Egyptian Journal of Anaesthesia

ISSN: (Print) 1110-1849 (Online) Journal homepage: https://www.tandfonline.com/loi/teja20

Propofol dexmedetomidine versus propofol ketamine for anesthesia of endoscopic retrograde cholangiopancreatography (ERCP) (A randomized comparative study)

Mai W. Abdalla, Sahar M. El Shal, Ahmed I. El Sombaty, Nasr M. Abdalla & Rasha B. Zeedan

To cite this article: Mai W. Abdalla, Sahar M. El Shal, Ahmed I. El Sombaty, Nasr M. Abdalla & Rasha B. Zeedan (2015) Propofol dexmedetomidine versus propofol ketamine for anesthesia of endoscopic retrograde cholangiopancreatography (ERCP) (A randomized comparative study), Egyptian Journal of Anaesthesia, 31:2, 97-105, DOI: 10.1016/j.egja.2014.12.008

To link to this article: https://doi.org/10.1016/j.egja.2014.12.008

Published online: 17 May 2019.

Egyptian Journal of Anaesthesia (2015) **31**, 97–105

HOSTED BY

ELSEVIER

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

www.elsevier.com/locate/egja
www.sciencedirect.com

Research Article

Propofol dexmedetomidine versus propofol ketamine for anesthesia of endoscopic retrograde cholangiopancreatography (ERCP) (A randomized comparative study)

Mai W. Abdalla [a], Sahar M. El Shal [a,*], Ahmed I. El Sombaty [a], Nasr M. Abdalla [a], Rasha B. Zeedan [b]

[a] *Department of Anesthesia, Faculty of Medicine, Cairo University, Cairo, Egypt*
[b] *Department of Anesthesia, Liver and Tropical Research Institute, Cairo, Egypt*

Received 20 September 2014; revised 16 December 2014; accepted 22 December 2014
Available online 24 January 2015

KEYWORDS

ERCP;
Dexmedetomidine;
Propofol;
Ketamine

Abstract *Objectives:* The aim of this study was to compare the effects of propofol/dexmedetomidine and propofol/ketamine combinations for anesthesia in patients undergoing ERCP regarding hemodynamic changes, propofol requirements and the recovery criteria.
Patient and methods: Sixty patients aged 20–50 years ASA II or III scheduled for ERCP were enrolled in this study. Patients were randomly allocated into two equal groups: dexmedetomidine/propofol (DP) group and ketamine/propofol (KP) group. DP patients received a loading dose of iv dexmedetomidine 1 μg/kg over 15 min then maintained by a 0.5 μg/kg/h. Group KP patients received a loading dose of iv ketamine 1 mg/kg over15 min then maintained by 0.5 mg/kg/h. Induction of anesthesia was achieved with propofol 2 mg/kg, atracurium 0.5 mg/kg to facilitate endotracheal intubation. Anesthesia was maintained by propofol infusion 5 mg/kg/h, intermittent iv propofol boluses (0.5 mg/kg) were administered if needed. MAP and HR were recorded before loading of study drugs (baseline) and recorded every 5 min after beginning of loading throughout the procedure and just after intubation, then every 15 min for one hour post-operative. Total propofol consumption, recovery time, VAS and postoperative complications (PONV, cognitive dysfunction, and respiratory complications) were recorded.
Results: The intra-procedural HR and MAP showed high statistical significant differences between both groups throughout the procedure with lower values in DP group ($p < 0.01$ or < 0.001). During the post-procedural period, the HR and MAP were significantly lower in DP group. Propofol consumption was comparable in both groups (268.0 ± 122.3 mg) in DP group versus (304.7 ± 142.0 mg) in KP group. Postprocedural recovery time was significantly shorter in DP

* Corresponding author at: 23 Ahmad Mokhtar Hagazy, Elmanayl, Cairo, Egypt. Tel.: +20 1114616555.
E-mail address: sasmed_2006@yahoo.com (S.M. El Shal).
Peer review under responsibility of Egyptian Society of Anesthesiologists.

http://dx.doi.org/10.1016/j.egja.2014.12.008

group (5.7 ± 1.7 min) compared with (22.2 ± 8.2 min) KP group ($p < 0.01$). VAS was comparable in the two groups. PONV was 46.67% of KP group, while it was absent in DP group. Post-operative cognitive disorders showed a high statistical significant difference between both groups ($p < 0.001$) with no cases was reported in DP group. No respiratory complications in both groups. *Conclusion:* Dexmedetomidine–propofol combination as TIVA during ERCP showed better intra- and post-procedural hemodynamic stability, less PONV, less postoperative cognitive dysfunctions and shorter recovery time when compared with ketamine–propofol combination.

1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is commonly used in the management of many pancreatobiliary disorders. ERCP is the ideal method for extraction of common bile duct stones; it reduced the need for the more invasive surgical procedures associated with high morbidity particularly in old age patients. ERCP with stent placement can be very effective for the palliation of obstructive jaundice In pancreatic cancer patients [1,2].

In comparison with upper gastrointestinal endoscopic procedures, ERCP is a longer and more complex procedure, with a substantially higher complication rate [3]. Sedation for gastrointestinal endoscopic procedures has gained much interest in recent years. Sedation obviously ensures comfort for the patients and endoscopists during the procedure, but sometimes sedation in ERCP may be responsible for some postoperative adverse events [4,5].

In fact, most complications in GI endoscopy are related to sedation; including cardiopulmonary events such as hypoxemia, hypoventilation, airway obstruction, apnea, arrythmia, hypotension, and vasovagal episodes [6]. Raymonds and his colleagues supported a continued preference for GA rather than conscious sedation for ERCP especially when complex and painful interventions are planned in prone position [7].

The introduction and availability of different pharmaceutical agents such as propofol, ketamine and dexmedetomidine allow rapid induction of anesthesia while enabling rapid recovery.

Dexmedetomidine is a stereoisomer of medetomidine. It is a highly selective α2-agonist; eight times higher specificity for receptors compared with clonidine. It seems to have better hemodynamic parameters. It has a perioperative sedative, analgesic and anxiolytic properties similar to benzodiazepines but being α2 adrenoceptor agonist it has less side effects. Dexmedetomidine provides analgesia with ceiling effect at doses >0.5 μg/kg thus this effect is dose-dependent. Dexmedetomidine is not a powerful anti-emetic and it has been shown to cause much less respiratory depression than other sedatives. However, co-administration of dexmedetomidine with other anesthetic agents, sedatives, hypnotics, or opioids is likely to cause additive effects, it attenuates but not completely abolishes stress-induced sympatho-adrenal responses protecting the patients from noxious sympathetic stimulation and hemodynamic changes and that is one of the main anesthetic goals [8–11].

Propofol is a non barbiturate sedative hypnotic; it has a favorable pharmacokinetic profile as the lipid solubility confers a quick onset and short recovery time. It has also an anti-emetic, anticonvulsant, antipruritic and amnestic effects. Although it is extremely effective and potent, propofol use is limited by a relatively high incidence of dose-dependent hypotension and respiratory depression [12].

Ketamine is a phencyclidine derivative. It provides excellent amnesia and analgesia, preserves muscle tone with maintaining airway reflexes and spontaneous respiration. Despite its obvious advantages over other agents, some practitioners are hesitant to use ketamine alone secondary to its ability to cause frightening emergent reactions; additionally it has significant adverse effects including; sympathomimetic effects, vomiting and excessive salivation even when administered in sedating doses [13].

It is postulated that combining propofol–ketamine may preserve sedative and analgesic efficacy while minimizing their respective adverse effects, this is partially due to the fact that many of the adverse effects are dose-dependent and when the two drugs used in combination the doses administered of each can be reduced. Also, the CVS effects of each are opposing in action, thus theoretically balancing each other when used together. The theoretical advantages of this combination produce more stable hemodynamic and respiratory profile that were tested and found to be true in group of patients receiving GA [14,15].

We hypothesized that the combination of propofol with either dexmedetomidine or ketamine will improve the analgesic and anesthetic effects of these drugs with lower doses and less side effects. This will later help in providing adequate anesthesia and analgesia in ERCP procedures requiring general anesthesia.

This randomized comparative study was performed to compare the effects of propofol/dexmedetomidine and propofol/ketamine combinations in patients undergoing ERCP regarding hemodynamic effects, intra-procedural propofol requirements as well as the recovery criteria and side effects.

2. Subjects and methods

The study was conducted after approval of the ethical and scientific committee of the department of anesthesia in Kasr El Aini hospital-Cairo University, and a written informed consent was obtained from each participant in this study. Sixty patients of both sexes aged 20–50 years scheduled for diagnostic or therapeutic ERCP were enrolled in this study which was conducted from March 2013 to March 2014. All patients were of American Society of Anesthesiologist (ASA) class II or III. Exclusion criteria included patients with allergy to study drugs, patients with cardiovascular disease (hypertension, congestive heart failure, and coronary artery disease), cerebrovascular

insufficiency, increased intracranial tension, personality disorders or suspected pregnancy in addition to those receiving antipsychotic or sedative medication.

Patients were randomly allocated into one of two parallel treatment groups with allocation ratio of 1:1 and thirty patients in each group. The allocation sequence was generated using a randomized computer-generated sequence held by an investigator not involved with the clinical management or data collection.

- Dexmedetomidine/propofol (DP) group received iv dexmedetomidine (1 μg/kg loading), followed by (0.5 μg/kg/h infusion) and iv propofol infusion (5 mg/kg/h).
- Ketamine/propofol group (KP) group received iv ketamine (1 mg/kg loading, followed by 0.5 mg/kg/h infusion) and propofol infusion (5 mg/kg/h).

Pre-procedural evaluation included history taking, physical examination and laboratory investigations (complete blood picture, liver and kidney function tests, and coagulation profile) and ECG. All patients were made familiar with the use of 10 cm visual analogue scale score (VAS) identifying 0 as no pain and 10 as the worst imaginable pain.

Before induction of anesthesia the study drugs (propofol, dexmedetomidine, and ketamine) were prepared in identical 50 ml infusion syringes, the drugs were prepared as the following:

- The propofol infusion syringe: A 50 ml syringe contained 10 mg/ml propofol (1% Fresenius Kabi Austria Gmbh 20 ml).
- Dexmedetomidine infusion syringe contained 100 μg dexmedetomidine (precedex®; united pharmaceutical group company, USA) diluted by normal saline to have 50 ml filled syringe (2 μg/ml).
- Ketamine infusion syringe contained 100 mg ketamine (Ketamine®; Sigma company) diluted with normal saline to have 50 ml filled syringe (2 mg/ml).

Blinding of the study was ensured for the patients receiving the treatment drugs, the investigators assessing the outcomes, and the people analyzing the results/data. The study medications were prepared, and coded by an independent observer who was not participating in any other part of the study and the study drugs were administered by an anesthesiologist who was not involved in the management of follow-up period to maintain the double-blind nature of the study. But no blindness to the propofol infusion syringe as sometimes there was a need to decrease the infusion rate on occurrence of hypotension (a decrease $>20\%$ of baseline value).

2.1. Anesthetic procedure

On arrival to the operating room standard monitoring were applied (ECG, automated non-invasive blood pressure monitoring and pulse oximetry) with recording of base line HR, MAP, and oxygen saturation, then a 20 gauge iv cannula was inserted on the dorsum of the hand and lactated ringer solution was infused (6–8 ml/kg/h). Group DP patients received a loading dose of iv dexmedetomidine 1 μg/kg over 15 min then maintained throughout the procedure by a rate of 0.5 μg/kg/h. Group KP patients received a loading dose of iv ketamine 1 mg/kg over 15 min then maintained throughout the procedure by a rate of 0.5 mg/kg/h.

After insertion of another 20 gauge iv cannula induction of anesthesia was achieved with iv lidocaine 0.5 mg kg^{-1} to decrease pain induced by propofol injection, then propofol 2 mg/kg IV bolus, atracurium 0.5 mg/kg was used to facilitate endotracheal intubation using a suitable sized cuffed endotracheal tube. Controlled mechanical ventilation was instituted with 100% oxygen. Capnography was applied and mechanical ventilation was adjusted to maintain Et-CO_2 at 30–35 mmHg. Anesthesia was maintained by iv propofol infusion 5 mg/kg/h, intermittent iv propofol boluses (0.5 mg/kg) were administered to the patient guided by patient's hemodynamic parameters (20% increase in HR, and MAP above baseline values) and atracurium top up doses 0.1 mg/kg was given every 20 min. All operations were performed in the prone position. At the end of the procedure all infusion drugs discontinued and reversal of neuromuscular block was done by 0.05 mg/kg prostigmine and 0.01 mg/kg atropine followed by suctioning of secretions and awake extubation after fulfilling the criteria of extubation (patient is conscious, hemodynamic stability, spontaneous breathing and oxygen saturation $>95\%$). Finally patients will be transferred to recovery room.

The primary outcome was: assessment of heart rate and mean arterial blood pressure changes during the procedure and for one hour post-procedure. Secondary outcomes were as follows: total propofol consumption by both groups recorded at the end of the procedure, recovery time, level of postoperative pain assessed by visual analogue scale, and incidence of side effects (nausea and vomiting, postoperative cognitive dysfunction, and any respiratory complications).

2.2. The recorded data

Mean arterial pressure (MAP) and heart rate (HR) were recorded before administration of dexmedetomidine or ketamine loading (baseline), and continued every 5 min after beginning of loading throughout the course of the procedure and just after intubation. Any hemodynamic complications were observed and recorded which included hypotension (a decrease $>20\%$ of baseline value) or bradycardia (HR $<$ 50 beat/min) and they were treated according to the cause, in hypotension infusion rate of propofol decreased, iv fluids would be rapidly infused and iv ephedrine 3–6 mg incremental doses repeated after 5 min if no improvement. If bradycardia occurred the endoscopist was asked to stop stimulation, and atropine 0.01 mg/kg was given. Hypertension or tachycardia (an increase $>20\%$ of baseline values) also managed by giving 0.5 mg/kg iv propofol boluses to increase depth of anesthesia.

- MAP and HR were also recorded every 15 min for one hour postoperatively.
- Propofol consumption was calculated and recorded at the end of the procedure.
- Recovery time (time from extubation to spontaneous eye opening) was recorded.
- After the procedure, patients were assessed every 15 min for 60 min regarding pain which was assessed by VAS, if VAS $>$ 3 pain was treated by 10–15 mg/kg paracetamol IV infusion.

- Postoperative nausea and vomiting (PONV) managed by giving iv 4 mg ondansetron.
- Postoperative cognitive dysfunction (hallucination, agitation, or excitation) assessed and recorded every 15 min for one hour postoperative.
- Any respiratory complications as labored breathing, respiratory depression (RR < 10 bpm), or oxygen desaturation ($SpaO_2$ < 92%) were recorded. Oxygen mask was applied to improve oxygen saturation.
- Procedural complications as bleeding, duodenal perforation and cholangitis were recorded.
- Patients were discharged from recovery room when an Aldrete score ⩾9 was obtained (Table 1).

Statistical analysis: The sample size was based on data of previous study [17] which indicated that a total sample size of 60 patients (after exclusion of the drop out) randomly allocated into two equal groups (30 patients in each group) is sufficient to ensure power 80% for detecting clinically meaningful attenuation of heart rate and mean arterial blood pressure changes by 10–20%, especially after induction of anesthesia and intubation. Student's *t* test for independent samples was chosen to perform the calculation. α-error level was fixed at 0.05 and the power was entered to be 80% and the groups are assumed to be of equal size. Calculations were done using PS Power and Sample Size Calculations Software, version 3.0.11 for MS Windows (William D. Dupont and Walton D. Vanderbilt, USA).

Data were analyzed using IBM SPSS Advanced Statistics version 20.0 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using independent sample *t*-test or Mann-Whitney test. Comparison of repeated measures was done using ANOVA test for repeated measures. A *p*-value <0.05 was considered significant.

3. Results

The current study was a comparative randomized study between two groups; group-DP and group-KP with 30 patients in each group (Fig. 1). Both groups had no statistical significant differences in demographic data (age, weight and sex), ASA classification and duration of the procedure, also, there were no statistical significant differences between both groups as regard baseline of hemodynamic parameters (HR and MAP) (Table 2).

The intra-procedural heart rate decreased significantly in DP group at 10 min till end of the procedure ($p < 0.01$), while it increased significantly in KP group ($p < 0.001$) from 5 min till the end of the procedure with a high statistical significant differences between both groups throughout the procedure (at 5 min, intubation time (I.T.), 10 min, 15 min, 20 min, 25 min, 30 min and 35 min); *p*-value was <0.01 at all measured times except at intubation time and 35 min *P* value was <0.001; HR values were lower in dexmedetomidine–propofol group (Fig. 2).

The intra-procedural MAP decreased significantly in DP group ($p < 0.01$) from measuring at 5 min till end of the procedure, while it increased significantly in KP group ($p < 0.01$) from IT till the end of the procedure except at 15 and 20 min ($p > 0.05$).

Table 1 Modified Aldrete recovery score [16].

Score	Score		
	0	1	2
Activity (able to move voluntary or on commands)	0 extremities	2 extremities	4 extremities
Respiration	Apneic	Dyspnea, shallow or limited breathing	Able to deep breathe & cough freely
Consciousness	Unresponsive	Responding to stimuli	Fully awake
SpO_2	O_2 saturation is <90% even with O_2 supplementation	Needs O_2 to maintain O_2 saturation >90%	Able to maintain O_2 saturation >92% on room air
Circulation	BP ± 50 mmHg of preanesthetic level	BP ± 20–50 mmHg of preanesthetic level	BP ± 20 mmHg of preanesthetic level

Table 2 Demographic and clinical characteristics and duration of the procedure in the two studied groups.

	DP group (n = 30)	KP group (n = 30)	*p* value
Age (years)	42.7 ± 8.7	38.0 ± 10.7	0.067
Weight (kg)	60.7 ± 8.5	61.8 ± 9.7	0.687
Sex (male/female)	20/10	16/14	0.292
ASA (II/III)	24/6	26/4	0.674
Duration of the procedure (min)	30.3 ± 8.2	24.5 ± 7.5	0.134
Baseline MAP (mmHg)	101.9 ± 8.2	100.8 ± 11.3	0.686
Baseline HR (beats/min.)	85.4 ± 10.0	82.6 ± 11.4	0.316

Data are mean ± SD, or numbers.
P value >0.05 was considered statistically not significant. *P* value <0.05 was considered statistically significant.
Group DP; dexmedetomidine/propofol group, Group KP; ketamine/propofol group.

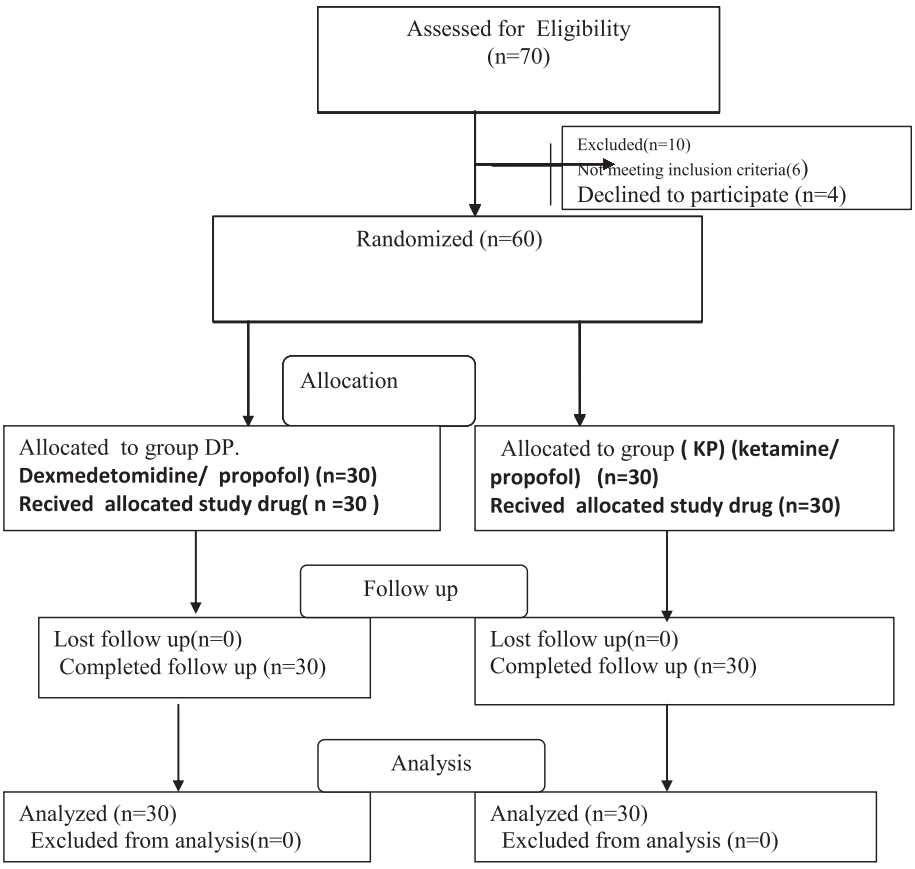

Figure 1 Flow diagram displaying the progress of all participants through the study.

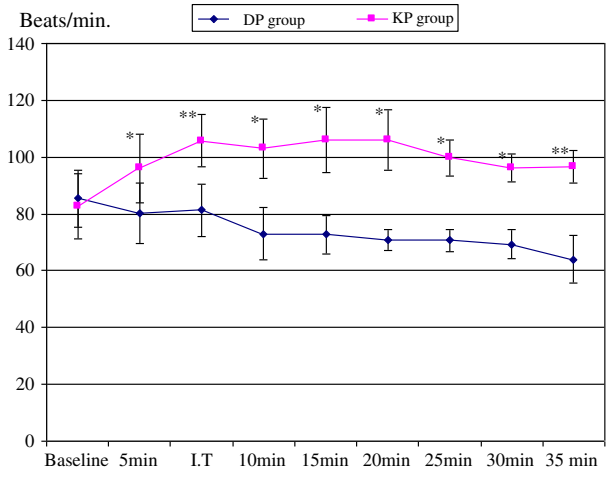

Figure 2 Mean intra-procedural HR changes in the two studied groups I.T.: intubation time, $^{*}P < 0.01$, $^{**}P < 0.001$ between both groups.

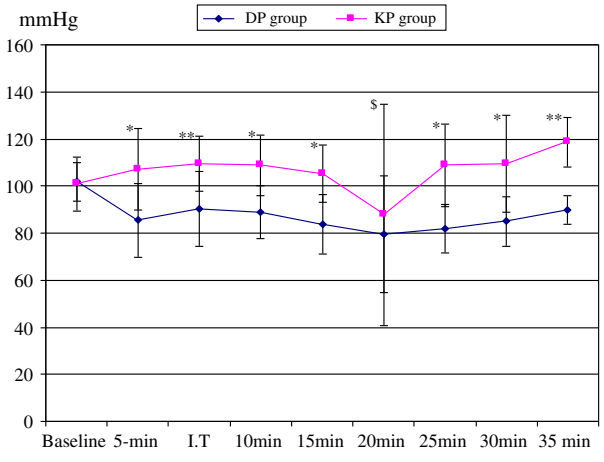

Figure 3 Mean intra-procedural MAP changes in the two studied groups I.T.: intubation time $^{*}P < 0.01$, $^{**}P < 0.001$, \$: $P = 0.036$ between both groups.

The MAP had a high statistical significant difference between both groups; p-value was <0.001 at (5-min, 10-min, 15-min, 25-min, 30-min), while at IT and 35 min P value was <0.001, and P-value at 20-min was 0.036 denoting statistical significant difference between both groups; MAP values were lower in dexmedetomidine–propofol group (Fig. 3).

During the post-procedural period, the HR and MAP were significantly lower in DP group compared with KP group starting from 15 min to 60 min after the end of the procedure with p-value was <0.01 at all measured times except at 60 min for measuring MAP $p = 0.035$ (Figs. 4 and 5).

No atropine or ephedrine required for management of bradycardia or hypotension.

The total dose of propofol was comparable in the two groups (268.0 ± 122.3 mg) in DP group versus (304.7 ± 142.0 mg) in KP group ($p = 0.288$) (Table 3).

Postprocedural recovery time (time from extubation to spontaneous eye opening) was significantly shorter in DP group (5.7 ± 1.7 min) compared with (22.2 ± 8.2 min) in KP group ($p = 0.01$) (Table 3).

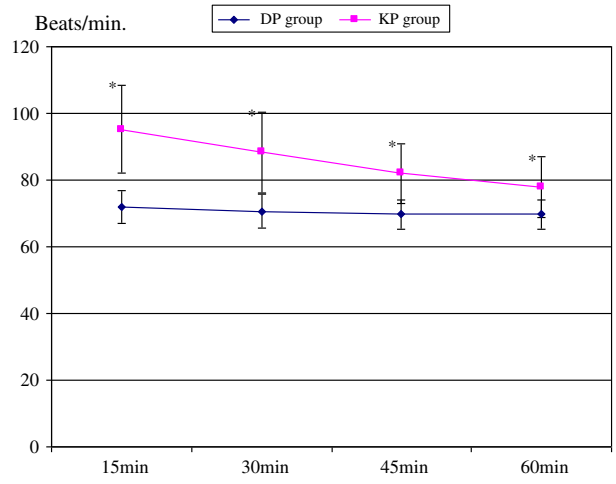

Figure 4 Comparison between dexmedetomidine/propofol (DP) and ketamine/propofol (KP) groups as regard post-procedural HR (beats/min). $^{*}P < 0.01$ between both groups.

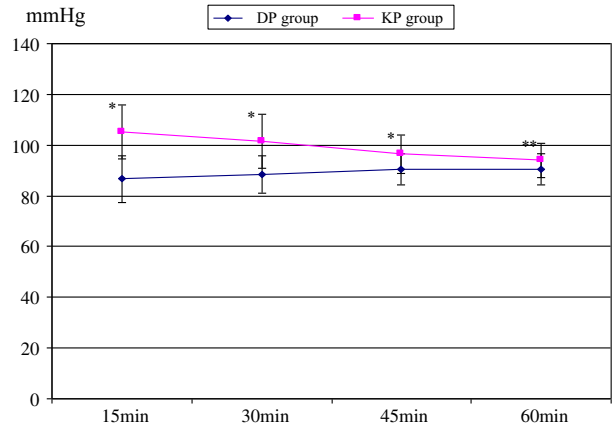

Figure 5 Comparison between dexmedetomidine/propofol (DP) and ketamine/propofol (KP) groups as regard post-procedural MAP $^{*}P < 0.01$, $^{**}P = 0.035$ between both groups.

Post-procedural pain as assessed by VAS was comparable in the two groups as 26 patients in DP group and all patients in KP group (30 patients) had VAS 1–2 ($p = 0.12$) and only 4 patients in DP group had VAS of (3–5) (Table 3).

PONV occurred in about 46.67% of patients in KP group, while it was absent in DP group ($p < 0.001$) it was managed by giving 4 mg iv ondansetron. Post-operative cognitive disorders (in the form of hallucination, agitation and excitation) showed a high statistical significant difference between both groups; p-value was <0.001; no cases were reported in dexmedetomidine–propofol group.

Modified Aldrete recovery score at 15 min was comparable in both groups (9.16 ± 0.68 in DP group versus 9.02 ± 0.64 in KP group with $p > 0.05$). There were no respiratory complications (labored breathing, apnea, or $SPO_2 < 92\%$) in both groups.

Surgical complications were comparable in the two groups (Table 3).

4. Discussion

The results of this study indicate that GA with Dexmedetomidine–propofol combination provided more hemodynamic stability, with shorter recovery time, less PONV, and no postoperative cognitive dysfunction compared with ketamine–propofol combination in anesthesia for ERCP.

Patients planned for ERCP often have additional co-morbidities that may make them candidates for GA. GA may be required especially in high ASA, high BMI, gastrointestinal bleeding, expected prolonged procedures, and previous failed procedure [18,19]. Manukyan et al. [20] demonstrated that GA shortened the duration of ERCP, increased the success rate and prevented respiratory complications.

The current study demonstrated greater intra-procedural, hemodynamic stability in dexmedetomidine–propofol group in comparison with ketamine–propofol group. HR and MAP values were lower in dexmedetomidine–propofol group throughout the procedure, this may be related to the effect of dexmedetomidine as highly selective α2-agonist so it has a strong sympatholytic effect, while in ketamine and propofol group mean arterial pressure was elevated above the base line, this was due to increased diastolic pressure owing to increased systemic vascular resistance.

Kang and his colleagues [17] supported the hemodynamic stability of dexmedetomidine as they evaluated the effect of

Table 3 Total dose of propofol, recovery time, post-procedural VAS score and complications in the two studied groups.

	DP group ($n = 30$)	KP group ($n = 30$)	p value
Total dose of propofol (mg)	268.0 ± 122.3	304.7 ± 142.0	0.288
Recovery time (min.)	5.7 ± 1.7	22.2 ± 8.2	<0.01
VAS score			
1–2	26 (86.67%)	30 (100.0%)	0.120
3–5	4 (13.33%)	0 (.0%)	>0.05
PONV	0 (0.0%)	14 (46.67%)	<0.001
Hallucination or excitation (cognitive dysfunction)	0 (0.0%)	10 (33.33%)	<0.001
Surgical complication	2 (6.67%)	1 (3.33%)	0.554

Data are means ± SD, or numbers and %.
P value >0.05 was considered statistically not significant. P value <0.05 was considered statistically significant.
Group DP; dexmedetomidine/propofol group, Group KP; ketamine/propofol group.

dexmedetomidine on intra-operative hemodynamics during remifentanil-based anesthesia on 20 patients that were randomly divided into two groups one of them received dexmedetomidine as adjuvant to propofol remifentanil based anesthesia and the other group received only propofol remifentanil, with lower intra-procedural HR and MAP values at induction and incision times in dexmedetomidine group. The study performed by Tsai et al. [11] agreed the intraoperative hemodynamic stability of dexmedetomidine as the current study, they evaluated dexmedetomidine hemodynamic stability in comparison with propofol in sedation for fiber-optic naso-tracheal intubation in 40 patients with anticipated difficult airway undergoing elective surgery. Intra-procedural hemodynamic stability was also supported by another study performed by Sethi et al. [21] who studied dexmedetomidine versus midazolam for conscious sedation in ERCP. They observed decreased HR and comparatively stable MAP values in dexmedetomidine group.

Contrary to these results another study by Muller et al. [22] reported intra-procedural hemodynamic instability of dexmedetomidine as they studied dexmedetomidine alone against propofol–fentanyl for conscious sedation during ERCP. 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.

Bajwa et al. [23] compared two drugs combinations in Total Intravenous Anesthesia: propofol–ketamine (group-I) versus propofol–fentanyl (group-II), there was an increase in intra-operative HR and MAP values in group-I while they decreased in group-II after induction and intubation with a statistical significant difference between both groups; these results were in accordance with results of ketamine propofol group in the current study.

On the other hand Mahajan et al. [24] compared ketamine and fentanyl with propofol and fentanyl in TIVA and found that there was slight increase in intra-procedural pulse rate after induction in both groups that was statistically non significant. The difference between Mahajan et al. study and the current study might be due to the different lower basal pulse rate and MAP in their study, also the premedication with 0.03 mg/kg midazolam IV, and the different type of patients as Mahajan's et al. patients were ASA I, II while the current study patients were ASA-II and III with controlled co-morbidities like DM and hypertension.

Post-procedural HR and MAP changes in the current study showed high statistical significant difference between both groups throughout PACU-period; with HR and MAP values lower in dexmedetomidine–propofol group, this was supported by a study performed by Sethi et al. [21] using dexmedetomidine versus midazolam for conscious sedation in ERCP with stable post-procedural MAP and lower HR values in dexmedetomidine group compared with midazolam group.

Demiraran et al. [25] compared dexmedetomidine and midazolam for sedation of upper endoscopy. There was no statistical significance between both groups as regards postoperative hemodynamic parameters HR and MAP (p-value >0.05).

Bajwa et al. [23] studied two drugs combinations: propofol–ketamine and propofol–fentanyl in TIVA. They noticed that post-procedural HR in both groups increased at 1 and 5 min after extubation, this was in agreement with the current study. On the other hand post-procedural hemodynamic derangement did not occur in patients received ketamine–propofol combination in a study performed by Aydogan et al. [26] who studied ketamine–propofol combination versus propofol alone in upper GI-endoscopy in adults.

Total propofol consumption by the end of the procedure in the current study was lower in dexmedetomidine–propofol group but with no statistical significant difference ($p = 0.288$).

Kang et al. [17] studied dexmedetomidine versus placebo in remifentanil-based anesthesia. They reported significant difference in total propofol consumption by the end of their procedure (63.9 ± 16.2 μg/kg/h) in dexmedetomidine, versus (96.4 ± 10.0 μg/kg/h) in placebo with P-value <0.001. 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 remifentanil infusion to anesthetic technique might play a synergistic role in Kang et al. study.

On the other hand propofol consumption in a study performed by Saric et al. [27] was (352.65 ± 109.44 mg) in ketamine–propofol group versus (380 ± 135.4 mg) in propofol alone for deep sedation during ERCP in elderly, P-value was 0.0268. This was more than the propofol consumption reported in the current study; this might be due to the lower dose of ketamine as they administered ketamine as a single bolus (25 mg) after losing ciliary reflex by propofol bolus.

Total propofol consumption by patients received ketamine–propofol combination was reported by a study performed by Aydogan et al. [26]. They found that ketamine–propofol group consumed (72 ± 12 mg) versus (92 ± 10 mg) consumed by propofol group; the consumed amount of propofol by ketamine–propofol group in Aydogan et al. study was less than that reported by the current study, this might due to the duration of the endoscopy that appeared to be shorter than ERCP (5.5 ± 0.096 min) in Aydogan et al. study versus (24.50 ± 7.51 min) in the current ERCP study.

Post-procedural recovery time of the current study (time from extubation to spontaneous eye opening) was significantly shorter in dexmedetomidine–propofol group than ketamine–propofol group. Sethi et al. [21] supported this finding as they reported shorter recovery time for dexmedetomidine group in patients undergoing ERCP under conscious sedation; and 90% of patients received dexmedetomidine achieved Alderte score 9–10 within 5 min. These results were contrary to Demiraran et al. study [25] that demonstrated prolonged recovery time of dexmedetomidine (42 ± 12.5 min) which was more than the current study, this may be due to difference of the procedure in both studies. The duration of their simple procedure (upper endoscopy) was (8.9 ± 1.3 min) in dexmedetomidine group compared with (30.3 ± 8.2 min) in the current study as ERCP is more complex, prolonged and painful procedure than the upper endoscopy.

Aydogan et al. [26] 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 undergoing upper gastro-intestinal endoscopy. The difference between recovery time reported in Aydogan et al.; and that recorded in KP group by the current study might be due to the different type of their procedure; that lapse for (5.516 ± 0.096 min), more simpler and less complex, in addition to the lower ketamine dose (0.25 mg/kg bolus).

Recovery time in Hasanein and El-Sayed [28] study was shorter (11.19 ± 19 min) than that detected by the current study (22.2 ± 8.2 min) as regard ketamine–propofol group; this might be due to the lower ketamine dose that was administered in conjunction with propofol (1:4) for induction of deep sedation in their study while the current study used GA as an anesthetic plan that required more anesthetic doses.

Post-procedural nausea and vomiting in the current study showed a high statistical significant difference between both groups; *P*-value <0.001. The incidence was higher in ketamine–propofol group (14 cases i.e. 46.67%), while no reported cases in dexmedetomidine–propofol group.

Demiraran et al. [25] supported the current study as they studied midazolam versus dexmedetomidine for sedation of patients undergoing upper endoscopy. There were no reported cases of PONV in dexmedetomidine group.

PONV was 2% in patients received ketamine–propofol combinations by Aydogan et al. [26] versus no case reported in the other group received propofol alone in patients undergoing upper gastro-intestinal endoscopy; this was much lower than the incidence reported in the current study, this might be due to different type of the procedure and the lower ketamine dose (0.25 mg/kg as one bolus dose) used in their study.

The incidence of PONV detected by Hasanein and El-Sayed [28] was 3% in patients received ketamine propofol for sedation of obese patients undergoing ERCP without statistical significant difference with the other group that received fentanyl–propofol combination. The reported PONV by Hasanein and El-Sayed; was less than that detected by the current study as they used lower ketamine dose and the intention was for sedation not GA.

Post-procedural pain in the current study was assessed by VAS showed no statistical differences between both groups, with all patients of ketamine propofol group were VAS (1–2), compared with 26 patients from the dexmedetomidine–propofol group, this high analgesic effect of ketamine is related to being NMDA receptor antagonist, also ketamine has agonist activity at mu-opioid receptors, while the anti nociceptive action of dexmedetomidine is due to being selective α2-agonist. Dexmedetomidine provides analgesia with a ceiling effect at doses >0.5 μg/kg. Previous study detected that opioid requirements in the intraoperative period and in the post-anesthetic care unit (PACU) are reduced by dexmedetomidine [11].

Demiraran et al. [25] results supported the current study finding as regard incidence of pain. As they assessed the incidence of post-procedural abdominal discomfort in patients undergoing upper endoscopy received dexmedetomidine versus midazolam, there was a lower pain incidence in patient receiving dexmedetomidine than those receiving midazolam but this difference did not reach statistical significance ($p = 0.21$).

The current study reported post-operative cognitive disorders in the form of hallucination, agitation and excitation, it showed a high statistical significant difference between both groups; with higher incidence in ketamine–propofol group (33.33%) and no cases in DP group. Agitation and irritability reported by Hasanein and El-Sayed study [28] was 2% in patients receiving ketamine–propofol combination versus no reported cases in the other comparative group that received propofol–fentanyl. This incidence was lower than that reported in ketamine–propofol group of the current study, this might be due to their lower ketamine dose used for sedation.

Mahajan et al. [24] also reported lower incidence of post-operative cognitive dysfunction (8/50) than the current study; they studied ketamine–propofol versus fentanyl–propofol for TIVA, despite the higher ketamine dose used in their study (1 mg/kg ketamine + 2 mg/kg propofol) for induction followed by (2 mg/kg/h ketamine + 4 mg/kg/h propofol) for maintenance. This lower incidence might be due to different type of patients as patients in the current study had liver impairment, and elevated liver enzymes with hyperbilirubinemia that may alter the pharmacokinetics and pharmacodynamic effects of ketamine.

Respiratory adverse events did not occur in both groups of the current study.

Demiraran et al. [25] studied the dexmedetomidine versus midazolam for sedation in upper endoscopy. In midazolam group, apnea was developed in one patient and two patients suffered from desaturation (SPO2 < 90%) while no deterioration in respiratory parameters (respiratory rate, desaturation) were observed in dexmedetomidine group; this result was in accordance with that reported in the current study.

On the other hand Bajwa et al. study [23] and a study performed by Aydogan et al. for upper GI endoscopy [26] did not report any cases of respiratory impairment in ketamine–propofol group; this was compatible with the current study.

The current study has some potential limitations as the small sample size, so further studies with larger number of patients are needed to test the efficacy and safety of the study drugs when used as TIVA technique to maintain better intra- and post-procedural hemodynamic stability with lower post-operative complications. Another limitation was inability to assess intraoperative depth of anesthesia and incidence of intraoperative awareness as the BIS monitor was unavailable, however the intensity of noxious stimuli that the patients received during surgery might be relatively homogeneous because of the uniform surgery. Therefore, we believe that there may have been only a small difference in anesthetic depth between the groups during the study period. Also the duration of assessment of postoperative hemodynamic changes, and VAS as well as complications were limited to one hour in PACU, so further studies with extended period of postoperative assessments are required as those patients may have different drug metabolism due to their liver impairment. Finally the cost effectiveness was not evaluated in the current study.

Dexmedetomidine–propofol combination as TIVA technique requires further studies to be adequately evaluated with recommendation to include larger number and different types of patients; as elderly and critically ill patients.

5. Conclusion

Dexmedetomidine–propofol combination as TIVA during ERCP showed better intra- and post-procedural hemodynamic stability, less PONV, less postoperative cognitive dysfunctions and shorter recovery time when compared with ketamine–propofol combination.

Conflict of interest

No conflict of interest to declare.

References

[1] Fanti L, Testoni P. Sedation and analgesia in gastrointestinal endoscopy: what is new? World J Gastroenterol 2010; 16(20):2451–7.

[2] Adler DG, Baron TH, Davila RE, Egan J, Hirota WK, Faigel DO, Fanelli R, et al. Standards of Practice Committee of American Society for Gastrointestinal endoscopy. ASGE guidelines: the role of ERCP in diseases of the biliary tract and the pancreas. Gastrointest Endosc 2005;62(1):1–8.

[3] Fisher L, Jain R, Ikenberry SO, et al. Complications of ERCP. Gasterointestinal Endoscopy 2012;75(3):467–73.

[4] Khan K, Steven O, Bo Shen Stewart L, Vargo JJ, et al. Sedation and anesthesia in GI endoscopy. Gastrointest Endosc 2008;68(5):815–26.

[5] Chainaki Irene G, Manolaraki Maria M, Paspatis Gregorios A. Deep sedation for endoscopic retrograde cholangiopancreatography. World J Gastrointest Endosc 2011;3(2):34–9.

[6] Beeton A. Refresher course; Quoted ERCP: sedation or anaesthesia? South Afr J Anaesth Analg 2011;17(1):124–5.

[7] Raymondos K, Panning B, Bachem I, Manns MP, Piepenbrock S, Meier PN. Evaluation of endoscopic retrograde cholangiopancreatography under conscious sedation and general anesthesia. Endoscopy 2002;34(9):721–6.

[8] Lee SK. Clinical use of dexmedetomidine in Monitored Anesthesia Care. Korean J Anesthesiol 2011;61(6):451–2.

[9] Hoy SM, Keating GM. Dexmedetomidine: a review of its use for sedation in mechanically ventilated patients in an intensive care setting and for procedural sedation. Drugs 2011;71(11): 1481–501.

[10] Afonso J, Reis F. Dexmedetomidine: current role in anesthesia and intensive care. Rev Bras Anestesiol 2012;62(1):118–33.

[11] Tsai CJ, Chu KS, Chen TI, Lu DV, Wang HM, Lu IC. A comparison of the effectiveness of dexmedetomidine versus propofol target-controlled infusion for sedation during fiberoptic nasotracheal intubation. Anaesthesia 2010;65(3):254–9.

[12] Fechner J, Ihmen H, Hatterscheid D, et al. Comparative pharmacokinetics and pharmacodynamic of the new propofol prodrug GPI 15,715 and propofol emulsion. Anesthesiology 2004;101:626–39.

[13] Himmelseher S, Durieux ME. Ketamine for perioperative pain management. Anesthesiology 2005;102(1):211–20.

[14] Kayan GE, Yucel A, Colak YZ, Ozgul S, Yologu S, et al. Ketofol (mixture of ketamine and propofol) administration in electroconvulsive therapy. Anaesth Intensive Care 2012;40(2):305–10.

[15] Daabiss M, El Sherbiny M, Alotibi R. Assessment of different concentration of ketofol in procedural operation. Brit J Med Practitioners BJMP 2009;2(1):27–31.

[16] Erhan E, Ugur G, Anadolu O, Saklayan M, Ozyar B. General anesthesia or spinal anesthesia for outpatient urological surgery. Eur J Anaesthesiol 2003;20:647–52.

[17] Kang WS, Sung YK, Jong CS, Ju DK, Muhammad HB, Seong HK, Yoon TG, Kim TY. The effect of dexmedetomidine on the adjuvant propofol requirement and intraoperative hemodynamics during remifentanil based anesthesia. Korean J Anesthesiol 2012;62(2):113–8.

[18] Goudra BG, Singh PM, Sinha A. Outpatient endoscopic retrograde cholangio-pancreatography: safety and efficacy of anesthetic management with a natural airway in 653 consecutive procedures. SJA 2013;7(3):259–65.

[19] Cotton PB, Eisen G, Romagnuolo J, et al. Grading the complexity of endoscopic procedures: results of an ASGE working party. Gastrointest Endosc 2011;73(5):868–74.

[20] Manukyan MN, Deveci U, Kebudi A, Şimşek S, Çubuk Rve Gökçe K. General anesthesia versus deep sedation and superficial sedation in endoscopic retrograde cholangiopancreatography. J Surg Arts 2012;5(2):31–4.

[21] Sethi P, Mohammed S, Bhatia PK, Gupta N. Dexmedetomidine versus midazolam for conscious sedation in endoscopic retrograde cholangiopancreatography: an open-label randomized controlled trial. Indian J Anaesth 2014;58(1):18–24.

[22] Muller S, Borowics SM, Fortis EA, Stefani LC, Soares G, Maguilnik I, Breyer HP, Hidalgo MP, Caumo W. Clinical efficacy of dexmedetomidine alone is less than propofol for conscious sedation during ERCP. Gastrointest Endosc 2008; 67(4):651–9.

[23] Bajwa SJS, Bajwa SK, Kaur j. Comparison of two drug combinations in total intravenous anesthesia: propofol–ketamine and propofol–fentanyl. Saudi J Anaesth 2010;4(2):72–9.

[24] Mahajan R, Swarnkar N, Ghosh A. Comparison of ketamine and fentanyl with propofol in total intravenous anesthesia: a double randomized clinical trial. Internet J Anesthesiol 2009;23(2).

[25] Demiraran Y, Korkut E, Tamer A, Yorulmaz I, Kocaman B, Sezen G, Akcan Y. The comparison of dexmedetomidine and midazolam used for sedation of patients during upper endoscopy: a prospective randomized study. Can J Gastroenterol 2007;21(1):25–9.

[26] Aydogan H, Aydgoan T, Uyankoglu A, Kucuk A, Yuce HH, Alpkarahan M, Buyukfrat E, Yalcin S. Propofol–ketamine combination has shorter recovery times with similar hemodynamics compared to propofol alone in upper gastrointestinal endoscopy in adults: a randomized trial. Acta Medica Mediterranea 2013;29:259–64.

[27] Saric PJ, Matasic H, Zenko J, Ivanov N. Comparison of propofol and ketamine for deep sedation during ERCP in elderly 2AP1-2. Eur J Anaesthesiol 2012;29:31.

[28] Hasanein R, Sayed EL. Ketamine–propofol versus fentanyl–propofol for sedating obese patients undergoing endoscopic retrograde cholangiopancreatography (ERCP). Egyptian J Anaethesia 2013;29(3):207–11.