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Original Article

Comparing the Cardiac Outcomes of Mild and Moderate Hypothermic Cardiopulmonary Bypass in Children Undergoing Congenital Heart Surgery.

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ABSTRACT

Objectives: This single-blind, parallel-design randomized clinical trial aimed to assess the impact of mild and moderate hypothermia on brain oxygenation changes in pediatric patients with noncyanotic cardiac disorders undergoing cardiac surgery.

Methods: In this trial, 68 pediatric patients undergoing noncyanotic cardiac surgery at Rajaie Cardiovascular, Medical, and Research Center were included. Participants were randomly allocated to mild hypothermia (32 ˚C) and moderate hypothermia (28 ˚C) groups. Outcomes were measured and compared between the groups at baseline, during, and after cardiopulmonary bypass.

Results: The mean bypass and cross-clamp times were 147.72±68.30 minutes and 92.03±54.91 minutes, respectively. There were no significant differences between the groups in terms of bypass time, ICU length of stay, and ventilation time. The frequency of neurological complications was also similar between the groups (P>0.05).

Conclusions: The results of this trial demonstrated no significant differences in perioperative and postoperative outcomes, including ICU length of stay, mechanical ventilation time, and neurological outcomes, between the groups managed with mild or moderate hypothermia during cardiopulmonary bypass in noncyanotic pediatric patients undergoing surgery for the correction of congenital heart anomalies. ***(Iranian Heart Journal 2024; 25(3): 6-15)***

KEYWORDS: Mild hypothermia; Moderate hypothermia; Cerebral oxygenation; Cardiopulmonary bypass

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Hypothermic cardiopulmonary bypass (CPB) is commonly used for congenital heart defect surgeries in pediatric patients.[1] This technique aims to reduce metabolic demand during CPB and increase operational safety.[2] In pediatric patients, hypothermic CPB has been modified by lowering CPB temperature and shortening cooling and rewarming durations.[3] Unfortunately, some complications associated with hypothermic CPB have been reported, potentially impacting clinical outcomes negatively.[3-5]

Core temperature control is essential for cardiac and pediatric surgeons, as unexpected changes in normal core temperature may impair the function of vital organs.[6] During the cooling phase of hypothermic CPB, blood concentration increases, and plasma volume decreases due to interstitial plasma trapping.[7, 8]

In the normothermia method, patients' temperature decreases spontaneously to 35 °C without topical cooling. The efficacy and postoperative complications of hypothermic and normothermic CPB have been compared in the literature. Some researchers suggest that hypothermia reduces body metabolism and inflammatory responses in pediatric patients.[9] In contrast, potential negative effects on enzyme function, energy production, and cellular integrity have been reported as common complications of hypothermia-CPB methods.[10, 11]

In the normothermic method, cerebral blood flow autoregulation is maintained in neonates and pediatric patients, potentially leading to better cardiac and neurologic system outcomes.

Better hemodynamic stability, reduced inotropic drug usage, and shorter mechanical ventilation times have been suggested as benefits of the normothermic-CPB method, potentially improving postoperative clinical outcomes.[12, 13]

Moderate hypothermia has been found to provide better brain protection compared to deep hypothermia methods during cardiac surgeries.[14] Decreases in brain oxygenation during these operations can have several consequences, and monitoring oxygen saturation can help reduce the likelihood of organ failure.[15-17] While the prevalence of cardiovascular disorders among Iranian pediatric patients is high, necessitating open-heart surgery for many of them, few studies have investigated the complications of mild and moderate hypothermia in this population. Therefore, it is important to assess the impacts of mild and moderate hypothermia on brain oxygenation changes during open cardiac surgery among Iranian pediatric patients with congenital noncyanotic cardiac disorders.

PATIENTS AND METHODS

Trial Design

We conducted a single-blind, parallel-design clinical trial involving pediatric patients with congenital noncyanotic disorders undergoing cardiac surgery at Rajaie Cardiovascular Medical and Research Center. The trial protocol was approved by the Ethics Committee of Rajaie Cardiovascular Hospital (IR.RHC.REC1398.082) and registered on the IRCT trial registration website (IRCT20201217049741N1).

Participants

We included patients aged 1 day to 14 years with congenital noncyanotic cardiac disorders undergoing cardiac surgery with CPB (5–20 kg) and without a history of neurological, hepatic, or renal failure (Cr>2 mg/dL), preoperative anemia, or cardiopulmonary resuscitation. Patients with unstable hemodynamics during the operation, those requiring urgent cardiac surgery, or those whose temperature decreased below the expected level were excluded.

Intervention and Outcomes

Study investigators informed trial participants (>7 y) or their parents and

obtained signed consent forms. In the operating room, electrocardiography and radial artery pressure monitoring were commenced. Peripheral venous, central venous, and urethral catheters were inserted. Body temperature was monitored with rectal and esophageal probes.[18]

All patients received 300 IU/kg heparin, with additional heparin administered for activated clotting times less than 400 seconds.[19] Del Nido cardioplegia was administered for both groups as previously described.[20]

The following variables were assessed as trial outcomes: age, gender, weight, body surface area, operation type, ejection fraction, operation time, CPB, aortic clamp, intubation time, neurological complications, ICU length of stay, and mortality. Additionally, the minimum and maximum hemoglobin levels during CPB, temperature, serum lactate, blood urea nitrogen (BUN), and creatinine (Cr) were assessed (T1: before the operation, T2: ICU entrance, T3: 24 hours after ICU entrance), and the use of inotropic agents was evaluated. PaO_2, pH, rSO_2, and $PaCO_2$ were measured at 5 time points (T1: before the operation, T2: cooling down temperature to 34 °C, T3: temperature reduction to the lowest temperature (28 or 32 °C in the corresponding group), T4: rewarming to 34 °C, and T5: after the operation). Cerebral oximetry measurements were recorded at different time points before anesthesia induction, cooling to 34 °C, the lowest temperature, rewarming to 34 °C, and the end of CPB.

Sample size

Based on similar studies[14] and the sample size formula, a minimum of 30 patients was determined for each trial group (α=0.05 and β=80%) using the following formula:

$$n = \frac{\left[Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right]^2 \left[S_1^{\,2} + S_2^{\,2}\right]}{(\mu_1 - \mu_2)^2}$$

Randomization

Randomization was performed using a table of random numbers and a list of patients undergoing cardiac surgery.

Allocation

Patients who met the inclusion criteria were randomly allocated to the mild (32 °C) and moderate (28 °C) hypothermia groups.

Blinding

The trial was single-blind, with only the patients unaware of their trial group assignments.

Statistical Analysis

Trial data were analyzed using SPSS v.21 (IBM Corporation, NY, USA). Mean ± standard deviation and frequency/relative frequency percentage were used to describe quantitative and qualitative variables, respectively. Independent sample *t* and χ^2 tests were used to compare quantitative and qualitative variables between the 2 groups. Trends in trial variables were assessed at different time points using repeated measures analysis. If the data distribution deviated from normal, nonparametric tests were used. For such data, between-group comparisons were made using the Mann-Whitney *U* test, and the Friedman test was used for repeated measures comparisons. *P* values <0.05 were considered statistically significant.

RESULTS

Finally, data analysis was performed on 68 patients (41 males), with 35.51% in the mild hypothermia group and 48.53% in the moderate hypothermia group. The mean age, height, and weight were 41.24±41.89 months, 99.29±21.75 cm, and 13.34±10.49 kg, respectively. The mean values of the CPB time, the cross-clamp time, and blood flow-adjusted arterial oxygen saturation were 146.72±68.03 minutes, 92.02±54.91 minutes, and 0.7540±1.47 M^2, respectively. The male-to-female ratio was 12.23 in the

mild hypothermia group and 15.8 in the deep hypothermia group (*P*=0.35). The mean ICU length of stay (140.27±128.79 vs 105.08±88.50), CPB, and ventilation time were similar between the 2 groups (*P*>0.05). Only 3 patients (4.41%) died within the study period, all belonging to the mild hypothermia group. Neurological complications were observed in 4 patients in the moderate group and 3 patients in the mild group, with no significant difference in frequency between the 2 groups (*P*>0.05). One patient in each group required a return to the operating room. The mean ventilation time was similar between patients in the mild and moderate hypothermia groups (78.32±122.29 vs 63.86±71.69 min; *P*=0.11). Although the mean rSO_2 and hemoglobin levels in 5 measurements were higher in the moderate hypothermia group than in the mild hypothermia group, the difference was not statistically significant. Details of the measurements in each group are presented in Table 1 and Figure 1.

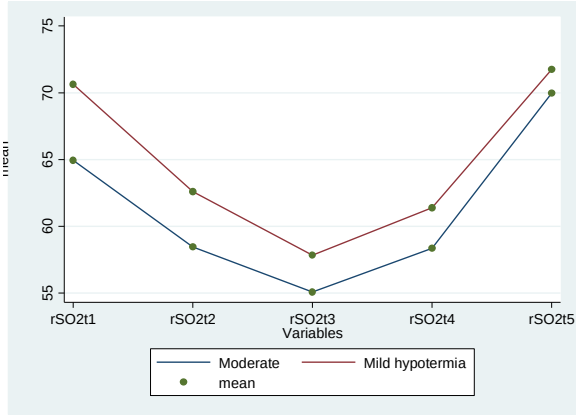


Figure 1: A repeated measures analysis was used to compare the rSO_2 measurements among the study participants. The trends in values were similar between the 2 groups.

T1: before the operation, T2: cooling down to 34 °C, T3: temperature reduction to the lowest temperature (28 °C or 32 °C in the respective group), T4: rewarming to 34 °C, T5: postoperative measurement

P value for interaction: 0.738

The mean ejection fraction before the operation was similar between patients in the moderate and mild hypothermia groups (50.01±8.52 vs 47.29±8.53; *P*=0.21). A similar ejection fraction was observed in the postoperative period among patients in both groups (51.61±10.91 vs 46.57±12.71; *P*=0.09). Renal function parameters (BUN and Cr) were similar between patients in both groups. The frequency of inotropic agent usage in the operating room and ICU was also similar between patients in the moderate and mild hypothermia groups. Details of these comparisons are presented in Table 2 and Table 3.

Analysis of blood gas demonstrated an equal shift in metabolism to anaerobic in both groups at the cooling and rewarming stages, with no significant differences between the 2 groups in pH, PaO_2, and $PaCO_2$, except for $PaCO_2$ at the cooling down to 34 °C. However, since this difference occurred before the final hypothermia in both groups (28 °C or 32 °C in the moderate or mild hypothermia groups, respectively), it cannot be attributed to the extent of hypothermia. These values were corrected following appropriate measures taken during the rewarming and postoperative stages (Fig. 2).

Table 1: The Mean of rSO_2 and Hemoglobin in 5 Measurements Among the Study Population

		Groups Measurement Time Points	Moderate Hypothermia	Mild Hypothermia	*P* value
rSO_2		T1	64.94±16.16	70.63±9.75	0.08
		T2	58.45±14.34	62.60±9.02	0.16
		T3	55.09±12.48	57.83±9.19	0.31
		T4	58.36±14.15	61.40±11.90	0.34

		T5	69.97±14.47	59.93±13.03	0.59
Hemoglobin		T1	12.46±2.15	12.18±2.81	0.65
		T2	14.52±22.50	8.75±2.06	0.22
		T3	8.61±1.39	8.56±3.90	0.94
		T4	9.48±1.76	9.84±1.98	0.44
		T5	10.35±1.82	10.83±1.65	0.26

T1: before the operation, T2: cooling down the temperature to 34 ˚C, T3: temperature reduction to the lowest temperature (28 or 32 ˚C in the corresponding group), T4: rewarming to 34 ˚C, T5: after the operation

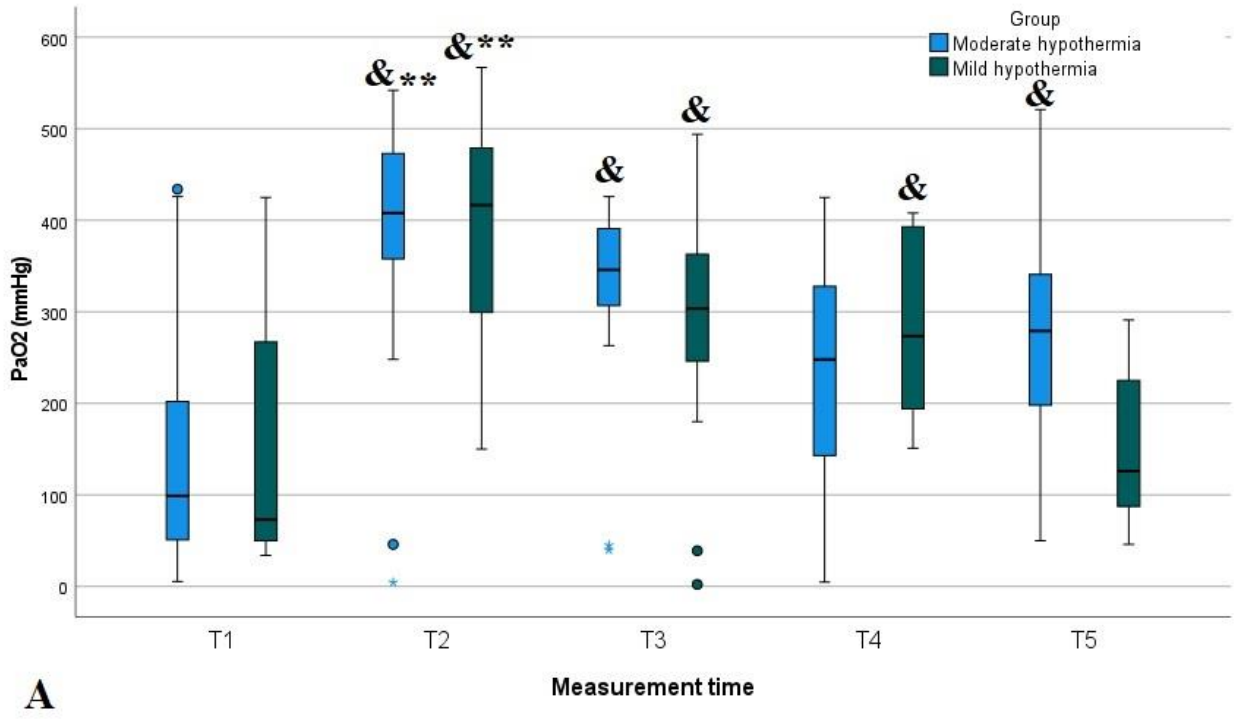
Table 2: Renal Function Markers in 3 Measurements Among the Study Population

	Groups Measurement Time Points	Moderate Hypothermia	Mild Hypothermia	*P* value
BUN (mg/dL)	T1	14.96±16.93	15.19±22.27	0.97
	T2	11.66±4.25	11.90±2.54	0.78
	T3	11.03±5.51	12.09±4.82	0.43
Creatinine (mg/dL)	T1	0.51±0.15	0.50±0.13	0.71
	T2	0.52±0.12	0.50±0.14	0.54
	T3	0.61±0.14	0.53±0.19	0.98

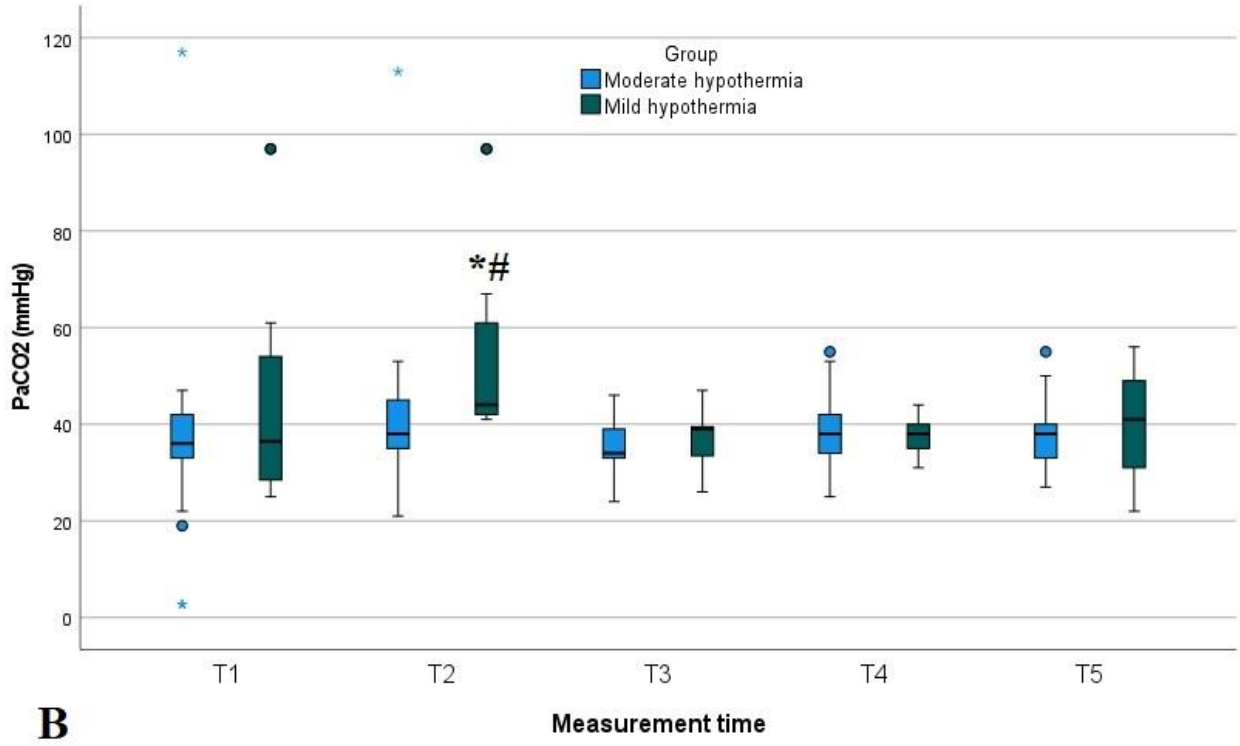
T1: before the operation, T2: ICU entrance, T3: 24 hours after ICU entrance

Table 3: The Mean Inotropic Agent Usage in the Operating Room and ICU Among the Study Participants

Study Groups Inotropes		Moderate Hypothermia		Mild Hypothermia		*P* value
		N	%	N	%	
Operating Room	Epinephrine	16	48.5	18	51.4	0.81
	Norepinephrine	1	3	1	2.9	0.97
	Phenylephrine	5	15.2	5	14.3	0.92
	TNG	3	9.1	3	8.6	0.94
	Milrinone	11	33.3	8	22.9	0.34
ICU	Epinephrine	-	-	1	2.9	0.52
	Norepinephrine	2	6.1	-	-	0.14
	Phenylephrine	1	3	-	-	0.30
	Milrinone	20	60.6	25	71.4	0.16


Group
Moderate hypothermia
Mild hypothermia
PaO2 (mmHg)
600
500
400
300
200
100
0
&**
&**
&
&
&
&
T1
T2
T3
T4
T5
Measurement time

A


Group
Moderate hypothermia
Mild hypothermia
PaCO2 (mmHg)
120
100
80
60
40
20
0
*#
T1
T2
T3
T4
T5
Measurement time

B

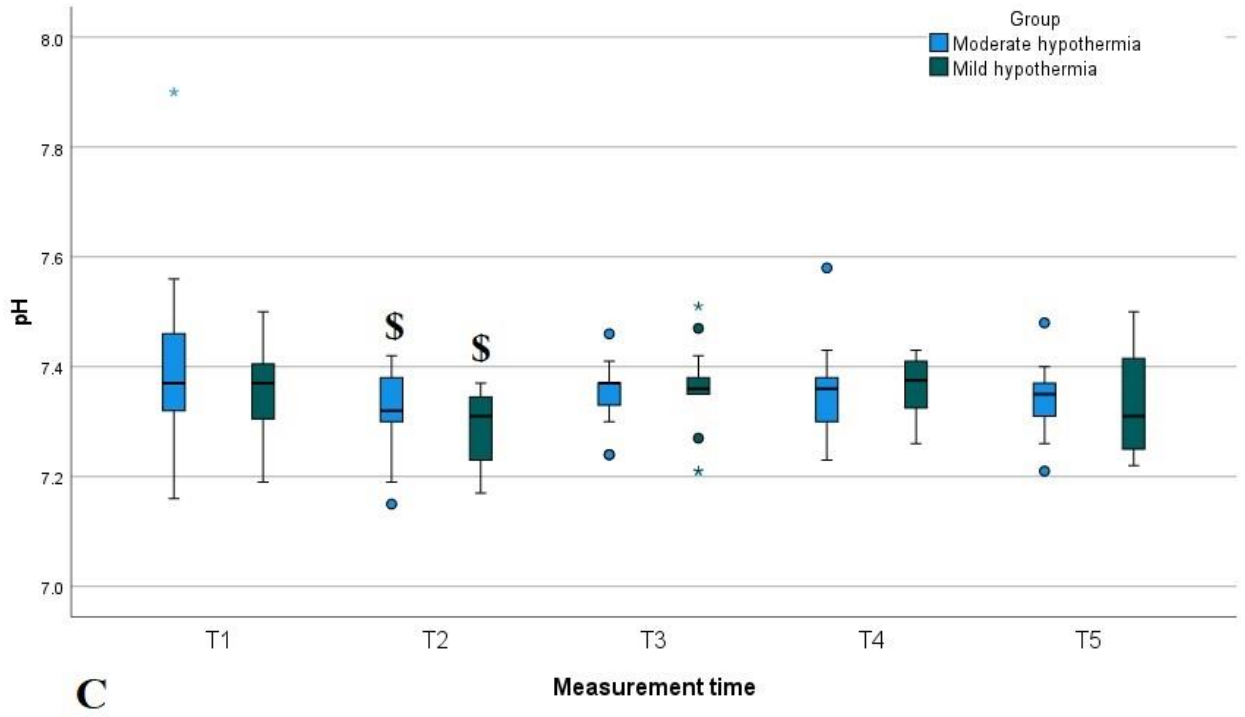


Figure 2: Comparisons of PaO_2 (A), $PaCO_2$ (B), and pH (C) between groups of patients receiving mild and moderate hypothermia during cardiopulmonary bypass (CPB). Time points: T1 (before the operation), T2 (reducing temperature to 34 °C), T3 (temperature reduction to the lowest temperature [28 °C or 32 °C in the respective group]), T4 (rewarming to 34 °C), and T5 (postoperative measurement). There was a similar trend between the groups, and no significant between-group differences were observed at equivalent measurement times, except for $PaCO_2$, which was significantly higher in the mild hypothermia group. However, since this difference occurred during cooling to 34 °C and before the target hypothermia of 32 °C or 28 °C in the respective groups, it cannot be attributed to hypothermia and is considered a chance observation.
*P<0.05 compared with the other group at the same time point, # P<0.05 compared with other time points within the same group, & P<0.05 compared within the same group at T1, **P<0.001 compared with T5 within the same group, $ P<0.05 compared with T1, T3, and T4 measurements within the same group

P values for interaction were 0.657 for pH, 0.017 for PaO_2, and 0.146 for $PaCO_2$ across the groups over time.

DISCUSSION

Our study included 68 pediatric patients who underwent surgery for noncyanotic congenital cardiac disorders. The findings showed that operation-related variables such as CPB, ventilation and clamping times, ICU length of stay, mortality rate, and neurological complications were similar between patients in both groups. Brain oxygenation status and hemoglobin levels were nonsignificantly lower among patients in the moderate hypothermia group than among those in the mild hypothermia group. Moreover, preoperative and postoperative ejection fraction, inotropic agent dosage, and renal function parameters were similar between patients in both groups. Overall, hypothermia during CPB can protect myocardial tissue by decreasing blood flow and oxygen consumption during CPB.

Zhu et al[21] compared the short-term outcomes following aortic arch surgery in adult patients who experienced deep, moderate, and mild hypothermia during CPB. They found that mild hypothermia offers acceptable protection during CPB while reducing the incidence of major adverse effects. While they reported reduced postoperative and total transfusion of packed red blood cells in the mild hypothermia group compared to the moderate

hypothermia group, we observed no significant differences in these criteria between patients in the mild and moderate hypothermia groups.

The discrepancies between the results could be attributed to several reasons. One is the age of the patients in each study. While the research conducted by Zhu et al[21] focused on adult patients, our investigation involved pediatric patients, who have different anthropometric characteristics, metabolic demands, and hemostasis control mechanisms. Moreover, their study was not randomized and included a diverse cohort of patients undergoing various types of corrective surgeries, which resulted in significant variations in the duration of surgery and other related outcomes, such as cross-clamp and CPB duration. These variations may confound their findings, as operations with longer cross-clamp, CPB, and overall operation times may be associated with increased blood loss and a higher need for transfusions.

Aydemir et al[22] reported the advantages of mild hypothermia over moderate hypothermia in terms of inotropic support need, ICU length of stay, and hospital stay in neonates undergoing arterial switch operations (ASO). ASO is a complex operation with a median cross-clamp duration of 124 to 127 minutes in their study, while the mean cross-clamp time in our study was approximately 92 minutes, which is significantly longer. This difference in duration affects metabolic demand and may, in turn, influence the outcomes of the operation. Although many studies advocate the advantages of mild hypothermia over moderate hypothermia, others challenge these findings. Bianco et al[23] reported in a retrospective study of 6525 patients that normothermia is superior to hypothermia in terms of postoperative renal failure incidence and the length of intensive care unit stay.

While hypothermia is a common practice during CPB in both adult and pediatric patients, a growing body of evidence questions its benefits for patients. Many studies have challenged the hypothesis that deeper hypothermia may offer better protection of the brain and remote organs during surgery and improve patient outcomes.[24, 25] Our study contributes to the current evidence and supports the notion that deeper hypothermia is not superior to mild hypothermia for organ protection during CPB.

CONCLUSIONS

The results of the current trial demonstrate that there are no significant differences in peri- and postoperative outcomes, including ICU length of stay, mechanical ventilation time, and neurological outcomes, between groups managed with mild and moderate hypothermia during CPB in noncyanotic pediatric patients undergoing surgery for the correction of congenital heart anomalies. However, we suggest considering other factors and long-term postoperative follow-ups to clarify the potential long-term risks and benefits associated with both interventions.

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