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Effectiveness of Dexmedetomidine to Midazolam as Premedication for Sedation in Patients undergoing Endoscopic Retrograde Cholangiopancreatography

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ABSTRACT
Background: *Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive procedure and produces substantial discomfort to the patient. Conscious sedation is preferred for sedation in ERCP. Most commonly used drug for conscious sedation is propofol. Different adjuvants are also used with propofol as premedication like midazolam, fentanyl, remifentanil, dexmedetomidine etc.*
Objective: *The aim of the study was to evaluate the effectiveness of dexmedetomidine and midazolam as premedication for sedation in patients undergoing Endoscopic Retrograde Cholangiopancreatography (ERCP).*
Methods: *This Randomized Controlled Trial was carried out in Dhaka Medical College Hospital, Dhaka. A total sixty patients were enrolled according to inclusion and exclusion criteria. Patient randomization were done by computer generated random number table. They were divided into two groups, 30 in each. Group A (n=30) patients received midazolam 0.05 mg/kg IV bolus and group B (n-30) patients received dexmedetomidine 1 µg/kg IV bolus over 10 min prior to propofol administration. Depth of sedation by Ramsay Sedation Scale, hemodynamics, spo_2, pain by F-PRS, recovery time, total requirement of propofol, surgeon's satisfaction by Likert scale were noted and analyzed statistically by SPSS version 24.*
Results: *After statistical analysis there were no statistically significant difference found in demographic characteristics of the patients in between two groups. Among hemodynamics, HR of group B patients were comparatively lower than that of group A patient which was statistically significant as p value was <0.05. In respect of onset of sedation and recovery time, statistically significant difference was found between two groups as p value was <0.05. There was no statistically significant difference in F-PRS between two groups except in 20min time of interval. There was statistically significant difference found in total propofol consumption in between two groups as p value were <0.05. Surgeon's satisfaction was more in group B than group A, which was also statistically significant as p value was <0.05.*
Conclusion: *Dexmedetomidine as premedication is more effective than midazolam for sedation in patients undergoing ERCP.*
Keywords: *Conscious sedation, Dexmedetomidine, Midazolam, Propofol, ERCP.*

I. INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) plays very important role in the diagnosis and treatment of the pancreaticobiliary pathologies and its use has been increased in recent years. It is a complex and potentially uncomfortable procedure that necessitates adequate sedation for successful completion. ERCP procedure involving papillotomy, sphicterotomy, dilatation of ampulla of vater, stent removal needed for moderate sedation. [1] There are many challenges during moderate sedation for ERCP in endoscopy unit; as remote location, less familiar area, semi prone position, lengthy procedure and shared airway. [2] It should ensure immobility,

sufficient analgesia, avoid coughing or gagging and allow patient comfort to avoid any complication as perforation or peritonitis.

There has been a considerable progress in practice of sedation and analgesia in the era of endoscopy. ERCP performed under moderate sedation, a practice that is referred to as "conscious sedation". At the level of moderate sedation, the patient, while maintaining ventilatory and cardiovascular function, is able to make purposeful response to verbal or tactile stimulation. [3] Conscious sedation is required mainly to minimize patient anxiety, discomfort and enhance patient co-operation throughout the procedure and facilitate the performance of the procedure by the endoscopists. [4] Propofol is a widely used agent for conscious sedation during ERCP. It is an alkylphenol, has sedative-hypnotic effects mediated by GABA receptor with faster onset of action and shorter recovery time. It also has anticonvulsant, amnestic and antiemetic properties. It has dose dependent cardiac effect which together with respiratory depression and insufficient analgesia present the common adverse effects observed with it. [5]

Hence adjunct use of drug, of different pharmacological properties, as premedication may decrease total propofol requirement and consequently its adverse effects while increasing the level of analgesia. There are various agents used as premedication such as midazolam, fentanyl, remifentanil, dexmedetomidine etc. Most endoscopists favor midazolam because of its faster onset and shorter duration of action. It is water soluble and the shortest acting benzodiazepine available. [6] The repeated doses of midazolam lead to prolonged sedation because of accumulation of its active metabolites. It can produce respiratory depression also, as being a benzodiazepine, it decreases the sensitivity of respiratory center to carbon dioxide. [7] Dexmedetomidine, the selective α-2 adrenergic agonist, though has sedative and analgesic role without major changes in respiratory parameters, was found inferior to propofol in ERCP sedation as a single agent. Still, the drug was able to gain popularity in different other types of procedural sedations, sedation in intensive care setting and also as an adjunct in anesthesia practice. [8]

In past few years dexmedetomidine has been widely used for minor procedure needing conscious sedation. Dexmedetomidine because of its unique properties such as analgesia and minimal respiratory depression is considered a useful and safe drug for day care procedures. The patient who had received dexmedetomidine for sedation during surgical period had significantly decreased pain scores and reduces analgesic. [9] It provides excellent sedation that can be easily titrated, especially in non-intubated patients. Hypotension, hypertension, bradycardia, dry mouth and nausea is the common adverse effects. [10] For providing unique conscious sedation which agent premedication is very important to make the procedure safer and more comfortable both for the patient and endoscopist. For this reason, the aim of this study to assess the effectiveness of dexmedetomidine to midazolam as premedication for sedation in patients undergoing ERCP.

II. METHODOLOGY

This is a randomized controlled trial study. This study was carried out on 60 patients in the department of Anesthesia, Analgesia, Palliative and Intensive care medicine, Dhaka Medical College Hospital, Dhaka, Bangladesh in the period from March 2019 to July 2022. Adult patients scheduled for ERCP with ASA I, II, III were included in this study. Patients with known hypersensitivity to study drug, difficulty in communication due to language problem or distress, long term opioid use or alcohol use, uncontrolled comorbidity and whom converted to general anaesthesia were excluded from the study. Purposive sampling technique was followed. Patients enrolled and divided into two groups, 30 in each. Randomization was done by computerized random number table Group A patients received midazolam 0.05mg/kg I/V bolus and group B patients dexmedetomidine 1µg/kg I/V bolus over 10 minutes. After receiving premedication, propofol 1 mg /kg I/V bolus was used in both groups then given intermittently 20mg I/V to achieve Ramsay sedation scale-4, Depth of sedation, haemodynamic, SPO_2, pain during procedure, recovery time, total requirement of propofol, adverse effects, surgeon's satisfaction were observed and noted. After collection, the data were checked, followed by editing, compiling and coding. Statistical analysis of the results obtained by using Statistical Packages for Social Sciences (SPSS-24).

III. RESULTS

Table 1: Distribution of the patients according to the demographic characteristics in both groups. (n=60)

Characteristics		Group A (n=30)	Group B (n=30)	P value
Age(years)		57.6±4.7	55.4±4.2	0.65
Weight(kg)		55.3±5.2	54.6±5.4	0.53
ASA				
	Class I	10(32.3%)	11(36.7%)	0.69
	Class II	20(67.7%)	19(63.3%)	0.72
Gender				
	Male	11(36.7%)	12(40%)	0.73
	Female	19(63.3%%)	18(60%)	0.72
Duration of procedure (min)		28.4±4.7	27.8±4.9	0.531

Values are expressed as Mean±SD and within parenthesis percentage (%) over column in total. Student t-test and chi-squared Test (x^2) were performed. P value <0.05 considered statistically significant.

On the basis of demographic characteristics of the patients, the mean age of patient was 57.6±4.7 years in group A and 55.4±4.2 years in group B. Maximum patient had ASA Class II in both groups. Most of the patients had female gender in both groups. Average duration of procedure was (28.4±4.7 and 27.8±4.9) min in group A and group B.

There had no statistically significant difference in any characteristics of the patients between two groups as p value was not <0.05.

Table 2: Assessment of onset of sedation time by RSS score in two groups.

Variables	Group A (n=30)	Group B (n=30)	P value
Onset of sedation time (RSS>4) (min)	3.68±1.25	6.25±2.45	0.009ss

Values are expressed as Mean±SD. Student t-test was performed to analyze the data. P <0.05 considered as statistically significant. ss statistically significant.

On assessment of onset of sedation time by RSS score, onset of sedation was earlier in group A than group B. The difference was statistically significant as p value was
<0.05.

Table 3: Comparison of RSS scores of the patients between two groups (n=60)

RSS score	Group A (n=30)	Group B (n=30)	P value
Beginning of ERCP	4.1±0.8	4.15±0.8	0.174
5 min	4.2±0.6	4.1±0.7	0.173
10 min	3.1±0.5	4.2±0.5	0.033ss
15 min	3.6±0.9	4.1±0.6	0.031ss
20 min	3.3±0.6	4.3±0.5	0.028ss
25 min	4.2±0.7	4.15±0.6	0.163
30 min	3.9±0.8	4.10±0.4	0.141
35 min	3.6±0.6	3.8±0.8	0.128
40 min	3.7±0.9	3.5±0.8	0.216

Values are expressed as Mean±SD. Student t-test was performed to compare the mean RSS score of both groups. P value <0.05 considered as statistically significant.
ss= statistically significant.

RSS score was higher among group Bat all the time of interval. The RSS score had been significantly low in group A at 10min, 15min and 20min time of interval, which was also statistically significant as p value was <0.05 at those points of time, The scores were higher at this point of time where the patients deeply sedated. In both groups RSS score was increased after giving rescue sedative, At the end of procedure there was no significant difference in RSS score between two groups as p value was not <0.05**.**

Table 4: Comparison of Heart rate of the patients between two groups. (n=60)

Heart rate (beat/min)	Group A (n=30)	Group B (n=30)	P value
Baseline	79.2±6.8	78.8±5.6	0.726
5 min	74.9±5.5	73.9±5.3	0.728
10 min	74.5±5.5	62.6±5.1	0.034ss
15 min	80.8±5.6	67.3±5.3	0.013ss
20 min	78.4±8.3	63.2±5.5	0.017ss
25 min	79.5±6.9	64.3±6.2	0.021ss
30 min	78.7±5.2	66.3±5.8	0.024ss
35 min	80.1±5.9	68.5±6.3	0.025ss
40 min	79.4±6.3	67.2±6.3	0.016ss

Values are expressed as Mean±SD. Student t-test was performed to compare the mean heart rate of both groups. P value <0.05 considered statistically significant.
ss= statistically significant.

In respect to heart rate, group B patient had comparatively lower HR than group A throughout the procedure which was statistically significant as p value was <0.05.

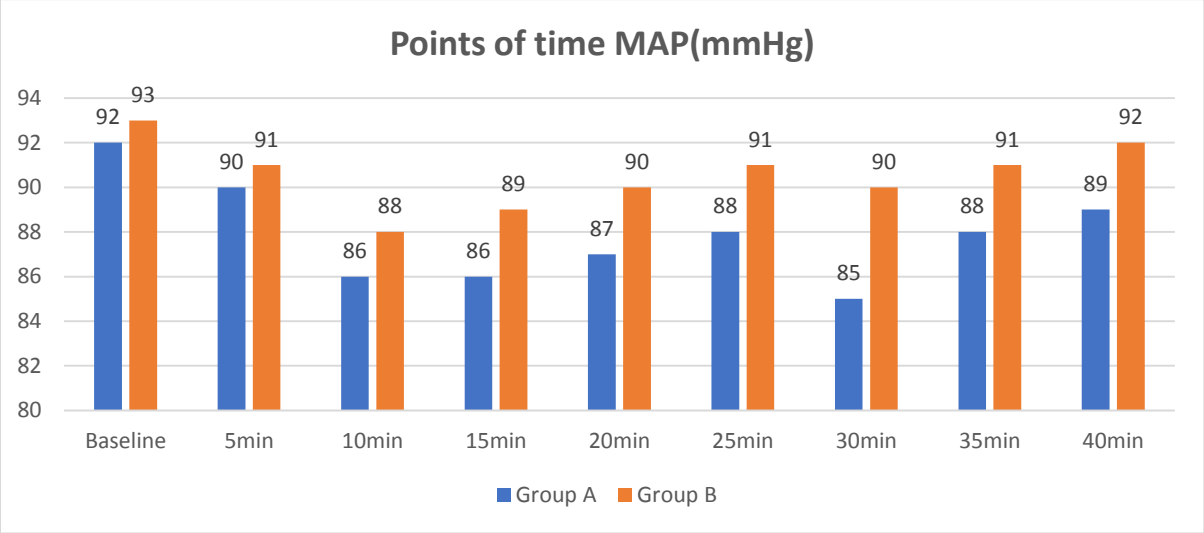

Figure 1: Mean arterial pressure (MAP) during ERCP period between two groups. Student t-test was performed to compare the mean of MAP.

There had been no significant difference in mean arterial pressure (MAP) between two groups as p value was not <0.05 during the ERCP procedure.

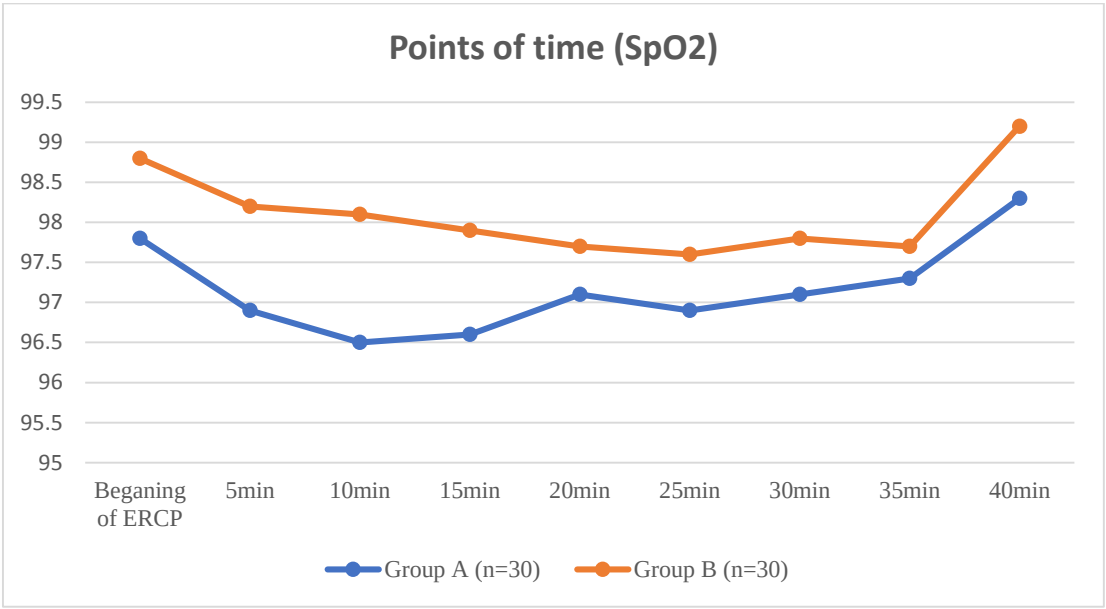

Figure 2: Comparison of SpO_2, during ERCP period between two groups. Student t-test was performed to compare the mean SpO_2, of both groups.

On consideration of SpO_2, of the patients during ERCP period, there were no statistically significant difference was found between two groups as p value was not <0.05.

Table 5: Comparison of F-PRS of patients during ERCP period in two groups

F-PRS	Group A (n=30)	Group B (n=30)	P value
Baseline	1.5±0.3	1.3±0.2	0.143
5 min	1.8±0.4	1.5±0.2	0.148
10 min	2.2±0.5	1.8±0.4	0.136
15 min	2.3±0.4	1.9±0.5	0.127
20 min	3.5±0.6	2.1±0.4	0.016[ss]
25 min	3.3±0.5	2.9±0.6	0.134
30 min	3.1±0.4	2.8±0.5	0.141
35 min	2.7±0.3	2.6±0.4	0.169
40 min	2.5±0.4	2.4±0.5	0.165

Values are expressed as Mean±SD. Student t-test was performed to compare the mean F-PRS of both groups. ss= statistically significant.

F-PRS score was not statistically significant between two groups at all-time interval except around 20 min which is statistically significant as p value was <0.05 at those point of time, Mean value of F-PRS was very low in group B and the patients seldom need additional analgesia, but in group A patient need additional dose of analgesia as they maintain high F-PRS. This might be due to cause of pain during the procedure.

Table 6: Assessment of total propofol consumption and total opioid consumption of the patients during ERCP period. (n=60)

Variable	Group A (n=30)	Group B (n=30)	P value
Total propofol consumption(mg)	109.8±9.3	75.5±6.2	0.011[ss]
Total opioid consumption (µg)	70.7±9.4	52.5±6.7	0.011[ss]

Values are expressed as Mean±SD. Student t-test was performed to analyze data. P<0.05 considered statistically significant. ss= statistically significant. Total propofol consumption was greater (109.8±9.3 vs 75.5±6.2) mg in group A than group B. Patients in group B had significantly lower opioid requirements compared to group A during the ERCP procedure. Both variables were statistically significant as p value was <0.05.

Table 7: Assessment of Recovery time of the patients in two groups. (n=60)

Variable	Group A (n=30)	Group B (n=30)	P value
Recovery time after ERCP procedure (Modified Aldretes Score>9) (min)	10.70±2.65	5.65±1.45	0.015[ss]

Values are expressed as Mean±SD. Student t-test considered as statistically significant. ss= statistically significant.

After observing recovery time, mean recovery time after ERCP procedure was earlier in group B than group A. After statistical analysis the difference was statistically significant as p value was <0.05.

Table 8: Assessment of Adverse effects of the patients during ERCP period. (n=60)

Adverse effects	Group A (n=30)	Group B (n=30)	P value
Gagging	4 (13.34%)	2(6.67%)	0.028[ss]
Cough	6(20.0%)	2(6.67%)	0.021[ss]
Desaturation	3(10.00%)	1(3.33%)	0.061
Bradycardia	1(3.34%)	4 (13.34%)	0.025[ss]
Hypotension	5(16.67%)	2(6.67%	0.023[ss]

Values are expressed within parenthesis percentage (%) over column in total. Chi square test (x^2) was done to analyze the data. ss= statistically significant.

Table 9: Comparison of the level of satisfaction among the surgeons between two groups. (n=60)

Level of satisfaction	Group A (n=30)	Group B (n=30)	P value
Very Satisfied	3(10.00%)	7(23.4%)	0.017[ss]
Satisfied	19(63.4%)	21(70.00%)	0.074
Dissatisfied	6(20.00%)	1(3.3%)	0.012[ss]
Very Dissatisfied	2(6.3%)	1(3.3%)	0.083

Values are expressed within parenthesis percentage (%) over column in total. Chi square test (x^2) was done to analyze the data. ss= statistically significant.

The level of satisfaction was much higher in group B. In case of group B 23.4% of the ERCP procedure were very satisfied by the surgeon where as 10% in group A, the difference was statistically significant because p value was <0.05. In group A 20% of the ERCP was also procedure dissatisfied in comparison to group B 3.3%, which was also statistically significant as p value was <0.05.

IV. DISCUSSION

This study was conducted in Department of Anaesthesia, Analgesia, Palliative and Intensive care Medicine, Dhaka Medical College and Hospital to assess the effectiveness of Dexmedetomidine as premedication in patient undergoing ERCP. Sample size was reduced than calculated size, and it was 60 (30 in each group) due to lack of time and covid pandemic situation. When we observed the demographic characteristics of the patients, such as age, gender, BMI, ASA class and the duration of procedure, there had been no statistically significant difference in any characteristics of the patients between two groups as p value was not <0.05. Another study also

compared two groups in respect to demographic characteristics and found no significant difference between two groups as p value was not <0.05. [1]

In this study, onset of sedation was early in group A but level of sedation (RSS) was more stable in group B. RSS score frequently fall below 4 in group A in comparison to group B. The RSS score were significantly low in group A at 10min, 15 min, 20 min of time interval, RSS score was higher among group B at all the time of interval.

In a study, patients had rapid onset of sedation in midazolam group but did not achieve the adequate depth of sedation as compared to dexmedetomidine group, probably because of method of administration IV bolus versus infusion. [11] Muller et al., (2008) concluded that dexmedetomidine associated with higher hemodynamic instability. [7] This finding is different from our study. This difference may be due to high doses of dexmedetomidine, which was used alone during the entire procedure. In other study, also found statistically significant lower heart rates in dexmedetomidine group compared with midazolam group and comparatively stable MAP in dexmedetomidine group. [12, 13]

In this study, on consideration of SpO_2, of the patients during ERCP period in both groups, there had no statistically significant difference in any change of SpO_2, of patients between two groups as p value was not <0.05.

In a study, there was also no statistically significant decrease in SpO_2; during the procedure when comparable in between two groups. [4] Emad Salem et al. (2019) used dexmedetomidine during sedation of obstructive sleep apnea obese patients for upper gastro endoscopic procedures and concluded that dexmedetomidine can reduce the incidence of respiratory depression. [14]

In this study, after observing F-PRS between two groups statistically significant difference was found at 20 min time of interval as p value <0.05. Mean value of F-PRS was very low in group B and the patients seldom need additional analgesia. But in group A patients need additional dose of analgesia as they maintain high F-PRS. Dexmedetomidine binds with alpha 2 receptors at dorsal horn of spinal cord and seems to employ analgesic effect. [10]

Another study found statistically significant difference in F-PRS at 5 and 10 min in between two groups. And dexmedetomidine showed better F-PRS Score. At 15 min of procedure, both groups had similar F-PRS. [4] Kilic et al., (2011) found that there were no significant differences in F-PRS score between two groups during the procedure. [15]

In this study, total propofol requirement was less in group B than group A during the procedure and the difference was statistically significant as p value was <0.05. A synergistic effect was seen when these sedative drugs were used in combination with propofol. Synergism was more in dexmedetomidine group than midazolam group.

Mukhopadhyay et al., (2015) evaluated the efficacy of a dexmedetomidine as an add-on for prolonged deep sedation for ERCP and to compare three deep sedation regimens regarding safety and efficacy. [16] They concluded that the sedato-analgesic propofol-midazolam regimen, cocktail was superior to the conventional dexmedetomidine as add-on increased the efficacy and safety of sedato-analgesic cocktail. It reduces propofol requirement, helps to maintain the patient in a safe and more stable level of sedation and increases satisfaction of the anesthetist. Similar observation also found another study. [17]

In this study, after observing recovery time (10.70+2.65 vs 5.65+1.45) min after ERCP procedure in both groups, statistically significant difference was found as p value was <0.05. Midazolam when used with propofol provide faster onset of sedation but did not produce quality sedation. So, need more incremental sedative and analgesic to maintain expected level of sedation, thus leads to prolong recovery time. The characteristic arousable sedation action of dexmedetomidine can be explained by its action on alpha 2 adrenoceptors in locus ceruleus in the brain stem.

Similar observation also found by Tomar GS et al. [18] But another study showed recovery times between two groups were very similar. The reason for this might be their duration of procedure relatively short compared to our study. Adverse effects like gagging, cough, desaturation and hypotension were more in group A than group B. Bradycardia was more in group B than group A and the difference was statistically significant as p value was <0.05. In other study, no intraoperative or post operative adverse effects were reported in dexmedetomidine group. [19]

In this study, surgeon's satisfaction was assessed by Likert scale and there was statistically significant differences found between two groups. Surgeon's satisfaction was more in group B than group A. This may be explained, as adequate sedation depth, less pain, less adverse effects like gagging, cough, agitation in dexmedetomidine group facilitate surgeon to perform successful intervention. Other study found similar observation that surgeon satisfaction was more in dexmedetomidine group. [15]

It was observed that the dexmedetomidine group had a stable level of sedation, rapid recovery time and less adverse events compared with the midazolam group. On the other hand, our study suggests that adjunctive

use of dexmedetomidine reduces propofol and fentanyl requirements and increase surgeon's satisfaction during ERCP.

Limitation of the study

The limitations of the study as follows: a) Sample size was small due to lack of patient availability in the situation of COVID-19 pandemic. b) Bispectral index (BIS) monitoring did not used for assessing the adequacy of sedation.

V. CONCLUSION

Dexmedetomidine as premedication is more effective than midazolam for sedation in the patient undergoing ERCP.

RECOMMENDATION

Dexmedetomidine as premedication can be used for sedation in patient undergoing ERCP.

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