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Automated oxygen control in preterm babies on respiratory support: protocol for a randomised crossover trial

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ABSTRACT

Introduction Respiratory support is frequently needed for babies admitted to the neonatal intensive care unit. Among them, preterm babies are most likely to have issues of respiratory distress, and they may need invasive or non-invasive breathing support. Providing respiratory support, keeping the oxygen saturation (SpO2) in the target range (TR) and preventing abnormal high and low oxygen levels should be the aim of providing respiratory therapy. Usually, this control is achieved by manual adjustment of FiO2 (fraction of inspired oxygen) by bedside staff nurses to keep SpO2 in TR. However, the latest ventilators have automated oxygen control devices that adjust the FiO2 to keep SpO2 in TR. This study protocol is prepared to assess the effectiveness of automated versus manual oxygen control in keeping SpO2 in TR.

Methods and analysis This is a single-centre, non-blinded, randomised crossover trial that aims to recruit 26 preterm babies who may need invasive or non-invasive respiratory support. The 12-hour periods of automated oxygen control by ventilator will be compared with 12 hours of manual oxygen control by bedside staff nurse. The primary outcome will compare both interventions and will assess their efficacy to keep SpO2 in TR. Secondary outcomes will compare abnormal high and low SpO2 levels, and number and duration of fluctuations in both interventions. Median FiO2 values and median number of manual adjustments of FiO2 will also be compared. Secondary outcomes will also look for the impact of sedative and respiratory stimulant medications on target oxygen saturation.

Ethics and dissemination The ethics review committee at Aga Khan University Hospital Karachi has given ethical approval for this trial (approval number: 2024-10189-30775). Results from this trial will be published in journals.

Trial registration number NCT06622161.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Respiratory disease in preterm babies leads to impaired oxygen levels. However, it is difficult to achieve target oxygen saturation via manual control due to the need for frequent adjustments by the bedside staff nurse. Automated oxygen control, now being introduced in many countries, aims to achieve target SpO2 more effectively. This reduces staff workload and helps prevent abnormal oxygen levels, particularly in vulnerable preterm babies.

WHAT THIS STUDY HOPES TO ADDS

⇒ Our study will compare manual and automated oxygen control to determine the better method for maintaining SpO2 in the target range. Limited research has been done on automated oxygen control in developing countries.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study will provide insights to neonatal intensive care unit medical professionals on managing respiratory distress in preterm infants using better oxygen control systems. While not directly addressing morbidity and mortality, it may contribute to improved care practices that influence long-term outcomes.

⇒ This study will encourage medical professionals, particularly in underdeveloped nations, to explore further research on automated versus manual oxygen control. Such investigations may contribute to optimising neonatal care practices in resource-limited settings, which will help in improving morbidity and mortality.

INTRODUCTION

Babies admitted in neonatal intensive care unit (NICU) often need supplemental oxygen to keep their oxygen saturation (SpO2) in target range (TR). Hypoxia and hyperoxia episodes should be avoided while working towards this goal. Preterm babies are particularly vulnerable to abnormal oxygen levels, and adverse effects of hyperoxia and oxygen toxicity may result in retinopathy of prematurity and bronchopulmonary dysplasia.[1] Similarly, mortality may rise due to hypoxic events.[2 3] In routine practice, SpO2 target is usually achieved by manual adjustment of FiO2 (fraction of inspired oxygen), but it usually does not accomplish the desired SpO2 target, leading to the episodes of hyperoxia and hypoxia and increased risk of complications.[4] A study

was conducted in multiple centres involving extremely preterm babies, the results of which depicted that the babies on manual control of FiO2 spent only 48% of their time with SpO2 in the TR, 16% below the TR and 36% above it. The compliance of the SpO2 TR was also variable in these centres.[5] There is a need to improve compliance by using automated oxygen control systems.

At the Aga Khan University Hospital (AKUH), investigators have included SLE 6000 (SLE, Croydon, UK) ventilators in their NICU, which have automated oxygen control device 'OxyGenie' that continuously adjusts FiO2 (fraction of inspired oxygen) of the patient to keep SpO2 in the TR, avoiding abnormal high- or low-oxygen levels.[6] This also reduces the workload on staff and improves patient care.[7] Investigators usually put the preterm babies on these ventilators so that SpO2 can be kept most of the time in the TR. When the OxyGenie and SpO2 monitoring are added to the SLE 6000 ventilator, it becomes possible to accurately regulate and deliver closed-loop oxygen to preterm infants. This automated oxygen control system limits the episodes of both hypoxia and hyperoxia by using the VDL 1.1 algorithm that uses an adaptive proportional–integral–derivative (PID) algorithm to control the FiO2 adjustments in response to changes in SpO2.[8 9] This keeps SpO2 within a TR, which is selected by user. A randomised crossover trial comparing two devices for automated oxygen control in preterm infants included the SLE 6000 ventilator as one of its devices.[10 11] The purpose of this study is to establish whether, in preterm babies, OxyGenie device functions efficiently to keep SpO2 in the TR between 90% and 94% as per European guidelines[12] and also avoids abnormal oxygen levels.

Objectives

To assess the effectiveness of automated inspired oxygen control versus manual oxygen control in keeping SpO2 within TRs for preterm babies needing respiratory support at a tertiary care hospital, Karachi, Pakistan.

Hypothesis

The primary outcome variable, which is the percentage of time with SpO2 within the designated TR of 90%–94%, would not differ between the automated and manual control periods of 12 hours each, when on supplemental oxygen.

As per the secondary outcome variable, there would be no difference in the percentage of time spent in severe hyperoxia defined as SpO2 ≥98% and severe hypoxia defined as SpO2<80% between the automated and manual control periods.

METHODS AND ANALYSIS

We used Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.[13]

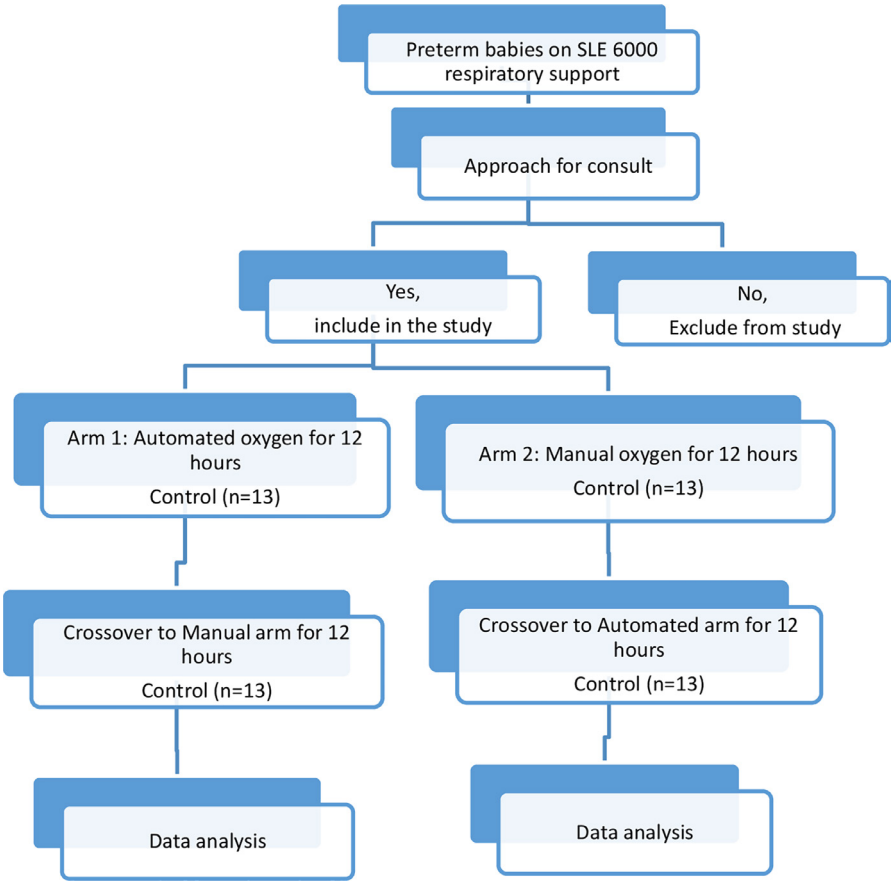

Figure 1 Study methodology flowchart.

Box 1 Patient demographics and ventilator and blood gas parameters

Patient demographics

⇒ Gestational age at birth (week), median (IQR).
⇒ Birth weight (grams), median (IQR).
⇒ Age (day/days), median (IQR).
⇒ Postmenstrual age at start of study (week), median (IQR).
⇒ Weight at start of study (grams), median (IQR).

Ventilator and blood gas parameters at start of study.

⇒ Mode of ventilation (n=number).
⇒ nHFOV (n).
⇒ NIPPV (n).
⇒ NCPAP (n).
⇒ PTV (with volume guarantee) (n).
⇒ P-SIMV (n).
⇒ HFOV (n).
⇒ Peak inspiratory pressure (cm H2O), median (IQR).
⇒ Positive end expiratory pressure (cm H2O), median (IQR).
⇒ FiO2 (%), median (IQR).
⇒ pH, median (IQR).
⇒ PCO2 (mm Hg), median (IQR).

HFOV, high-frequency oscillatory ventilation; NCPAP, nasal continuous positive airway pressure; nHFOV, nasal high-frequency oscillatory ventilation; NIPPV, nasal intermittent positive pressure ventilation; PCO2, partial pressure of carbon dioxide; P-SIMV, pressure control synchronised intermittent mandatory ventilation; PTV, patient-triggered ventilation.

Trial design

This single-centre, non-blinded, randomised crossover study will be conducted in two consecutive 12-hour periods using automatic and manual FiO2 control in a randomly assigned sequence.

Settings and protocol

The study will be conducted in a 24-bed NICU at AKUH, Karachi, treating both inborn and outborn term and extreme preterm babies. Nursing allocation will follow standard practice: one nurse per intubated baby (1:1) or one nurse for two babies on non-invasive support (1:2). Patients will be randomly assigned to 12-hour periods of automatic and manual oxygen control alternatively, aiming to keep SpO2 within 90%–94%. NICU staff are trained to use both modes on SLE 6000 ventilators. All planned and elective procedures will be completed before the study. During the 24-hour study period, routine patient care and procedures, including blood sampling, endotracheal tube suction, chest physical therapy, kangaroo care and insertion of lines, cannulas and catheters, will be recorded.

Table 1 Percent of times with SpO_2 values within and outside the TR (90%–94%) proportion of time

SpO_2 range	Automated Median (IQR)	Manual Median (IQR)	P
SpO_2 of 90%–94%			
SpO_2 of<90%			
SpO_2 of<80%			
SpO_2 of>94%			
SpO_2 of≥98%			

Note: SpO_2 >94%, and ≥98% is excluded when FiO_2=0.21 (21%).
P≤0.05 (statistically significant result).
TR, target range.

Table 2 Episodes of SpO_2 fluctuations, prolonged hypoxia and hyperoxia

Episodes of SpO_2 fluctuations	Automated Median (IQR)	Manual Median (IQR)	P
Episodes of SpO_2<80% for ≥10 s			
Number per 12 hours			
Duration (minutes)			
Episodes of SpO_2≥98% ≥10 s			
Number per 12 hours			
Duration (minutes)			
SpO_2 of<80% for ≥1 min			
SpO_2 of<80% for ≥3 min			
SpO_2 of≥98% for ≥1 min			
SpO_2 of≥98% for ≥3 min			

IQR; number of episodes per 12 hours; ≥98% SpO_2 is excluded when FiO_2=0.21 (21%).
P≤0.05 (statistically significant result).

Automated FiO_2 system OxyGenie

The OxyGenie algorithm is a closed-loop PID controller that continuously adjusts FiO2 to suit the patient.[10] It is a part of the SLE 6000 infant ventilator (SLE Limited, South Croydon, UK). The proportional term reflects the current error, defined as the deviation from the TR's midpoint (eg, 92% for a 90%–94% range). The integral term sums prior errors, and the derivative term considers the direction of the SpO2 error.[14] The FiO2 change is determined by adding the P, I and D terms. The radical neonatal pulse oximeter (Masimo, Irvine, CA, USA) automatically adjusts FiO2 to maintain SpO2 within the TR. Before activating OxyGenie, FiO2 is manually adjusted to achieve SpO2 in the TR. Once SpO2 is in TR, OxyGenie is turned on, which maintains SpO2 by adjusting FiO2 based on SpO2 trends. The pulse oximeter settings include normal sensitivity, a 2–4 s average time, a 20-s

Table 3 FiO_2 values and manual adjustments to FiO_2 during automated and manual periods

FiO_2 values	Automated Median (IQR)	Manual Median (IQR)	P
12-hour FiO_2			
Manual FiO_2 adjustments, no. per 12 hours			

P≤0.05 (statistically significant result).

Table 4 Percent of time with SpO_2 in TR (90%–94%), <90% and>94%, with and without use of sedative and respiratory stimulant medications

Medication	Group	SpO_2 (90%–94%) Median (IQR)	SpO_2<90% Median (IQR)	SpO_2>94% Median (IQR)	P value
Sedative (Morphine)	With Morphine (n=X)				
	Without Morphine (n=Y)				
Stimulant (Caffeine)	With Caffeine (n=X)				
	Without Caffeine (n=Y)				

SpO_2 >94% is excluded when FiO_2=0.21 (21%).
P≤0.05 (statistically significant result).
TR, target range.

alarm delay and alarm limits of 89% and 95% SpO2. The right wrist is used for the Masimo neonatal probe when feasible. The user will be advised on screen if the SpO2 signal will be lost. OxyGenie would display a blue waiting signal and maintain the current FiO2 for 60 s. If SpO2 is within TR, it continues at the current FiO2. If SpO2 is above TR and FiO2 is 10% above the reference range, it decreases to the reference value. If SpO2 is below TR and FiO2 is more than 5% below the reference FiO2, it increases to the reference level. The reference FiO2 value is updated every 30 min based on the last 60-min average.[8]

Study methodology

Refer to figure 1, study methodology flowchart.

Trial population

Eligibility criteria

Inclusion

Premature babies (born before 37 weeks) on SLE 6000 ventilator needing additional oxygen therapy or respiratory support due to respiratory dysfunction. Criteria: (1) receiving respiratory support via mechanical ventilation (non-invasive or invasive); (2) receiving supplemental oxygen at inclusion and (3) written informed parental consent.

Exclusion

(1) Babies with major congenital anomalies (eg, neural tube defects, neuromuscular disorders, congenital heart diseases and syndromic conditions). (2) Resuscitation, termination of mechanical ventilation during the study. (3) Withdrawal of parental consent.

Interventions

26 preterm babies will be recruited from October 2024 to March 2025, approximately 6 months, after ethics review committee (ERC) approval. Patient characteristics, ventilator and blood gas parameters will be shown in box 1. Initially, half of the babies will be randomly assigned to a 12-hour manual period where a nurse adjusts FiO2 based on SpO2 levels, and the other half to a 12-hour automated period where OxyGenie adjusts FiO2. After 12 hours, they will switch interventions. Ventilator parameters (peak inspiratory pressure, positive end expiratory pressure and rate) and time spent within different SpO2 ranges will be compared and shown in tabular form. *Discontinuation Criteria*: (1) deterioration in clinical status not improving with corrective measures; (2) baby no longer needs respiratory support and (3) withdrawal of consent by family.

Table 5 Study timeline outlining key phases: Enrolment, Eligibility Screen, Informed Consent, Allocation, and Interventions (A and B), with corresponding time points, and post-allocation close-out

	Study period						
	Enrolment	Allocation	Postallocation				Closeout
TIMEPOINT*	–T1		T1	T2	T3	T4	
Enrolment:							
Eligibility screen							
Informed consent							
Allocation							
INTERVENTIONS:							
Intervention A:							
Intervention B:							

*Specific timepoints will be mentioned in this row.

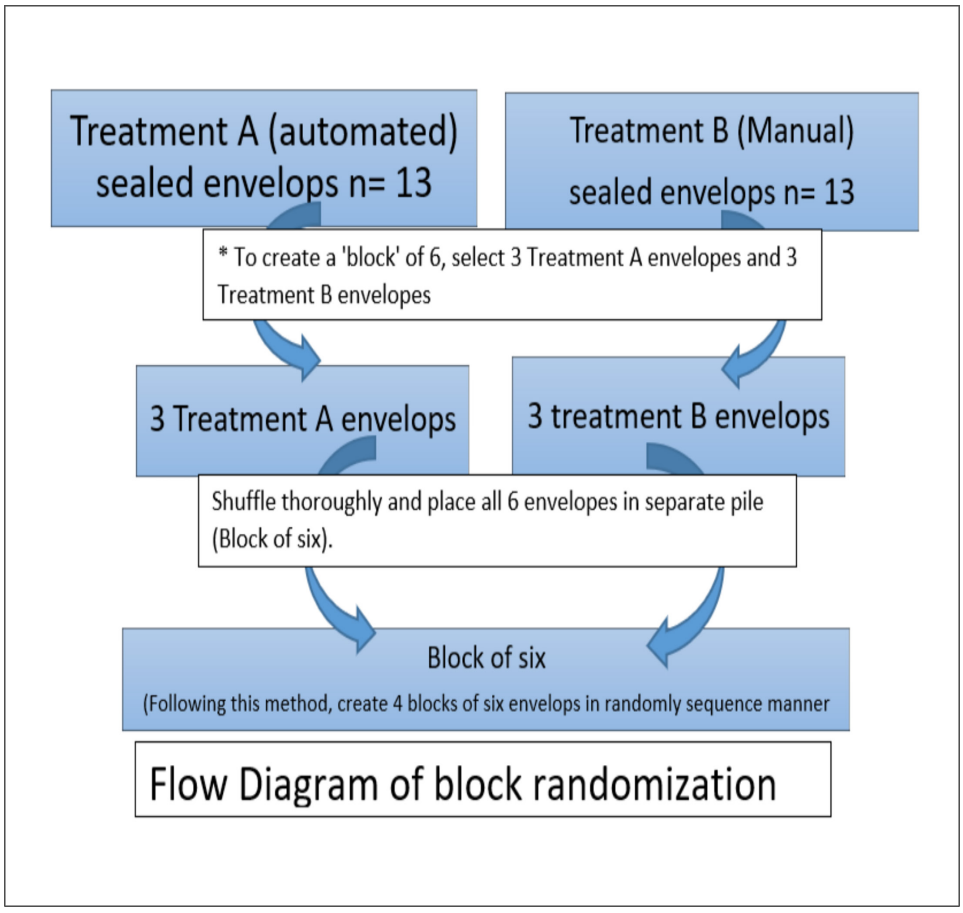

Figure 2 Block randomisation. *To create a block of 2, select 1 treatment A envelope and 1 treatment B envelope.

Study outcomes

Primary outcome

Time with SpO2 within the TR of 90%–94% will be compared between automated and manual periods.

Secondary outcomes

- Percentage of time with SpO2 below (<90% and <80%) and above (>94% and ≥98%) the TR with FiO2>0.21 (21%) will be compared between both interventions (table 1, page 10).
- Number and median duration of SpO2 fluctuations below 80% and ≥98% plus episodes of prolonged hypoxia and hyperoxia of 1 and 3 min will be tracked between automated and routine care (table 2, page 11).
- Median FiO2 values and median number of manual FiO2 adjustments will be compared between automated and manual control periods (table 3, page 11).
- The percentage of time with SpO2 in the TR (90%–94%), below (<90%) and above (>94%) the TR when FiO2>21%, in babies with and without sedative and respiratory stimulant medication use (eg, Morphine and Caffeine) will be compared (table 4, page 12).

Participant timeline

Refer to following table (table 5).

Sample size calculation

In a prior study,[15] the use of an automated oxygen control system was linked to a decrease in the number of severe desaturation episodes from 5 to 0 in babies receiving non-invasive ventilatory support. Our primary outcome is the average percent of time when SpO2 is in the TR in automated versus manual control periods. The study sample size has been calculated using PASS software. Reference is 'Senn, Stephen. 2002. Cross-Over Trials in Clinical Research. Second Edition. John Wiley and Sons. New York.'

We will measure the average percent of time when SPO2 is in the TR for which we will require a sample size of 24 babies to detect a mean difference of at least 10% in both groups with a power of 90% and significance level of 5%. We plan to enrol 26 babies in the study to adjust for attrition.

Methods: assignment of interventions

This non-blinded, randomised crossover trial will use opaque, sealed envelopes with sequential numbers to assign automated and manual periods in four blocks of 6 and one block of 2. Refer to the flow diagram (figure 2) for the allocation sequence and randomisation procedure, which will be created by an individual not affiliated with the research team. Block randomisation will

be employed. The envelopes will be stored in a secure cabinet until they are used for interventions. A member from research team will take consent from parents, will enrol the patients and will assign participants to interventions.

Recruitment, data collection and analysis

After ERC approval and trial registration, all eligible preterm babies will be approached through their parents/guardian. Those meeting the inclusion criteria and consenting will be recruited. Consent will be obtained by a trained research team member. Clinical and demographic information, such as gestational age, birth weight, clinical condition specifics and respiratory support level, will be documented (box 1page 9). The SLE 6000 ventilator will store data on SpO2, FiO2, ventilator settings and monitoring parameters. Data will be extracted via USB and stored offline using specialised PC software. Extracted data will include time with SpO2 within the TR (90%–94%), time in hypoxaemia (SpO2<80%) and hyperoxaemia (SpO2≥98%), SpO2 distribution during each 12 hours, mean FiO2 during each 12 hours, hourly inspired O2 level, time spent in room air, number of manual FiO2 changes, duration and severity of episodes and time below and above the target SpO2 range. For participant timeline, refer to table 5 (page 7).

Shapiro–Wilk test will check for normalcy. Non-parametric Wilcoxon signed-rank tests will determine statistical significance if differences are found. Results will be presented as mean, median and IQR. P values<0.05 will be considered statistically significant. IBM SPSS Statistics V.21.0 will be used for all statistical purposes.

In addition, the data on the administration of sedative and respiratory stimulant medications (eg, Morphine and Caffeine) will be collected and documented during the study period. This will allow for a comprehensive analysis of their potential impact on maintaining oxygen saturations within the TR.

Data storage

Data will be stored in allocated computers, with storage and archiving duration following hospital policy.

Monitoring of trial

Before beginning the trial, Aga Khan Hospital's Clinical Trial Unit (CTU) gave its approval. The study does not conflict with CTU's interests. It has complete control over the monitoring and auditing of the trial's data and the right to end the research at any moment.

Any adverse event (AE)/serious adverse event (SAE) occurring during the intervention will be reported to the CTU or ERC within 24 hours.

The definitions are as follows.

AE: any untoward medical occurrence to a participant that does not necessarily have a causal relationship with the treatment.

SAE: any untoward medical event related or unrelated to the study intervention/procedures that is life threatening or results in death, hospitalisation (or its prolongation), disability/incapacity or is a congenital anomaly/birth defect or is a medically important event.

ETHICS AND DISSEMINATION

The ERC of AKUH Karachi approved the study in August 2024. Before a neonate is chosen for the study, parental informed consent will be obtained in a private room by a research team member. Parents will be fully informed about the research's goals, methodology, possible risks and advantages, and they can leave the study at any time. Participation will be entirely voluntary, with no coercion. Fair research practices will be followed, ensuring equal sharing of risks and rewards. Any AEs occurring due to study will be reported to the ERC and CTU of AKUH, Karachi. Patient confidentiality and privacy will be guaranteed, with anonymity maintained throughout the study. Each subject will receive a unique ID from 001 to 026, and information will be securely stored and protected against unauthorised access. If it becomes necessary for ERC and CTU to review the study records, information that can be linked to the patient will be protected to the extent allowed by law. The data may be made available to other researchers in the future for research purposes without identification. In these cases, the data will have no identifying information that could associate it with patient. Routine hospital standard operating procedures shall be followed for any AEs that occur in order to compensate for harms.

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Contributors ASH and HMAY planned the trial idea. ASH, HMAY, GMS and ZH designed the trial. HMAY drafted the protocol, which was edited by ASH, GMS and ZH. RM and UK helped make parental consent forms and will take part in collecting consent and data. HMAY will do data extraction and help with data analysis. AR helped with sample size calculation and will assist with statistical ansalysis. HMAY is the guarantor of this work and accepts full responsibility for the overall content and integrity of the study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The ethics review committee at Aga Khan University Hospital Karachi has given ethical approval for this trial (approval number: 2024-10189-30775). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data will be available on reasonable request.

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