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ORIGINAL ARTICLE

Fentanyl-Propofol Versus Ketamine-Propofol Combination for Sedation and Recovery in ERCP: A Double-Blinded Randomized Clinical Trial

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ABSTRACT

Objective: The main goal of this study was to investigate the groups receiving fentanyl-propofol (fentP) against ketamine-propofol (ketP) in ERCP in terms of sedation, rescue sedation requirement, and recovery scores. Additionally, evaluated were the procedure's hemodynamic changes, postoperative pain score, complications, and endoscopist satisfaction.

Methodology: A double-blinded randomized clinical trial was undertaken at the Dr. Ruth K.M. Pfau Civil Hospital Karachi's endoscopic room (DUHS) for six months. By using OPEN EPI sample size calculator, sample size was calculated. A total of 124 patients for elective ERCP were randomized into two groups by SNOSE protocol. Groups A and B, fentanyl-propofol (fentP) and ketamine-propofol (ketP), respectively, each contain 62 patients. All patients were given a loading dose of propofol 0.5 mg/kg, followed by a 75 ug/kg/minute infusion. The group fentP received fentanyl 1ml/kg (1 ug/kg) and the group ketP received ketamine 1ml/kg (0.5mg/kg). Ramsay sedation scores, the necessity for rescue sedation, and the Aldrete score post-operatively were noted. Hemodynamics during surgery and complications were also noted.

Results: Sedation began noticeably earlier than usual in the group B at 0, 2 and 4 minutes (p-value <0.05), whereas sedation scores were higher in the group A at 8,10, and 15 minutes (p-value <0.05). Early sedation in the group B led to less consumption of rescue sedation doses (p-value <0.01). However, recovery scores were comparable in each groups (p-value >0.05).

Conclusion: We were able to conclude that during ERCP, ketP had a significantly faster sedative onset than fentP, with less complication and a quicker recovery.

Keywords: Propofol, KetP, FentP, ketamine, fentanyl, Sedation, Analgesia, ERCP, Monitored Anesthesia care.

INTRODUCTION

Better patient compliance and comfort during the surgery are guaranteed by closely monitored anaesthesia care. [1, 2] ERCP involves sedation, by lowering pain, discomfort, and stress, this helps patients tolerate unpleasant and time-consuming procedures (like ERCP). [3,4] Additionally, they can make the task of the endoscopist simpler and reduce the risk of harm during ERCP. [1,5,6] Adverse intraoperative and postoperative events that have been recorded during sedation for ERCP include hypoventilation, hypoxemia, respiratory arrest, airway obstruction, dysrhythmias, hypotension, and vasovagal episodes. [1,4,5]

The gold standard diagnostic and therapeutic approach for pancreaticobiliary diseases is the ERCP, which is frequently carried out in daycare. [2] Through ERCP, procedures like stenting, stone removal, pancreatic-biliary tract visualization, laser lithotripsy, and sphincterotomy can all be carried out. [3,6] It is necessary to have a sufficient depth of sedation or general anaesthesia for immobility, analgesia, and patient comfort. [2,7] Due to the confined access to the airway prone and semi-prone position, airway management can turn out to be difficult.[6]

The ideal sedative–analgesic mixture ought to preserve a patient's hemodynamic status and ought to cause no breathing depression, a quick onset and reversal to initial values, and a small occurrence of postoperative nausea and vomiting.[1,2,6]

Several pharmacological medicines, including dexmedetomidine, fentanyl, ketamine, and propofol, are now widely accessible, taking into consideration short induction, rapid recovery, and lessening complications associated with using a single drug.[6] Additional small doses of supplementary medicines example ketamine and fentanyl are recommended as propofol, if administered in excess to deepen anaesthesia can have significant cardiac adverse effects. [8]

Ketamine, phencyclidine derivative, is a preferable alternative to opioids because of its exceptional ability to generate analgesia without respiratory depression. [5] Furthermore, because of the actions of local anaesthetics, it can currently lessen the discomfort of propofol injections. [5,6,9]

The popular Ketofol protocol is extensively used due to the paucity of research and clinical experience with fenofol.[10] Given the limited availability and consumption of opioids in our society, we might want to evaluate fentanyl and ketamine in combo with propofol as our rationale. The findings of this study may influence the formulation of new regional guidelines for the combination of drugs that is usable in place of fentanyl in sedative techniques for ERCP procedures with fewer complications and side effects.

Using a modified Ramsay scale, the primary endpoint compared the effects of fentP and ketP combinations on sedation and recovery. The secondary endpoint was hemodynamic changes during the procedure, postoperative pain score, complications, and endoscopist satisfaction.

METHODOLOGY

After approval of research synopsis from the College of Physicians and Surgeons of Pakistan (Ref: CPSP/REU/ANS-2017-183-1736, REU number 38795), This double-blinded, randomised clinical trial was undertaken at the Dr. Ruth K. M. Pfau Civil Hospital in Karachi from September 2019 to March 2020 in the endoscopic suite. The study included a total of 124 patients with hepatobiliary diseases who were sent to Dr. Ruth K.M. Pfau Civil Hospital Karachi for elective ERCP. Sample size was calculated by openEpi version 3 by employing Mean ± SD(M1) of Ramsay score at 4min of group PF= 4.17±0.45 [6] and Mean ± SD(M2) of Ramsay score at 4min of group PK= 4.43±0.57.[6] Confidence level of 95% and power of 80% was taken. Sample size came out to be 62 patients in each group. Sampling technique was Consecutive non-probability sampling technique. To avoid drop outs, total 170 patients were enrolled to determine their eligibility.

Only ASA I and II patients with a BMI of less than or equal to 25 kg/m2 and aged 18 to 50 years, regardless of gender, were scheduled for ERCP. Patients who refused to participate in the trial or had a history of medication allergy, cardiac disease, difficulty breathing, acute GI haemorrhage, prior GI surgery, or were pregnant or nursing were also not allowed to participate. Patients with a history of drug dependence and those requiring procedures that took longer than an hour were also not eligible. Patients fulfilling the inclusion criteria, had been provided relevant information regarding the study before taking written informed consent by the primary investigator. All giving written informed consent were randomized into one of the study arms by the study researcher via sealed envelope method. Information had been kept confidential. An experienced endoscopist with at least 10 years of ERCP experience and a qualified anesthesiologist with at least 4 years of experience performed each ERCP. Under the direction of the principal investigator, the research study pharmacist made two syringes labelled study medications A (fentP) and B (ketP), which contained fentanyl and ketamine, respectively. Syringe A contained fentanyl 250 ug diluted in 250 ml of normal saline (1 ug/ml of fentanyl) and syringe containing ketamine 125 mg and normal saline 250 ml (0.5 mg/ml of ketamine) was prepared with label B and After labelling, a serial number was assigned to each syringe. The provided sealed envelope by DUHS Clinical research unit with arm allocation provision held the drug protocol. The envelopes followed the SNOSE protocol (i.e. sequentially numbered, opaque sealed envelopes). Patient record number, date was noted on envelope and signed by research nurse. Carbon paper was used to transfer data allocation paper inside that was dispatched to the ERCP suite.

A detailed pre-anesthetic evaluation was done before surgery day.

Standard noninvasive blood pressure, continuous three-lead electrocardiography, and oxygen saturation (SpO2) monitoring were applied and after application baseline readings of MAP and HR were noted, a large-bore intravenous line was cited by research nurse, and injection ringer lactate was attached. Both groups received 1-mg midazolam in the pre-anesthesia area. A loading dosage of propofol of 0.5 mg/kg was given when the patient was brought to the procedure suite and positioned for ERCP, and then a 75 ug/kg/minute infusion was started. The research medicines were to be administered by the consultant anesthesiologist at a dosage of 1ml/kg. Fentanyl 1 mg/kg (1 ml/kg) was administered to group A (fentP), and ketamine 0.5 mg/kg (1 ml/kg) was administered to group B (ketP). Heart rate and MAP were again noted 1min after study drug infusion completed (noted as point 0) and at 10 minutes after the start of the procedure. The Modified Ramsay sedation score was noted at point 0(1 min after study drug infusion completed), 2nd, 4th, 8th, 10th, 15th, and 20th minutes of start of procedure, and then every 5 minutes until the procedure was completed, sedation was measured on modified Ramsey sedation score (1= awake and alert and 8=unresponsive).

In the event that the modified Ramsay Sedation Scale score was less than two, propofol (20 mg) was administered as a rescue dosage. Additionally, highlighted was the need for propofol rescue doses. Oxygen was given using a nasal cannula during ERCP. In situations of loss of consciousness (based on the modified Ramsay scale), respiratory depression, Sp02 of less than 90%, or a halt of respiratory effort for longer than 10 seconds, the drug infusion was stopped and jaw-thrust maneuver and mask ventilation were initiated. A complication was noted for the event. The patient was intubated and removed from the research if the apnea persisted in spite of therapy. Another main goal was the duration it took the patient to score a 9 on the Aldrete scale for recovery. The patient was released 20 minutes later with an Aldrete score of 9. At the time of arrival in recovery and at the time of discharge from recovery, the effectiveness of analgesia was evaluated after the procedure using a VAS scale of 0 to 10, with 0 being the least painful and 10 representing the most painful. During the surgery and afterward in the PACU, the patient was monitored for any drug-related side effects, such as bradycardia, hypotension, and hypertension, and was treated appropriately. The surgeon's satisfaction and the length of the procedure were recorded thereafter.

The data was all entered into the statistical analysis programme Statistical Packages for Social Science (V.20, SPSS Inc., Chicago, IL, USA). Age, BMI, the Ramsay sedation score, the Aldrete score, the visual analogue score, the MAP, heart rate, recovery time, and operation length were quantitative factors that were measured as mean and standard deviation. The frequency and percentage of qualitative characteristics such as gender, ASA status, need for rescue drugs and surgeon satisfaction were measured (ordinal scale). An independent T-test was used to compare the Ramsay scores at 0 min, 2 min, 4 min, 8 min, 10 min, 15 min, and 20 min between the two groups. Stratification was used to control effect modifiers such gender, age, BMI, ASA status, and procedure length. A P-value of 0.05 or less was considered statistically significant when performing a post-stratification independent T-test.

RESULTS

128 patients were enrolled after 170 patients fulfilled eligibility screening. The most frequent grounds for exclusion were lack of interest (n=17), presence of significant comorbidities (n=11), lack of informed permission (n=10), and BMI >25 mg/kg2 (n=4). Following randomization, two patients in group fentP and one in group ketP withdrew from the study. One patient in the ketP group declined to participate after giving her consent, and the endoscopist cancelled the procedure for the other patient. Table 1

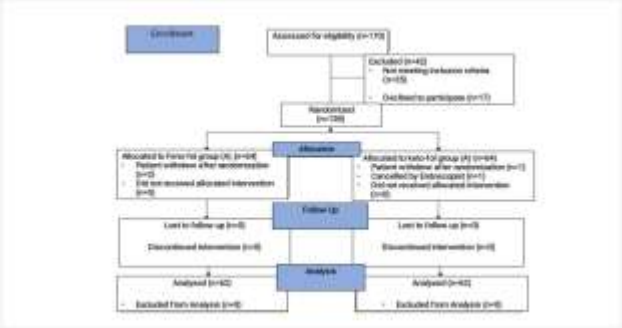

Figure 1: Consort Flow Diagram

124 patients—62 in each group—were successfully completed the trial. Table 1 compares patient characteristics in terms of gender, age, baseline MAP, HR, and BMI between the two groups.

The American Society of Anesthesiology (ASA) categorized the majority of patients as class one (85 percent). Upper endoscopy was most frequently performed for therapeutic rather than diagnostic objectives (65.3%).

Table 1: Comparison and distribution of patient characteristics (gender, age, BMI and baseline MAP & HR)

Variables			Groups		P-value
			Group A (FentP)	Group B (KetP)	
Gender	Male	Total no.	30	22	0.145
		Percentage	48.4%	35.5%	
	Female	Total no.	32	40	
		Percentage	51.6%	64.5%	
Baseline	MAP (mean mmHg)		91.05 ± 28.94	95.14 ± 20.13	0.59
	HR (mean bpm)		84.1 ± 15.15	85.02 ± 15.2	0.7
Age (in years)	Mean		38.68±12.7	38.90±13.1	0.06
Body mass index	Mean		24.54±2.7	25.22±2.5	0.140

At 0, 2, 4, 8, 10, and 15 minutes, there was a significant difference in the Ramsay score, but after 20 minutes, there was no evident difference between the groups. (P=0.2). (Table 2)

Ramsay scores at 0, 2, and 4 minutes in group A (fentP) are significantly lower, suggesting that patients in group B (ketP) experience early sedation (p-value 0.000). However, the fentP group had significantly greater sedation scores at 8, 10, and 15 minutes (p-value 0.05). There was no difference between the two groups in terms of recovery time. Although the differences between the two groups were not statistically significant (p-value >0.05), fentP caused a delayed recovery.

Table 2: Data and comparisons between the two groups' results (Ramsey score and recovery time):

Variable	Groups	N	Mean	Standard Deviation	P-values
Ramsey score					
0 minute	A (FentP)	62	4.16	1.162	0.00
	B (KetP)	62	5.27	1.416	
2 minutes	A (FentP)	62	4.90	0.53	0.00
	B (KetP)	62	5.69	0.66	
4 minutes	A (FentP)	62	5.05	0.38	0.00
	B (KetP)	62	5.92	0.27	
8 minutes	A (FentP)	62	5.85	0.35	0.00
	B (KetP)	62	5.10	0.78	
10 minutes	A (FentP)	62	5.84	0.37	0.00
	B (KetP)	62	5.53	0.93	
15 minutes	A (FentP)	62	4.73	0.50	0.03
	B (KetP)	62	4.24	0.46	
20 minutes	A (FentP)	62	4.70	0.55	0.2
	B (KetP)	62	4.61	0.82	
Recovery time (in minutes)	A (FentP)	62	14.40	2.03	0.47
	B (KetP)	62	14.14	1.93	

At baseline, point 0 (1 minute after study medication infusion), and point 10 (10 minutes after procedure start), hemodynamics between the two study groups were evaluated. At baseline, points 0 and 10, heart rate and MAP did not differ significantly (P-value > 0.05); but, at 10 minutes, MAP in group A (FentP) was lower than baseline (79.64 mmHg vs 91.05 mmHg); this suggests that ketP provides better hemodynamic stability than fentP, but the difference was not statistically significant.

There was a significantly reduced requirement of rescue sedation in group B (p-value <0.01). Figure 2

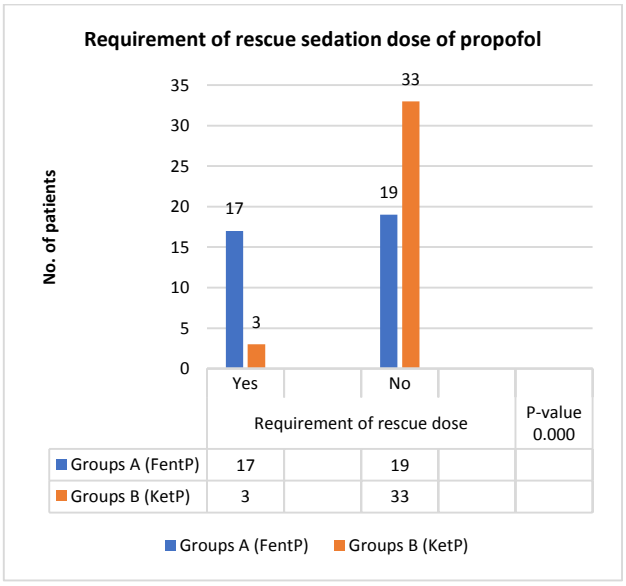

Figure 2: Comparison Of Propofol rescue dose requirements in Group A and Group B

The average pain score at entry into recovery (P-value: 0.06) and at the time of shifting from recovery was lower in the fentP group than in the ketP group when pain score and pain intensity were compared between the study groups (P-value: 0.000). As demonstrated in Figure 3, a comparison of the intensity between the two study groups showed that overall, fentP and ketP both have more potent pain-relieving capabilities.

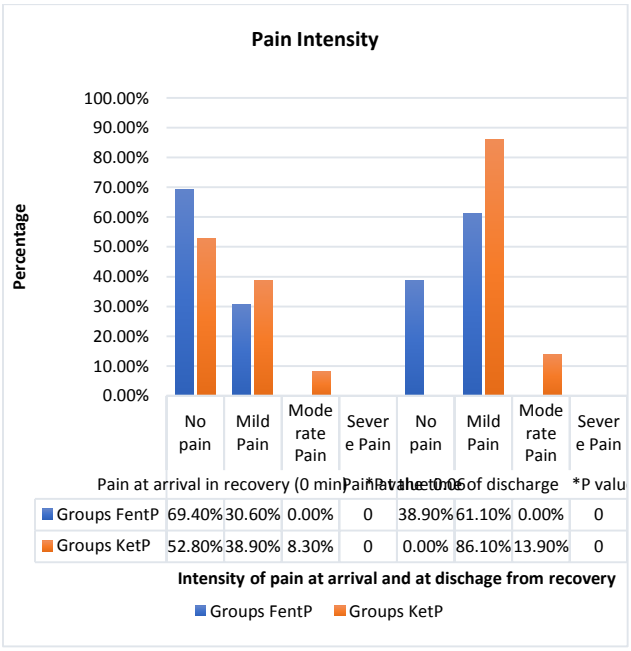

Figure 3: Comparison Of pain intensity scores between two groups

FentP and ketP demonstrated comparable non-significant results when comparing surgeons' satisfaction and operation length (p-value 0.527). Of noted complications, there was more frequency of apnea in fentP group (7 vs 5 patients) than ketP group (p-value = 0.56).

DISCUSSION

For diagnostic and therapeutic ERCP, adequate patient sedation is required. Propofol intravenous sedation is more effective and safe when administered under close patient monitoring, and it is associated with faster post-procedure recovery, however, it is well known that propofol alone is ineffective because it does not relieve pain.[7,8]

Various studies [4,5,11,12] using a combination of medications for different procedures have recorded sedation and recovery responses, but little is known about ERCP in the Southeast Asian population, which was the primary goal of our investigation.

Unlike the findings of multiple researcher[3,6,7,13], who found no significant differences in sedation scores while comparing these drugs, we have found that KetP had a faster onset and higher level of sedation during the initial phase of the procedure (0-4 mins), while fentP had better sedative properties during the mid-phase (8-15 min). After 20 minutes, there was no noticeable difference. This could be due to ketamine's shorter duration of action. Several investigations[5,8,11,12] have found similar outcomes.

In our study, a combination ketP (ketamine and propofol) was found to significantly minimize overall propofol use, despite the fact that earlier research had found no significant differences in additional doses of propofol between the two groups.[3,7]

Similar to our study, results that were found by Gorji et al[6] and Gad el Rab et al[7] showed that both groups have comparable recovery times, however, other trials have found considerable early recovery in the fentP group.[4,8] In the ketP group, Ayodghan[14] et al discovered remarkable early recovery. In previous research,

surgeons were equally satisfied with both medications group as in our study. [6,8]

According to the current study, ketP provided improved hemodynamic control since at 10 minutes after the procedure began, MAP in the FentP group was lower than the initial MAP. However, the results were not statistically significant. Ebru et al.[2] and Gad al Arab et al.[7], concluded results in concordance with our results. Due to the sympathomimetic effects of ketamine, several studies suggested that fentanyl had better hemodynamic control than ketamine; nonetheless, they recovered to baseline values postoperatively.[8]

Pain following ERCP was less in the FentP group than in the KetP group at the time of recovery and discharge in our investigation, which is consistent with the findings of Gorji et al.[6], and Nazemroaya et al. [9] trials. In contrast to our findings, Kurdi et al.[11] discovered that the KetP group had improved pain control.

While numerous studies have found that the fentP group had a higher rate of apnea, which could contribute to respiratory depression,[3,4,6,7,8,12,14] the results in our study group were not significant. As a result, a combination ketP (ketamine and propofol) may be recommended for our patients.

The strength of our study is that it's a double-blind randomized control on a specific patient population with minimum biasness.

As a single-centered study with a small sample size since some patients did not meet the inclusion criteria, our study had some drawbacks. Intraoperative and post-recovery pain scores were not noted. Despite the continuous monitoring used in other research, hemodynamics was only noticed at two times, giving insignificant results even though there was a decrease in MAP after 10 minutes with the use of fentanyl in our trial. The patient's experience and any adverse effects, such as nausea, vomiting, and hallucinations, were not recorded. They could have an impact on the criteria for discharge and length of stay. This study opens the door for future research using the same medication combinations or alternative drug combinations for various endoscopic procedures or procedures needing simply sedation. This study may serve as a springboard for additional research in a different patient population, such as pediatrics.

CONCLUSION

Although fentanyl-propofol produces better postoperative pain scores, ketP (ketamine-propofol) offers greater sedation, faster recovery with better hemodynamics, and fewer complications. In terms of procedure time and endoscopist satisfaction, these combinations are equivalent. Based on the results of this study, we will advise using ketP for ERCP. Ketamine and propofol together are advised for patients at risk for respiratory depression. Additional research can be done to examine the post-procedure side effects of these medication combinations, including as nausea, vomiting, and hallucinations, which may show additional advantages of fentP over ketP.

Recommendation: By the end of this study, we can confidently suggest that a ketamine-propofol combination may be used to lessen respiratory and hemodynamic abnormalities during ERCP in those with underlying comorbidities.

Conflicts of interest: No conflict declared by the authors

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Ethical Approval: Approval from College of physician and surgeon of Pakistan (CPSP)

Ref: CPSP/REU/ANS-2017-183-1736

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