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RESEARCH ARTICLE

COMPARISION OF INTRAVENOUS MIDAZOLAM/ KETAMINE WITH DEXMEDETOMIDINE-PROPOFOL COMBINATION FOR SEDOANALGESIA IN ENDOSCOPIC RETROGRADE CHOLANGIO PANCREATOGRAPHY(ERCP) PROCEDURES IN TERTIARY CARE HOSPITAL

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Bispectral Index (BIS), Dexmedetomidine, ERCP Endoscopic Retrograde Cholangio Pancreatography, Ketamine, Midazolam, Recovery Time, Sedation

Abstract

Background: Endoscopic retrograde cholangiopancreatography (ERCP), often require sedation during the procedure. The most commonly used drugs for this purpose are midazolam and propofol, which are used as sedative and hypnotic agents with minimal analgesic potential.

Aims & objectives: Effects of Sedoanalgesia with Midazolam/ ketamine long with Dexmedetomidine nfusion & Rescue propofol alliquotes regimes on hemodynamic and respiratory variables& recovery profile in patients undergoing ERCP.

Methods: In this Retrospective observational study adult patients of ASA grade l- lll were enrolled after taking inform consent from patient & their relatives. Premedication was given in form of inj.Midazolam 0.02 mg/kg iv in Group l,.inj ketamine 0.5 mg/kg iv was given in group ll. Inj.Dexmedetomidine (bolus dose of 1 µg/kg over 10 min) followed by 0.5µg/kg/hour as maintenance in both the groups.intermittent Intravenous Propofol alliquotes was used for maintain BIS 70-80 in both groups. Amount of propofol used during procedure was notified.. Hemodynamic and respiratory variables, recovery time and adverse events were monitored & recorded.

Results: The hemodynamic and respiratory variables were similar in both groups. Total propofol consumption was significantly lower in the group ll. (205+/-80 mg vs.155+/-20 mg; $p < 0.001$). The recovery period was shorter in group ll (time to achieve the Aldrete score 9 was 9.0 ±2.2 vs. , 6.2+/-1.1min; $p < 0.001$).Adverse events were comparable between the two groups.

Conclusion: Ketamine-Dexmedetomidine combination with propofol may be a safe and useful alternative for sedation for ERCP patients.

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Introduction:-

Endoscopic Retrograde Cholangio Pancreatography (ERCP), requires sedation. Multimodal Anaesthesia in form of Sedoanalgesia to General Anaesthesia with endotracheal intubation are used by anaesthesia worldwide.Gastroentrologists prefer Sedoanalgesia morethan Genral Anaesthesia.

The most commonly used agent for this purpose is midazolam because it has a short elimination half-life and has amnestic and anxiolytic effects [1].

Propofol is a widely used sedative and hypnotic agent with minimal analgesic potential. Propofol may cause respiratory depression, especially in high doses [2]. To reduce cumulative propofol doses, it may be used in combination with other drugs, such as midazolam or dexmedetomidine. Propofol and midazolam act synergistically in combination and may be more effective than when used alone [3]. Dexmedetomidine is a highly selective α2-adrenergic receptor agonist that has analgesic and sedative effects with minimal depression on ventilation [4]. It has been reported that dexmedetomidine reduces the recruitment of propofol during anaesthesia because dexmedetomidine has analgesic effects [5].

Ketamine is a phencyclidine derivative. It provides excellent amnesia and analgesia, preserves muscle tone with maintaining airway reflexes and spontaneous respiration.

It is postulated that combining propofol–ketamine may preserve sedative and analgesic efficacy while minimizing their respective adverse effects, this is partially due to the fact that many of the adverse effects are dose-dependent and when the two drugs used in combination the doses administered of each can be reduced. Also, the CVS effects of each are opposing in action, thus theoretically balancing each other when used together. The theoretical advantages of this combination produce more stable hemodynamic and respiratory profile that were tested and found to be true in group of patients receiving GA (27)

The level of sedation can easily shift from conscious to deep sedation and result in the loss of protective reflexes and may cause problems in airway control [3]. Therefore, the sedation level should be monitored and managed carefully. For assessment of the level of sedation, bispectral index (BIS) monitoring may be used; it is an objective method and provides titration of drugs [6, 7]. The BIS is a complex mathematical evaluation of relevant, descriptive electroencephalographic parameters of the frontal cortex corresponding to varying levels of sedation [8]. Patients undergoing general anaesthesia require a BIS level of 40 to 60, and a level of approximately 80 is adequate for less invasive procedures, such as ERCP and endoscopic interventions [9].

Methods:-

After taking written inform consent, total 700 adult patients scheduled for therapeutic ERCP in VS General hospital during February 2017 to February 2018,were enrolled in the study. All patients were in ASA I–III physical status.

Study period:
February 2017 to February 2018

Study place:
VS General hospital & NHLM medical college, Ahmedabad,Gujarat, India.

Exclusion criteria:
Patients under the age of 18, those who were pregnant, chronically using opioid or α2 agonist drugs, had a history of allergy to one of the drugs used in the study, had severe cardiac or respiratory comorbidity, had second- or third-degree heart block, had ASA IV-V status, had a body mass index (BMI) over 36 kg/m2, patients with hypertensive disorders and those who refused to participate in the study were excluded from the study.

The patients were randomized to two groups by odd & even numbers put in opaque sealed envelopes. Execution of Randomisation at time of Premedication.

Group Allocation

Group l : Inj Midazolam-0.02 mg/ kg+ Dexmedetomidine 1 mcg/kg bolus followed by 0.5 mcg/ kg/ hour+ Iv propofol alliquotes to maintain BIS 70-80

Group ll inj.Ketamine 0.5 mg/kg+Dexmedetomidine 1 mcg/kg bolus followed by 0.5 mcg/ kg/ hour+ Iv propofol alliquotes to maintain BIS 70-80

In the operating room, baseline haemodynamic & respiratory parameters of patients were monitored like heart rate (HR), mean arterial blood pressure (MAP), respiratory rate (RR) and arterial oxygen saturation (SpO2), BIS Monitoring was also applied to all patients. Nasal cannula was inserted & 4 litres oxygen started.BIS values range between 0 and 100 (0: no cortical activity or coma; 40–60: unconscious; 70–90: varying levels of conscious sedation; 100: fully awake). In this study, the BİS value was maintained at 70–80, which was sufficient for conscious sedation.Lateral/ semiprone position for ERCP was given to patients.

Propofol was given as 50 mg first bolus dose and intermittent alliquotes of 20 mg to achieve a BIS score between 70 and 80) was given for sedation in both groups. ERCP was initiated after achieving an adequate sedation level (BIS: 70–80). The ERCP was performed by an experienced gastroenterologist in a standard manner. The vital data (HR, MAP, RR and SpO2) were recorded periodically during the procedure. When there was more than a 20% increase or decrease in heart rate and blood pressure, it was evaluated as a side effect. Other side effects (such as arrhythmias, nausea-vomiting and shivering) were also recorded. In the case of bradycardia (HR < 40 beat/min), hypotension (MAP < 50 mm Hg), bradypnea (RR < 10/min) or desaturation (SpO2 < 92%), adequate therapeutic applications were carried out in each situation (atropine 0.5 mg for bradycardia, 0.9% saline infusion (500 ml/h) for hypotension, In case of respiratory depression, patients were planned to be supported with a jaw thrust maneuver and ventilation with a bag&mask & changing position to supine. During the procedure, Any airway intervention required was notified& patients were managed by Endotracheal intubation & Standard General anaesthesia instead of Sedoanalgesia. propofol doses were also administered to maintain BIS levels between 70 and 80, and the cumulative dose was recorded. With termination of ERCP, drugs were ceased, and Duration of procedure was notified & defined as time at which Gastroenterologist started procedure to end of procedure where endoscope removed from patients. patients were evaluated with an Aldrete score [10] for defining the recovery period . The period between the termination of ERCP and time to achieve an Aldrete score of 9 was accepted as the recovery time,time to eye-opening,verbalres verbal response& cooperation time also noted..

Results:-

Table 1:- Demographic parameters.

Parameters	Group ll (n=350)	Group ll (n=350)	P value	Inferences
Age(yrs)	58+/-4	54+/-6	>0.05	NS
Gender(M:F)	250:100	245:105	>0.05	NS
BMI	23+/-2	22+/-3	>0.05	NS
ASA grade(l/ll/lll)	150/100/100	148/102/100	>0.05	NS
Duration of procedure (mins)	24+/-8	22+/-9	>0.05	NS

Table 2:- Mean BIS score.

BIS	Group l (n=350)	Group ll (n=350)	P value	Inferences
Baseline	90+/-1.2	92.2+/-0.8	>0.05	NS
5 min After premedication	82+/-0.6	82+/-1	>0.05	NS
10 min	74.4+/-1.3	75.2+/-0.6	>0.05	NS
20 min	71.6+/-1.8	70+/-2.1	>0.05	NS
30 min	71+/-1.0	70+/-2	>0.05	NS

Table 3:- Recovery parameters.

Recovery Parameters (In mins)	Group l (n=350)	Group ll (n=350)	P value	Inferences

Time to modified alderte score of 9	9.0+/-2.2	6.2+/-1.1	<0.001	HS
Eye opening	6.9+/-2.2	4.2+/-2.1	<0.001	HS
Verbal response	8.1+/-3.2	6.1+/-2.1	<0.001	HS
Cooperation time	10.7+/-3.8	7.4+/-1.4	<0.001	HS

Table 4:- Mean arterial pressure.

Mean arterial pressure (mm of Hg)	Group l (n=350)	Group ll (n=350)	P value	Inferences
Base line	84+/-4	82+/-2	>0.05	NS
5 min after Premedication	78+/-2	84+/-2	>0.05	NS
10min after premedication	75+/-2	80+/-2	<0.05	S
20 min after Premedication	68+/-2	78+/-2	<0.05	S
30 min after Premedication	70+/-2	77+/-3	<0.05	S

Table 5:- Heart Rate.

Heart Rate (beats/ min)	Group l (n=350)	Group ll (n=350)	P value	Inferences
Baseline	78+/-4	76+/-5	>0.05	NS
5 min after Premedication	76+/-2	74+/-3	>0.05	NS
10 min after Premedication	66+/-1	74+/-2	<0.05	S
20 min after Premedication	64+/-4	72+/-2	<0.05	S
30 min after Premedication	68+/-6	72+/-4	<0.05	S

Table4&5 show stable haemodynamic variables in group ll in comparison to group l.

Table 6:- Total propofol consumption.

Total propofol (mg)consumed	(Group l n=350)	Group ll (n=350)	P value	Inferences
Propofol	205+/-80	155+/-20	<0.001	HS

Table 6 showed less total propofol required in group ll.

Table 7:- Complications.

Complications	Group l (n=350)	Group ll (n=350)	P value	Inferences
Nausea Vomiting	7(2%)	5(1.4)	>0.05	NS
Shivering	0	0	-	-
Aponea	0	0	-	-
Arrythmia	0	0	+	-
Airway interventions	7(2%)	5(1.4%)	>0.05	NS

Complications were similar & minimum in both groups (not more than 2 %). There was no in-hospital mortality was there in any patients in both groups.

Discussion:-

ERCP are done as diagnostic & therapeutic purpose world wide since last decade.Most of them are done under sedation.Adequate sedation during endoscopic procedures, especially for therapeutic ERCP, directly affects the procedure time and success. Propofol is widely used for this purpose, and it is postulated to be effective in sedation

for ERCP. In a meta-analysis, propofol-induced respiratory depression and hypotensive effects were shown to be more common than in single use. In the same article, it was reported that recovery time was shorter and patient cooperation was better when used with opioids or midazolam [11]. However, higher doses of propofol may cause platelet aggregation [12], metabolic acidosis [13], delayed awakening [14], depression of the hypoxic ventilator response, and cardiorespiratory depression. Therefore, to decrease these adverse effects of propofol, it is commonly combined with other sedatives. Peden et al. [15] reported that the addition of dexmedetomidine to propofol caused a reduction in the propofol requirement and a decrease in the plasma concentrations of propofol. In our study, we found statistically significantly lower propofol consumption in the dexmedetomidine group.

In a study, it was demonstrated that conscious sedation for diagnostic and therapeutic ERCP can be successfully and safely achieved using midazolam [16].

Seifert et al. [3] compared propofol alone and propofol-midazolam combinations in interventional endoscopy. The authors found similar sedative efficacy in both groups but longer recovery times in the propofol-midazolam combination group (19 ±7 vs. 25 ±9 min; $p < 0.01$). This finding may be due to the relatively slower elimination half-life of midazolam. In our study, the shorter recovery time in the dexmedetomidine group may be secondary to both the short elimination half-life of dexmedetomidine and less propofol consumption.

A study by **Lee etal**. [18] compared the sedative effect and adverse events of midazolam–meperidine–dexmedetomidine and midazolam–meperidine during ERCP and found that adding dexmedetomidine to the midazolam–meperidine regimen was more effective and safe during ERCP compared with a midazolam–meperidine regimen.

We used BIS measurements to objectively achieve adequate sedation levels. Thus, the total sedative agent dose did not depend on the operator's subjective evaluation. We found that the total propofol consumption was lower in group ll compared to Group l as shown in table 6. This result is important, and it may be postulated that dexmedetomidine might be a good alternative for sedation with the propofol sparing effect. It can be postulated that due to less propofol consumption in the dexmedetomidine group, cost-effectiveness in this group is better. This approach reduces the possible respiratory depressive effect of propofol by decreasing the total consumption. In an experimental study with a rabbit model, the researchers found that ventilator depression was higher in treatment with propofol and midazolam. The depression was lowered with dexmedetomidine [19]. This outcome is an important respiratory protective effect for ambulatory sedation.

In a study,**Muller S& Erdman MJ** significant decreases in MAP and HR occurred if dexmedetomidine was used as monotherapy [17, 20]. This effect may be due to the higher doses of the drug, and decreased sympathetic outflow and circulating catecholamine levels [21]. Gastrointestinal endoscopy studies using dexmedetomidine and midazolam showed that the two agents do not differ from each other in terms of hypoxia, bradycardia and hypotensive effects [22]. Again,**Nishizama T** in his meta-analysis, patients who were treated with dexmedetomidine for longer procedures, such as ERCP or endoscopic mucosal resection, reported less restlessness [23]. In our study, we did not find any respiratory or hemodynamic differences (MAP and HR) between the groups. In group analysis, the MAP decreased during the procedure but did not exceed 20% compared to the baseline values. **Jackob SM** showed that the most important cause of hemodynamic side effects due to dexmedetomidine is the high-speed and long-term induction dose [24]. It has also been reported by **Kontak AC** that it may have hypertensive effects when used as the sole agent [25].

When the side effects were examined in our study, no difference was observed in terms of restlessness between the groups, since sedation was achieved at the same level as BIS monitorization.There was no difference in nausea-vomiting between the groups because antiemetic treatment was applied in both groups.**P.Sethi,**etal have compared Dexmedetomidine & Midazolam for ERCP & concluded that Dexmedetomidine provide better sedation for ERCP.(28)

Conclusion:-

Ketamine -Dexmedetomidine combination with propofol is a more safe alternative than Midazolam-Dexmedetomidine combination with propofol for sedation in ERCP patients.

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