Dexmedetomidine *versus* Ketofol for Moderate Sedation in Endoscopic Retrograde Cholangiopancreatography

Nida Aqeel, Muhammad Qamar Abbas, Syed Muhammad Abbas, Muhammad Faisal Farooq, Muhammad Siddique and Shakeel Malik

Department of Anaesthesia, SICU and Pain Management, Sindh Institute of Urology and Transplantation, Karachi, Pakistan

ABSTRACT

Objective: To compare the efficacy of dexmedetomidine *versus* ketofol for moderate sedation in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP).

Study Design: Randomised controlled trial.

Place and Duration of the Study: Department of Anaesthesia, SICU and Pain Management, Sindh Institute of Urology and Transplantation, Karachi, Paksitan, from December 2021 to June 2022.

Methodology: Sixty-two patients aged 20-60 years of any gender scheduled for elective ERCP were included. Patients were randomly divided into Dexmedetomidine group (2ml ampule of 100ug/ml diluted in 18ml of normal saline) and Ketofol group (2ml ketamine and 10ml of propofol 1% diluted in 8ml of normal saline) for sedation. The mean difference in time to achieve Ramsay Sedation Scale (RSS) score of 4 and Modified Aldrete's Score (MAS) of 9 were noted as outcomes in each group. In addition, complications during the procedure and recovery were also noted.

Results: The mean age was 39.15 ± 9.82 years. There were 33 (53.2%) males and 29 (46.8%) females. The mean time to achieve RSS 4 was significantly lower in patients who were treated with Dexmedetomidine as compared to Ketofol, i.e., 11.84 ± 1.77 minutes *vs.* 13.10 ± 1.64 minutes respectively (p-value 0.005, 95% CI -2.12 to -0.39). Similarly, the mean time to achieve MAS score 9 was significantly lower in patients who were treated with Dexmedetomidine as compared to Ketofol, i.e., 11.19 ± 1.72 minutes *vs.* 12.23 ± 1.84 minutes, respectively (p-value 0.026, 95% CI -1.94 to -0.13).

Conclusion: Dexmedetomidine proved to be more effective than Ketofol for sedation in ERCP, achieving faster sedation and quicker recovery.

Key Words: *Dexmedetomidine, Ketofol, Sedation, Endoscopic Retrograde Cholangiopancreatography*.

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INTRODUCTION

The utilisation of endoscopic retrograde cholangiopancreatography (ERCP) for both diagnosis and treatment of pancreaticobiliary diseases has witnessed a significant surge in recent times.[1,2] Conscious sedation is routinely administered during ERCP procedures to enhance patient comfort and facilitate gastroenterologist interventions.[3,4] However, it is essential to acknowledge that sedation in ERCP carries the potential for adverse intraoperative events.[5,6] Various pharmacological agents, including midazolam, propofol, ketamine, and dexmedetomidine are available, offering rapid induction and smooth recovery.[3-8]

Correspondence to: Dr. Syed Muhammad Abbas, Department of Anaesthesia, SICU and Pain Management, Sindh Institute of Urology and Transplantation, Karachi, Pakistan
E-mail: smabbas69@hotmail.com
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Dexmedetomidine, a relatively recent addition to the pharmacological arsenal, has gained prominence as an alternative sedative in conscious sedation. It acts as a potent and highly selective α-2 adrenergic receptor agonist, demonstrating sympatholytic, sedative, amnestic, and analgesic properties.[9] Dexmedetomidine stands out for its unique ability to provide conscious sedation and analgesia without inducing respiratory depression. However, it is crucial to note the potential side effects, such as bradycardia and hypotension.[10]

Ketamine, characterised as an N-methyl-D-aspartate (NMDA) receptor antagonist, offers sedative, analgesic, and amnestic effects without causing respiratory depression. On the other hand, propofol, a sedative-hypnotic agent, boasts a rapid onset and fast recovery time.[6]

The ERCP procedure, vital for diagnosing and managing biliary and pancreatic disorders, has become increasingly common. Recognised as a complex, protracted, and uncomfortable procedure, ERCP necessitates adequate sedation and analgesia to mitigate agitation and discomfort, which have been identified as potential factors contributing to ERCP failure. Despite the escalating demand for ERCP, there remains a dearth of local and international studies comparing the efficacy of these two phar-

macological agents in patients undergoing ERCP, leading to clinical equipoise. Sedation in gastrointestinal endoscopy not only alleviates patient discomfort but also enhances operator performance. This study aimed to address this gap by providing current, locally relevant statistics, with the objective of determining the comparative effectiveness of dexmedetomidine and ketamine-propofol combination during the ERCP procedures. The outcomes of this study could contribute to the refinement of management protocols, optimising the balance between the patient comfort and procedural success.

METHODOLOGY

This randomised controlled trial was conducted at the department of Anaesthesia, SICU and Pain management, Sindh Institute of Urology and Transplantation, Karachi, Pakistan, from December 2021 to June 2022. Ethical approval was obtained from the Ethical Review Committee prior to the commencement of the study (ERC # SIUT-ERC-2021/PA-268). Signed informed consent was also obtained from the study participants prior to the enrolment in the study.

Patients aged 20-60 years of either gender scheduled for elective ERCP were included. All these patients had American Society of Anaesthesiologists (ASA) classification I or II. While those who were allergic to Dexmedetomidine, Ketofol, or related medications, BMI over 40 kg/m^2 (morbidly obese), had a history of stroke, renal impairment, chronic obstructive pulmonary disease, asthma, chronic liver disease, hypothyroidism, and congestive cardiac failure were excluded. Furthermore, pregnant, or breastfeeding women, and patients who reported chronic use of sedative medications or substance abuse, known contraindications to ERCP, and already enrolled in another clinical trial study were excluded.

The sample size of 62 patients was calculated by using the OpenEpi software where alpha was taken as 5%, power of the test 1-beta as 90, mean time to good recovery as 11.4 ± 0.5 minutes *versus* 12.5 ± 1.8 minutes.[10]

A brief history of demographic data was taken from each patient. Preoperative assessment included history, general physical examination, systemic examination, and routine laboratory investigations.

Sixty-two patients were randomly divided into two equal groups, 31 in each group, using computer randomisation (Figure 1). All patients were taken to the procedure room and venous access was secured on a non-dominant hand by 20G IV cannula, intravenous (I/V) fluid (ringer lactate or normal saline) was started by 8 ml/kg/h, and oxygen support was provided by nasal cannula at 4 litres per minute. Standard monitors were attached for heart rate (HR), non-invasive blood pressure (systolic and diastolic), mean arterial blood pressure (MAP), and peripheral oxygen saturation (SpO_2). Injection midazolam 0.05 mg/kg was also given I/V to every patient in both groups to decrease the anxiety of patients.

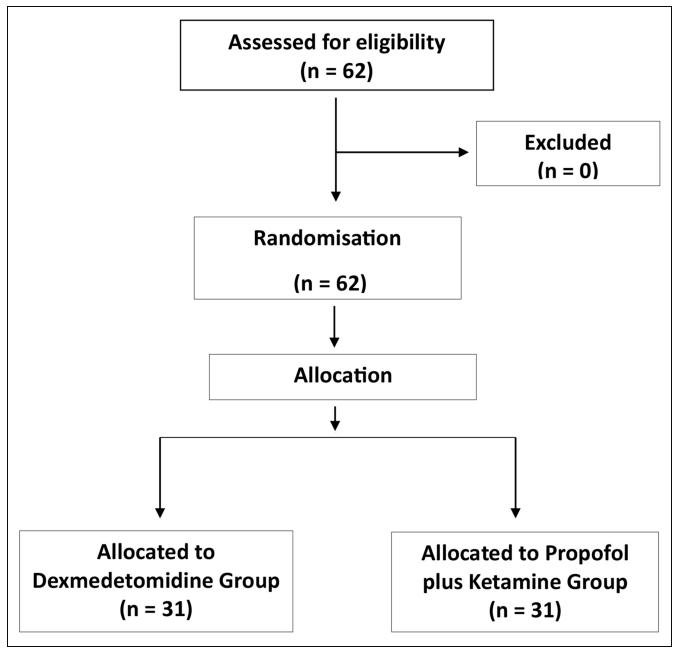

Figure 1: Consort flow diagram showing recruitment of the patients.

Patients received either Dexmedetomidine or Ketofol for sedation. All syringes and infusion sets were covered by silver paper and these infusions were labelled as infusion 1 or 2. In patients who received Dexmedetomidine, a 2ml ampule of 100ug/ml was diluted in 18ml of normal saline, making a total volume of 20ml. Patients received Dexmedetomidine as a bolus over 10 minutes in a dose of 1ug/kg followed by an infusion at the rate of 0.5 ug/kg/hr and it was labelled as "infusion 1". In the Ketofol group, 2ml ketamine (50mg/ml) and 10ml of propofol 1% (10mg/ml) were diluted in 8ml of normal saline. This mixture was 20ml each, making 5mg/ml of ketamine and propofol. Patients received 1mg/kg over 10 minutes followed by 50 ug/kg/min of infusion, labelled as "infusion 2".

During infusion, vitals were recorded at 0,1,3,5, and 10-minute intervals from the start, and the Ramsay Sedation Scale (RSS) score was recorded after every 1 minute. The RSS score was first noted at the initiation of the procedure and then monitored continuously at one-minute intervals. Both infusions were started as per the randomisation of groups. The mean difference in time to achieve adequate sedation and time to good recovery were noted as outcomes in each group. In addition, complications during the procedure and recovery were also noted. Adequate sedation was defined as the time from initiation of infusion to achieve an RSS score of 4. While Modified Aldrete's Score (MAS) was used to assess the recovery. Time from discontinuation of the infusion to achieving an MAS score of 9 was labelled as a good recovery.

Statistical Package for Social Sciences (SPSS) version 26 was used for the purpose of statistical analysis. Mean ± Standard Deviation (SD) was computed for quantitative variables such as age, time to achieve RSS, and time to achieve MAS. Frequency and percentages were calculated for gender, ASA status, diabetes, hypertension, smoking, cough during procedure, gagging during procedure, apnoea during procedure,

apnoea during recovery, and post-operative nausea and vomiting. A comparison was done to see the association of baseline characteristics, complications during procedure, and complications during recovery on the outcome. Chi-Square test was applied. Moreover, the mean difference of time to achieve RSS and time to achieve MAS were explored using Independent t-test. A p-value of ≤0.05 was considered significant.

RESULTS

Among 62 patients, mean age was 39.15 ± 9.82 years. Most of the patients were presented with ≤40 years of age, i.e., 39 (62.9%). There were 33 (53.2%) males and 29 (46.8%) females. ASA status I was observed in 17 (27.4%) patients and ASA status II was observed in 45 (72.6%) patients. Diabetes was observed in 13 (21.0%), hypertension in 14 (22.6%), and smoking in 21 (33.9%) patients. An insignificant association of baseline characteristics was observed in between the Dexmedetomidine group and the Ketofol group, except for smoking (Table I).

Table I: Baseline characteristics of the patients (n = 62).

Items	Dexmedetomidine Group	Keofol Group	p-value
Age, years			
≤40	22 (71.0)	17 (54.8)	0.189
>40	9 (29.0)	14 (45.2)	
Gender			
Male	18 (58.1)	15 (48.4)	0.445
Female	13 (41.9)	16 (51.6)	
ASA			
I	8 (25.8)	9 (29.0)	0.776
II	23 (74.2)	22 (71.0)	
Diabetes Mellitus	25 (80.6)	24 (77.4)	0.755
Hypertension	23 (74.2)	25 (80.6)	0.544
Smoking	17 (54.8)	4 (12.9)	<0.001

Chi-Square test was applied, p-value ≤0.05 was considered as significant. Group D; Dexmedetomidine group, Group K; Ketofol group, RSS; Ramasy Sedation Score, MAS; Modified Aldrete's Score.

Table II: Mean difference of time to achieve RSS 4 and MAS 9 (n = 62).

Items	Group	Mean ± SD	p-value	95% CI
Time to achieve RSS 4 (in minutes)	Group D	11.84 ±1.77	0.005	-2.12 to -0.39
	Group K	13.10 ±1.64		
Time to achieve MAS 9 (in minutes)	Group D	11.19 ±1.72	0.026	-1.94 to -0.13
	Group K	12.23 ±1.84		

Independent t-test was applied, p-value ≤0.05 was considered as significant. CI: Confidence Interval, Group D; Dexmedetomidine group, Group K; Ketofol group, RSS; Ramasy Sedation Score, MAS; Modified Aldrete's Score.

The mean time to achieve RSS 4 was significantly lower in patients who were treated with Dexmedetomidine as compared to those who were treated with Ketofol, i.e., 11.84 ± 1.77 minutes *vs.* 13.10 ± 1.64 minutes, (p=0.005, 95% CI -2.12 to -0.39). Similarly, mean time to achieve MAS score 9 was significantly lower in patients who were treated with Dexmedetomidine as compared to those who were treated with Ketofol, i.e., 11.19 ± 1.72 minutes *vs.* 12.23 ± 1.84 minutes, (p=0.026, 95% CI -1.94 to -0.13, Table II).

No complications were reported during the procedure, whereas postoperative nausea and vomiting were insignificantly higher in the Ketofol group compared to the Dexmedetomidine group, i.e., 7 (22.6%) and 4 (12.9%, p = 0.319).

DISCUSSION

The current study demonstrates that Dexmedetomidine achieves a significantly faster time to achieve adequate sedation, as indicated by a lower RSS score of 4, compared to Ketofol. Similarly, the time to achieve MAS of 9, representing a state of good recovery, is significantly shorter with Dexmedetomidine compared to Ketofol. These findings suggest that Dexmedetomidine may offer a more efficient and prompt onset of sedation during the ERCP procedures. In a previous study, there was a slightly longer time to achieve RSS of 4 in Ketofol group than Dexmedetomidine similar to the current study findings. However, the author stated that it was still in the acceptable range and due to slow onset of action of ketamine.[11] Moreover, recovery time was also good in Dexmedetomidine group than that of Ketofol.[11] Another study reported that Dexmedetomidine-propofol combination has shown better results than ketofol.[12] It is reported in the literature that variations in outcomes are attributed to the diverse proportions of the ketamine and propofol combination employed. A higher proportion of propofol in ketofol results in a more rapid initiation and cessation of the sedative effect.[13]

It is pertinent to acknowledge the current ambiguity surrounding the optimal sedation techniques for complex endoscopic procedures. The absence of a global consensus further extends to uncertainties regarding the choice of practitioners responsible for administering sedation and the most advantageous sedation approach specifically tailored for ERCP.[14] According to a research investigation, sedation administered by an anaesthesiologist proves to be a secure approach for patients undergoing ERCP. This method is correlated with a heightened success rate in ERCP, reduced procedural duration, and accelerated recovery post-anaesthesia.[14-16] Furthermore, both patients and endoscopists express a high level of satisfaction with this sedation approach.[14] However, few studies have also reported the favourable outcomes of patient-controlled sedation in ERCP.[17,18]

The quicker attainment of adequate sedation with Dexmedetomidine is a crucial consideration in the context of ERCP, a procedure known for its complexity and potential patient discomfort.[19,20] This advantage may contribute to improved procedural conditions, making it more feasible for both the patient and the gastroenterologist. The observed shorter recovery times with dexmedetomidine also hold implications for the overall efficiency and safety of the procedural sedation process. Comparatively, Ketofol, a combination of ketamine and propofol, is recognised for its sedative, analgesic, and amnestic properties. While the current study indicates a longer time to achieve adequate sedation and good recovery with Ketofol, it is crucial to consider the overall safety profile and potential advantages of each sedative in the specific clinical context of ERCP. A recent randomised controlled trial has reported more efficacy of the combination of ketamine and dexmedetomidine compared to Ketofol.[21]

The contribution of the current study lies in its focus on both the induction of sedation and the recovery phase, providing a comprehensive assessment of the two sedative agents. The results provide valuable insights for clinicians and anaesthesiologists in selecting the most suitable sedative for ERCP, taking into account factors such as procedural efficiency, patient comfort, and safety.

Despite the strengths of this study, including its randomised controlled design and focus on a specific patient population, certain limitations should be acknowledged. The sample size is relatively small, and the study duration is limited to a specific time-frame. Future research with larger cohorts and longer follow-up periods would enhance the generalisability and robustness of the findings.

The current study suggests that dexmedetomidine may offer advantages in terms of faster onset of sedation and shorter recovery times compared to ketofol in patients undergoing ERCP. However, the choice between these sedatives should be made based on a careful consideration of their respective benefits and potential side effects, tailored to the individual patient and procedural requirements. Further research and clinical trials are warranted to validate and expand upon these findings, ultimately refining sedation protocols and improving the overall experience and safety of ERCP procedures.

CONCLUSION

The study findings showed that dexmedetomidine is more effective than ketofol for sedation during elective ERCP procedures. Patients sedated with dexmedetomidine achieved the desired sedation level and recovery milestones more rapidly than those sedated with ketofol. Additionally, dexmedetomidine was associated with fewer haemodynamic fluctuations and post-procedural complications, suggesting it provides a more stable and comfortable sedation experience.

ETHICAL APPROVAL:
Ethical approval was obtained from the Institute's Ethical Review Committee prior to the commencement of the study (ERC # SIUT-ERC-2021/PA-268).

PATIENTS' CONSENT:
Signed informed consent was obtained from study participants prior to their enrolment in the study.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
NA: Conceived the idea, literature search, synopsis writing, data collection, and manuscript writing.
MQA, SMA, MFF, MS, SM: Literature search, synopsis writing, data collection, and manuscript writing.
All authors approved the final version of the manuscript to be published.

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