, further studies are needed to compare effect of different doses of dexmedetomidine aiming to detect the optimal dose that provides more reduction in the incidence of gag reflex with least side effects.

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