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A comparison between magnesium sulphate and fentanyl as adjuvants to propofol infusion for sedation in endoscopic retrograde cholangiopancreatography: A randomized controlled trial

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ABSTRACT

Background: Propofol-based sedations are used widely during endoscopic retrograde cholangiopancreatography (ERCP) procedures. However, respiratory depression and cardiovascular adverse events commonly occur. Therefore, we designed this study to evaluate the effects of adding a single boules induction dose of fentanyl or magnesium sulphate to propofol infusion for sedation of patients subjected to ERCP.

Methods: This randomized parallel double-blind controlled trial included 60 adult patients scheduled for ERCP procedures. Before starting the propofol infusion, patients immediately received either magnesium sulphate 50 $mg.kg^{-1}$ intravenously (IV) over 10 min (Group M) (n = 30) or fentanyl 2 $\mu g.kg^{-1}$ IV over 10 min (Group F) (n- = 30). Continuous propofol infusion was given with a syringe pump for maintenance, with the initial rate set at 25–75 mic/kg/min IV during the first 10–15 min.

Results: The magnesium group had significantly reduced the total propofol consumption and increased the onset time of sedation than the fentanyl group ($P < 0.05$). Heart rate and mean arterial pressure were statistically lower after adjuvant bolus injection and 15 min in the magnesium group than in the fentanyl group ($P < 0.001$). Procedure time, involuntary movement, physician satisfaction, and complications exhibited no significant differences between both groups.

Conclusions: During ERCP, adding a single bolus of magnesium sulphate to propofol was associated with a lower total propofol consumption and better hemodynamics than fentanyl but with a delayed onset time of sedation and comparable respiratory depression.

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ERCP; propofol; fentanyl; magnesium; sedation

1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) represents the gold standard for biliary and pancreatic disease detection and treatment [1].

During ERCP, painful procedures may be performed including stone removal, stenting, visualization of the pancreaticobiliary tract, sphincterotomy, and laser lithotripsy. Therefore, ERCP should be performed under general anesthesia or deep sedation to ensure the patient is immobile, pain-free, and relaxed during the procedure [2,3].

The choice of anesthetic strategy is considered a significant challenge during ERCP due to patient conditions and procedural complications. Consequently, general anesthesia is the preferred option for most individuals [4,5].

Propofol is a lipophilic, short-acting intravenous (IV) anesthetic most often used in ERCP. Propofol has amnestic and sedative properties with no analgesic properties [2,6,7]. Higher dosages of propofol are administered to achieve a deeper level of anesthesia, which causes cardiovascular adverse effects. Thus, it is suggested to add minimal dosages of other sedative medications, such as fentanyl [2,7,8].

During ERCP, fentanyl is used to help with sedation and pain relief. Fentanyl may cause hypotension and respiratory depression, often needing emergency airway management. Therefore, evaluating a non-opioid adjuvant to propofol sedation is crucial to reduce propofol consumption and its adverse effects [2,6,7].

Magnesium has analgesic and moderate sedative effects as a non-specific calcium channel inhibitor and a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist [9]. Magnesium sulphate IV injection has successfully reduced intraoperative propofol and the need for postoperative analgesia in several surgical procedures [10,11]. However, there is a scarcity of literature comparing the effects of fentanyl and magnesium sulphate as adjuvants to propofol sedation for ERCP procedures.

We hypothesized that magnesium sulphate might be beneficial for ERCP patients. Therefore, this study

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was designed to compare the effects of adding fentanyl or magnesium sulphate as a single boules induction dose to propofol infusion for sedation in patients undergoing ERCP.

2. Patients and methods

This randomized double-blind controlled trial enrolled 60 adult patients of both sexes aged between 21 and 60 years, with physical classes I or II according to the American Society of Anesthesiologists (ASA), scheduled for ERCP procedures at Tanta University Hospitals from December 2022 to March 2023.

The study was started after being approved by the Medical Ethics Committee, Faculty of Medicine, Tanta University, Tanta, Egypt (Code: 36161/12/22). Written consent was obtained from all participants.

Exclusion criteria were hypersensitivity for any drug used in the study, receiving magnesium sulphate supplementation, receiving drugs known to interact with magnesium sulphate, kidney disease, neuropathy, myopathy, and ischemic, hypertensive, or valvular heart disease.

3. Preoperative evaluation

All cases were subjected to history taking, laboratory investigation and clinical examination.

4. Randomization and blindness

The cases were randomized using a computer-generated sequence by sealed opaque envelopes in a parallel manner. Before starting the propofol infusion, patients immediately received either magnesium sulphate 50 mg.kg^{-1} IV as a bolus in 100 ml of 0.9% normal saline over 10 min (Group M) or fentanyl bolus dose of 2 µg.kg^{-1} as infusion in 100 ml saline 0.9% over 10 min (Group F).

The anesthesiologist and patients were all blinded to the given study drugs, and the envelopes were opened immediately before administration. A pharmacist formulated the research solutions without further involvement in the trial. Intraoperative and postoperative parameters were examined by another anesthesiologist, unaware of the group assignment.

5. Intraoperative management

Patients were placed in prone positioning, 20 G peripheral IV cannula was placed. Electrocardiogram (ECG), mean blood pressure (MAP), Heart rate (HR), end tidal CO_2 by capnography, peripheral oxygen saturation, and body temperature were monitored.

Continuous propofol infusion was given with a syringe pump for maintenance, with the initial rate set at 25–75 mic/kg/min IV during the first 10–15 min.

To avoid administering sedatives at rates greater than clinically necessary, infusion rates were gradually titrated to 25–50 mic/kg/min and regulated with the clinical response, with an onset of peak drug action expected to occur within 2 min.

The total amount of propofol consumed, onset time of sedation, and procedure time were recorded.

The study ends when the patients had any disturbed level of consciousness or occurrence of hemodynamic instability or respiratory problems.

For optimal sedation level, the Ramsay Sedation Scale was used (RSS 1 = anxious and agitated or restless, or both; 2 = cooperative, oriented, and tranquil; 3 = responding to commands only; 4 = exhibiting brisk response to a light glabellar tap or loud auditory stimulus; 5 = exhibiting sluggish response to light glabellar tap or loud auditory stimulus; 6 = no response to stimulus).

A bolus of propofol at 0.25 mg/kg was administered as rescue medication if the patient's score was less than 5 or if they showed signs of pain (such as involuntary movement or grimacing) or difficulties with endoscope manipulation. Meanwhile, the rate at which propofol is infused was increased by 0.5 mg/kg/h, with the procedure repeated if required.

If the patient suffered from respiratory depression (SpO_2 <90% for >10 s), the essential respiratory supports were immediately provided until SpO_2 reverted to normal.

HR and MAP were measured before induction, after adjuvant bolus injection, 15 min, 30 min, 45 min, and 60 min after propofol infusion.

Involuntary movement, physician satisfaction (values recorded for the 6-point Likert-scale (1: very satisfied and 6: very dissatisfied)), and adverse events such as desaturation (represented by O2 sat < 90% for at least 2 min), interruption of the procedure, hypotension (MAP reduction by >20% of baseline Or: MAP < 80% of baseline was overcome by ephedrine 5 mg IV and/or normal saline IV), hypertension (MAP) (higher than 110 mmHg or 20% increase from the baseline), antispasmodic need, sore throat, and bloating were recorded.

The 1st outcome was the total propofol consumed, and the 2nd outcomes were hemodynamic measurements, RSS, patient movement during procedure, physician satisfaction, need for antispasmodics, sore throat, and bloating,

6. Sample size calculation

The sample size calculation was done by G*Power 3.1.9.2 (Universitat Kiel, Germany). Depending on a previous study [12], the mean ± SD of propofol consumption was 276.67 ± 76.06 mg with fentanyl and expected to decrease by at least 25% with adding Mg. The sample size was based on the following

considerations: 0.909 effect size, 95% confidence limit, 90% power of the study, group ratio 1:1, with additional three cases to each group to overcome dropout. Therefore, 30 patients were enrolled in each group.

7. Statistical analysis

Using IBM-SPSS 24.0, data were analysed (IBM-SPSS Inc., Chicago, IL, USA). Comparing the two groups using an unpaired Student's *t*- test, quantitative data were provided as mean and standard deviation (SD). When applicable, qualitative variables were given as frequency and percentage and evaluated using the Chi-square test or Fisher's exact test. *P* value less than 0.05 was significant.

8. Results

In this study, 82 patients were evaluated for eligibility, 16 were excluded, and 6 refused to participate. The remaining patients were allocated randomly into two equal groups (30 patients each). All allocated patients were followed-up and analyzed statistically. Figure 1

Demographic data and indications of ERCP were insignificantly different between both groups. Table 1

The total amount of propofol consumed (74.37 ± 7.38 mic/kg/min) was significantly lower in group M than group F (79.83 ± 6.88 mic/kg/min) ($P = 0.004$). The onset time of sedation was significantly delayed in

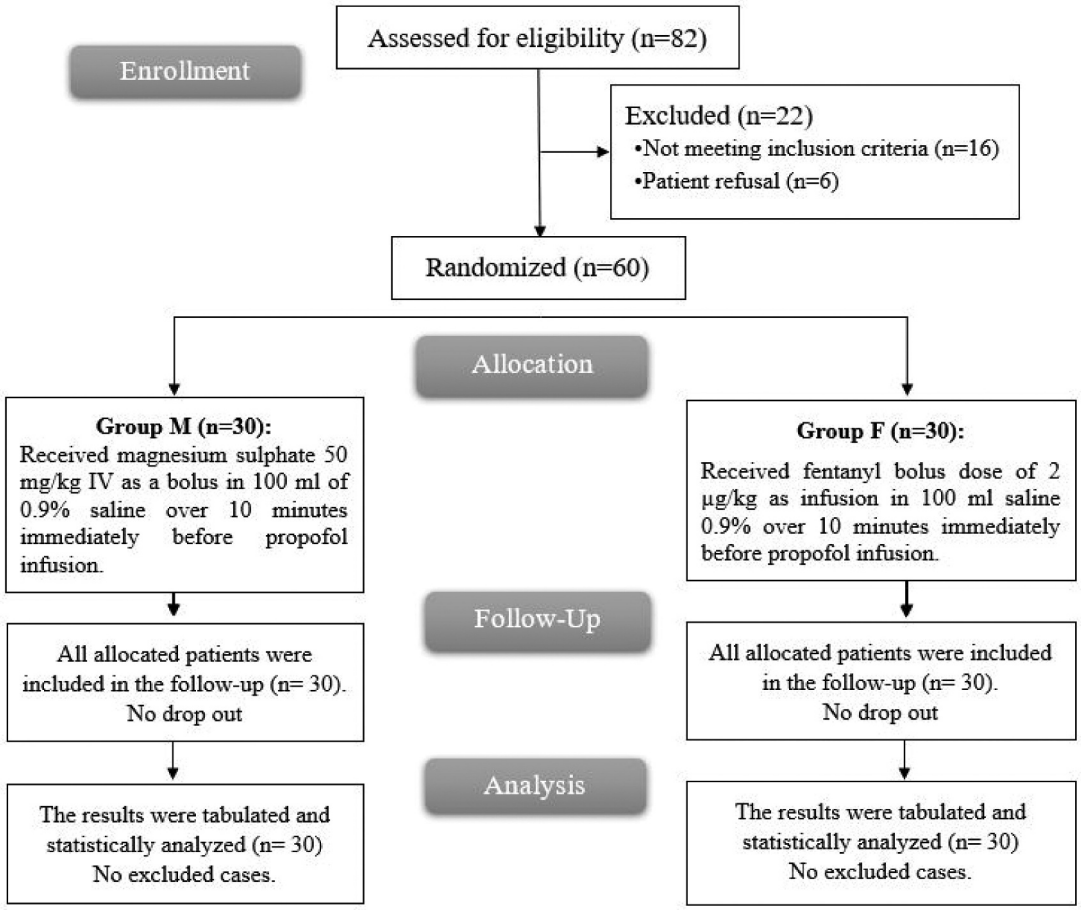

Figure 1. CONSORT flowchart of the enrolled patients.

Table 1. Demographic data and indications of ERCP of the studied groups.

			Group M ($n = 30$)	Group F ($n = 30$)	P value
Age (years)			43.87 ± 10.27	44.7 ± 8.72	0.736
Sex n (%)		Male	12(40%)	14(46.7%)	0.598
		Female	18 (60%)	16(53.3%)	
BMI(Kg/m^2)			25.97 ± 2.89	24.90 ± 3.44	0.197
ASA physical classes		I	11 (36.7%)	13 (43.3%)	0.598
		II	19 (63.3%)	17 (56.7%)	
Indication for ERCP	Biliary stones		14 (46.7%)	16 (53.3%)	0.852
	Biliary or pancreatic tumors		12 (40%)	11 (36.7%)	
	Other		4 (13.3%)	3 (10%)	

Data are presented as mean±SD and frequency (percentage). BMI: Body mass index; ASA: American society of Anesthesiologists; ERCP; Endoscopic retrograde cholangiopancreatictography.

Table 2. Total amount of propofol consumed, onset time of sedation, and procedure time of the studied groups.

	group M ($n = 30$)	group F ($n = 30$)	P value
Total amount of propofol consumed (mic/kg/min)	74.37 ± 7.38	79.83 ± 6.88	**0.004***
Onset time of sedation (min)	4.56 ± 1.21	3.45 ± 1.63	**0.002***
Procedure time (min)	25.21 ± 18.31	23.43 ± 17.32	0.402

Data are presented as mean±SD. * $P < 0.05$ is statistically significant.

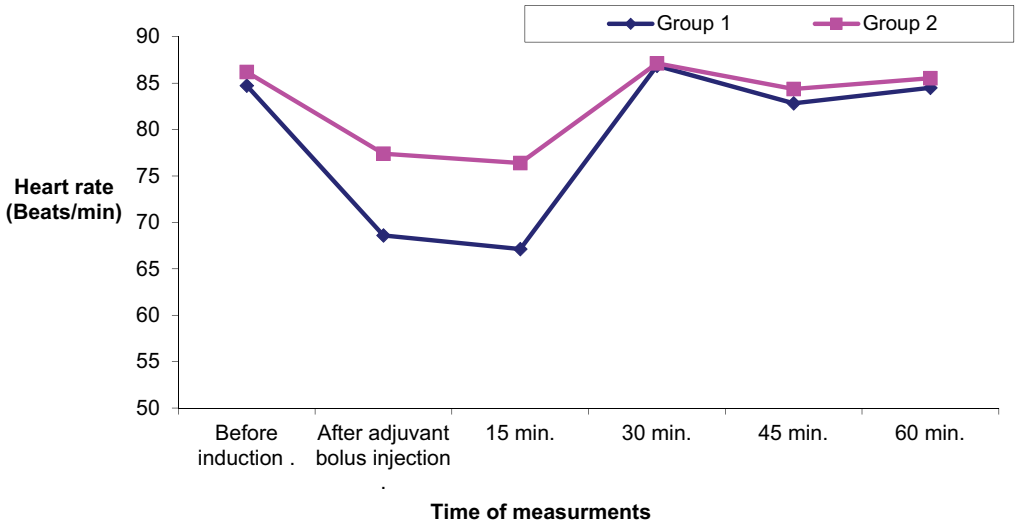

Figure 2. Heart rate (HR) of the studied groups.

group M (4.56 ± 1.21 min) than in group F (3.45 ± 1.63 min) ($P = 0.002$). Procedure time was insignificantly different between both groups. Table 2

HR and MAP measurements before induction, at 15, 45 min, and 60 min were insignificantly different between both groups and were significantly lower after adjuvant bolus injection and 15 min in group M than in group F (P value < 0.001). Figure 2, Figure 3

Involuntary movement and physician satisfaction were insignificantly different between both groups. Complications (desaturation, interruption of the procedure, hypotension, hypertension, antispasmodic need, sore throat, and bloating) were insignificantly different between both groups. Table 3

9. Discussion

Without sufficient sedation, patients often cannot undergo the ERCP due to pain, difficulty, anxiety, and nausea [13]. Therefore, ERCP is often carried out under varying degrees of sedation and adequately anesthesia to increase the probability of a desirable outcome and boost patient satisfaction [14].

Propofol is an IV mild analgesic and sedative-hypnotic drug used commonly by endoscopists to provide adequate sedation as an induction agent for general anesthesia that starts working in 0.5 to 1 min and lasts 4–8 min [15]. Respiratory depression and hypotension (due to decreased cardiac output and

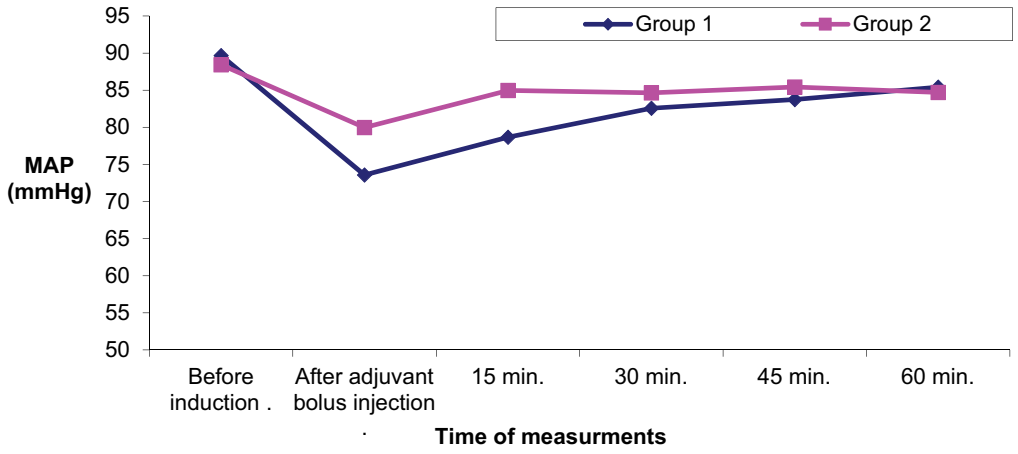

Figure 3. Mean blood pressure (MAP) of the studied groups.

Table 3. Involuntary movement and physician satisfaction and complications of the studied groups.

		Group M ($n = 30$)	Group F ($n = 30$)	P value
Involuntary movement	Yes	6 (20%)	8 (26.7)	0.542
	No	24 (80%)	22 (73.3%)	
Physician satisfaction	High	13 (43.3%)	10 (33.3%)	0.698
	Medium	11 (36.7%)	12 (40%)	
	Low	6 (20%)	8 (26.7%)	
Desaturation		2 (6.7%)	3 (10%)	0.640
Interruption of the procedure		3 (10%)	4 (13.3%)	0.688
Hypotension		3 (10%)	2 (6.7%)	0.640
Hypertension		1 (3.3%)	3 (10%)	0.301
Antispasmodic need		7 (23.3%)	10 (33.3%)	0.390
Sore throat		4 (13.3%)	5 (16.7%)	0.718
Bloating		6 (20%)	8 (26.7%)	0.542

Data are presented as frequency (percentage).

systemic vascular resistance) are major side effects in addition to absence of pharmacologic antagonist [16].

Administering propofol alone during ERCP provides insufficient sedation and analgesia, leading to an increase in unnecessary drug consumption and associated adverse effects, using adjuvant sedative agents has become more widespread [17].

Fentanyl is a very potent synthetic opioid used as a pain medication. Combining propofol with fentanyl for ERCP has the potential to reduce the overall propofol dose, lower pain, boost physician satisfaction, and ensure haemodynamic stability, but it also has the potential to cause respiratory depression, stiff muscles, and airway obstruction [18,19]. Thus, it is suggestive to validate a non-opioid adjuvant for elderly patients with propofol sedation to reduce propofol consumption and related side effects [20].

Magnesium sulphate has an analgesic effect and reduces the requirement for anesthetics and/or muscle relaxants and decreases the incidence of post ERCP pancreatitis [21].

Our findings indicated that the magnesium group had significantly reduced the total propofol consumption and increased the onset time of sedation than fentanyl group. HR and MAP measurements were significantly lower after adjuvant bolus injection and 15 min in magnesium group than fentanyl group. Procedure time, involuntary movement, physician satisfaction and complications were insignificantly different between both groups.

Consistent with our results, Fahmy et al. [22] reported that magnesium sulfate infusion provided a more favorable hemodynamic profile and lower incidence of complications during sedation for chronic subdural hematoma evacuation in comparison with fentanyl infusion. Besides, magnesium sulfate provided a propofol-sparing effect comparable to fentanyl.

Moreover, Hasanein et al. [8] and Tosun et al. [23] showed that fentanyl and propofol combination resulted in lower sedation quality than of ketamine and propofol in obese patients undergoing ERCP.

There was a significant risk of postinduction hypotension when fentanyl-propofol was used to initiate anesthesia. The negative inotropic effect of fentanyl is likely to be responsible for the elevated rate of hypotension [24]. Fentanyl, like other opioids, has a direct stimulation on the chemoreceptor-triggering zone, which in turn stimulates the vomiting center in the medulla [25].

Magnesium sulfate has a well-known vasodilatory effect; however, its use as an adjuvant to general anesthesia was associated with modest hypotension, and it has no cardiac inhibitory effect. The incidence of nausea and vomiting was lower in the magnesium sulfate group compared with the fentanyl group [26].

Yoldas et al. [27] concluded that the magnesium sulphate added to propofol improved respiratory and hemodynamic complications and decreased propofol use during colonoscopy, making it a preferable safety precaution.

Likewise, Olgun et al. [10] showed that magnesium sulphate decreased the consumption of sedative agents such as propofol, desflurane and morphine after laparoscopic cholecystectomy. Seyhan et al. [11] demonstrated to reduce intraoperative propofol consumption by 13.5% when administered with single dosage (40 mg/kg) magnesium sulfate.

In this regard, Semeda et al. [28] reported that magnesium sulfate infusion with propofol in patients undergoing colonoscopy under sedation decreases the total amount of propofol used.

Altan et al. [29] showed that magnesium sulphate was shown to significantly reduce the dosage of propofol used for induction and maintenance of anesthesia. No effects on hemodynamics or cardiovascular function were seen in the magnesium sulphate group, however extubation took longer in patients having spinal surgery.

Theoretically, magnesium inhibits the calcium channel activation and antagonizes NMDA receptors in the central nervous system and consequently modified the anesthetic effects [9,30]. Another mechanism involves that magnesium inhibits the release of catecholamines through reduced sympathetic outflow, which may decrease peripheral nociceptor sensitization or the stress response to surgery [30].

The study had few limitations, the sample size was relatively small, it was a single-centered study; therefore, the findings cannot be generalized. Further studies using different additives, types, and concentrations of the sedative agents are recommended.

10. Conclusion

During ERCP, adding a single boule of magnesium sulphate to propofol was associated with a lower total propofol consumption and better hemodynamics than fentanyl but with a delayed onset time of sedation.

Acknowledgments

There are none to be declared.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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