Research Article

Effectiveness of Dexmedetomidine versus Ketamine for Control of Shivering and Hemodynamic Stability in Vaginal Hysterectomy under Spinal Anesthesia

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Abstract: Background: Shivering is an attempt by the body to increase the generation of heat through metabolism in response to core hypothermia. Ketamine and dexmedetomidine have been used to prevent shivering during anesthesia with variable findings.

Objective: To determine effectiveness of dexmedetomidine versus ketamine for control of shivering and comparing hemodynamic stability in vaginal hysterectomy under spinal anesthesia.

Materials and Methods: This double blinded randomized control trial was performed in Hamdard University Hospital during January to October, 2023. Before commencing the study, formal permission was taken from Ethics Committee of Hamdard University Hospital (Ref#H-CM&D/20/2022). Patients of age 45-55 years undergoing vaginal hysterectomy with ASA grade of I-II were enlisted. Group D was given a prophylactic dose of dexmedetomidine (1mcg/kg) and Group K was given a prophylactic low dosage of ketamine (0.25 mg/kg). Blood pressure (mmHg), heart rate (bpm), oxygen saturation (%) and mean arterial pressure (mmHg) were recorded after every 15 minutes throughout the procedure.

Result: Total 104 patients were enrolled into the study with equal allocation in both the groups. In dexmedetomidine group, only 2 (3.8%) patients experienced shivering whereas in Ketamine group shivering was seen among 9 (17.3%). Among dexmedetomidine group, both of the patients developed shivering at 98 minutes. In ketamine group, average shivering onset time was 84 ± 29.8 minutes with range of 60-105 minutes. Average duration of shivering in dexmedetomidine group was 20±2.1 minutes whereas average duration of shivering for ketamine group was 26.1 ± 9.6 minutes.

Conclusion: The present study demonstrated that dexmedetomidine is superior to ketamine in shivering prevention and control following spinal anesthesia. This study also found that dexmedetomidine is also effective in maintaining hemodynamic stability throughout the procedure.

Keywords: Anesthesia, Dexmedetomidine, Hysterectomy, Ketamine, Shivering, Vaginal hysterectomy.

INTRODUCTION

Shivering is an attempt by the body to increase the generation of heat through metabolism in response to core hypothermia [1]. Heat loss, elevated sympathetic tone, discomfort, and the systemic release of pyrogens are the primary causes of both intraoperative and postoperative shivering [2]. The two most common causes of shivering in surgical patients are anesthesia and operation [3]. Shivering resulting from neuraxial anesthetic administration is a common occurrence, with a reported incidence as high as 40–70% [4]. Shivering causes discomfort for the patient and makes it difficult to monitor blood pressure, oxygen saturation, and ECG. It may cause lactic acidosis and raise carbon dioxide and oxygen consumption. Additionally, it raises intraocular and intracranial pressure [5]. Humans typically have a core temperature between 97.7°F and 99.5°F [6]. The anterior hypothalamus is where thermoregulation, a component of the homeostatic mechanism, takes place. When evaluating peripheral inputs, the anterior hypothalamus compares them to a predefined point or threshold value. A cooling response will occur if the temperature is higher than this set point, whereas specific reflexes to warm the body will be activated if the temperature is lower than this set point [7].

With encouraging results, ketamine and dexmedetomidine have recently been used to stop shivering during anaesthesia. At different doses, ketamine, a competitive antagonist of NMDA receptors, which interferes in thermoregulation. In the locus ceruleus, serotonergic and noradrenergic neurons are modulated by the NMDA receptor. Ketamine was administered intravenously at a dose of 0.25–0.75 mg/kg as an antishivering medication. Ketamine most likely regulates shivering through nonshivering thermogenesis, either through its effects on the hypothalamus or through noradrenaline's beta-adrenergic activity [8, 9]. Non-shivering thermogenesis is quickly triggered by direct pharmacological activation or physiological activation of brown fat β3-AR via cold stress. The biochemical process by which brown fat generates heat is mediated by mobilized fatty acids acting as allosteric activators of uncoupling protein 1 (UCP1) [10].

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Dexmedetomidine exhibits strong effects on the central nervous system and is a highly selective α-2-adrenergic receptor agonist [11, 12]. While there are a number of drugs used to treat shivering, dexmedetomidine's antishivering effects during central neuroaxial blockage have not yet been studied. The primary mediator of dexmedetomidine's anti-shivering action may be the hypothalamic α2-adrenoceptor. Dexmedetomidine lowers central thermosensitivity, inhibits the rate at which neurons fire spontaneously, and ultimately lowers the thresholds for shivering and vasoconstriction [13]. Research conducted outside of Pakistan has examined the effects of ketamine and dexmedetomidine on shivering control, with varying degrees of success [14, 15]. On the other hand, local statistics on this topic are scarce. Thus, the primary purpose of this study was to determine effectiveness of dexmedetomidine and ketamine in reducing shivering in vaginal hysterectomy procedures performed under spinal anaesthesia. Secondary objective is to evaluate hemodynamic stability among patients receiving dexmedetomidine and ketamine.

MATERIALS AND METHODS

This double blinded randomized control trial was performed in Department of Anesthesia, Hamdard University Hospital, Karachi, during January to October, 2023. Before commencing the study, formal permission was taken from Ethics Committee of Hamdard University Hospital (Ref#HCM&D/20/2022). The trial was prospectively registered in registry of clinical trial with trial number of "NCT05481281". Patients of age 45-55 years undergoing vaginal hysterectomy with ASA grade of I-II were enlisted. Patients with uncontrolled hypertension, vascular or coronary disease, patients with increased intraocular, intracranial pressure, bleeding disorders and psychiatric disorders were excluded. A written inform consent was taken from all patients prior to their recruitment.

Sample size was estimated using online available calculator Open-EPI by taking time for cessation shivering of 35.17 ± 6.13 seconds and 39.13 ± 8.11 seconds in dexmedetomidine and ketamine group respectively [16]. Using power of 80% and 95% confidence interval, a sample of total 104 patients needs to be studied with 1:1 ratio in each group (i.e. 52 patients per group). Patients were enrolled into the study using non-probability consecutive sampling technique. Fig. (**1**) depicts consort diagram of the study.

Patients planned for vaginal hysterectomy were advised to admit a night before surgery in the hospital. All patients were clinically evaluated for medical fitness to undergo surgery. All the patients were premedicated with tablet Alprazolam 0.25mg a night before the surgery. As per the schedule, patients were moved to operation theatre. After transferring the patients to operation room, each patient received 10ml/kg of lactated Ringer's solution. Before performing spinal anesthesia, standard monitoring of heart rate (HR), non-invasive blood pressure (NIBP), oxygen saturation (SPO_2) and body temperature (axillary) were recorded and then every 15min. Subarachnoid anesthesia was

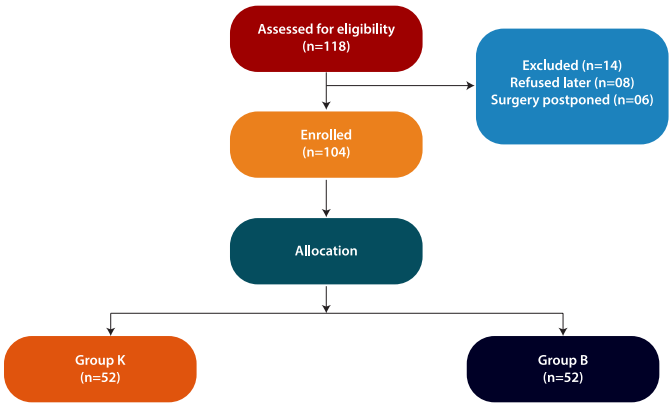

Fig. (1). Consort Diagram of the Study.

administered at either L3/L4 or L4/L5 interspace with 3ml of 0.5% hyperbaric bupivacaine using a 25G pencil point spinal needle and blockade up to T9-T10 dermatome was achieved. At this stage, patients were assigned to the study groups. Group K was ketamine group whereas Group D was dexmedetomidine group. Patients were randomly assigned to both the groups using sequentially numbered opaque sealed envelope protocol [17]. In two groups, the anesthesiologists and the patients were blinded to the medicine being provided. Double blinding was achieved by preparing the study drugs in identical syringes. Both of the syringes were labelled with a code Group D and Group K. The anesthesiologist who prepared the study drugs was not involved in drug administration and outcome assessment. Coding was kept confidential until the data analysis was performed.

Following the delivery of spinal anaesthesia, group D was given a prophylactic dose of dexmedetomidine (1mcg/kg) and group K was given a prophylactic low dosage of ketamine (0.25 mg/kg). 200 mcg of dexmedetomidine ampule was diluted in 50 ml of diluent so 4mcg/ml strength of dexmedetomidine was made. Normal saline was used as a diluent solution. Using a syringe pump, patients were given a dose of 1 mcg/kg dexmedetomidine over a 10-minute period. During the procedure, they were then continuously infused with dexmedetomidine at rate of 0.4 mcg/kg/hr, which was terminated when the procedure was over. 100mg of ketamine ampule was diluted in 50ml of normal saline so that 2mg/ml strength of ketamine was made. Patients in group K got 0.25 mg/kg IV bolus of ketamine as an 20ml solution, and continued at a rate of 0.1 mg/kg/hr, till the end of surgery, while patients in group D received an intravenous I/V bolus of dexmedetomidine 1mcg/kg /hr as a 20 ml solution. A constant 22–24°C was maintained in the chamber. An axillary thermometer was used to check the patients' temperatures. A core temperature of less than 96.8°F was thought to be hypothermic. Without using an inline warming system, room temperature irrigation and IV fluids were given. No further warming apparatus was employed. A protocol to administer 0.5 mg of atropine was set to be used in case the heart rate drops below 50 BPM.

Each patient in the recovery area got a blanket and a face mask that delivered 4 L of oxygen per minute. The degree of shivering was measured prior to the surgery (0 min) and then every

minute till 15 min later. Prior to and following therapy, patients' arterial oxygen saturation (%), heart rate (bpm) temperature and non-invasive blood pressure (systolic, diastolic pressure in mmHg, and mean arterial blood pressure), were measured at every 15 minute. Control of shivering is defined as prevention of shivering events. Shivering was assessed using 4 point scale ranging from 0-3. Score of 0 denoting no shivering, A score of 1,2, and 3 denotes mild shivering (shivering localized to the neck and/or thorax only), moderate shivering (shivering involved gross movement of the upper extremities (in addition to neck and thorax) and severe shivering (shivering involved gross movements of the trunk and upper and lower extremities) [18]. The length of shivering was defined as the time interval between the start of shivering and the end of shivering during the study follow-up period (i.e. till 180 minutes after the procedure). For assessment of hemodynamic stability following variables were evaluated; systolic and diastolic blood pressure (mmHg), heart rate (bpm), temperature (°F), saturation level (SPO_2) (%) and mean arterial pressure (%).

STATISTICAL EVALUATION

Data was entered in SPSS version 26 for statistical analysis. Frequencies and percentages were computed categorical variables. Numerical were expressed as mean ± standard deviation when normally distributed otherwise summarized as median with inter-quartile range (IQR). Normality assumption was tested. Patients' age, BMI, surgery duration, blood pressure, heart rate, saturation level, temperature and mean arterial pressure were non-normal and expressed as median with inter-quartile range (IQR). Numerical variables were compared among the two study groups using Mann-Whitney U test. P-values less than or equal to 0.05 were deemed as statistically significant.

RESULT

Socio-Demographic and Baseline Clinical Features

Total 104 patients were enrolled into the study with equal allocation in both the groups. Table **1** displays comparison of patients' demographic and baseline features among the two groups. None of patients' features including age, gender, surgery duration and baseline systolic blood pressure, diastolic blood pressure, temperature and heart rate were significantly different among the two groups.

Table 1. Patients' Demographic and Baseline Features among Dexmedetomidine and Ketamine Group.

Variables	Combined (Group D & Group K)	Group D	Group K	p-value
Age (in years)	49 (46-57.8)	48 (45-57.5)	50.5 (48-57.8)	*0.029
Body mass index (Kg/m^2)	23.1 (21.1-25.8)	22.2 (20.6-25.8)	23.9 (22.4-25.9)	*0.016
Surgery duration (in minutes)	120 (110-125)	120 (112-125)	120 (105-130)	0.475
Systolic blood pressure (mmHg)	126.5 (119-130.8)	130 (120-139.5)	125 (119-130)	0.169
Diastolic blood pressure (mmHg)	80 (75.3-86)	80 (73.7-90)	80.5 (75.5-85)	0.692
SPO_2 (%)	99 (98-100)	99 (99-100)	99 (98-99)	0.105
Temperature (°F)	98.2 (98-98.6)	98 (98-98.6)	98.5 (98-98.6)	0.432
Heart rate (BPM)	81 (78-89)	81 (80-88.8)	81.5 (77.3-92)	0.863

All of the variables were non-normal and expressed as median with inter-quartile range (Q1-Q3), *Significant at $p<0.05$.

Shivering Onset among the Two Groups

In dexmedetomidine group, only 2 (3.8%) patients experienced mild shivering whereas in Ketamine group shivering was seen among 9 (17.3%). Out of 9, 6 patients developed mild shivering and 3 developed moderate shivering. Among dexmedetomidine group, both of the patients developed shivering at 98 minutes. In ketamine group, average shivering onset time was 84 ± 29.8 minutes with range of 60-105 minutes. Duration of shivering in dexmedetomidine group was 20 minutes for both of the patients whereas average duration of shivering was 26.1 ± 9.6 minutes (Table **2**).

Table 2. Details of Shivering Events among the Two Study Groups.

Shivering Details	Group D	Group K
Shivering event, n(%)	2(3.8)	9 (4.5)
Shivering Grade		
Mild, n(%)	2(100)	6 (66.7)
Moderate, n(%)	0(0)	3 (33.3)
Shivering onset time, (mean ± SD)	98 ± 0	84 ± 29.8
Duration of shivering, (mean ± SD)	20 ± 0	26.1 ± 9.6

Comparison of Hemodynamic Stability among the Study Groups

Median systolic blood pressure was significantly lower at 15 minutes and 45 minutes in ketamine group whereas systolic blood pressure was found to be significantly increasing in ketamine group from 150-180 minutes. Diastolic blood pressure was significantly lower at 15, 45, 60 and 75 minutes in ketamine group than Group D. SPO_2 was not significantly different at any time point throughout the procedure. Temperature was also found to be non-significant among the two groups throughout the study. Heart rate was significantly higher in ketamine group and dexmedetomidine group except at 30 minutes. MAP was higher in Group D at 15 minutes and 90 minutes than Group K. At 150 and 165 minutes, MAP was lower Group D as compared to Group K (Table **3**).

Table 3. Comparison of Hemodynamic Parameters among the Two Study Groups.

Variable	Group D	Group K	p-value
Systolic Blood Pressure			
at 15 minutes	127(114-142.3)	123(114-128.8)	*0.012
at 30 minutes	122.5(119-135)	121(118-127)	0.128
at 45 minutes	123(113-133)	115.5(112-123)	**0.004
at 60 minutes	117(106.5-130)	115.5(108.5-120)	0.735
at 75 minutes	118(99-127.5)	118(111-120)	0.825
at 90 minutes	114(104.5-122)	116(107-124.8)	0.553
at 105 minutes	108(95-119)	115.5(97-124.3)	0.324
at 120 minutes	107.5(96.8-114.8)	111(98-122.8)	0.174
at 135 minutes	108.5(100.3-116)	114.5(104-121)	*0.028
at 150 minutes	105(100-113.5)	119(112-122)	*<0.001
at 165 minutes	104.5(101-117.3)	114(108-119)	**0.001
at 180 minutes	106.5(100-119.5)	111(106.3-120.8)	*0.041
Diastolic Blood Pressure			
at 15 minutes	80(77-90)	77(69-82)	*0.014
at 30 minutes	82(77.3-85)	76(70-82)	0.128
at 45 minutes	78.5(73-85)	73(67-75)	**0.004
at 60 minutes	76.5(68-80)	70.5(67-78)	**<0.001
at 75 minutes	75(63.8-80)	72(67-76.5)	*0.031
at 90 minutes	74(67-80.5)	71.5(60-79)	0.556
at 105 minutes	69(52.3-74)	70(59-74.8)	0.547
at 120 minutes	70(59.3-74)	70.5(61-74.8)	0.235
at 135 minutes	70(60.5-77.8)	70(66-78)	0.662
at 150 minutes	69(63.3-76.8)	70.5(64.3-80.5)	0.555
at 165 minutes	69(63.3-76.8)	70(64-78.8)	0.181
at 180 minutes	70(64-77.5)	70(63.3-76.5)	0.500
SPO_2			
at 15 minutes	99(99-100)	99(98-99)	0.105
at 30 minutes	100(99-100)	99.5(99-100)	0.358
at 45 minutes	100(99-100)	100(99-100)	0.903
at 60 minutes	100(99-100)	100(99-100)	0.651
at 75 minutes	100(99-100)	99(99-100)	0.977
at 90 minutes	100(99-100)	100(99-100)	0.539
at 105 minutes	99(99-100)	100(99-100)	0.358
at 120 minutes	100(99-100)	100(99-100)	0.467

Continue

Continue

at 135 minutes	100(99-100)	99(99-100)	0.261
at 150 minutes	100(99-100)	99.5(99-100)	0.137
at 165 minutes	100(99-100)	100(99-100)	0.123
at 180 minutes	100(99-100)	99(99-100)	0.119
Temperature			
at 15 minutes	98 (98-98.6)	98 (98-98.2)	0.327
at 30 minutes	98 (98-98.6)	98 (98-98.2)	0.327
at 45 minutes	98 (98-98.6)	98 (98-98.2)	0.314
at 60 minutes	98 (98-98.6)	98 (98-98.2)	0.314
at 75 minutes	98 (98-98.6)	98 (98-98.2)	0.314
at 90 minutes	98 (98-98.6)	98.6 (98-98.6)	0.078
at 105 minutes	98 (98-98.6)	98 (98-98.6)	1.000
at 120 minutes	98 (98-98.6)	98 (98-98.6)	0.843
at 135 minutes	98 (98-98.6)	98 (98-98.6)	1.000
at 150 minutes	98 (98-98.6)	98 (98-98.2)	0.314
at 165 minutes	98 (98-98.6)	98 (98-98.2)	0.314
at 180 minutes	98 (98-98.6)	98 (98-98.2)	0.314
Heart Rate			
at 15 minutes	79(72-85)	82(78.3-88)	*0.048
at 30 minutes	80(73-81)	81(77-93)	0.115
at 45 minutes	75.5(70-83)	83(72-91)	*0.006
at 60 minutes	71(68-75)	79(69.3-90)	**<0.001
at 75 minutes	71(68-74)	75.5(71-81)	**<0.001
at 90 minutes	71(68-75.8)	75(70-86)	**0.001
at 105 minutes	69(66-71)	79(69.3-89.5)	**<0.001
at 120 minutes	67(66-70)	80(70.3-88)	**<0.001
at 135 minutes	68(64-70)	82(69-92)	**<0.001
at 150 minutes	67(66-71.5)	81.5(70-86)	**<0.001
at 165 minutes	67.5(65-75.8)	82.5(72-88)	**<0.001
at 180 minutes	67(64-75)	83.5(72-87.8)	**<0.001
Mean Arterial Pressure			
at 15 minutes	93.5(89-100)	89(84.3-95)	*0.022
at 30 minutes	95(89.3-98)	94(80.8-96)	0.136
at 45 minutes	86.5(80.5-97)	86(80.8-88)	0.083
at 60 minutes	87.5(77.8-94.5)	85.5(80-92.5)	0.742
at 75 minutes	89.5(75.5-99.8)	86.5(83-91.8)	0.176
at 90 minutes	86(78.5-94.8)	82(74-89)	*0.040
at 105 minutes	82(65-91.8)	82(74-89)	0.904
at 120 minutes	82.5(72.8-87)	83(74-92)	0.421
at 135 minutes	83(73-90.8)	84(82.3-92)	0.096
at 150 minutes	80(73.3-88.5)	87.5(80-92)	*0.001
at 165 minutes	79(73.3-90)	84.5(79-92)	*0.034
at 180 minutes	80(73.3-91)	84(79-92)	0.167

*Significant at p<0.05, ** Significant at p<0.01.

DISCUSSION

The present study demonstrated that patients' features including gender and their surgery duration and baseline systolic blood pressure, diastolic blood pressure, temperature and heart rate were not significantly different among the two groups. Age and BMI were significantly different but this difference of magnitude of smaller and of no clinical importance. This finding depicts that randomization was correctly done for allocating patients among the two groups. Similar studies also showed the same pattern that patients' features such as age, gender and surgery duration were significantly different among the two study groups, providing the evidence of randomization was done when allocating study participants to study groups [8, 14].

In the current investigation, Group D experienced considerably less shivering (3.8% versus 17.3%) than Group K. Lower shivering rates among patients who received dexmedetomidine as compared to those who received ketamine is also reported in a similar Indian study (24% versus 46%) [14]. Another similar study from India enrolled 30 patients in each group and followed them from baseline till 120 minutes and reported among both of groups shivering was seen in only 1 patient at 30 minutes [19]. After spinal anaesthesia, none of the patient developed shivering in dexmedetomidine group whereas 6.6% patients developed shivering in ketamine group [20, 21]. A study was performed in Egypt evaluating the efficacy of dexmedetomidine alone, ketamine alone and their combination. The study analyzed that 6.67% had shivering in dexmedetomidine cohort, 10% shivering incidence in ketamine group and 16.67% shivering in cohort received combination drugs [16]. A study performed in Pakistan also found that dexmedetomidine was superior to ketamine in terms of absence of shivering till 45 minutes post operatively with 57% efficacy in ketamine group and 76.7% efficacy in dexmedetomidine group [17].

In the present study it is found that shivering onset time in Group D was 98 minutes. On the other hand, in Group K, median shivering onset time was 90 minutes with range of 60-105 minutes. Many authors investigating dexmedetomidine and ketamine effects in shivering control did not report shivering onset time [14, 16, 22]. However, some of the studies reported shivering onset time which is quite lower than present study [19, 23]. The shivering onset time was same i.e. 30 minutes for ketamine and dexmedetomidine group [19]. Time from spinal anesthesia to beginning of shivering in ketamine group was reported to be 41.6 ±20.7 minutes which is lower than this study [23]. The reason of higher onset time in present study could be due to different drug doses, method of drug infusion like through IV or injectable or infusion rate and overall technique differences of anesthesia induction.

In this study, systolic blood pressure was significantly lower in Group K at 15 minutes, 45 minutes but higher at 150 minutes, 165 minutes and 180 minutes it was greater in than Group D. This finding is consistently reported in literature that in late peri-operative period systolic blood pressure is higher in ketamine group than dexmedetomidine group [16, 24]. However, in the present study, from 90 to 180 minutes we found no significant difference in diastolic blood pressure among the two groups. In the present study, SPO_2 throughout the peri-operative period was not significant different among the groups which is comparable to finding of Houssein MM and coworkers [16]. In this study, except at baseline and 30 minutes heart rate was significantly lower in dexmedetomidine group than ketamine group which corroborates to the existing literature [14, 16]. Mean arterial pressure was lower in dexmedetomidine group at 150 and 165 minutes but clinically this difference is unimportant. There was no difference in MAP among the two drugs except at 15 minutes, 90 minutes, 150 minutes and 165 minutes. This pattern gives impression that MAP was inconsistently differing among the two groups. The pattern needs to be investigated in another similar study. However, existing literature reports that MAP in Ketamine group than dexmedetomidine group is higher at 10 min, 15 min, 20 min, 25 min and 30 min [25].

LIMITATIONS

This study had some limitations as this was a single centre, conducted on a relatively small sample size. In this study, for hemodynamic stability parameters we evaluated only blood pressure, heart rate, SPO_2 and mean arterial pressure. Results could vary if formal criteria was applied. Further randomized controlled trials are required to confirm the findings of this study.

CONCLUSION

The present study demonstrated that dexmedetomidine is superior to ketamine in shivering prevention and control following spinal anesthesia. This study also found that dexmedetomidine is also effective in maintaining hemodynamic stability parameters throughout the procedure.

AUTHORS' CONTRIBUTION

Nida Shahid: Conceptualization, Study design, Methodology, Data analysis and interpretation, Critical review and revision the manuscript, Final approval, final proof to be published.

Asim Masroor Rashid: Study design, Methodology, Data analysis and interpretation, Writing draft, Final approval, final proof to be published.

Atia Kazim: Writing draft, Final approval, final proof to be published.

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Declared none.

ETHICAL DECLARATIONS

Data Availability Statement

Data are available upon reasonable request. The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

Ethical approval for this study was granted by the Ethical Committee of the Institute of Hamdard University Hospital (Ref#HCM&D/20/2022).

Clinical Trail Registry

This study was registered with ClinicalTrials.gov under identifier NCT05481281 (https://clinicaltrials.gov/study/NCT05481281).

Consent to Participate

Informed consented.

Consent for Publication

Consented.

Conflict of Interest

Declared none.

Competing Interest/Funding

Declared none.

Use of AI-Assisted Technologies

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were utilized in the writing of this manuscript, in the creation of images/graphics/tables/captions, or in any other aspect of its preparation.

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