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Original Article

Sedation for Endoscopic Retrograde Cholangiopancreatography (ERCP) – A comparative study between propofol-fentanyl with Propofol-fentanyl-ketamine Combination

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Abstract

Background: *Endoscopic retrograde cholangiopancreatography (ERCP) is a painful and long procedure requiring transient deep sedation and analgesia. The purpose of our study was conducted to evaluate and compare the sedation efficacy and propofol-fentanyl-ketamine could be a better regime than propofol-fentanyl for sedation in ERCP.* ***Material and Method*** *100 ASA II-III patients, 18-60 yrs old schedule for planned ERCP procedure in the Dept. of Hepatobiliary Surgery & Gastroenterology of BSMMU. They were selected by inclusion and exclusion criteria and allocated to one of the two groups: group PF (n=50) and group PFK (n=50) by randomization. Group PF received propofol 1mg/kg + fentanyl 1µg/kg and group PFK received propofol 1mg/kg + fentanyl 1µg/kg + ketamine 0.25mg/kg and subsequent doses of propofol were given as a dose 0.5mg/kg accordingly. Recovery time was assessed from the discontinuation of procedure to modified aldrete recovery score ≥ 9. All result was expressed as number or mean ± SD or in frequencies (percentage) as applicable. The result were compiled and analyzed using SPSS-16, Student unpaired t test, Chi-square test.* ***Result*** *The average age of group PF and group PFK study population was 40.16(±9.34) and 44.56(±3.75) respectively whereas there average weight in initial group was 60.83(±5.54) and in the second group 58.39(±7.37). Male patients were more in both the groups. Group PF belongs to ASA II 35(70%) patients and ASA III 15(30%) patients whereas group PFK belongs to 30 (60%) and 20(40%) patients respectively. In the peroperative vital parameters, sedation related side effect as hypotension 10(20%) patients was observed in group PF and 3(6%) patients was observed in group PFK which was found statistically significant (p value 0.032) and apnea has been found 7(14%) patients in group PF and 2(4%) patients in PFK group. Which was found statistically significant (p value 0.018). No post-operative vital parameters were found statistically significant (p value >0.05). Total doses of propofol consumed was significantly higher in group PF (p<.05) than group PFK (190.45±12.8 mg and 140.67 ± 10.23mg). Time needed to achieve Aldrete recovery scale score of 9 in between PF group and PFK group were 18.25±6.76 min and 12.24 ±5.45 min respectively and the result found statistically significant (p value <0.001).* ***Conclusion:*** *Propofol-fentanyl-ketamine provided better sedation quality over propofol-fentanyl combination in term of less side effects, early recovery, cost effectiveness in patients undergoing ERCP procedure.*

Key wards: *Sedation, ERCP,Propofol-fentanyl, Propofol-fentanyl-ketamine combination*

Introduction: Endoscopic Retrograde Cholangio pancreatography (ERCP) is a minimal invasive procedure that helps endoscopist to diagnose primarily the hepatobiliary-pancreatic pathology as well as some effective therapeutic procedure.[1] This is the radiographic examination which is done via endoscopicallycannulated duodenal papilla. By insertion of duodenoscope and filling the stomach and small intestine with air or carbon dioxide; the procedure is being started. There after cannulation

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done to access the duodenal papilla. Then contrast media is injected through the catheter under fluoroscopic guidance. Biliary or pancreatic duct system can be visualized. Sphincterotomy of the bile or pancreatic duct might be performed in order to facilitate stent placement or removing of the stones. Existing biliary/pancreatic stricture may be dilated with the use of hydrostatic wire-guided balloon. Dilation of pancreatic duct is often very painful while sphincterotomy and biliary dilations are significantly less painful. Other stages of ERCP are not very much painful. ERCP duration differs markedly (range 10-120 minutes) depending on expertise of man behind the machine and complexity of procedure. In most difficult cases, such as altered gastrointestinal anatomy, duration of ERCP usually exceeds 90 minutes [2]

ERCP is commonly performed for diagnosis and management of choledocholithiasis, primary sclerosing cholangitis, chronic pancreatitis, biliary and pancreatic neoplasm, and biliary perioperative complications. ERCP has been practiced for over 30 years being firstly described in 1968[3]

As ERCP is a complex, lengthy and potentially uncomfortable procedure that needs moderate of deep sedation or even general anesthesia to achieve success and patients' compliance.[4,5] Between them, general anesthesia is usually useful in failure of sedation and in case of children. On the contrary, sedation is an effective measure to reduce patients' consciousness, anxiety, discomfort and pain.

Sedation may be defined as a drug-induced depression in the level of consciousness whereas deep sedation may be defined as a drug-induced depression of consciousness which patients cannot be easily aroused but respond purposefully after repeated verbal or painful stimulation.[6,7] Deep but conscious sedation in ERCP should be maintained as for assurance of the maintenance of cough reflex, spontaneous breathing and cardiovascular stability.[8]

But different opinions for sedation procedure about the sedative agents are going on whole over the world. For that reason, different studies are also going on about the combination of sedative agents. There are much unpredictability of drug interactions and unwanted effects made the debate more complicated.

Among them, Propofol (2,6 diisopropylphenol) is a phenol derivative. It is a short acting potent hypnotic drug (t1/2 distribution 2-4 min) introduced by Kay and Rolly introduced propofol in 1977. It shows also a more rapid recovery time (10-20 min).[9,10] But on the contrary, it may cause respiratory depression, airway obstruction and pain at the site of injection.[11]

Fentanyl is a synthetic opioid analgesic drug, derived from pethidine and it is 100 times as potent as morphine and as a part of balanced anesthesia it relieves pain, reduces somatic and autonomic response to airway manipulation, provides haemodynamic stability and lesser respiratory depression.[12]

Ketamine is an NMDA receptor antagonist. It has the ability to bind to opioid receptors and sigma receptors. These bindings can make a condition which is termed as, "Dissociative anesthesia"[13] Ketamine has significant disadvantages like hypertension, tachycardia, psychomimmetic effect and long recovery time.[14] Combination of Propofol and Fentanyl are a preferred regimen for sedation during ERCP procedure. Here both the drugs are short acting where Propofol produces sedation and amnesia and Fentanyl produces analgesia and sedation.[15,16]

On the other hand, Ketamine in combination with Propofol can achieve satisfactory analgesia and relatively comfortable respiration. The sympathomimmetic actions of Ketamine may be effective in counteracting the hemodynamic depression of Propofol. [17,18]

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Thus the combination of Propofol and Ketamine may minimize the need for supplemental opioid analgesics and has the potential to provide better sedation with less toxicity than either drug alone.

The main objective of this study is to compare the sedation efficacy, patients and endoscopist's satisfaction, haemodynamicparameters, sedation related untoward effects, recovery score and total drugs consumption between propofol-fentanyl with propofol-fentanyl plus low dose ketamine combination for sedation during ERCP in a randomized fashion.

RATIONAL OF THE STUDY

For successful ERCP, moderate to deep level of sedation needed for throughout the procedure. Now a daypropofol is widely used for sedation in ERCP. But it has no analgesic property. So patients undergoing ERCP under propofor alone could be suffered from pain and high doses related adverse effect like hypotension and respiratory depression. Highly potent short acting opioid like fentanyl is usually added with propofol to make a balance sedation and anaesthesia. Combination of sedative drugs reduce its does that also reduce its does related adverse effects. Again which combination is better is a long term question. Propofol and fentanyl both causes more or less cardio-respiratory depression. So combined administration of these two drugs in ERCP might causes hypotension and desaturation. As we know ketamine is a potent bronchodilator, maintain spontaneous breathing, and have sympathomimetric actions, so we hypothizedthat low dose ketamine in combination with propofol-fentanyl might have been providing adequate analgesia and would prevent respiratory related desaturation and might be effective in counteracting the haemodynamic depression of propofol and fentanyl As well as early recovery for relatively decrease total propofol-fentanyl consumption. There is relatively lack of such study in Bangladesh. So the outcome of the study is expected to ensure the anesthesiologists as well as physicians to find out a better combination of sedation for their patients undergoing ERCP.

OBJECTIVES:

General Objectives:

To compare the advantage of addition of low dose ketamine with propofol and fentanyl over propofol and fentanyl combination for sedation in ERCP.

Specific Objectives:

1) To evaluate sedation efficacy.
2) To evaluate haemodynamic stability.
3) To compare the patients and endoscopist's satisfaction.
4) To compare the perioperative untoward effects.
5) To compare the recovery status and total drugs consumption.

MATERIALS AND METHODS

Place of study

Bangabandhu Sheikh Mujib Medical University, Shahbagh, Bangladesh.

Period of study

September, 2019 to February, 2020.

Study population

This study was designed to be conducted among the indoor patients of general surgery and Hepatobiliary Surgery Ward and Gastroenterology Department who underwent ERCP for biliary and pancreatic pathology in BSMMU, Shahbagh, Dhaka.

Study design

This is a Randomized Controlled Trial. There were 2 groups for this comparative study.

Group PF: (Patients were sedated here by Propofol plus Fentanyl)

Group PFK: (Patients were sedated here by Propofol, Fentanyl and Ketamine)

Sample size and statistical basis of it

Sample size determination depends on time and resources. Estimated population will be calculated by using the following statistical formula:

$$n = \frac{P^1 (1- P^1) + P^2 (1- P^2)}{(P^1 - P^2)^2} \times (Z\alpha + Z\beta)^2$$

Where

n= the desired sample size
P1= proportion of patients developing outcome in control group
P1 = proportion of patients developing outcome in treatment group.
Zα = Z-value (two tail) at a definite level of significance.
Zß= Z-value (one tail) at a definite level of significance.
So from the previous study of

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P1 = 67% =0.67

P2 = 92% = 0.92

Zα = 1.96 } at 5% level of significance &

Zß= 1.28 } 90% power

$$n=\frac{0.67(1-0.67)+0.92(1-0.92)}{(0.67-0.92)^2}\times(1.96+1.28)^2$$

$$n=\frac{0.2211+0.0736}{0.0625}\times(3.24)^2$$

n= 49.5

approx. 50. (total sample size 50x2= 100)

So, Group PF = 50

Group PKF = 50

Methods of estimating sample size and the detailed samplingtechniques

The sample size has been selected by using the formula

$$n=\frac{P^1(1-P^1)+P^2(1-P^2)}{(P^1-P^2)^2}\times(Z\alpha+Z\beta)^2$$

Group samplings were selected by randomization by lottery method.

Inclusion Criteria

1) Age ranging between 18 - 60 years.
2) Both genders eligible for the study.
3) Patients scheduled for elective ERCP.
4) ASA grade II & III

Exclusion Criteria

1) Patient not willing to participate in study and not co-operative.
2) Patients with history of sulfate, egg or soy bean allergy,
3) Patients undergoing emergency ERCP
4) Patients with anatomic airway abnormalities.
5) Patients with severe cardiovascular and respiratory diseases like uncontrolled hypertension, ischemic heart disease, aortic stenosis, left ventricular failure, presence of arrhythmia, atrioventricular conduction block, COPD,
6) Morbidly obese patients.
7) Patients having Severe psychological disorder

Procedures of preparing and organizing materials

One hundred (100) patients were selected in the pre anaestheticcheck up room on the basis of inclusion and exclusion criteria who were scheduled for ERCP. They were divided into two groups, Group PF and group PFK. Verbal and a written informed consent were be taken from all selected patients. Patients were advised to fast for at least 8 hours before intervention. Premedication was not given to the patients. An 20G intravenous cannula were inserted on the dorsal side of the hand 45-60 minutes before the procedure and crystalloids infusion (like-Ringer lactate iv fluids) was started and continued according to requiring doses. Randomization was done by simple lottery technique preoperatively and ERCP procedures were performed by an experienced endoscopist/surgeon. In the ERCP room patients were attached with monitors and base line parameters such as pulse, Noninvasive blood pressure, respiratory rate, SpO_2, ECG were recorded. All patients were placed in left lateral semi prone position. All patients were given Oxygen (O_2) 2L/m via nasal cannula. Group PF (n=50) was administered fentanyl 1 µg/kg plus propofol 1mg/kg and Group PFK (n=50) was administered fentanyl 1µg/kg plus and propofol 1mg/kg and ketamine 0.25mg/kg. ERCP procedure was started by endoscopist/ surgeon after ensuring the sedation level of the patient, according to Ramsay sedation score 4 or 5, then subsequently propofol 0.5mg/kg was given according to the patient's response to sedation. If the patients were still show discomforted (moved or cried), fentanyl 0.5µg/kg was added. Throughout the ERCP procedure, the Ramsay sedation score was used to assess the sedation level and sedation was adjusted to target a score of 4 or 5. Medication doses, administration time and total procedure time were recorded. Drugs were administered by investigator and he was constantly available in the ERCP room and was observed and recorded patient's pulse, blood pressure, respiratory rate, SpO_2 and continuous ECG in lead II in every 5 minute and till the end of the procedure. During each procedure adverse events were noted. After completion of ERCP, patient was sent to post anaesthetic care unit (PACU) where patients was placed on left lateral recovery position. Patient's level of consciousness and all the previously said vitals parameters was recorded in every 5 minutes. Recovery status was assessed by Modified Aldrete recovery score. A full sets of resuscitation equipments including laryngoscope, endotracheal tube, suction apparatus, oxygen, a bag valve mask, appropriate size airway, defibrillators and resuscitation drugs including naloxone, atropine, adrenaline, flumazenil was available throughout the

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procedure and recovery room to combat any adverse event. Side effects during sedation or in the recovery room like desaturation, hypotension, arrhythmia, vomiting, agitation was observed, recorded and managed accordingly in both groups. All the events were recorded in the Data Collection sheet.

Procedures of data analysis and interpretation

In this clinical study, both manual and computer based statistical analysis of the data were done. Data were analyzed manually and then rechecked with SPSS-16 (Statistic package for social science) computer package programmer. The survey data were analyzed using both analytic as well as descriptive statistic. Such as; mean, SD, percentage, co-efficient of variation. Chi-square test and unpaired student's t-test. Level of significance will be set as <0.05 and p- value significance level will be considered as <0.05 Report was produced by computer based program- Microsoft Word, Power point, Photoshop, Adobe and other accessories.

RESULTS

The mean age and weight of the patients underwent ERCP with the sedation of propofol-fentanyl and propofol-fentanyl-ketamine was stated below. The age of patients in both groups were between 30 to 58 years, the mean age in group PF was 40.16±9.34 and group PFK was 44.56±3.76. The mean body weight in group PF and group PFK were 60.83±5.54 and 58.39±7.37 respectively. In the sex distribution, there were male predominance in both groups. Analyzing the ASA grading, both groups were ASA II predominance observed (Table-I). The p value was not significant.

Table-I: Patients characteristics between the groups (n=50 in each group)

SL	Demographic variables	Group PF (n=50)	Group PFK (n=50)	p value	Remarks
1.	Age in years	40.16±9.34	44.56±3.76	0.345	NS
2.	Weight in Kg	60.83±5.54	58.39±7.37	0.497	NS
3.	**ASA grading**				
	ASA II	35 (70%)	30(60%)	0.205	NS
	ASA III	15(30%)	20(40%)	0.301	NS
4.	**Sex**				
	Male	33(66%)	31(62%)	0.173	NS
	Female	17(34%)	19 (38%)	0.269	NS

Values are expressed as number and percentage over column total.

Statistical analysis was done by unpaired student's't' test (SL. 1 & 2) and by chi-square test (SL. 3 & 4).

Sex distribution in Group PF (n=50):

Out of 50 patients in Propofol-Fentanyl Group 17 was female and 33 were male.

Figure-IV: Sex distribution in Group PF (n=50)

Sex distribution in Group PFK(n=50):

Out of 50 patients underwent ERCP in Propofol-Fentanyl-Ketamine Group 19 was female and 31 were male.

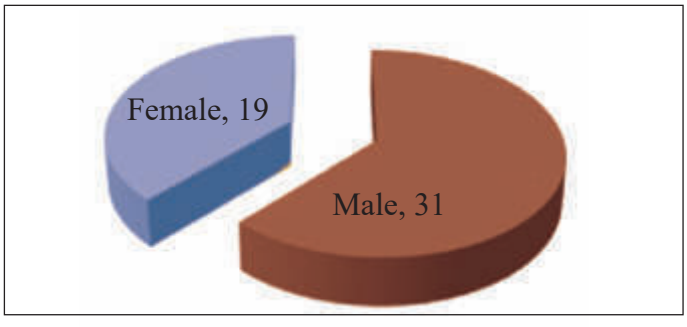

Figure-V: Sex distribution in Group PFK (n=50)

ASA grading of study population(n=50 in each group):

The patients with ASA grade II in PF and PFK group were respectively 35 (70%) and 30(60%) patients whereas ASA III in the said groups were 15(30%) and 20(40%) respectively.

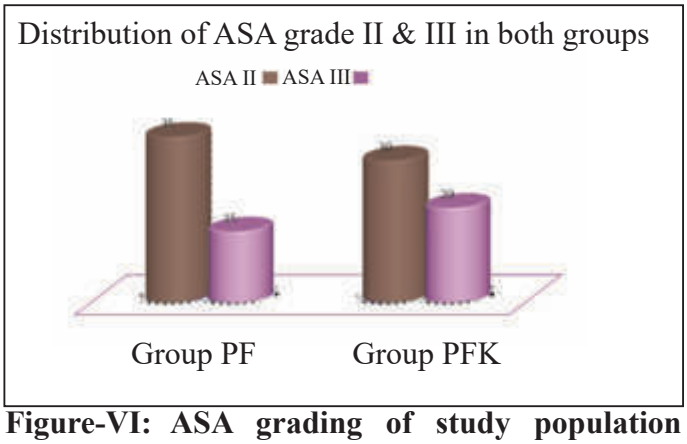

Figure-VI: ASA grading of study population (n=50 in each group):

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Co morbidities (n=50 in each group) :

Out of 50 patients in Group PF 12 (24%) had the associated comorbidities whereas out of 50 patients in PFK 15 (30%) had the same types of comorbidities. The including co-morbidities were IHD, DM, CKD, Bronchial asthma etc.

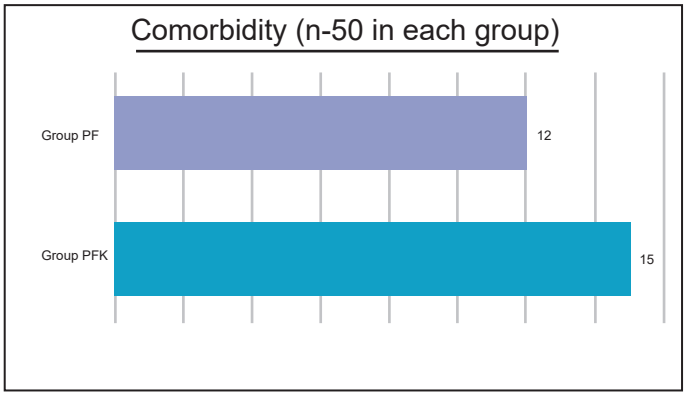

Figure-VII: Comorbidities (n=50 in each group)

Table-II: Changes of Systolic blood pressure at different time period of the studied groups

Change in systolic blood pressure (SBP) between two groups shown in Table-IV. Values are presented as mean±SD. After 5 minute of the procedure SBP was 110±7.52 in group PF and 115±3.91 in group PFK and at the end of the procedure it was 112±3.93 and 114±3.132 respectively but there was no significant different between the groups. The level of significance is p<0.05.

Time	Group-PF (n=50)	Group-PFK (n=50)	P value	Remarks
Baseline	126±6.36	124±5.966	0.192	NS
Before induction	127±6.12	125±3.54	0.178	NS
After 5 min	110±7.52	115±3.91	0.09	NS
After 10 min	114±1.31	117±3.53	0.101	NS
After 15 min	112±1.57	116±2.98	0.129	NS
After 20 min	111±1.26	115±3.95	0.102	NS
At the end of procedure	112±3.93	114±3.132	0.109	NS
In the recovery room				
After 5 min	117±3.92	118±1.57	0.201	NS
After 10 min	117±6.25	118±2.14	0.205	NS
After 15 min	119±5.27	120±1.22	0.109	NS
After 20 min	118±1.26	120±3.27	0.108	NS

Values are presented as mean ± SD
Statistical analysis was done by student's't' test.
Significant, p value < 0.05.

Table-III: Changes of Diastolic blood pressure at different time period of the studied groups

Diastolic blood pressure (DBP), after 5 minute of induction was 69.1±1.75 in group PF and 73.1±3.51 was group PFK and 73.4±3.91 and 74.9±4.12 was at the end of the procedure between the groups respectively. The mean of the diastolic pressure was noted lower in PF group than group PFK mainly after the induction of the procedure but there was no significant different between the groups. The level of significance is p<0.05.

Time	Group-PF (n=50)	Group-PFK (n=50)	P value	Remarks
Baseline	79.8±6.79	79.7±5.91	0.651	NS
Before induction	80.2±5.29	79.9±5.12	0.512	NS
After 5 min	69.1±1.75	73.1±3.51	0.095	NS
After 10 min	70.1±3.25	72.1±5.12	0.105	NS
After 15 min	72.3±3.12	73.1±1.91	0.309	NS
After 20 min	72.4±4.12	73.4±3.21	0.201	NS
At the end of procedure	73.4±3.91	74.9±4.12	0.301	NS
In the recovery room				
After 5 min	74.1±3.12	74.3±5.51	0.601	NS
After 10 min	74.4±4.12	75.3±4.98	0.201	NS
After 15 min	74.3±3.12	75.9±1.25	0.209	NS
After 20 min	74.9±1.25	75.7±2.35	0.193	NS

Values are presented as mean ± SD
Statistical analysis was done by student's't' test.
Significant, p value < 0.05.

Table-IV: Changes of Mean blood pressure at different time period of the studied groups

Mean blood pressure of group PF and group PFK after 5 minute of induction were 85±6.25 and 91±3.75. That was found statically significant (p value <0.05). Mean blood pressure remain comparably slight lower in group PF than PFK during the procedure as well as in postoperative recovery room.

Time	Group-PF (n=50)	Group-PFK (n=50)	P value	Remarks
Baseline	97±6.39	96±5.12	0.409	NS
Before induction	98±5.25	97±3.51	0.306	NS
After 5 min	85±6.25	91±3.75	0.045	S
After 10 min	86±3.29	90±6.12	0.09	NS
After 15 min	87±1.35	89±7.31	0.102	NS
After 20 min	86±6.51	88±5.25	0.205	NS
At the end of procedure	85±9.31	89±1.25	0.101	NS
In the recovery room				
After 5 min	86±5.12	88±1.25	0.107	NS
After 10 min	86±3.95	88±3.35	0.201	NS
After 15 min	86±4.32	87±6.35	0.201	NS
After 20 min	87±3.25	88±5.35	0.197	NS

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significant, p value < 0.05.

Table-V : Changes of pulse rate at different time period of the studied groups.

Changing in heart rate are showing in Table-II. The mean of the values of during procedure and during recovery was calculated and considered as mean±SD of the values. Heart rate was 77.2±10.12 in PF group and 78±10.24 in PFK group at the beginning of the procedure. 79.9±9.97 in group PF and 80.6±10.52 was in group PFK after the 5 minute of procedure. 78.2±4.10 and 80.2±3.46 was in group PF and group PFK after 5 minute of the end of the procedure. Mean of the heart rate of PFK group remain slightly higher in comparison to group PF but there was no significant different between the groups. The level of significance is p<0.05.

Time	Group-PF (n=50)	Group-PFK (n=50)	P value	Remarks
Baseline	77.9±9.84	78.1±11.43	0.312	NS
Before induction	77.2±10.12	78±10.24	0.301	NS
After 5 min	79.9±9.97	80.6±10.52	0.219	NS
After 10 min	78.4±7.85	79.1±8.53	0.196	NS
After 15 min	77.2±4.51	78.3±5.59	0.175	NS
After 20 min	79.1±3.53	80.2±4.25	0.297	NS
At the end of procedure	77.2±4.19	81.4±2.51	0.115	NS
In the recovery room				
After 5 min	78.2±4.10	80.2±3.46	0.182	NS
After 10 min	77.9±3.16	79.5±2.94	0.199	NS
After 15 min	77.7±2.90	79.9±2.13	0.213	NS
After 20 min	78.1±1.21	80.1±1.11	0.192	NS

Values are presented as mean ± SD
Statistical analysis was done by student's 't' test.
significant, p value < 0.05.

Table-VI : Changes of respiratory rate at different time period of the studied groups

There were no significant differences of respiratory rate between two groups. Decreased respiratory rate was observed in PF group than PFK group after 5 minute of induction, 12.9±1.28 and 14.2±1.53 were respectively but there was no significant different between the groups. The level of significance is p<0.05.

Time	Group-PF (n=50)	Group-PFK (n=50)	P value	Remarks
Baseline	16.6±2.51	16.1±1.91	0.105	NS
Before induction	16.6±2.92	16.5±3.27	0.109	NS
After 5 min	12.9±1.28	14.2±1.53	0.09	NS
After 10 min	13.9±1.53	14.2±1.39	0.101	NS
After 15 min	14.1±1.27	14.9±1.19	0.303	NS
After 20 min	15.1±1.25	15.6±2.56	0.401	NS
At the end of procedure	15.2±1.77	15.9±2.31	0.391	NS
In the recovery room				
After 5 min	14.3±1.57	15.2±3.24	0.293	NS
After 10 min	15.5±2.59	16.1±1.19	0.119	NS
After 15 min	14.7±1.32	15.1±1.35	0.137	NS
After 20 min	15.1±1.28	15.3±1.91	0.427	NS

Values are presented as mean ± SD
Statistical analysis was done by student's't' test.
Significant, p value < 0.05.

Table-VII: Changes of saturation at different time period of the studied groups

There is no significant difference of SPO_2 between the groups but after 5 minutes of induction, it was 94.41±1.01 for group PF and 96.31 ±1.02 for group PFK. All the time of procedure SPO_2 of group PF were slightly lower than group PFK but there was no significant different between the groups. The level of significance is p<0.05.

Time	Group-PF (n=50)	Group-PFK (n=50)	P value	Remarks
Baseline	97.31±1.05	97.34 ±1.05	0.315	NS
Before induction	97.31±1.06	97.34 ±1.07	0.299	NS
After 5 min	94.41±1.01	96.31 ±1.02	0.195	NS
After 10 min	96.31±1.05	97.34 ±1.11	0.201	NS
After 15 min	95.33±1.21	96.14 ±1.41	0.295	NS
After 20 min	95.41±1.13	96.41 ±1.13	0.271	NS
At the end of procedure	96.15±1.33	96.32 ±1.11	0.412	NS
In the recovery room				
After 5 min	96.11±1.32	97.71 ±1.12	0.301	NS
After 10 min	96.32±1.15	97.34 ±1.05	0.107	NS
After 15 min	97.14±1.23	97.51 ±1.15	0.301	NS
After 20 min	97.14±1.11	97.31 ±1.12	0.301	NS

Values are presented as mean ± SD
Statistical analysis was done by student's't' test.
Significant, p value < 0.05.

Distribution of operation (n=50):

Out of 50 patients in PF group the maximum 35(70%) underwent ERCP due to choledocholithiasis whereas in PFK group 33(66%) underwent ERCP for the same region. The test was not statistically significant.

Table-VIII: Distribution of indication of operation (n=50 in each group)

Indication (%)	Group PF (n = 50)	Group PFK (n = 50)	p value	Remarks
choledocholithiasis	35	33	0.601	NS
Biliary stricture	2	2	0.921	NS
Cholangio carcinoma	7	8	0.526	NS
Periampulary carcinoma	2	1	0.152	NS
Carcinoma head of the pancrease	4	6	0.135	NS

Values were expressed as numbers.
Statistical analysis was done by chi-square test.

Duration of the procedure & recovery time (n=50 in each group):

The mean of procedure and recovery time are plotted below where it can be seen that the difference of procedure time between the groups found statistically not significant whereas recovery time was found statistically significant.

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Table-IX: Duration of the procedure and recovery time, (n=50 in each group)

Parameters	PF(N=50)	PFK(N=50)	p value	Remarks
Duration of the procedure(min)	41.82 ± 10.12	39.79±9.87	0.167	NS
Recovery time (min)	18.25±6.76	12.24 ±5.45	<0.001[S]	S

Recovery time considered to modified aldrete recovery score ≥9
Values are presented as mean ± SD
S: significant.
NS : Not significant
Statistical analysis was done by student's t test.
significant, p value < 0.05.

Sedation related peroperative complications (n=50 in each group):
The following parameters were observed peroperatively between the groups to compare the efficacy of the proposed combination of sedatives. Among the parameters only Hypotension and Apnea were found statistically significant. The level of significance was p<0.05.

Table-X: Peroperative complication (n=50 in each group)

Variables	Group PF (n = 50) No(%)	Group PFK (n = 50) No (%)	p value	Remarks
Hypotension	10(20%)	3(6%)	0.032	S
Hypertension	0(0%)	1(2%)	0.301	NS
Bradycardia	3 (6%)	1(2%)	0.153	NS
Tachycardia	2 (4%)	5 (10%)	0.09	NS
Apnea	7 (14%)	2 (4%)	0.018	S
Respiratory depression	4(8%)	3(6%)	0.109	NS
Desaturation	3(6%)	1(2%)	0.162	NS
Shivering	1(2%)	1 (2%)	0.931	NS
Agitation	2 (4%)	3(6%)	0.105	NS
Per operative Nausea & Vomiting	0 (0%)	0 (0%)	1.00	NS

Values are presented as number & percentage over column total
S: significant p value < 0.05.
NS : Not significant p value > 0.05.
Statistical analysis was done by chi-square test.

Post operative complications (n=50 in each group):

The following parameters were observed postoperatively between the groups to compare the efficacy of the proposed combination of sedatives. Among the parameters no values were found statistically significant. The level of significance was p<0.05.

Table-XI: Post operative complication (n=50 in each group)

Variables	Group PF (n = 50) No (%)	Group PFK (n = 50) No (%)	p value	Remarks
Hypotension	0(0%)	0 (0%)	1.00	NS
Hypertension	0(0%)	0(0%)	1.00	NS
Bradycardia	1 (2%)	1(2%)	0.871	NS
Tachycardia	2 (4%)	3 (6%)	0.302	NS
Respiratory depression	0(0%)	0(0%)	1.00	NS
Apnea	0 (0%)	0 (0%)	1.00	NS
Desaturation	0(0%)	0 (0%)	1.00	NS
Shivering	1(2%)	1 (2%)	0.871	NS
Agitation	2 (4%)	3(6%)	0.201	NS
PONV	3 (6%)	2 (4%)	0.197	NS

Values are presented as number & percentage over column total
NS: Not significant
Statistical analysis was done by chi-square test.
significant, p value < 0.05.

Total amount of drugs needed in both groups (n=50)
The mean of drug of different drugs of both proposed combination are given below where the mean of propofol doses between the groups were found statistically significant. The level of significance was p<0.05.

Table –XII: Drug dosages in both groups (n=50 in each group)

Sl.	Drug	Group PF (n=50)	Group PFK (n=50)	p value	Remarks
1.	Propofol (mg)	190.45±12.8	140.67±10.23	0.047	NS
2.	Fentanyl (µg)	60.34±6.98	58.56±2.13	0.301	NS
3.	Ketamine (mg)	0	14.5±1.45	--	--

Values are presented as mean ± SD
NS : Not significant
Statistical analysis was done by student's test
Significant, p value <0.05

Peroperative sedation status (n=50 in each group)
Out of 50 patients in each group the Ramsay sedation scoring was determined group wise and the average scoring is being plotted below.

Table XIII: Peroperative sedation status (n=50 in each group)

SL	Group name	Ramsay sedation score	p-value	Remarks
1.	Pf Group	5±0.12	0.301	NS
2.	PFK group	5± 0.14		

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Values are presented as mean ± SD
NS: Not significant.
Statistical analysis was done by student's t test.
significant, p value < 0.05.

Patients' and endoscopists'satisfaction (n=50):
Patients satisfaction were noted according to VAS interview and endoscopist's satisfaction according to their interview statement. Out of 50 patients, patients and endoscopist's satisfaction found to be comparative satisfied predominantly in both group of study.

Table XIV: Patients and Endoscopist's satisfaction score

	Group PF (n=50)	Group PFK (n=50)	p value	Remarks
Patient satisfaction				
Extremely satisfied	5±0.12	6±0.75	0.702	NS
Satisfied	37±0.58	35±0.52	0.601	NS
Somewhat satisfied	7±0.30	7±0.63	0.512	NS
Endoscopist satisfaction was noted according to their statement				
Extremely satisfied	4 (8%)	4 (8%)	0.902	NS
Satisfied	35 (70%)	37 (74%)	0.401	NS
Somewhat satisfied	11 (22%)	9 (18%)	0.297	NS

Values are presented as mean ± SD and number & percentage over column total for endoscopist's satisfaction.
NS: Not significant.
Statistical analysis was done by student 't' test and Chi-square test.
Significant, p value < 0.05.

Comparison of cost status :
The difference between the cost status of drugs price in both groups found significant difference.

Table XV : Comparison of cost status

SL	Group Name	Cost	P value	Remarks
1.	PF Group	220.15± 5.45 BDT		
2.	PFK Group	170.56 ± 6.41 BDT	0.011	S

Values are presented as mean ± SD
S: Significant p value < 0.05
p-value was calculated by student's t test

DISCUSSION

According to the statistical analysis in our study, it has been tested that propofol-fentanyl-ketamine would have favorable effect over propofol-fentanyl combination in term of (1) haemodynamic parameters in peroperative period where it has been found hypotension 10 (20%) in patients in PF group and 3 (6%) patients in PFK group and the difference between two groups found statistically significant (<p.05) [Table-X]. Apnea has been observed 7 (14%) patient in PF group and 2(4%) patient in PFK group that was found significant (<p.05). (2) Mean recovery time was observed 18.25±6.76 min in group PF and 12.24 ±5.45 min in group PFK which was found statistically significant (<p.001). In term of cost effective issue it was 220.15± 5.45 BDT in group PF and 170.56 ± 6.41 BDT in group PFK. That is also found statistically significant (<p.05).

The result of our study favour the statement of addition of low dose ketamine with propofol-fentanyl combination decrease the propofol-fentanyl associated hypotension (p<.05) and apnea (p<.05) [Table-X]. But for the propofol-fentanyl associate desaturation, hypotension were found according to our statistical analytic result, not significant (p>0.05). This lack of significant might have been related to addition of lower doses of ketamine (0.25mg/kg) and 2LO2/min has been administrated to all of the patients with a nasal cannula thoughout the procedure as well as in the post operative recovery room.

In term of patient's characteristics duration of procedure, post operative complications, sedation status, patients' and endoscopits' satisfaction were found similar between group PF and group PFK and it has been found statically not significant (p>.05).

The combination of propofol and ketamine has many advantages and its use for procedural sedation and analgesia outside the surgical environment has grown in popularity[19]. The first advantage is the ability to decrease drug dosage, as exemplified by Akin et al. in pediatric patients undergoing cardiac catheterization [19] and auditory brainstem response testing[20]. They reported that the number of supplemental propofol doses was lower in the propofol ketamine group than in the propofol alone group in both their studies, which is similar to in our study.

Using lower doses of each agent may reduce their hemodynamic effects (e.g. hypertension and tachycardia for ketamine, low systemic vascular resistance with propofol). Guit et al.[21] reported that the combination of fentanyl with popofol depressed hemodynamics, but the combination of ketamine with propofol resulted in stable hemodynamics.

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However, in our study hypotension was observed in peroperative period. So that our results were consistent with the previous study.

Most importantantly, propofol is frequently combined with opioids to achieve analgesia, bringing extra risk of respiratory problems. The use of ketamine to produce sedation and analgesia potentially provides an advantage over opioids because it does not produce clinically significant respiratory depression and it also protect laryngeal and pharyngeal reflexes and induces bronchodilatation .Mortero et al.[22] reported that low-dose ketamine dramatically attenuated propofol induced hypoventilation based on the results of end-expiratory CO2 measurements. In a recent study, Godambe et al. [23] stated that in pediatric patients who received propofol-fentanyl combination, desaturation was reported in 31% of the cases. Skokan et al.[23] reported that oxygen desaturation was observed in 30% of the pediatric cases in which opioids and propofol were used for emergency interventions. Similarly, in our study the rate of desaturation was 6% in the propofol-fentanyl group, but only 2% in the propofol-fentanyl-ketamine group. Which has been co-related with our study but the percentage was less in both group in our study, very possibly due to continuous 2LO2/min was administrated throughout the procedure.

Ketamine, an NMDA receptor antagonist, is also a significant anesthetic agent. Cardiotoxicity and induction of psychotic episodes, and delayed recovery, are the main disadvantages for ketamine [24]. But in our study no statistically significant disadvantages of ketamine were found, thought to be its low doses application with propofol and fentanyl. The combination of propofol and ketamine has been efficiently used in separate syringes, as well as mixed in the same syringe, in a variety of settings, including coronary artery surgery in adults[25], interventional radiology, sedation for spinal anesthesia, gynecological and ophthalmological procedures[26]. Propofol-ketamine combination has also been effectively studied outside the operating room. When compared to a propofol-fentanyl combination, a combination of propofol-ketamine for deep sedation for burns dressings on the ward was associated with fewer episodes of restlessness and the 1:1 mixture in titrated bolus doses in the emergency department was proved to be an effective regimen [27]. Furthermore, it was pointed-out that propofol-ketamine combination effectively produced deep sedation for prolonged pediatric orthopedic procedures. However, there is a limited number of studies concerning the use of propofol-ketamine in upper gastrointestinal endoscopic (GIE) anesthesia [27]. Tosun et al. reported that there were no differences in propofol-ketamine and propofol-fentanyl group with respect to the endoscopist's rating and recovery time in upper GIE of pediatric population [28]. Some studies established synergism between ketamine and propofol. Ketamine is known to be an analgesic in sub dissociative doses, and when used in combination with propofol, it has been shown to diminish propofol expenditure and protect hemodynamic stability [29]. Additionally, it is assumed that the sedative and antiemetic effects of propofol may offset the nauseant and psychomimetic effects of ketamine. Some physicians prefer ketamine and propofol in combination over either agent alone for reasons of this possible balance of effects. Wathen et al.[29] reported children younger than 10 years of age who received ketamine, the frequency of vomiting was 19.4%. In children younger than of age, Green et al.[30] reported vomiting in 3.5%. But, emesis rarely complicates the use of propofol, probably because of its antiemetic property. Also, combinations with propofol have been reported to cause less postoperative nausea and vomiting. Probably because of this reason we observed only 6% and 4% cases of post operative nausea and vomiting in both PF and PFK group's patients.

Recovery time is very important in the interventional radiology unit, A shortened duration of recovery time is a valuable attribute of a procedural sedation and analgesia regimen. In our study, the mean recovery times were 18.25(±6.76) min in PF group and 12.24 (±5.45) min in PFK group which are similar with the data of Akin and colleagues study[31]. In developing country like Bangladesh cost of drug in a matter of consideration during sedation procedure in our study cost of sedation for group PF was 220.15± 5.45 BDT and 170.56 ± 6.41 BDT for group PFK. That is found significant.

CONCLUSION:

Result from our study noted that ERCP can be successfully done administrating both sedation regiment. But in addition of low dose ketamine to

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propofol-fentanyl combination decreased the risk of hypotension and it also decreased the need for supplemental propofol doses in patients undergoing ERCP procedures. But regarding the unwanted effects (hypotension, apnea), early recovery, cost effectiveness, PFK group patients showed better performances than those of PF group patients. So it can be recommended that Propofol- Fentanyl-Ketamine is a better combination of sedatives than Propofol-Fentanyl combination.

AUTHOR'S CONTRIBUTION

AtiqurRahman was involved in the conception, design, drafting, data collection, data analysis and report writing. Kutubuddin and Abbas Uddin were involved in conception, designing of the study, collection and supervision of data collection, preparation of manuscript and editing the research report. MizanurRahman and Ayesha hasina were involved in data collection, compilation and supervision.

COMPETING INTEREST

There is no competing interest

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