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Effectiveness of Fentanyl in Facilitating Cannulation of Ampulla of Vater during Endoscopic Retrograde Cholangiopancreatography

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ABSTRACT

Background: Endoscopic retrograde cholangiopancreatography is carried out under moderate sedation mostly by use of propofol, opioids and benzodiazepines. The aim of study is to assess difficulty in cannulation of ampulla of vater with the use of fentanyl.

Methods: A prospective randomized double blind comparative study was conducted at Bharatpur Hospital from August 2019 to August 2020 among patients undergoing Endoscopic retrograde cholangiopancreatography. Total 100 patients were enrolled in study and were divided in two groups – Group P (propofol and midazolam) and Group FP (propofol, midazolam and fentanyl). Ease of cannulation was determined using Freeman scale. Independent sample t-test was used to compare mean between two groups and Chi Square test was used to compare categorical variables.

Results: Mean age (51.36 ± 17.750 years versus 56.74 ± 16.995 years), weight (58.88 ± 8.151 kg versus 57.32 ± 8.431 kg) and gender distribution (14 versus 12 male patients and 36 versus 38 female patients) were comparable in both groups-Group P and Group FP. There were 34 patients in Group P and 37 patients in Group FP with easy cannulation and 16 patients in Group P and 13 patients in Group FP with difficult cannulation, which was comparable (p value=0.509)

Conclusions: Cannulation of ampulla of vater is not affected by the use of fentanyl in combination with propofol when compared to propofol alone and can be routinely used during endoscopic retrograde cholangiopancreatography.

Keywords: Ampulla of vater; endoscopic retrograde cholangiopancreatography; fentanyl; propofol

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a diagnostic and therapeutic endoscopic procedure for biliary tract and pancreatic diseases, done by cannulation of ampulla of vater mostly preformed under moderate sedation.^{1,2} However, sedation practices vary in different countries and the ideal sedation regimen for gastro endoscopy procedures is still debatable.^{3,4}

In our Government Hospital, ERCP is done under propofol plus midazolam sedation or in combination with fentanyl especially in those case which is posted for single session ERCP followed by laparoscopic cholecystectomy.^{5,6} Opioids like fentanyl are known to increase the intrabiliary pressure. There are various studies showing elevated basal pressure of Sphincter of Oddi (SO) by opioid, evaluated with manometry examination or by observational study during cholecystectomy.⁷⁻¹⁰ On the

other hand, there are also studies showing no difference of opioid in the spasmodic action of SO.¹¹⁻¹⁴

Therefore, the objective of our study was to see whether the addition of fentanyl to midazolam and propofol combination hindered the success rate of ampullary cannulation during ERCP.

METHODS

A prospective randomized double blind comparative study was conducted among patients undergoing ERCP at Bharatpur Hospital from August 2019 to August 2020. Ethical approval was taken from Institution Review Committee (IRC) Bharatpur Hospital (reference number 076/77-03) and informed written consent was taken from the patient.

All patient undergoing ERCP were included in this study

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and patient with ampullary carcinoma, previously cannulated ampulla of vater, patient refusal for consent were excluded from this study. For sample size estimation, we conducted a pilot study in 10 patients in which the proportion of patients with easy cannulation in Propofol Group was 0.6 and proportion of patient with easy cannulation in Propofol and Fentanyl Group was 0.4. Considering 95% confidence interval and 80% power and the proportion of patients with easy cannulation in Propofol Group which is taken as 0.6, the proportion of patients with easy cannulation in Propofol and Fentanyl Group which is taken as 0.4, the minimum total sample size for this study was calculated as 95. Taking 5% non-response rate the sample size is 100, with 50 patients in each group.

Patients were randomly assigned using computer generated random numbers into two groups - Group Propofol (P) and Group Fentanyl (FP). In Group P patients were sedated with injection (inj.) midazolam 0.05mg/kg intravenous (i.v), inj. normal saline 1ml/kg and propofol 1mg/kg i.v loading dose, maintained with propofol 100 µg/kg/min and titrated based on hemodynamic parameters (heart rate, mean arterial pressure and oxygen saturation) and subjective assessment of sedation (minimal, moderate and deep sedation). Similarly, in Group FP patients were sedated with injection midazolam 0.05mg/kg i.v, fentanyl 1 µg/kg (diluted at 10 µg/ml and administered at 1 ml/kg) and propofol 1mg/kg loading dose, maintained with propofol 100 µg/kg/min and titrated according to hemodynamic parameters and level of sedation. Drugs were given by anesthetist and drugs label were kept blind to the surgeon, the principal investigator. Intra-operatively in both the groups, patients were given injection Ondansetron 4 mg as antiemetic. The difficulty of cannulation for ampulla of vater was assessed using Freeman Scale¹⁵; defined by the presence of one or more of more than 5 contacts with the papilla whilst attempting to cannulate, more than 5 minutes spent attempting to cannulate following visualization of the papilla, more than one unintended pancreatic duct cannulation or opacification.

Data were analyzed using statistical package for the social sciences (SPSS) version 16. Independent sample t-Test was used to compare mean between two groups and Chi Square test was used to compare categorical variables.

RESULTS

The totals of 100 patients, 50 patients in each group

were used in this study. Socio-demographic parameters like age, weight, sex distribution were comparable in both the groups. The mean age was 51.36 ± 17.750 years in Group P and 56.74 ± 16.995 years in group FP (p value= 0.553), which showed that there is no any statistically significance difference between two groups. Mean weight was 58.88 ± 8.151 kg and 57.32 ± 8.431 kg in Group P and Group FP which was comparable (p value=0.941), showed that there is no any statistically significance difference between two groups. In group P, 14 patients were male and 36 patients were females and 12 patients were male and 38 patients were females in Group FP, showed that there is no any statistically significance difference between two groups.

Table 1. Demographic variable.

Demographic Variable	Group P	Group FP	p-value
Age Mean(SD)	51.36 ± 17.750	56.74 ± 16.995	0.553*
Gender			
Male	14	12	0.648**
Female	36	38	
Weight Mean(SD)	58.88 ± 8.151	57.32 ± 8.431	0.941*

*: Independent sample t-Test, **: Chi Square test

Similarly, the distribution of American Society of Anesthesiologists - Physical Status (ASA- PS) in both the groups was comparable (p value= 0.858) which showed that there is no any statistically significant difference between two group.

Table 2. ASA-PS distribution.

Group	ASA -PS I	ASA-PS II	ASA-PS III	p value
Group P	7	37	6	0.858
Group FP	9	35	6	

Ease of cannulation was assessed using chi-square test and was found to be comparable in both the groups. There were 34 patients with easy cannulation and 16 patients with difficult cannulation in Group P. Similarly, there were 37 patients with easy cannulation and 13 patients with difficult cannulation in Group FP which was comparable (p value=0.509).

Table 3: Ease of cannulation.

	Easy cannulation	Difficult cannulation	p value
Group P	34	16	0.509
Group FP	37	13	

DISCUSSION

Fentanyl is a synthetic opioid which has rapid onset, short duration of action, lack of direct myocardial depressant effects and absence of histamine release. The action of the drug is related to its agonism of the opioid receptors. It is highly lipid-soluble and also found to increase in biliary pressure.^{2,4,16} Direct Sphincter of Oddi (SO) manometry has demonstrated that SO is sensitive to fentanyl. It surges the amplitude and frequency of phasic wave and basal pressure through mu receptors and non-mu receptors respectively.^{17,18} whereas, propofol is commonly used ultra-short acting hypnotic drug for induction and maintenance of anesthesia, conscious sedation in minor procedures, sedation in intensive care unit patients and day care surgery.¹⁹⁻²¹ It has no effect in SO and lacks analgesic property on mild to moderate sedation.⁵

Various combinations of drugs along with propofol are used for sedation in ERCP procedure like propofol infusion and intermittent use of midazolam^{22,23}, regime like sedato-analgesic cocktail (midazolam, ketamine, and pentazocine plus propofol)²⁴ and balanced propofol sedation (BPS).²⁵ In BPS propofol, fentanyl and midazolam are used in adjunct. Their use has been found to improve patient tolerance, safety and even making it feasible to use in advanced liver diseases than propofol alone.^{26,27} In our hospital our anesthetist prefer either propofol infusion with intermittent use of midazolam or BPS. BPS reduces the risk of over-sedation as analgesia and amnesia can be achieved with less than hypnotic doses, mitigating the potential for deep sedation. Furthermore, pharmacologic reversibility can be obtained by using naloxone or flumazenil.²⁸⁻³⁰

In our study, total 100 cases were included with 50 patients on each group. We found the cannulation difficulty was not statistically significant in both groups. Besides gender, age and weight of the patient which was taken in account was also comparable. GuitronCanti A, Mexican endoscopist had done thorough research on effect of fentanyl on ampulla of vater. In animal module, he had seen effect of fentanyl and hyosine bromide in sphincter of oddi of rabbit where he found SO relaxed at the dose of 1ug/kg body weight of fentanyl and sphincter pressure was raised at 5ug/kg and 10ug/kg. This increase in pressure was antagonized by hyosine bromide. Thus he had concluded with potential benefit of fentanyl in ERCP for human trial.¹¹ Similarly in his human prospective, double blind randomized comparative study of 432 patients; he concluded fentanyl does not hinder the cannulation of ampulla of vater during ERCP.

Besides, he found that propofol dose was reduced with the use fentanyl.¹² Our results were comparable to his study.

Similarly, John R M et al observed incidence of sphincter spasm during fentanyl supplemented anesthesia in biliary surgeries. He studied sphincter spasm by viewing cholangiographic image. Thus, he reported fentanyl as a suitable anesthetic agent for biliary surgery.¹³ Likewise, Koo HC et al applied transdermal fentanyl patch (TFP) and monitored motility of sphincter of oddi by SO manometry (SOM) using triple-lumen catheters anterogradely inserted through the percutaneous transhepatic route during cholangioscopy. He found below a dose of 25µg/hr, motility of the SO was not affected and addressed TFPs at lower dosages to be a safe analgesic treatment for the pain control of patients with pancreatitis without affecting the function of the SO.¹⁴

In contrast McCammon R studied by injecting 100µg fentanyl and recording biliary pressure by cannulating CBD or cystic duct with 18 gauge catheter after removal of gallbladder. He found the flow rate of bile was decreased and biliary pressure increased after use of fentanyl.⁷ He also emphasized on fentanyl induced spasm in especially suspected or pre-existing gallbladder disease patient during his study on reversal of fentanyl induced spasm of sphincter of oddi.⁸ Kroesen G and colleges, found significant rise in common bile duct pressure with fentanyl only compare to halothane and fentanyl plus droperidol.⁹ Chessick KC et al reported fentanyl and morphine causing spasm of sphincter of oddi leading to misinterpretation of cholangiography and unnecessary indication of surgery.¹⁰ This variation might be due to the higher dose of fentanyl which is more than 5 µg/kg, however the dose of fentanyl was not mentioned in their study.

However, we observed a few limitations in our study. In this study we did not assess the total dose of propofol used during the procedure and hence the additional benefit of fentanyl in reducing the total propofol dose was unknown. Similarly, it would have been better, had we have measured sphincter of oddi pressure with manometry and results would have been more accurate.

CONCLUSIONS

The study showed that at the dose of 1 µgm/kg fentanyl has got no effect on the cannulation of ampulla of vater during ERCP. However, more studies are required to come on clear consensus regarding dose of fentanyl and SO relation.

CONFLICT OF INTEREST

None

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