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Original Article

Anaesthesia Section

Preprocedural Nebulisation with 4% Lignocaine and Ketofol Sedation during Endoscopic Retrograde Cholangiopancreatography Procedure for Abolition of Gag Reflex: A Randomised Double-blinded Study

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ABSTRACT

Introduction: Endoscopic Retrograde Cholangiopancreatography (ERCP) is preferably carried out under deep sedation with propofol alone or with adjuncts to reduce the dose of propofol thereby reducing the intraprocedural complications and improving the patient and endoscopist acceptance of the procedure. There is no consensus on the ideal dose of ketamine as adjunct to propofol to be used in such scenario.

Aim: To evaluate the sedation characteristics, abolition of gag reflex and haemodynamic profile of the patients undergoing ERCP under ketofol sedation, with or without 4% lignocaine prenebulisation.

Materials and Methods: This randomised double-blinded study was undertaken in Indra Gandhi Medical College, Shimla, from September 2018 to October 2019. Sixty patients of American Society of Anaesthesiologists (ASA) physical class I and II aged between 25-65 of both sexes posted for routine ERCP were included. In group 1, patients were nebulised with 6 cc normal saline, and group 2 with 6 cc 4% lignocaine 15 min prior to procedure in the recovery room. Entropy-guided ketofol induction (ketamine and propofol used in 1:2 concentration) was used, followed by propofol infusion at the rate of 8 mL/hr. Gag reflex, haemodynamic and sedation characteristics were observed peri and postoperatively.

Results: The mean time to onset of sedation and duration of recovery room stay were comparable in both the groups. Total mean dose of propofol and ketamine used was 105.67 mg, 55.33±18.75 mg in group 1 and 101.83 mg, 48.67±15.588 mg in group 2. Gag reflex was similarly obtunded and endoscopists' rating of the procedure were similar in both the groups perioperatively (p-value >0.05).

Conclusion: Target controlled entropy guided infusion with ketofol is an effective drug combination to achieve all aspects of safe sedation practice in ERCP procedure.

Keywords: Deep sedation, Entropy, Ketamine, Lidocaine, Propofol

INTRODUCTION

Endoscopic Retrograde Cholangiopancreatography (ERCP) is a gold standard procedure for the diagnosis and treatment of biliary and pancreatic diseases [1]. This procedure is preferably carried out under sedation by propofol for patient immobility, analgesia, patient comfort and endoscopist satisfaction. Although propofol is close to an ideal intravenous sedative hypnotic agent, it has a narrow therapeutic range without analgesia, with resultant rapid unpredictable progression from deep sedation to general anaesthesia [2].

The main approach to decrease the propofol-related complications would be to use adjuncts, monitor depth of anaesthesia thereby, decrease the dose of sedative drugs and use locally acting drugs like lignocaine to allow easy maneuverability of endoscope in a prone position. So, all these factors were taken into consideration in this study individually. Balanced propofol sedation is thus used for ERCP worldwide in combination with other drug like opioids, benzodiazepine, dexmedetomidine, etomidate and ketamine in various concentration to reduce the dose of propofol [3-5].

As propofol is a main constituent in all sedation technique, ketamine was used with propofol in the study. Ketamine may be closer as an ideal adjunct to propofol as it causes analgesia, amnesia, an anaesthesia in addition to requisite haemodynamic stability. Ketamine is being used with propofol in varying concentrations (1:1 to 1:4) but researchers used 1:2 concentration as increasing the ketamine concentration increases the emergence reactions and decreasing the dose will compromise with analgesic effect thereby researchers might have to increase the propofol dose to take care of patient's movement [6-8]. Opioids are also good analgesic but their use can lead to spasm of sphincter of Oddi. Dexmedetomidine is expensive and may lead to hypotension and bradycardia. Etomidate is known to suppress the adrenal function and so is also not a good choice as sedation agent in such scenario [3-5]. Sedation technique was chosen over general anaesthesia in the patients as most of the guidelines advocate moderate to deep sedation only for these procedures with better postoperative profiles and less postoperative complications [1].

Monitoring the depth of sedation by entropy can further reduce the amount of drugs used perioperatively there by reducing the sedation related complications. The entropy/BIS (Bispectoral Index) calculates and displays two indices, the State Entropy (SE) reflects the cortical state of the patients and is computed over the frequency range of 0.8 Hz-32 Hz corresponding to EEG dominated part of spectrum and (RE) Response Entropy in a range of 0.8-47 Hz frequency corresponds with EMG (Electromyography) dominated frequencies [9]. The computer-generated values range from 0 (Coma) to 100 (Fully awake). The normal trend is to keep the patient between 60-80 entropy during sedation. Since this is non invasive estimation of the depth of anaesthesia hence it was used in present study too [10].

In addition to sedation, the requirement of abolition of gag reflex is essential for easy insertion of endoscope in prone position. Therefore, the sedation has to be deepened to abolish gag reflex with resultant respiratory depression [11,12]. Lignocaine is used locally in different concentration and technique for this purpose namely as gargles, intraoral spray and nebulisation with varying results. Nebulised lidocaine is known to attenuate the heightened airway reflex sensitivity [13].

Thus, studies done so far on attenuating the pharyngeal reflexes used nebulised lignocaine preoperatively to help in the passage of flexible bronchoscope, reported varying results. In these studies, patients reported better satisfaction with nebulisation technique. As there is paucity of studies on patients undergoing ERCP procedures with pharyngeal reflex attenuation, hence the dilemma over the choice of particular technique over other remains unresolved [14,15].

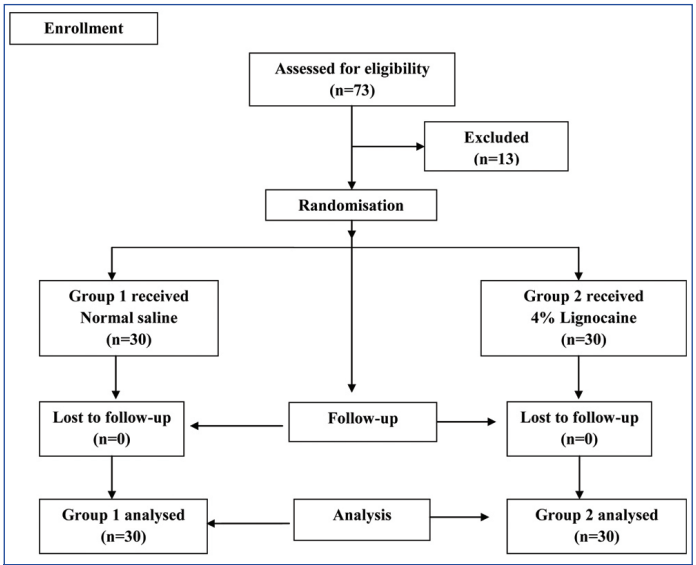
Hence, the hypothesis that preprocedural 4% lignocaine nebulisation by depressing the cough and gag reflex along with ketofol (ketamine and propofol in 1:2 concentration) induction and propofol target infusion could help in the easy maneuverability of the endoscope thereby increasing the patient comfort and endoscopist satisfaction was tested in the study. The primary objective was to evaluate the sedation characteristics, presence or absence of gag reflex and periprocedure haemodynamic profile of the patient in the two groups. Secondary objective was to determine endoscopist's satisfaction and recovery time seen after the procedure in the patients.

MATERIALS AND METHODS

This randomised double-blinded study was undertaken in Indra Gandhi Medical College Shimla, Himachal Pradesh, India, from September 2018 to October 2019. An Institutional Ethics Committee clearance was obtained vide letter no. HFW(MC)SURG/477 /30.10.2018.

Inclusion criteria: Total of 60 patients of ASA physical class I and II aged between 25-65 of both sexes posted for routine ERCP were included in the study.

Exclusion criteria: Patients aged below 25 yrs and above 65 yrs., of ASA class IV and above, having allergies to drugs, pregnant patients and patients with history of substance abuse, diastolic blood pressure more than 110 mmHg, asthmatic patients and patients with blood glucose level <60 were excluded from the study. Hence, total of 73 patients were assessed for the study but 13 patients were excluded [Table/Fig-1].



[Table/Fig-1]: CONSORT diagram.

Sample size calculation: The sample size was calculated using ClinCal.Com calculator, taking following assumptions as incidence of gag reflex in group 1-32% and it was assumed that nebulisation will abolish the gag reflex in group 2 hence the incidence will be 0% from the study by Abbas [7], Confidence interval of 95%, power of study 80%. Sample size was 19 in each group. Thirty patients in each group were studied to cover up for loss of patient data to any cause [16].

Study Procedure

Patients were examined and informed of the procedure to be carried out on them and written informed consent was undertaken. Patients were randomly divided into two groups, group 1 and group 2 using random allocation software [random Alloc.exe] [17] and record maintained by a separate anaesthetis not involved in recording variables perioperatively in the recovery room and disclosed at the end of the study. The nebulisation was also done by the same anaesthesia via nebulisation kit with oxygen face mask and flow at 7 litre/min. Endoscopist, patient, and the anaesthesia's recording perioperative measurements were blind to the drugs being used for nebulisation in the preprocedural room. The patients were kept fasting for 6-8 hours overnight. Intravenous access was secured in all patients (i.v. fluid started) and kept in place for administration of sedation and premedication. The groups were:

- **Group 1 (n=30):** Patients received nebulisation with normal saline 0.9% 6 cc 15 minute prior to endoscopy
- **Group 2 (n=30):** Patients received nebulisation with 4% lignocaine 6 cc 15 minute prior to endoscopy

Patients were monitored for Heart Rate (HR), lead II Electrocardiography (ECG), pulse oximetry (SpO_2) and Non invasive Blood Pressure (NIBP). All parameters were recorded at presentation, and after every five minutes during and after the procedure. Premedication of the patient was done with injection Glycopyrrolate (0.2 mg), inj. Ondansetron (4 mg i.v.), and inj. Midazolam (1 mg i.v.). Sedation was carried out in prone position. Ketofol in dose of 0.5 mg/kg ketamine and 1 mg/kg of propofol (1:2) was calculated and mixed in one syringe and was given slowly followed by propofol infusion at 8 mL/hr (80 mg). Sedation was maintained by entropy in the range of 60-80. In case of sedation level decreasing, with entropy level >80 then 2 mL of propofol bolus was given and this was recorded. If sedation deepened or entropy was <60 then researchers stopped the propofol infusion and this was recorded. If the patient moved with pain then 25 mg of ketamine was given and recorded.

Systolic Blood Pressure of <90 mmhg or Mean Arterial Pressure (MAP) decreased more than 30% from baseline was treated with inj. Mephentermine 6 mg and heart rate less than 50/min was treated by injection atropine 0.6 mg and was recorded. If any patient desaturated intraoperatively (SpO_2 less than 90%), plan was to increase Fraction of inspired oxygen (FiO_2). If patient did not improve, endoscopist was informed, procedure stopped, patient positioned supine, and oxygenated by bag and mask. Monitoring was continued after completion of endoscopy until regaining of full consciousness.

The primary objectives were to evaluate the sedation characteristics, abolition of gag reflex and haemodynamic profile of the patient in the two groups. The secondary objectives were to determine the physician's satisfaction and recovery time seen after the procedure, total amount of drug boluses (propofol and Ketamine) used in the procedure and adverse effects and complications, if any. Onset of sedation was taken as time when entropy was <80 and patient stopped responding to verbal commands. Time of endoscopy was taken as time from insertion to taking out of endoscope.

The observations were recorded at baseline before nebulisation (presentation), at the time of induction of sedation (0 min) and then followed every five min till completion of the procedure. At the end of the procedure, the endoscopist was asked to rate the ease of procedure on a four-point scale (very easy, easy, adequate, impossible). Modified Aldrete score was used to assess the sedation level in recovery. Patients were discharged to postoperative ward only when they achieved a score of >9 [5].

STATISTICAL ANALYSIS

Associations between intervention groups and other co-variables were tested using Chi-square tests and two Student t-test. Difference between the two tailed groups at different time points was reported as mean difference with 95% CI. Significance level was set at p-value ≤0.05. All statistical analysis was performed using software "Epi Info version 7.1.5 CDC Atlanta, USA".

RESULTS

The mean age (years) in groups 1 and 2 was 45.07±14.198 and 50.83±12.485, respectively (p-value=0.100) [Table/Fig-2].

Parameters	Group 1	Group 2	Total	p-value
Age (in years) Mean±SD	45.07±14.198	50.83±12.485	47.95±13.570	0.100
Weight (in Kg) Mean±SD	56.20±7.369	53.63±8.869	54.92±8.187	0.228
Gender n (%)				
Male	10 (33.3%)	12 (40%)	22 (36.7%)	0.789
Female	20 (66.7%)	18 (60%)	38 (63.3%)	
ASA, n (%)				
I status	20 (66.7%)	22 (73.3%)	42 (70%)	0.389
II status	10 (33.3%)	8 (26.7%)	18 (30%)	

[Table/Fig-2]: Demographic profile of the patients.
N=60 and n=30 in each group

The mean time of onset of sedation in group 1 was 0.72±0.26 min, while it was 0.65±0.24 min in group 2 (p-value=0.303). In group 1, 4 patients (13.3%), while 7 patients (23.3%) patients in group 2 moved with endoscopy manipulation during the procedure (p-value=0.506). Perioperative gag reflex to endoscope insertion was abolished similarly in both the groups. There was no significant difference in endoscopist's satisfaction grading between the two groups (p-value=0.112). The mean duration of endoscopy was 17.33±5.371 min. in group 1, and 17.17±5.522 min in group 2 (p-value=0.906). Endoscopist graded the procedure 'easy' in 26 patients (86.7%) in group 1 and in all 30 patients (100%) of group 2. Mean duration of recovery room stay was comparable in both the groups (p-value=0.935) [Table/Fig-3]. The mean Response Entropy (RE) and State Entropy (SE) were comparable between both the groups at various time intervals (p-value >0.05).

When mean arterial pressure, mean heart rate, and respiratory rate was compared between both the groups, it was noted that there was no statistically significant difference at any period of time (p-value >0.05). One patient in each group underwent post-ERCP laparoscopic cholecystectomy, hence, they were shifted to the surgery OT on completion of the ERCP-guided CBD stone retrieval. So their Aldrete score was not assessed and these two patients were not included in post-op assessment. Hence, the number of patients in postoperative period was 29, making up a total of 58 patients [Table/Fig-4,5].

The mean SpO_2 was comparable between the groups at various time intervals perioperatively (p-value >0.05). The mean ketamine bolus dose, rescue dose, and total dose given to patients was comparable in the two groups (p-value >0.05) [Table/Fig-6].

There was no incidence of any adverse effect like apnoea, uncontrolled hypotension, bradycardia, desaturation, nausea, vomiting and emergence reaction in both the groups at any time interval.

Parameters	Group 1	Group 2	Total	p-value
Onset of sedation (min)	0.72±0.26	0.65±0.24	0.69±0.25	0.303
Duration of endoscopy (min)	17.33±5.371	17.17±5.522	17.25±5.401	0.906
Patients movements present perioperatively	26 (86.7%)	23 (76.7%)	49 (81.7%)	0.506
Movements absent	4 (13.3%)	7 (23.3%)	11 (18.3%)	
Recovery room stay (min)	14.33±2.881	14.40±3.420	14.37±3.135	0.935
Endoscopist easy grading	26 (86.7%)	30 (100%)	56 (93.3%)	0.112
Endoscopist adequate grading	4 (13.3%)	-	4 (6.7%)	

[Table/Fig-3]: Sedation and perioperative period characteristics and recovery room time.
N=60 and n=30 in each group

Mean arterial pressure (mm Hg)										
Groups		Presedation	0 min	5 min	10 min	15 min	20 min	25 min	30 min	Postoperative MAP
1	Mean±SD	101.13±12.142	101.10±11.394	105.50±12.423	105.73±12.564	105.19±11.836	102.82±12.048	111.00±15.100	105.00±1.414	99.21±9.969
	n	30	30	30	30	26	11	5	2	29
2	Mean±SD	97.07±13.272	96.77±12.334	106.33±14.742	106.53±13.985	108.67±13.114	108.31±16.332	119.75±13.574	126.50±12.021	98.41±11.879
	n	30	30	30	30	24	13	4	2	29
Total	Mean±SD	99.10±12.777	98.93±11.973	105.92±13.522	106.13±13.186	106.86±12.461	105.79±14.494	114.89±14.295	115.75±14.245	98.81±10.876
	N	60	60	60	60	50	24	9	4	58
p-value		0.221	0.163	0.814	0.817	0.330	0.367	0.397	0.129	0.784

[Table/Fig-4]: Intergroup comparison of Mean Arterial Pressure (MAP) (mm Hg).

Heart rate (beats per min)										
Group		Presedation	0 min	5 min	10 min	15 min	20 min	25 min	30 min	Postop HR
1	Mean±SD	84.90±16.775	85.17±16.948	94.77±15.673	96.80±13.775	94.23±14.728	92.00±11.705	94.40±7.127	97.00±1.414	86.07±14.575
	n	30	30	30	30	26	11	5	2	29
2	Mean±SD	87.40±11.003	89.77±11.440	100.23±9.975	102.47±14.323	104.04±13.839	104.00±11.923	103.25±11.057	94.50±13.435	88.24±9.448
	n	30	30	30	30	24	13	4	2	29
Total	Mean±SD	86.15±14.122	87.47±14.522	97.50±13.313	99.63±14.222	98.94±15.003	98.50±13.078	98.33±9.644	95.75±7.932	87.16±12.223
	N	60	60	60	60	50	24	9	4	58
p-value		0.498	0.223	0.112	0.124	0.019	0.021	0.187	0.818	0.503

[Table/Fig-5]: Intergroup comparison of Heart Rate (HR) (beats per min).

Group (Mean±SD)	Ketamine bolus dose in mg	Ketamine rescue dose in mg	Ketamine total dose in mg	Propofol bolus in mg	Propofol infusion in mg	Propofol rescue dose in mg	Propofol total dose in mg
1 (n=30)	28.03±3.917	28.33±17.036	55.33±18.751	55.67±7.29	24.83±8.251	25.33±14.794	105.67±24.095
2 (n=30)	27.33±4.498	21.33±13.705	48.67±15.588	53.83±8.777	23.67±7.420	24.33±16.543	101.83±27.180
Total (N=60)	27.68±4.196	24.83±15.730	52.00±17.423	54.75±8.048	24.25±7.802	24.83±15.567	103.75±25.539
p-value	0.5229	0.523	0.085	0.382	0.140	0.806	0.565

[Table/Fig-6]: Amount and number of propofol, ketamine doses used as rescue drug during the ERCP procedure.

DISCUSSION

The ERCP is routinely performed by either trained persons other than anaesthetists as NAAP (Non anaesthesiologist Administered Propofol) or is performed under the supervision of anaesthetist by BPS (Balanced Propofol Sedation) technique with addition of opioids, benzodiazepines, ketamine or dexmedetomidine with propofol for achieving moderate to deep sedation required for the procedure [1]. Propofol sedation although has fast onset and is still considered a gold standard for these techniques but achieving all aspects of sedation with a single drug leads to most of the adverse events associated with its use [2]. Patients movement, gag reflex and vomiting associated with endoscope insertion prompt the care giver to deepen the level of sedation culminating into respiratory depression and other side effects [8]. Exaggerated patient reflexes movements can lead to problems with endoscopist and even cause injury to the oesophagus and the procedure execution can become difficult. Too deep sedation can lead to hypoxemia, desaturation, aspiration and late emergence from anaesthesia. Thus ideal technique should look into all these factors for safe anaesthesia practice [3].

The incidence of gag reflex varies between 20-32% and pharyngeal anaesthesia is an essential part of the sedation to improve patient acceptance of the procedure with least respiratory depression and other complications [18,19]. In two separate experimental studies on rats, ketamine sedation was considered superior in terms of depression of superior laryngeal nerve stimulated gag reflex and maintenance of airway patency during sedation [20,21]. Yamagata R and Koga T reported that Neurokinin 1 antagonist (NK1) or NMDA (N-Methyl D-aspartate) antagonist dizocilpine in 1 mg/kg dose was able to diminish the gag reflex in decerebrated rats [20]. Eikermann M et al., et al., in a study on rats, and Mishima G et al., in a study on young healthy volunteers, concluded that ketamine stabilised the airway patency during sedation and anaesthesia [21,22]. Tandon M et al., used ketamine in 0.15 mg/kg dose with 50 mg propofol and reported 2.2% incidence of gag reflex over 17% in plain propofol group [23]. Thus, most of the studies find low dose ketamine as a superior adjunct to propofol in ERCP procedures in dose of 15 mg to 0.5 mg/kg for blunting the gag reflex, maintaining the upper airway collapsibility, stable haemodynamic profile and less desaturation episodes than observed with propofol alone. Higher than 0.5 mg dose is associated with more incidence of emergence delirium and desaturation perioperatively. Ketamine although depresses the gag reflex, but there is inconclusive data as to the dose at which it can optimally function in such scenario [5-7]. Hence current study used ketofol (ketamine 0.5 mg/kg: propofol 1 mg/kg) induction followed by entropy lignocaine nebulisation to improve the pharyngeal anaesthesia, thereby, leading to ease in insertion of endoscope and better patient profile perioperatively as few studies have reported persistence of cough and gag reflex at this dosage of drugs [10,18].

Pharyngeal anaesthesia during moderate to deep sedation can be augmented with various techniques like topical 10% spray, nebulisation with 4% lignocaine or superior laryngeal nerve blocks with varying results [10-12,14,15]. Researchers who have used ketamine in less than 0.5 mg dose have reported less but persistence of gag reflex in some patients [10]. Tsai HI et al., used 10% lignocaine spray with propofol, 6 and propofol and dexmedetomidine combination and observed 32% incidence of gag reflex in plain propofol group, 20% in ketofol group and 8% in dexmedetomidine with propofol group. They had used 0.2 mg ketamine with 50 mg propofol hence the incidence of gag reflex in patients was high (20%) [10]. Tandon M et al., used ketamine in 0.15 mg/kg dose with 50 mg propofol and reported 2.2% incidence of gag reflex over 17% in plain propofol group [23]. Tekeli AE et al., also reported persistence of cough during the procedure in his patients undergoing ERCP but they had used ketamine in 1 mg/kg dose with around 60 mg propofol bolus followed by infusion at the rate of 60 mg/hr [24]. Although Mathur PR et al., found better anaesthesia with nerve blocks in patients undergoing bronchoscopy over nebulisation method but routine invasive nerve block use is unwarranted in patients undergoing ERCP, when the similar effect can be achieved by the use of pharmacological drugs like ketamine [15]. Noitasaeng P et al., compared the effectiveness of spraying and nebulised lidocaine for patients undergoing ERCP. In their study, patients were more comfortable with nebulised technique whereas endoscopist were at ease with spray as you go technique with better patient's variable like less cough, secretions and less time to start the procedure [14]. In the present study, none of the patients in either group experienced gag reflex to endoscope insertion. Basturk A et al., used midazolam and ketamine in 0.5 mg/kg dose with lignocaine spray 10% at 1 mg/kg dose and observed that the gag reflex was reduced to 6.5% with lignocaine over 33.3% in patients without it. Hence, the incidence was less but not eradicated which could because propofol was not used in the study, but the dose of lignocaine was high in their patients [12]. Thus, there is no added advantage with nebulised lignocaine and hence its use is questionable in patients receiving ketofol as it will increase the procedural time, and unnecessary usage of additional drugs [25].

Hypotension was the main adverse event reported and was maximally seen when propofol was used alone or with dexmedetomidine and almost all studies like present study reported higher MAP with the use of ketamine as adjunct to propofol [18,23,26]. Airway assistance was also required maximally with the use of propofol or dexmedetomidine (12-20%) as compared to 0-8% with low dose ketamine [18]. Recovery time was least with propofol and maximum with dexmedetomidine and few have even reported more emergence delirium with propofol alone over ketamine used alone in ERCP procedures [26].

Target controlled entropy-guided ketamine and propofol combination helped in restricting the amount of these drugs to be used preoperatively thus minimising the adverse effects and also obtained the maximum results with these drugs.

Limitation(s)

The ASA III were not included in the study.

CONCLUSION(S)

Target controlled entropy guided infusion with ketofol (1:2) is an effective drug combination to achieve all aspects of safe sedation practice in ERCP procedure. Nebulisation with lignocaine 4% is not required as it only increases the procedure time and leads to unnecessary use of lignocaine in patients of choledocholithiasis.

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