BIOMEDICAL JOURNAL 39 (2016) 145–149

Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Original Article

A comparison between the effects of propofol–fentanyl with propofol–ketamine for sedation in patients undergoing endoscopic retrograde cholangiopancreatography outside the operating room

Reza Akhondzadeh [a,*], *Ali Ghomeishi* [a], *Sholeh Nesioonpour* [a], *Sanaz Nourizade* [b]

[a] *Department of Anesthesiology, Pain Research Center, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

[b] *Department of Anesthesiology, Pain Research Center, Razi Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

ARTICLE INFO

Article history:
Received 17 February 2015
Accepted 4 November 2015
Available online 21 June 2016

Keywords:
Deep sedation
Endoscopic retrograde cholangiopancreatography
Fentanyl
Ketamine
Propofol

ABSTRACT

Background: The efficient and secure techniques of anesthesia and sedation have always been needed for. One of these procedures is endoscopic retrograde cholangiopancreatography (ERCP), due to its painfulness and long duration, has high sensitivity. We compare the effects of propofol–fentanyl (PF) with propofol–ketamine (PK) to sedate patients undergoing ERCP.
Methods: In this clinical trial, patients were divided into two groups of 49 people. A group received a pharmaceutical combination of PK, and another group received a pharmaceutical combination of PF. Vital signs of patients, Ramsey Sedation Score, and pain of patients were assessed. The total dosage of used propofol was also recorded.
Results: There was no significant difference seen in the patients' hemodynamic characteristics in both groups. Pain at the end of surgery and an hour after it in the PK group was less that was not statistically significant. By Ramsey Sedation Score also significant differences were not seen between groups ($p = 0.68$). By using total dose of propofol used also a significant difference was not observed between the two groups ($p = 0.36$). Rate of apnea in PK group was 32% and in the PF group was 63%, which this difference was statistically significant ($p < 0.05$).
Conclusion: A comparison between the two drugs combination shows that although in terms of hemodynamic and sedation criteria both groups were similar, but because of the lower amount of pain and apnea in the PK group, this combination may generally in the ERCP procedure is more efficient and safer.

* *Corresponding author*. Department of Anesthesiology, Pain Research Center, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Box: 1519, 6193673166, Ahvaz, Iran. Tel.: +98 9161135201; fax: +98 6132220168.
E-mail address: rezaakh@hotmail.com (R. Akhondzadeh).
Peer review under responsibility of Chang Gung University.
http://dx.doi.org/10.1016/j.bj.2015.11.002

At a glance commentary

Scientific background

In 2012 Khutia et al. compared a combination of Propofol and fentanyl infusion with Propofol and ketamine infusion in the pediatric short-term procedures. In their study, in the propofol-fentanyl group more hypotension was seen compared with the propofol-ketamine group that was statistically significant as well, and this result is different with our study because hemodynamically differences was not observed in our study.

What this study adds to the field

By this study we will have guidelines about effective and with less side effects combination of drugs for sedation in ercp patients. The distinction between our study with other studies is that while comparison between the two medicinal compound has been applied in the studies of children limited studies have investigated its application in the endoscopic procedures of adults.

According to the multitude of surgical procedures outside the operating room, efficient and secure anesthesia techniques appreciably are required [1].

Sedation is a technique in which prescription of a tranquilizer medication leads to analgesia or without analgesic effects, creates a situation in which procedure can be tolerated while maintaining cardio-respiratory function [2].

One of these procedures is endoscopic retrograde cholangiopancreatography (ERCP), and because it is painful and also has long duration, ERCP needs more attention and is sensitive.

Sedation technique that used for this procedures should be in such a way that, despite to create analgesia and prevent cough, maintaining the spontaneous breathing and hemodynamic stability. Many drugs individually or in combination with each other, including benzodiazepines, opioids, propofol, and ketamine, can be used to create sedation [3].

Due to favorable features such as fast start and end of its effect, the short length of effects and quiet awakening, propofol is popular among certain outpatient procedures [4]. However, because it does not have analgesic effects in the painful procedures, large doses are used that may increase the risk of respiratory depression and hemodynamic consequences; for this reason the use of analgesic medicine in combination with propofol becomes essential [5].

Among the opioid drugs, fentanyl could lead to reducing the dosage of propofol and reduce its complications [6]. While it has been reported that alfentanil and remifentanil cause to worsen the cardio-respiratory depression effects of propofol [7].

Ketamine, a derivative of phencyclidine, has a noteworthy ability to create analgesia without respiratory depression that is considered beneficial compared to the opioids. Another advantage of it is sympathomimetic effects that can create the hemodynamic stability when using propofol. In addition to this, it can decrease the pain of propofol injection by local anesthesia effects [8–10].

On the other hand, the probability of occurrence of complications such as the increased blood pressure, the elevated intraocular pressure and or disorders, such as the bad dreams, will limit the usage of this medicine alone; as a result, it seems that better results can be achieved with a combination of propofol and ketamine by reducing the side effects of each other.

According to the lack of extensive studies about the combination of propofol and ketamine in endoscopic procedures, in this study we compared the effects of propofol–fentanyl (PF) with effects of propofol–ketamine (PK) for patients sedating undergoing ERCP outside the operating room.

Methods

After obtaining a written permission from the Ethics Committee (2013, 286, IRCT2014031316976N1), and the Pain Research Center (pain 2013–05), in this double-blind clinical trial, a total of 98 patients between 18 and 65 years old, who were referred to hospital during 2013–2014 to perform the ERCP (with a length of time of <45 min), were selected as inclusion criteria and were divided into two groups of 49 patients randomly (using odd and even numbers). Furthermore, in this study, the exclusion criteria were patients with allergies to medications, eggs, and soy, age <18 or more than 65 years, renal or hepatic failures, the difficult airway, ASA classes III and IV, having contraindications for propofol, ketamine, or fentanyl.

Based on previous studies, the sample size with a confidence level of 95% and a test power of 90% in each group were estimated to be 49, where 40% of the patients in both groups were women, and the remaining 60% were men.

At the beginning of a visit, the written consent was obtained for inclusion. Monitoring of patients, including systolic and diastolic blood pressure, heart rate, percentage of blood oxygen saturation and capnography, was measured and recorded in an interval time of each 5 min until the end of the procedure.

In the beginning, both groups of patients in the supine position received 0.05 mg/kg of intravenous midazolam (Chemie Tehran, Iran) and then, in the first group, 0.5 mg/kg of propofol (Claris, India) and 1 μg/kg of fentanyl (Caspian Tamin, Iran) were injected; also, in the second group, 0.5 mg/kg of propofol was injected and 0.5 mg/kg of ketamine (Rotex, Germany) was used for bolus injection, and after 90 s sedation level, the patient was assessed and recorded based on the criteria for Ramsey (1). A Ramsey score of five or six was considered as a desirable limit of sedation and score less than five was considered as insufficient rate of sedation. If the insufficient rate of sedation in a patient was seen, a bolus dose of propofol 0.5 mg/kg was prescribed. Then, if necessary, the dose can be repeated every 60 s. (1). The patient's respiration was controlled during a procedure with a bag and a mask.

At the end of surgery, patients were evaluated using Aldrete criteria (Aldrete postanesthetic recovery scoring) and time for reaching them to a score equal or more than eight was recorded.

The patients then were transferred to the postanesthesia care unit and were monitored with the help of a pulse and noninvasive blood pressure monitoring, and complications such as oxygen saturation percentage drop, systolic blood

pressure drop, or nausea and vomiting, psychiatric side effects, optical side effects, shivering, and vertigo were recorded. During this study, none of the patients were excluded from the study. After obtaining the scores equal to or greater than 9 based on the scoring system criteria for exit from monitoring care unit, patients were discharged, and the duration of hospitalization in recovery was also recorded.

At the start of a procedure, at the end of a procedure and an hour after finishing the procedure the amounts of pain assessed based on patients response to the Ambesh score [11]. Furthermore, all amount of propofol used, rate of nausea and vomiting, and apnea in both groups were recorded.

Statistical analysis

The data has been reported based on mean ± standard deviation. After assessing normal data distribution, by using the Kolmogorov–Smirnov test as well as the consistency of the variance using Loon test, to compare groups the independent *t*-test was used and if the data distribution is abnormal or ranked parameters, the Mann–Whitney *U*-test was used. Alpha at a level of 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA).

Results and discussion

Demographic characteristics of participants as well as the duration of anesthesia and surgery are displayed in [Table 1]. In each group, participants were 49 people, who did not have a significant difference with each other in terms of age, weight, gender, and time spent for doing procedure.

No significant difference was seen in the hemodynamic features of the patients (systolic blood pressure, diastolic blood pressure, and heart rate) between the two groups, both in the period before the procedure and in 5, 15, 10, and 20 min after the procedure [$p \geq 0.05$, Table 2].

In terms of the severity of the pain between the two groups, the pain at the end of the procedure and an hour after it in the PK group was lower, and there was statically a significant difference ($p = 0.63$; $p = 0.37$; $p = 0.59$) [Table 3].

In terms of the Ramsey criteria, 90 s after the start of sedation, also a significant difference was not observed between the groups (respectively, 4.42 ± 1.25; 4.51 ± 1.22; $p = 0.68$).

In terms of the total dose of propofol in two groups, also there was no significant difference (respectively, 134.42 ± 63.66, 148.67 ± 71.24; $p = 036$). For studying the amount of apnea, 16 cases (32%) in the PK group and 31 cases (63%) in the PF group were observed, which was statistically significant ($p < 0.05$). In none of the two groups, laryngospasm has been observed.

The results of this study showed that a significant difference was not seen among subjects in two groups in terms of hemodynamic characteristics, including heart rate, systolic, and diastolic blood pressure, in 5, 15, 10, and 20 min. No significant difference was observed between the groups in terms of Ramsey criteria. No significant difference was observed between the

Table 3 – The amount of pain in the two groups.

Pain 1 h after surgery	The pain at the end of surgery	Pain at the beginning of surgery	Groups and *p* value
1.30 ± 0.46	1.28 ± 0.45	1.14 ± 0.35	PF group
1.12 ± 0.33	1.10 ± 0.30	1.16 ± 0.37	PK group
0.028	0.22	0.78	*p*

Table 1 – Demographic characteristics of participants.

Procedure time (min)	Height (m)	Weight (kg)	Age (years)	Groups
162.18 ± 4.41	26.34 ± 3.23	66.09 ± 7.12	42.22 ± 7.10	PF group
163.65 ± 4.27	27.36 ± 2.26	67.94 ± 6.24	41.18 ± 5.98	PK group
$p = 0.88$	$p = 0.52$	$p = 0.67$	$p = 0.54$	Significance

Table 2 – The hemodynamic indices of groups.

Systolic blood pressure 20 min	Systolic blood pressure 15 min	Systolic blood pressure 10 min	Systolic blood pressure 5 min	Preoperative systolic blood pressure	Groups name and *p* value significance
139.84 ± 18.57	135.10 ± 18.24	133.02 ± 18.84	137.92 ± 18.70	137.82 ± 18.90	PF group
135.94 ± 18.57	131.24 ± 18.48	129.00 ± 18.85	134.20 ± 19.05	134.20 ± 19.05	PK group
$p = 0.30$	$p = 0.30$	$p = 0.29$	$p = 0.33$	$p = 0.34$	Significant
Diastolic blood pressure 20 min	Diastolic blood pressure 15 min	Diastolic blood pressure 10 min	Diastolic blood pressure 5 min	Preoperative diastolic blood pressure	
73.87 ± 18.77	74.93 ± 18.70	76.85 ± 18.79	75.79 ± 18.85	77.81 ± 18.83	PF group
70.02 ± 18.58	71.00 ± 18.62	72.93 ± 18.73	71.95 ± 18.75	73.93 ± 18.73	PK group
$p = 0.30$	$p = 0.29$	$p = 0.30$	$p = 0.31$	$p = 0.30$	Significance
Heart rate 20 min	Heart rate 15 min	Heart rate 10 min	Heart rate 5 min	Heart rate before surgery	
91.73 ± 18.74	88.61 ± 18.51	90.71 ± 18.69	76.61 ± 18.56	89.81 ± 18.83	PF group
87.93 ± 18.73	84.42 ± 17.97	86.73 ± 18.40	83.77 ± 18.49	85.93 ± 18.73	PK group
$p = 0.31$	$p = 0.25$	$p = 0.29$	$p = 0.30$	$p = 0.30$	Significance

groups in terms of the total dose of the consumed propofol. The intensity of the pain by the end of the procedure and an hour after it and the amount of apnea in the PK group were significantly less.

The results of this study indicated similar performance in a combination of PK and PF in terms of hemodynamic stability and sedation; although for measuring of the amount of pain and control of the apnea prevalence the combination of PK is more preferable. In an extensive study, Friedberg assessed a total of 1264 patients who had undergone 2059 procedure by 67 different surgeons during 5 years. All these patients receiving a pharmaceutical combination of PK have undergone the sedation along with spontaneous breathing. The results of their review showed that due to the oxygen saturation percentage drop, the procedure only in two patients was temporarily stopped. None of these patients needed to stay in the hospital due to pain after doing a procedure or nausea and vomiting. In addition, all the patients were satisfied with anesthesia method, and in none of them hallucination was seen [12].

It seems that addition of ketamine to propofol reduces the harmful heart effects of propofol, and propofol removes the psychosocial and nausea-inducing effects of ketamine. For this reason, the use of the combination of propofol and ketamine with different ratios has been accepted for doing sedation and analgesia in many surgeries such as cataract surgery [13].

In 2012, Khutia et al. compared a combination of propofol and fentanyl infusion with propofol and ketamine infusion in the pediatric short-term procedures. In their study, in the PF group more hypotension was seen compared with the PK group that was statistically significant as well, and this result is different with our study because hemodynamically differences were not observed in our study [14].

The difference between our study with other studies is that while the comparison between the two drugs compound has been applied in other studies for only children, our study has investigated its application in the endoscopic procedures for adults.

A question that can be raised is that can propofol be enough alone to make sedation or it is better to use an auxiliary medicine along with it? Different studies investigated this issue; some believe that the use of medication such as ketamine with its analgesic effect is able to reduce the consumption of extra propofol and consequently it can reduce the respiratory depression caused by propofol [15]. On the other hand, David and Shipp's study shows that the use of ketamine along with propofol has an effective role in reducing respiratory effects; however, it confirms the point that with the consumption of ketamine needs to an extra dose of propofol can be reduced and also a deeper sedation can be occurred [16]. In addition, in terms of the hemodynamic changes Phillips et al. showed that the use of ketamine provides a better hemodynamic stability [17].

Several studies agree with the use of ketamine to reduce the need of propofol and increase the depth of the anesthesia; furthermore, in our study, differences was not observed between two groups for additional doses of propofol , which can be concluded that both combinations have the ability to perform similar sedation in these cases.

Other indicators have been examined in some studies as well; for example, in a study by Shah et al., the satisfaction of patients and physicians was examined and that the results showed that a combination of ketamine–propofol is more acceptable than propofol [18] and or an assessment of recovery time in a study showed that the combination of PK compared with a combination of PF, has longer recovery time [14].

When talking about ERCP its complications also should be detected, an important problem, which might not be considered. The patient's pain during ERCP is important because studies show that pain while performing ERCP has a great relationship with its complications such as the occurrence of pancreatitis, as the most common complication of ERCP.

Hence, preparing a proper diet for pain control as a factor that causes side effects [19] is an important component of the sedation [20]. In this study, the pain of patients was studied; according to data analysis, a combination of PK is more appropriate in controlling the pain, and also the amount of apnea is less by this combination, so it can be concluded that a combination of PK generally is more efficient and safer in the ERCP procedure.

Conclusion

A comparison between the two drugs combination shows that while both groups were similar in terms of the hemodynamic and sedation criteria, because of the lower amount of pain and apnea in the PK group, the mentioned combination generally in the ERCP procedure is more efficient and more secure.

In the end, the broader spectrum studies are recommended for investigating and comparing other medicinal combinations and their effects to perform more secure sedation.

Financial support and sponsorship

Financial support was provided by Ahvaz Jundishapur University of Medical Sciences and Pain Research Center, Imam Khomeini Hospital, Ahvaz, Iran.

Conflicts of interest

There are no conflicts of interest.

Acknowledgment

The paper was issued from the thesis of Dr. Sanaz Nourizadeh. Hereby, we acknowledge the deputy vice-chancellor for research and technology affairs of Ahvaz Jundishapur University of Medical Sciences.

REFERENCES

[1] Akin A, Esmaoglu A, Tosun Z, Gulcu N, Aydogan H, Boyaci A. Comparison of propofol with propofol–ketamine combination in pediatric patients undergoing auditory brainstem response testing. Int J Pediatr Otorhinolaryngol 2005;69:1541–5.

[2] Krauss B, Green SM. Sedation and analgesia for procedures in children. N Engl J Med 2000;342:938–45.
[3] Joo JD, In JH, Kim DW, Jung HS, Kang JH, Yeom JH, et al. The comparison of sedation quality, side effect and recovery profiles on different dosage of remifentanil patient-controlled sedation during breast biopsy surgery. Korean J Anesthesiol 2012;63:431–5.
[4] Akcaboy ZN, Akcaboy EY, Albayrak D, Altinoren B, Dikmen B, Gogus N. Can remifentanil be a better choice than propofol for colonoscopy during monitored anesthesia care? Acta Anaesthesiol Scand 2006;50:736–41.
[5] Lichtenbelt BJ, Mertens M, Vuyk J. Strategies to optimise propofol-opioid anaesthesia. Clin Pharmacokinet 2004;43:577–93.
[6] Disma N, Astuto M, Rizzo G, Rosano G, Naso P, Aprile G, et al. Propofol sedation with fentanyl or midazolam during oesophagogastroduodenoscopy in children. Eur J Anaesthesiol 2005;22:848–52.
[7] Moerman AT, Struys MM, Vereecke HE, Herregods LL, De Vos MM, Mortier EP. Remifentanil used to supplement propofol does not improve quality of sedation during spontaneous respiration. J Clin Anesth 2004;16:237–43.
[8] Koo SW, Cho SJ, Kim YK, Ham KD, Hwang JH. Small-dose ketamine reduces the pain of propofol injection. Anesth Analg 2006;103:1444–7.
[9] Akhondzadeh R, Runassi N. Evaluation of analgesic effect of the ketamine on pain injection of propofol in patients undergoing general anesthesia 2014;3:72–5.
[10] Akhondzade R, Pipelzade MR, Gousheh MR, Sarrafan N, Mahmoodi K. Comparison of the analgesic effect of intra-articular and extra-articular injection of morphine and ketamine compound in arthrotomy lower limb surgery under spinal anesthesia. Pak J Med Sci 2014;30:942–5.
[11] Li L, Chen HZ, Long B, Meng LX. Preventive function of remifentanil to propofol injection pain. Pract Pharm Clin Remedies 2009;12:175.
[12] Friedberg BL. Propofol–ketamine technique: dissociative anesthesia for office surgery (a 5-year review of 1264 cases). Aesthetic Plast Surg 1999;23:70–5.
[13] Hui TW, Short TG, Hong W, Suen T, Gin T, Plummer J. Additive interactions between propofol and ketamine when used for anesthesia induction in female patients. Anesthesiology 1995;82:641–8.
[14] Khutia SK, Mandal MC, Das S, Basu SR. Intravenous infusion of ketamine–propofol can be an alternative to intravenous infusion of fentanyl–propofol for deep sedation and analgesia in pediatric patients undergoing emergency short surgical procedures. Indian J Anaesth 2012;56:145–50.
[15] Andolfatto G, Abu-Laban RB, Zed PJ, Staniforth SM, Stackhouse S, Moadebi S, et al. Ketamine–propofol combination (ketofol) versus propofol alone for emergency department procedural sedation and analgesia: a randomized double-blind trial. Ann Emerg Med 2012;59:504–12.
[16] David H, Shipp J. A randomized controlled trial of ketamine/propofol versus propofol alone for emergency department procedural sedation. Ann Emerg Med 2011;57:435–41.
[17] Phillips W, Anderson A, Rosengreen M, Johnson J, Halpin J. Propofol versus propofol/ketamine for brief painful procedures in the emergency department: clinical and bispectral index scale comparison. J Pain Palliat Care Pharmacother 2010;24:349–55.
[18] Shah A, Mosdossy G, McLeod S, Lehnhardt K, Peddle M, Rieder M. A blinded, randomized controlled trial to evaluate ketamine/propofol versus ketamine alone for procedural sedation in children. Ann Emerg Med 2011;57:425–33.e2.
[19] Nesioonpour S, Mokmeli S, Vojdani S, Mohtadi A, Akhondzadeh R, Behaeen K, et al. The effect of low-level laser on postoperative pain after tibial fracture surgery: a double-blind controlled randomized clinical trial. Anesth Pain Med 2014;4:e17350.
[20] Vandervoort J, Soetikno RM, Tham TC, Wong RC, Ferrari Jr AP, Montes H, et al. Risk factors for complications after performance of ERCP. Gastrointest Endosc 2002;56:652–6.