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Endoskopik Retrograd Kolanjiyo Pankreatografi için analjezi bazlı ve konvansiyonel sedasyon teknikleri

Analgesia – based vs conventional sedation techniques for endoscopic retrograde cholangiopancreatography: state of the art

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ÖZ

GİRİŞ ve AMAÇ: *Endoskopik retrograd kolanjiyopankreatografi (ERCP) ağrılı bir girişimdir ve genellikle anestezik uygulamalar gerektirir. Bu işlem sırasında işlemsel sedasyon için birçok ilaç kombinasyonu çalışılmıştır ve sonuçlar değişkenlik göstermektedir. Bu çalışmada remifentanil monoterapisini ERCP sırasındaki geleneksel sedasyon yöntemleriyle klinik güvenlik, derlenme profilleri, hasta ve endoskopist memnuniyeti açısından karşılaştırmayı amaçladık.*

YÖNTEM ve GEREÇLER: *18-80 yaşları arasındaki altmış hasta, işlemsel sedasyon için, remifentanil monoterapisi (bolus remifentanilin ardından infüzyon) ve geleneksel yöntemler (fentanil ile kombine edilmiş protafol ve / veya ketamin) olmak üzere rastgele iki gruba ayrıldı. Klinik özellikler, Ramsey Sedasyon Skoru (RSS), derlenme skoru (modifiye Aldrete skoru), hasta ve endoskopist memnuniyeti ölçülen sonuçlar olarak kabul edildi.*

BULGULAR: *Her iki hasta grubunda da kardiyorespiratuar parametreler ve advers reaksiyonlar benzerdi. Hasta ve endoskopist memnuniyeti, RSS ve derlenme özellikleri remifentanil monoterapisi ile anlamlı derecede daha iyiydi.*

TARTIŞMA ve SONUÇ: *Tek başına remifentanilin kullanılması, ERCP'de işlemsel sedasyon sırasında güvenli klinik performansı ve daha iyi sedasyon seviyesi, derlenme süresi ve memnuniyet sağlaması nedeniyle tercih edilen alternatif bir tedavi olarak düşünülebilir.*

Anahtar Kelimeler: : *Kolanjiyopankreatografi, Endoskopik Retrograd, bilinçli sedasyon, fentanil, propofol, remifentanil*

ABSTRACT

INTRODUCTION: *Endoscopic retrograde cholangiopancreatography (ERCP) is a painful intervention and usually requires anesthetic implications. Many drug combinations have been studied for procedural sedation during this procedure and the results show variability. In this study, we aimed to compare the remifentanil monotherapy with the conventional sedation methods during ERCP in terms of clinical security, recovery profiles and the satisfaction of the patients and endoscopists.*

METHODS: *Sixty patients aged between 18-80 years were randomly allocated into two groups to receive either remifentanil monotherapy (bolus dose of remifentanil followed by infusion) or conventional methods (propofol and/or ketamine combined with fentanyl) for procedural sedation. Clinical characteristics, Ramsey Sedation Score (RSS), recovery score (modified Aldrete score), the satisfaction of patients and endoscopists were considered as measured outcomes.*

RESULTS: *The cardiorespiratory parameters and adverse reactions were similar in both groups of patients. The endoscopist and patent satisfaction, RSS and recovery characteristics were significantly better with remifentanil monotherapy.*

DISCUSSION AND CONCLUSION: *The usage of remifentanil alone may be considered as an alternative treatment of choice during procedural sedation in ERCP due to its safety clinical performance and providing better sedation level, recovery period and satisfaction.*

Keywords: *Cholangiopancreatography, Endoscopic Retrograde, conscious sedation, fentanyl, propofol, remifentanil*

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly used in complex biliopancreatic diseases as it diminishes the need for percutaneous interventions and open surgery (1). However, the ideal sedation or anesthetic technique used during this procedure has not been identified yet. Guidelines for sedation and anesthesia in gastrointestinal endoscopy state that the use of a single agent reduces the risk of complications (2). Propofol is most commonly used as a single agent. However, sedation-related complications during propofol- mediated sedation restrict its use. Cardiorespiratory arrests, ventricular fibrillation and a respiratory arrest following aspiration were reported (3). Especially advanced age, prolonged intervention time, increased Body Mass Index (BMI), male sex, and American Society of Anesthesiologists (ASA) class of 3 or higher are independent risk factors for sedation related side effects. In a recent systematic review, propofol-induced acute pancreatitis was severe in 19 % of patients with a mortality rate related to acute pancreatitis of 14% (4). For this reason, it is reported that there are still limited data on safety of the propofol sedation (5). Higher risk of aspiration and vagally mediated hypotension are among these concerns. In their last review, Smith et al. (6) stated that the preferred method of anesthesia for the patients undergoing ERCP remains a highly debated topic. Remifentanil is a potent, ultra-short-acting μ-opioid receptor agonist with a fast onset of action. Remifentanil provides a rapid postoperative recovery (7, 8). The aim of this prospective randomized controlled, single-blinded study is to compare the efficacy of remifentanil as a single agent with conventional sedation techniques. We hypothesized that remifentanil infusion alone would be able to provide satisfactory sedation and analgesia with a better recovery period.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Ethics Committee (2019/514/151/3) and conducted according to the ethical principles outlined in the Helsinki Declaration and guideline of the Good Clinical Practice. The patients' written informed consents were obtained from all the participants.

Study population

Adult patients aged between 18-80 years with ASA physical status I-III scheduled for ERCP were recruited for this study between February-April 2019 in Kartal Dr. Lutfi Kırdar Training and Research Hospital (Figure 1). Patients with neurological and/or mental disturbances, pregnancy, known hypersensitivity or allergies to medications, renal or hepatic failure and anticipated difficult airway were excluded from the study. Patients were randomly assigned to either analgesia-based (Group R; n=30) or conventional sedation techniques (Group C; n=30) by a computer-generated randomization method (9).

In conventional sedation group, data were collected according to the attending anesthesiologist's preference during daily clinical practice. In analgesia-based sedation group, the study protocol has been preceded by the investigators. All interventions have been performed in a special fully equipped endoscopy unit designed for these procedures and experienced anesthesiologists administered all the anesthetic drugs. All ERCP procedures were performed by 5 endoscopists of similar experience. Anesthesiologists were not blinded for the administered drugs in both groups of patients. The recovery period, the satisfaction of the patients and endoscopists as well as the adverse reactions has been assessed by the recovery room nurse who was unaware of the anesthetic agent.

Patient monitoring

The monitoring included non-invasive systolic and diastolic blood pressure, heart rate, pulse oximetry and recorded before and just after the drug administrations. These parameters were recorded in an interval time of each 5 minutes throughout the procedure. In both groups of patients, Integrated Pulmonary Index monitoring (Capnostream 20 monitor, Medtronic, Israel) providing early warning of the altered respiratory pattern was applied (10). Ramsay sedation score was used to assess the level of sedation (11). Recovery score assessment was performed by another clinician blinded to the study at the end of the procedure with the modified Aldrete score (12) and was recorded at 5and 30. minutes. All patients received supplemental oxygen via nasal prongs at a 4 L/minute throughout the intervention and in the recovery room. Any uneventful reactions such as airway obstruction, hypoventilation (respiratory rate of <8/minute), apnea (>30 seconds), nausea, vomiting, hemodynamic instability (mean arterial blood pressure > or ≤30% of baseline value), arrhythmia or bradycardia (<50 beats/min) and decreasing of oxygen saturation percentage (<95%)were recorded. According to the study protocol, in case of hypotension and bradycardia, fluid replacement, bolus doses of ephedrine and intravenous atropine was the treatment of choice. If the respiratory depression developed, the endoscope was removed, and supplemental oxygen was increased. Jaw-thrust maneuver or bag-valve-mask ventilation was considered if necessary. In unresponsive cases, endotracheal intubation has been planned.

Study design and the definition of groups

When the patients arrived at the endoscopy unit, an18-G intravenous cannula was inserted on the dorsum of the hand and Normal Saline 0.9% infusion was administered. All patients fasted overnight and received 0.05 mg/kg intravenous midazolam for premedication before the procedure.

In conventional sedation group of patients, the drug of choice was left to the attending anesthesiologists' preference. In our clinical practice, fentanyl together with the propofol or ketamine was the most used anesthetic agents during procedural sedation. Initially, fentanyl was given as an analgesic agent at a dose of 1 μg/kg and then, propofol 0.5 mg/kg or ketamine 0.5 mg/kg was given to provide procedural sedation. If the patients have the complaint of pain and/or discomfort or when the endoscopists demand the deeper sedation, additional doses of propofol and/or ketamine were administered.

In the analgesia-based group, following premedication, remifentanil was diluted to a concentration of 40 μgr/ml and administered in a bolus dose of 0.2 μg/kg intravenously by using a syringe pump (Compact B, Braun, Germany). The sedation level was maintained by infusion of remifentanil in a dose of 0.05μg/kg/h.

The target sedation level was a Ramsay score of 4 or 5 in both groups. Below this level was considered as insufficient sedation and treated the increasing the rate of remifentanil infusion or additional doses of intravenous anesthetic agents.The level of 5 was considered as very deep sedation and the rate of remifentanil infusion was decreased. At the end of the procedure, all drugs were discontinued, and the patients were transferred to the recovery room. All monitoring was continued in the postoperative period. A modified Aldrete score of 9 or upper was targeted to discharge of the patients to the ward.

Outcome measures

The main outcome of this study was to compare the safety and efficacy of remifentanil alone during procedural sedation with conventional sedation techniques. Assessing the Aldrete Recovery Score at 5and 30. minutes in both groups of patients provided to compare the recovery profile of both techniques. The duration of the procedure was recorded as the time between the insertion of the endoscope through the oropharynx and the termination of the procedure. The ease of procedure was also an important issue in this study and the endoscopist was asked to give a satisfaction score (1: very bad, 2: mediate, 3: good, 4: very good). The patient's satisfaction was assessed at the recovery room by a nurse blinded to the study groups and when the patient was ready to discharge, he/she asked to give a satisfaction score for the

intervention (1: very bad, 2: mediate, 3: good, 4: very good).

Hemodynamic parameters and the adverse reactions during the procedural period were also evaluated as outcomes of this study.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 7. T-test was used to determine statistical difference between the groups. The differences were considered statistically significant when p values were were < 0.05 (*, p < 0.05; **, p < 0.01; ***, p < 0.001). The data has been reported as mean±standard deviation (SD).

The power analysis has been performed using GPower 3.1. To keep the study at a power level above %90 and a type I error level below %5, it is calculated that a total of 60 patients with 30 patients in each group must be included.

RESULTS

All patients completed the study and data were comparable including age gender, height, weight, and duration of the procedure. ASA physical status difference revealed statistical significance due to randomization, but this difference was underestimated (Table 1).

Table 1:Demographic characteristics (mean ±SD)

Variables	Group R	Group C	p
Age (years)	60.97±1.77	65.7±1.98	0.052
Gender (M/F%)	40/60	57/43	0.203
Height (cm)	165±1.33	167.30± 1.83	0.322
Weight (kg)	74.83±1.76	79.33 ±1.78	0.0078
ASA status (n) **I** **II** **III**	 9 21 -	 4 22 4	 **0.023***
Duration of the procedure (min)	30.33±1.76	35.17±1.77	0.058
The differences were considered statistically significant when p values were were < 0.05 (*, p < 0.05; **, p < 0.01; ***, p < 0.001).			

The mean amount of remifentanil was 113.6 ±7.16 µgr in Group R. The main drugs used in conventional sedation group were propofol (120.3±7.31 mg), ketamin (34.25±4.34 mg) and fentanyl (31.25±3.26 µgr). In terms of the patient' (p=0.024) and endoscopist' satisfaction (p= 0.007) and the Aldrete score at 30. minutes (p=0.0009) Group R indicated the significantly better results compared to Group C (Table 2).

Table 2: Clinical data related to the patients' groups.

Variables	Group R	Group C	p
The amount of drugs used **Remifentanil (µgr)** **Midazolam (mgr)** **Propofol (mgr)** **Ketamine (mgr)** **Fentanyl (µgr)**	 113.6 ±7.16 1.33±0.09 - - -	 1.6±0.9 120.3±7.31 34.25±4.34 31.25±3.26	 ---
The satisfaction score **Patient** **Endoscopist**	 3.83±0.07 3.80±0.07	 3.57±0.09 3.47±0.09	 0.024* 0.007**
Aldrete score **5 min** **30 min**	 8.27±0.18 9.97±0.03	 8.67±0.21 9.63±0.09	 0.15 0.0009**
The differences were considered statistically significant when p values were were < 0.05 (*, p < 0.05; **, p < 0.01; ***, p < 0.001)			

Because of the number of patients having the duration of procedure longer than 35 minutes difference, the statistical analysis was performed up to 35 minutes concerning SpO2, IPI, RSS and hemodynamic parameters. In Group R, the SpO2 values showed significantly lower values throughout the procedure (p<0.05) except 25. and 35. minutes but this difference had no clinical importance. IPI value indicated a significant difference only at 15. minutes in Group R (p=0.04) and at this period, RSS was better in this group (p=0.001). RSS was significantly better in Group R throughout the procedure up to 30. minutes which meant that the level of sedation with remifentanil infusion was provided better than conventional sedation methods (Table 3).

According to hemodynamic characteristics, both groups of patients represented similar results. The only significant difference between groups was the heart rate at 1. minute and the systolic arterial

pressure at 5. minutes which was clinically insignificant (Table 4).

In this study, all the cases were completed successfully with transient or minor side effects. In Group R, the adverse reactions were nausea (13.33%), hypotension (6.6%) and bradycardia (3.3%). In Group C, mostly encountered adverse reactions were hypotension (16.66%), nausea (6.6%) and desaturation (3.3%).

Table 3: The distribution of data concerning IPI, SpO_2(%) and RSS (mean ±SD)

Variables	Group R	Group C	P
Preoperative			
IPI	9.6±0.10	9.83±0.07	0.06
SpO_2	97.87±0.27	98.83±0.18	**0.004***
RSS	2±0	2±0	1.00
1.minute			
IPI	8.4±0.16	8.6±0.12	0.33
SpO_2	98.73±0.24	99.6±0.12	0.002*
RSS	2.73±0.08	4.53±0.15	**<0.0001***
5.minutes			
IPI	7.43±0.27	8±0.14	0.07
SpO_2	98.43±0.31	99.17±0.15	**0.04***
RSS	4.33±0.17	5.03±0.13	**0.002***
10.minutes			
IPI	7.23±0.26	7.77±0.08	0.05
SpO_2	98.17±0.28	99.03±0.16	0.01*
RSS	4.47±0.13	5.2±0.12	**0.0001***
15.minutes			
IPI	7.03±0.21	7.53±0.11	**0.04***
SpO_2	98.27±0.24	99.07±0.16	**0.01***
RSS	4.43±0.13	5.2±0.17	**0.001***
20.minutes			
IPI	7.33±0.20	7.3±0.14	0.9
SpO_2	98.33±0.30	99.13±0.16	**0.02***
RSS	4.47±0.13	5.53±0.09	**<0.0001***
25.minutes			
IPI	7.64±0.21	7.43±0.13	0.39
SpO_2	98.52±0.31	98.83±0.40	0.55
RSS	4.52±0.15	5.23±0.09	**0.0001***
30.minutes			
IPI	7.37±0.26	7.73±0.15	0.21
SpO_2	98.31±0.32	99.19±0.14	**0.01***
RSS	4.56±0.16	4.88±0.11	0.10
35.minutes			
IPI	7.87±0.40	7.79±0.20	0.8
SpO_2	98.38±0.56	99±0.20	0.22
RSS	4.75±0.31	5±0.20	0.48

The differences were considered statistically significant when p values were were < 0.05 (*, p < 0.05; **, p < 0.01; ***, p < 0.001) IPI: Integrated Pulmonary Index ; SpO_2: Peripheral oxygen saturation; RSS: Ramsay Sedation Score

Table 4: Hemodynamic parameters of the patients (mean±SD)

	Group R	Group C	P
Preoperative			
SAP (mmHg)	72.21±7.25	138.6±22.62	0.87
DAP (mmHg)	76.76±12.54	82.23±13.82	0.11
MAP (mmHg)	100.5±16.08	101.66±14.20	0.77
HR (beats/minute)	81.46±13.84	83.23±12.98	0.82
1.minute			
SAP	121.58±23.56	130.5±27.19	0.15
DAP	73.86±13.77	77.70±18.92	0.37
MAP	89.53±18.35	94.7±19.09	0.16
HR	80.46±12.68	87.3±13.34	**0.04***
5.minutes			
SAP	112.93±19.21	122.8±21.38	**0.04***
DAP	66.00±13.89	74.20±18.48	0.06
MAP	84.40±17.07	90.90±18.00	0.15
HR	81.43±16.02	87.43±13.75	0.12
10.minutes			
SAP	114.48±22.06	120.4±16.87	0.19
DAP	67.86±17.03	73.16±16.27	0.22
MAP	85.96±20.82	88.83±17.31	0.90
HR	84.46±16.53	86.43±13.47	0.61
15.minutes			
SAP	117.07±21.79	118.8±16.26	0.84
DAP	70.33±16.70	69.93±14.68	0.92
MAP	88.10±18.08	88.60±14.81	0.90
HR	84.43±17.00	83.40±14.15	0.80
20.minutes			
SAP	122.53±20.47	122.36±23.80	0.77
DAP	75.36±16.59	72.80±20.24	0.59
MAP	94.30±20.72	89.7±20.13	0.39
HR	84.23±19.20	80.46±11.69	0.36
25.minutes			
SAP	119.28±19.51	126.26±23.56	0.49
DAP	73.92±14.28	77.63±21.07	0.46
MAP	94.04±17.29	97.56±23.21	0.53
HR	81.32±16.05	77.40±12.19	0.31
30.minutes			
SAP	123.20±21.12	130.44±26.72	0.39
DAP	75.81±14.29	80.15±18.98	0.44
MAP	95.21±18.67	98.57±20.11	0.58
HR	80.75±17.29	77.33±7.50	0.37
35.minutes			
SAP	126.25±29.11	131.66±16.62	0.50
DAP	75.12±17.73	81.53±17.47	0.43
MAP	93.00±23.29	102.00±17.79	0.28
HR	73.50±9.48	74.61±7.85	0.77

The differences were considered statistically significant when p values were were < 0.05 (*, p < 0.05; **, p < 0.01; ***, p < 0.001). SAP: Systolic arterial pressure; DAP: Diastolic arterial pressure; MAP: Mean arterial pressure; HR: Hearth rate

DISCUSSION

The results of this study indicated that remifentanil infusion alone provided satisfactory procedural sedation during ERCP compared to the conventional sedation methods in terms of similar clinical performance and hemodynamic variability.

Fulfilling the discharge criteria and both patient' and endoscopist' satisfaction were significantly better in the remifentanil infusion-based group. Remifentanil alone may be a good treatment of choice during procedural sedation in selected patients.

Balanced-propofol sedation gained popularity during endoscopic procedures since 2000s but the discussions about the ideal drug combinations during procedural sedation have been going on. The important point is the characteristics of procedure which tailored the anesthetic drug requirements according to the target, duration and the nature of the intervention (13). During the procedural sedation, providing a sedation level from consciousness state to deep sedation is a dose-related issue and depends on the patient's response. So, the intended level of sedation may not be achieved all the time and the level of sedation varies patient to patient in similar doses of drugs (14).

During ERCP general anesthesia practice has been reported by some authors, but these patients have primary sclerosing cholangitis, liver transplantation and the pathologies requiring painful dilatation (15). A common practice during ERCP is the conscious sedation with a moderate level of sedation. Nevertheless, Patel et al (16) reported that the overall incidence of deep sedation during ERCP was 35% and ERCP was an independent risk factor of deep sedation.

In our study, ASA physical status of the patients was not homogenous due to the randomization. As the consequence of the increased number of patients with ASA II-III physical status in Group C, the mean Aldrete score of the patients in Group C was significantly higher at the 30.min of the postoperative period. However, this significance has no clinical importance. ASA physical status indicated as a predictive factor for the outcome of surgical patients. Chen et al. (17) reported that recovery period, mental and general health status was significantly better in patients with ASA I-II physical status. Similar significance was indicated in SpO2 values recorded in measurement times (preoperative and intraoperative 5, 15, 20 and 30. minutes). No hypoxic period was recorded during these time intervals so, this significance was comparable in the clinical aspect.

Mostly used sedative agents in ERCP are propofol monotherapy or in a combination of benzodiazepines or opioids. A recent study indicated that one-third to one-half of patients undergoing therapeutic ERCP experienced discomfort and pain during conscious sedation and the amount of opioid administration increased during these procedures under sedation of propofol infusion (18,19). In patients having the risk of respiratory depression, a combination of propofol-ketamine has been recommended during ERCP in comparative studies with propofol-fentanyl combination (1,20). As mentioned previously, in our conventional procedural sedation group, propofol and/or ketamine was used alone or in a combination with midazolam and fentanyl. Only one patient demonstrated a transient decrease in SpO2 treated with jaw- thrust maneuver. The measurements of SpO2 remained stable throughout the procedure.

Due to its ultra-short acting effect and brief duration, remifentanil has been used alone or as an adjuvant for sedoanalgesia, regional anesthesia and local infiltration anesthesia with few adverse events (21). The propofol-remifentanil combination has been reported as a treatment of choice for better pain control and shorter recovery time. Nevertheless, this combination caused respiratory side effects concerning apnea and oxygen requirement (22). In our remifentanil infusion group of patients, mean SpO2 levels in a few measurement times indicated a statistically significant difference compared to conventional sedoanalgesia administrations. This difference was not clinically important, and no desaturation, apnea and/or respiratory impairment has been recorded during procedural sedation based on remifentanil infusion alone.

Apart from conventional monitoring, capnography and Bispectral Index monitoring have been recommended to titrate the sedative agents according to provide the intended level of sedation (23). In addition to conventional monitoring, we

used the Integrated Pulmonary Index (IPI) monitoring which provided an early warning of altered respiratory patterns in both groups of patients. This respiratory monitoring during anesthesia includes end-tidal CO2 (EtCO2), respiratory rate (RR), oxygen saturation (SpO2) and pulse rate (PR) as an index score based on the integrating the real-time interaction of four parameters (10). Mean IPI measurements showed a significant decline in Group R only at the 15. minutes of the procedure (7.03±0.21 vs 7.53±0.11, $p<0.05$). Nevertheless, no desaturation episode was recorded in Group R.

Hemodynamic stability is an important point of issue during outpatient procedures. In previous studies, similar hemodynamic characteristics have been reported by using the propofol in a combination either fentanyl or ketamine during ERCP (1, 20). In a comparative study of conventional versus analgesia-oriented combination sedation during ERCP, there was no difference in respect of cardiovascular side effects between groups (13). In our study, the difference between groups concerning the hemodynamic variability was insignificant.

LIMITATIONS

Our study has some limitations. Our results represented the data of a single university affiliated tertiary hospital so, these results may not be generalized to the entire population. Also, the variability between hospitals and attendance of anesthesiologists may result in different outcomes. In this study, the anesthesiologist was not blinded to the study groups which have led to bias. The aged of the patients were between 18-80 years due to randomization so, the clinical efficacy of remifentanil monotherapy in octogenarians has not been evaluated. This wide range between patients' age may vary the threshold for respiratory depression. These issues may be subjects in further studies. The small sample size is another limitation in this study, so studies with a larger sample size may change the statistical results.

CONCLUSION

Remifentanil as monotherapy can be used with few adverse reactions during ERCP as an alternative to conventional sedation methods. Concerning the satisfaction and the rapid recovery after the procedure, it represents clinical superiority. Monitoring of the patients including capnography provides the early awareness of cardiopulmonary adverse reactions.

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