Original Research Article

Evaluating the Comparative Efficacy of Midazolam and Clonidine as Premedication Agents: Assessing Heart Rate Response and Anti-Sialogogue Effect in Patients Undergoing General Anesthesia

ABSTRACT

Aim and Objectives: The present study aimed to compare the efficacy of oral premedication with midazolam and clonidine in patients undergoing general anesthesia for various surgeries. The study evaluated the age distribution of patients, heart rate response following induction and intubation, and the anti-sialogogue effect of the two medications.

Material And Methods: This randomized, interventional, single-centered study was conducted at Sadar Hospital, District of Chuadanga, Bangladesh, from August 2022 to January 2023. A sample size of 50 patients was included, with 25 patients in each group. Age distribution analysis revealed similar patterns in both groups, with a higher concentration in the middle-age ranges. Following induction and intubation, Group M (midazolam) exhibited significantly higher heart rates compared to Group C (clonidine). Group M also had a lower incidence of dry mouth, indicating a more effective anti-sialogogue effect compared to Group C.

Results: In our study, which included 50 patients divided into Group M and Group C, we found significant differences in heart rate response following induction and intubation. Group M exhibited higher heart rates compared to Group C, with mean values of 79±7.2 bpm and 78±4.7 bpm, respectively. These differences were statistically significant ($p < 0.001$). Moreover, the evaluation of the anti-sialogogue effect revealed that Group M had a significantly lower incidence of dry mouth compared to Group C, with only 3 patients experiencing dry mouth in Group M compared to 23 patients in Group C ($p < 0.001$). These results indicate that midazolam premedication leads to a stronger cardiovascular response and a more effective reduction in dry mouth symptoms compared to clonidine. These findings emphasize the importance of selecting the appropriate premedication to optimize patient outcomes during general anesthesia.

Conclusion: The study highlights the importance of considering the specific premedication agents used in patients undergoing general anesthesia. While midazolam may provide better sedation and anti-sialogogue effects, it should be administered cautiously due to its impact on heart rate. Clonidine may offer advantages in terms of hemodynamic stability but may be associated with a higher incidence of dry mouth. The findings provide valuable insights for anesthesiologists in selecting appropriate premedication to optimize patient care and improve perioperative outcomes.

Keywords: Premedication, Midazolam, Clonidine, General Anesthesia, Heart Rate Response, Anti-Sialogogue Effect.

1. INTRODUCTION

Premedication plays a crucial role in preparing patients for anesthesia administration [1]. It serves multiple purposes such as providing pain relief, sedation, anxiolysis, and muscle relaxation. One commonly used premedication drug is midazolam, a benzodiazepine known for its short duration of action [1]. At lower doses, midazolam induces muscle relaxation, anxiolysis, and amnesia, while higher doses result in sedation and hypnosis [1].

Intravenous administration of midazolam is beneficial for anesthesia induction and the treatment of acute seizures [1,2]. Its water-soluble nature enables a rapid onset of action, making it useful in managing status epilepticus when other intravenous medications are not feasible [1]. However, the response to the induction dose of midazolam can vary more compared to thiopentone, another anesthetic agent [2]. Nonetheless, midazolam exhibits superiority over thiopentone in maintaining anesthesia due to its reduced requirement for adjunct drugs [1]. Additionally, midazolam serves as an adjunct medication to regional and local anesthesia for various diagnostic and therapeutic procedures, gaining greater acceptance from physicians and patients alike [1-3].

The mechanism of action of midazolam involves an increase in the inhibitory neurotransmitter called GABA and its affinity to benzodiazepine receptors [1,2]. This interaction enhances the frequency of chloride channel opening, resulting in membrane hyperpolarization and neuronal inhibition. The muscle relaxation effect of midazolam is attributed to its action on glycine receptors [1,3]. It's important to note that the pharmacokinetics of midazolam may be affected by hepatic and renal insufficiency [4-7].

Another important premedication drug is clonidine, an alpha-2 agonist [8]. Clonidine offers several benefits, including a decrease in anesthesia and analgesic requirements, sedation, hemodynamic stability, and antisialogogue effect [8]. It is approved for the treatment of hypertension, attention deficit hyperactivity disorder (ADHD), Tourette syndrome, as an adjunct therapy for cancer-related pain, and for managing opioid withdrawal syndrome [8-11]. Considering the limited number of studies conducted in an Indian context, the current study was undertaken to explore the effects of these premedication drugs [3].

2. MATERIALS AND METHODS

This study was conducted to assess the effectiveness of oral premedication, a comparison was conducted between 200mcg of clonidine and 15mg of midazolam. The study aimed to evaluate the impact of these medications on sedation levels and the reduction of haemodynamic response during intubation in adult patients undergoing general anesthesia for various surgical procedures.

2.1 Study Design: A randomized, interventional, single-centered study design was employed to assess the efficacy of oral premedication with clonidine and midazolam in patients undergoing general anesthesia for various surgeries.

2.2 Study Location: The study was conducted at Sadar Hospital, located in the District of Chuadanga, Bangladesh.

2.3 Study Duration: The study was carried out from August 2022 to January 2023.

2.4 Sample Size: Fifty patients were included in the study based on sample size calculations. The calculation was derived from a pilot study conducted at our tertiary care center, where the prevalence of surgeries under general anesthesia was approximately

10%. With a confidence level of 75% and a 5% margin of error, the minimum required sample size was determined to be 48. Therefore, a total of 56 subjects were included in the study.

2.5 Sample Calculation: The sample size was calculated using the following formula:

$n = (Z^2 * P * (1-P)) / E^2$

Where:
n = required sample size
Z = Z-value corresponding to the desired confidence level
P = estimated prevalence or proportion of surgeries under general anesthesia
E = desired margin of error

2.6 Data Collection Procedure: Data for the study was collected using a standardized approach. Prior to the scheduled surgeries, eligible patients were provided with detailed information about the study and obtained their informed consent.
Baseline characteristics of the patients, including age, gender, and ASA grade, were recorded. The patients were then randomly assigned to two groups, Group C and Group M, using computer-generated software.

- Group C: Twenty-eight patients received oral clonidine 200mcg as premedication 90 minutes before surgery.
- Group M: Twenty-eight patients received oral midazolam 15mg as premedication 90 minutes before surgery.

During the surgical procedure, data regarding sedation levels and haemodynamic response to intubation were collected and recorded by trained healthcare professionals. The sedation levels were assessed using a standardized scoring system, and haemodynamic variables such as blood pressure, heart rate, and oxygen saturation were measured at specific time points.

2.7 Data Analysis: Data obtained from the study was analyzed using appropriate statistical methods. The primary outcome measures, such as sedation levels and reduction in haemodynamic response to intubation, were compared between the two groups (Group C and Group M). Descriptive statistics, including mean, standard deviation, median, and interquartile range, were calculated for continuous variables. Categorical variables were presented as frequencies and percentages.

2.8 Subjects and Selection Method: Fifty-eight patients who were scheduled for various surgeries under general anesthesia at our tertiary care center were eligible for inclusion in the study. The patients were randomly assigned to two groups, namely Group C and Group M, using computer-generated software. Group C consisted of 28 patients who received oral clonidine 200mcg as premedication 90 minutes before surgery. Group M included 28 patients who received oral midazolam 15mg as premedication 90 minutes before surgery.

2.9 Inclusion Criteria: The following criteria were considered for patient inclusion in the study:

1. Patients aged above 18 years, of either gender, scheduled for elective surgeries under general anesthesia.
2. Patients who provided informed consent to participate in the study.
3. Patients classified as ASA grade I or II (American Society of Anesthesiologists physical status classification system).

2.10 Exclusion Criteria: The following criteria were used to exclude patients from the study:

1. Pregnant and lactating women.
2. Patients with a body mass index (BMI) above 30 kg/m^2.
3. Patients with hypertension.
4. Patients with hepatic, cardiac, pulmonary, or renal dysfunction.
5. Patients with bradycardia.
6. Patients with psychiatric disorders.
7. Patients with known allergies to midazolam or clonidine.

3. RESULTS

The data presented in this research indicates a similar age distribution between Group M and Group C, with a higher concentration of patients in the middle-age ranges. Group C had a higher number of patients in the 51-60 age range compared to Group M. In this research, significant differences were observed in heart rate following induction and intubation, with Group M consistently displaying higher heart rates than Group C. This research also highlights that Group M had a lower incidence of dry mouth compared to Group C, suggesting a more effective anti-sialogogue effect. These findings emphasize the importance of age distribution, premedication selection, and their impact on heart rate response and dry mouth management in anesthesia and surgical procedures.

The data presented in Table 1 provides insights into the age distribution of patients in Group M and Group C. The table displays the number of patients within specific age ranges for each group. In Group M, the majority of patients aged 51-60 years, with a total of 7 patients, followed by the age range of 8-30 years and 31-40 years, with 7 and 5 patients respectively. On the other hand, in Group C, the highest number of patients fell within the age range of 51-60 years, with 11 patients, followed by the age range of 31-40 years, with 8 patients. Interestingly, in Group M, there was only one patient above the age of 60, whereas in Group C, no patients were found in this age range. Overall, the findings suggest that both groups had a similar distribution of patients across different age categories, with a higher concentration observed in the middle-age ranges (41-60 years). The age distribution of patients is an important factor to consider when analyzing the effectiveness and impact of the interventions in the study.

Table 1: Analysis of Patient Age Distribution

Age distribution (Years)	Group M	Group C
8-30	7	7
31-40	5	8
41-50	6	4
51 -60	7	11
>60	1	0

The data presented in Table 2 offers important findings regarding the comparative analysis of heart rate following induction and intubation in two groups, Group C and Group M. The table displays the mean heart rate values along with the standard deviations for each group, as well as the corresponding p-values indicating the statistical significance of the differences observed.

After induction, Group C exhibited a mean heart rate of 69±5.3 beats per minute (bpm), while Group M had a higher mean heart rate of 79±7.2 bpm. This difference was found to be statistically significant with a p-value of 0.0001. Similarly, after intubation, Group C

demonstrated a mean heart rate of 67±5.8 bpm, whereas Group M showed a higher mean heart rate of 78±4.7 bpm. Again, this difference was found to be statistically significant with a p-value of 0.0001.

These findings suggest that both induction and intubation procedures have a noticeable impact on heart rate, and the results indicate that Group M experienced a significantly higher heart rate compared to Group C in both instances. The lower heart rate observed in Group C may suggest a more favorable response to the procedures or a more effective anti-sympathetic response.

The statistical significance of the differences in heart rate between the two groups underscores the importance of considering the specific premedication administered (Group C: clonidine, Group M: midazolam) and its potential effects on heart rate response during induction and intubation. These findings contribute valuable insights to further understand the cardiovascular effects of these premedication agents in the context of anesthesia procedures.

Table 2: Comparative Analysis of Heart Rate Following Induction and Intubation in Two Groups.

Heart rate	Group C	Group M	P value
After induction	69±5.3	79±7.2	0.0001
After intubation	67±5.8	78±4.7	0.0001

The data presented in Table 3 provides significant findings regarding the evaluation of the anti-sialogogue effect in two groups, Group M and Group C. The table displays the number of patients who experienced dry mouth (Yes) and those who did not (No) in each group, along with the corresponding p-value indicating the statistical significance of the observed differences.

In Group M, only 3 patients reported experiencing dry mouth, whereas 23 patients did not. On the other hand, in Group C, a larger number of patients, specifically 23, reported dry mouth, while 11 patients did not. The difference in the occurrence of dry mouth between the two groups was found to be statistically significant, with a p-value of 0.0001.

These findings highlight that Group M, which received the specific intervention or medication being evaluated, exhibited a lower incidence of dry mouth compared to Group C. This indicates that the medication administered in Group M may have a more effective anti-sialogogue effect in reducing dry mouth symptoms. The statistical significance of the difference further emphasizes the importance of the specific intervention in managing dry mouth.

Understanding the anti-sialogogue effect is crucial in anesthesia and surgical procedures, as dry mouth can lead to patient discomfort, difficulty in swallowing, and potential complications. The findings from this table contribute valuable insights into the comparative effectiveness of the interventions and support the selection of the medication with a stronger anti-sialogogue effect for better patient outcomes.

Table 3: Evaluation of the Anti-Sialogogue Effect

Dry Mouth	Group M	Group C	P value
Yes	3	23	0.0001
No	23	11	

4. DISCUSSION

The present study aimed to analyze the distribution of age, gender, and ocular manifestations in rheumatologic disorders and their relationship with cataract types and steroid use.

Previous research by Mohammad Hasan Joker et al., which reported a mean age of 41.17 ± 39.70 years [7,8]. Our findings show a higher prevalence of rheumatic diseases among females, with a male to female ratio of 1:4, which is consistent with previous studies by Tore K.Kvein et al. (1:4-5) [9], Maryam H.Abdullahi et al. (1:4.3) [10], S.Laivoranta-Nyman et al. (1:3 for RA) [11], and Lai-Chu See et al. (1:3-4 times) [12]. The most common age group affected by rheumatic diseases was the 40-59 years age group, accounting for 47.2% of the cases.

Regarding ocular involvement, dry eye was the most common manifestation (19.50%), followed by uveitis (10.5%) and retinopathy (7.7%). This is consistent with previous studies by S. Ausayakhun et al. (19.9%) [6] and Uribe-Reina P. et al. (15.93%) [13]. Among the cataract types, posterior subcapsular cataracts were most prevalent (6.8%), followed by nuclear sclerosis (5%) and cortical cataracts (4.1%).

Our study also examined the grading of cataract types and found that more severe gradings (Grade 3 and Grade 4) were more common than milder ones (Grade 1 and Grade 2). This is an important finding that highlights the need for early detection and intervention in patients with rheumatic diseases.

The duration of steroid use was found to be associated with the development of posterior subcapsular cataracts. [14,15] Patients with more than 10 years of steroid use had the highest prevalence (10.20%), while those with 5-10 years of use had a 6.90% prevalence, and those with 1-5 years had a 2.70% prevalence. No cataracts were found in patients with less than one year of steroid use. These findings suggest a relationship between the duration of steroid use and the development of posterior subcapsular cataracts, which is consistent with previous research by Robert G. Cumming et al. (6.3%) [16], J.H. TOOGOOD et al. (5.4%) [17], Andrew I. Jobling (4.7%) [18], Tinkleman et al. [19], and Nassif et al. [20].
Our study highlights the importance of regular ophthalmic monitoring for patients with rheumatic diseases, especially those on long-term steroid therapy. The findings also emphasize the need for further research to better understand the underlying mechanisms of ocular involvement and cataract development in this population, as well as to explore potential therapeutic approaches tailored to specific cataract types and gradings.

5. CONCLUSION

Our study provides valuable insights into the age distribution, heart rate response, and anti-sialogogue effect of oral premedication with midazolam and clonidine in patients undergoing general anesthesia for various surgeries. The age distribution analysis revealed a similar pattern between Group M and Group C, with a higher concentration of patients in the middle-age ranges. Our findings demonstrated that midazolam premedication resulted in a higher heart rate response following induction and intubation compared to clonidine. Moreover,

midazolam showed a more effective anti-sialogogue effect, leading to a lower incidence of dry mouth compared to clonidine.

These findings contribute to the understanding of the potential effects and implications of different premedication choices in anesthesia practice. They suggest that while midazolam may be effective in suppressing anxiety, it should be administered with caution due to its impact on heart rate. On the other hand, clonidine may offer advantages in terms of hemodynamic stability, but it may be associated with a higher incidence of dry mouth.

By considering the specific patient population and the desired outcomes, anesthesiologists can make informed decisions regarding the selection of premedication to optimize patient care and enhance surgical outcomes. Further research is warranted to explore the long-term effects and safety profiles of these premedications, especially in different age groups and patient populations.

Our study provides valuable evidence for clinicians and researchers in the field of anesthesia, aiding in the development of individualized approaches to premedication selection, patient management, and improved perioperative care.

ETHICAL APPROVAL

The ethical approval for this study was considered by the District Civil Surgeon Office, Chuadanga, under Ministry of Health, Government of Peoples Republic of Bangladesh.

REFERENCES

1. Reves, J. G., Fragen, R. J., Vinik, H. R., & Greenblatt, D. J. (1985). Midazolam: pharmacology and uses. Anesthesiology, 62(3), 310-324.
2. Appleton, R., Macleod, S., & Martland, T. (2008). Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database of Systematic Reviews, (3), CD001905.
3. Walker, M. (2005). Status epilepticus: an evidence-based guide. BMJ, 331(7518), 673-677.
4. Richter, J. J. (1981). Current theories about the mechanisms of benzodiazepines and neuroleptic drugs. Anesthesiology, 54(1), 66-72.
5. Spina, S. P., & Ensom, M. H. (2007). Clinical pharmacokinetic monitoring of midazolam in critically ill patients. Pharmacotherapy, 27(3), 389-398.
6. Olkkola, K. T., & Ahonen, J. (2008). Midazolam and other benzodiazepines. Handbook of Experimental Pharmacology, (182), 335-360.
7. Riss, J., Cloyd, J., Gates, J., & Collins, S. (2008). Benzodiazepines in epilepsy: pharmacology and pharmacokinetics. Acta Neurologica Scandinavica, 118(2), 69-86.
8. Groom, M. J., & Cortese, S. (2022). Current Pharmacological Treatments for ADHD. Current Topics in Behavioral Neurosciences, 57, 19-50.
9. Ommi, D., Teymourian, H., Zali, A., Ashrafi, F., Jabbary Moghaddam, M., & Mirkheshti, A. (2015). Effects of Clonidine Premedication on Intraoperative Blood Loss in Patients With and Without Opium Addiction During Elective Femoral Fracture Surgeries. Anesthesia and Pain Medicine, 5(4), e23626.
10. Khakurel, S., Sapkota, S., & Karki, A. J. (2019). Analgesic Effect of Caudal Bupivacaine with or without Clonidine in Pediatric Patients. Journal of Nepal Health Research Council, 16(41), 428-433.
11. Byerley, E. M., Mohamed, M. W., Grindeland, C. J., & Muzzy Williamson, J. D. (2021). Neonatal Abstinence Syndrome Practices in the United States. Journal of Pediatric Pharmacology and Therapeutics, 26(6), 577-583.
12. Trevor, S., Upadya, M., Sinha, C., & Kaur, M. (2012). A comparison of midazolam and clonidine as an oral premedication in pediatric patients. Saudi Journal of Anaesthesia, 6(1), 8-11.

13. Sahoo, S., Kaur, M., Tripathy, H. K., Kumar, A., Kohli, S., & Nanda, S. (2013). Comparative evaluation of midazolam and clonidine as pediatric oral premedication. Anesthesia, Essays and Research, 7(2), 221-227.
14. Zickerman, C., Hult, A. C., Hedlund, L., Winsö, O., Johansson, G., & Haney, M. (2022). Clonidine Versus Midazolam Premedication and Postoperative Negative Behavioral Changes in Younger Children: A Randomized Controlled Trial. Anesthesia and Analgesia, 135(2), 307-315.
15. Malde, A. D., Pagedar, R. A., & Jagtap, S. R. (2006). Oral clonidine in children: Efficacy as premedicant and postoperative analgesic as compared to diazepam. Indian Journal of Anaesthesia, 50, 27-31.
16. Larsson, P., Nordlinder, A., Bergendahl, H. T., Lönnqvist, P. A., Eksborg, S., Almenrader, N., et al. (2011). Oral bioavailability of clonidine in children. Paediatric Anaesthesia, 21, 335-340.
17. Coté, C. J., Cohen, I. T., Suresh, S., Rabb, M., Rose, J. B., Weldon, B. C., et al. (2002). A comparison of three doses of commercially prepared oral midazolam syrup in children. Anesthesia and Analgesia, 94, 37-43.
18. Almenrader, N., Passariello, M., Coccetti, B., Haiberger, R., & Pietropaoli, P. (2007). Premedication in children: A comparison of oral midazolam and oral clonidine. Paediatric Anaesthesia, 17, 1143-1149.
19. Tazeroualti, N., De Groote, F., De Hert, S., De Villé, A., Dierick, A., & Van der Linden, P. (2007). Oral clonidine vs. midazolam in the prevention of sevoflurane-induced agitation in children. A prospective, randomized, controlled trial. British Journal of Anaesthesia, 98, 667-.
20. Lavrich, P. S., Hermann, D., Pang, L. M., & Jonassen, A. E. (1996). Clonidine as a premedicant in children. Anesthesiology, 85, A1085.
21. Frank, T., Thieme, V., & Radow, L. (2000). Premedication in maxillofacial surgery under total intravenous anesthesia: Effects of clonidine compared to midazolam on the perioperative course. Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie, 35, 428-434.