RESEARCH PAPER

Epinephrine Plus Vasopressin vs Epinephrine Plus Placebo in Pediatric Intensive Care Unit Cardiopulmonary Resuscitation: *A Randomized Double Blind Controlled Clinical Trial*

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Objective: To compare the efficacy of epinephrine plus vasopressin vs epinephrine plus placebo in the pediatric intensive care unit (PICU) cardiopulmonary resuscitation (CPR).

Design: Randomized, double-blind controlled clinical trial.

Setting: PICU in a tertiary care institute from February, 2019 to May, 2020.

Participants: Children aged one month to 13 years who required CPR during PICU stay. Patients in whom vascular access was not available or return of spontaneous circulation (ROSC) was achieved by defibrillation without epinephrine were excluded.

Intervention: Patients were randomized to receive vasopressin 0.1 mL per kg (=0.8 unit per kg) or placebo (0.1 mL per kg normal saline) in addition to epinephrine (1:10000) 0.1 mL per kg. The drugs were given as bolus doses every three minutes until the ROSC or up to a maximum of five doses, whichever was earlier.

Outcome Measure: The primary outcome was the proportion of patients who achieved ROSC. The secondary outcomes were survival rate and functional status (at 24-hour, PICU, hospital, and 90-day post-discharge), need for organ supports, length of stay (PICU and hospital), and adverse effect(s) of the study drugs.

Results: 90 patients (epinephrine plus vasopressin group, *n*=45 and epinephrine plus placebo group, *n*=45) were analyzed on intention-to-treat basis. There was no significant difference in the primary outcome between epinephrine plus vasopressin (*n*=25, 55.5%) and epinephrine plus placebo groups (*n*=24, 53.3%) (Relative risk 1.04, 95% CI 0.71 to 1.52). There was no significant difference in survival rate at 24-hour (*n*=7, 15.6% vs. *n*=8, 17.8%), at PICU, hospital, and 90-day post-discharge (*n*=1, 2.2% vs *n*=1, 2.2%). There was no difference in other secondary outcomes. No trial drug-related serious adverse events were observed.

Conclusion: A combination of epinephrine plus vasopressin did not improve the rate of return of spontaneous circulation in the pediatric intensive care unit cardiopulmonary resuscitation as compared with epinephrine plus placebo.

Keywords: *In-hospital cardiac arrest*.

Trial Registration: CTRI/2019/01/017200.

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Cardiac arrest is a dreadful event in pediatric intensive care unit (PICU). Cardiopulmonary resuscitation (CPR) involves chest compression and manual ventilation at appropriate intervals. Return of spontaneous circulation (ROSC) is the initial therapeutic goal in cardiac arrest and is a measure of initial success. Vasopressor medications are often used during CPR. These medications increase aortic diastolic pressure, thereby improving coronary perfusion pressure, which facilitates ROSC [1]. Epinephrine is the most widely studied and the first line vasoactive drug as per the pediatric advanced life support (PALS) guidelines [2]. Vasopressin, a potent vasoconstrictor, is well studied in adult cardiac arrest [3]. The recent advanced cardio-vascular life support guideline recommends that Vaso-pressin, combined with epinephrine, may be considered in adult cardiac arrest resuscitation [3]. Though the pediatric in-hospital cardiac arrest (IHCA) outcome has improved from 39% to 77% in high-income countries, data from low-and middle-income countries are lacking or are under-reported [2]. Animal studies, case series, and feasibility pilot studies have shown encouraging results for the use of vasopressin in pediatric cardiac arrest [4-6]. This study hypothesized that epinephrine plus vasopressin would be associated with a higher rate of ROSC as compared to epinephrine plus placebo in the pediatric intensive care unit cardiopulmonary resuscitation.

METHODS

This randomized, double-blind controlled clinical trial was undertaken in PICU of a tertiary care academic hospital from February, 2019 to May, 2020. Ours is a 19 bedded

level-III PICU, receiving critically ill children 24 hours a day throughout the year. Though our PICU is a predominantly medical ICU, it also receives complicated surgical and trauma patients. The PICU has facilities for providing multimodal hemodynamic and neuromonitoring, mechanical ventilation, and high-frequency ventilation. It is also equipped with an in-house blood gas analyzer with a co-oximeter module, osmometer, therapeutic plasma exchange, and renal replacement therapy. During the study period, the baseline mortality in our PICU was 20%, and the average length of PICU stay was six days, with a bed occupancy rate of 80%.

The trial was approved, and its progress was reviewed yearly by the institute ethics committee. Written informed consent was obtained from the parent/legally authorized representatives of all patients getting admitted to PICU at the time of transfer-in, stating that their child might be enrolled in the study if the child required CPR during the PICU stay. Children aged one month to 13 years, admitted in PICU, and who required CPR during their PICU stay were enrolled. Children who had a cardiac arrest outside of PICU and were shifted to PICU for post-cardiac arrest care were not enrolled. Children with either of the following conditions were also excluded (*i*) patients in whom vascular access was not available (*ii*) ROSC was achieved by defibrillation without the requirement of Epinephrine.

A computer-generated, unstratified, block randomization with variable block sizes of four, six, and eight was used with an allocation ratio of 1:1 by a person not involved in the study. Individual assignments were kept in serially numbered boxes. Each box contained ten identically looking one mL ampoules of either vasopressin or placebo (normal saline). The original label in each ampoule was removed and replaced by an opaque paper. Each box was serially numbered and allocated to the patient according to the random sequence. The serially-numbered trial drug boxes were kept in a separate place in PICU to avoid the wrong allocation in the stressful environment. Only one trial drug box was kept in the crash cart, which contained all the emergency drugs and equipment required for CPR. The nurses were instructed to open the trial drug box, which was kept in the crash cart during CPR. The investigator ensured the replacement of the trial drug box in the crash cart according to the serial number once the trial drug was used. Multiple simulation sessions were carried out and discussed before the start of the study. Injection normal saline (sodium chloride 0.9%, 1 mL, Serum Institute of India Pvt Ltd), injection epinephrine (Bioaderna, 1 mg per 1 mL, Health Biotech Ltd) and injection vasopressin (Vascel 20, 20 Unit per mL, CELON laboratories Pvt Ltd) were used in this study. The institute's central pharmacy supplied the trial drugs. The participants, treating team and nurses administering the medications, and the investigators, were unaware of the treatment assignments. The person who collected and entered the data into the datasheet and the study statistician were unaware of the treatment assign-ment throughout the analyses. The treatment assignment was disclosed, after the first draft of the result was finalized.

All patients received CPR in accordance with the PALS-2015 guidelines established by the American Heart Association (AHA) [2]. This includes the support of airway, breathing, including supplemental oxygen, evaluation of cardiac rhythm, high-quality CPR with minimally interrupted chest compressions, electrical defibrillation if appropriate, and medications except for the trial drugs. The resuscitation team members were trained to provide CPR as per the PALS 2015 guidelines [2]. The facility for standby extracorporeal membrane oxygenation (ECMO) is not available in the study site (PICU). Our hospital has no approved guidelines for 'Do not resuscitate' instructions. Epinephrine plus vasopressin group received intravenous epinephrine (1:10000) 0.1 mL per kg and vasopressin (1:1.5 dilution in normal saline) 0.1 mL per kg (=0.8 unit per kg; maximum dose of 5 mL, 40 unit). Epinephrine plus placebo group received intravenous epinephrine (1:10000) 0.1 mL per kg and placebo (1:1.5 dilution in normal saline) 0.1 mL per kg. The trial drugs were given as bolus doses, concurrently if two vascular accesses were available or within 10 seconds gap if one vascular access was available. The trial drugs were given at an interval of every three minutes until ROSC or a maximum of five doses, whichever was earlier. Three mL normal saline flush was given after adminis-tration of each dose of the trial drug. Subsequently, if needed, epinephrine was continued as per protocol. Post-resuscitation care was provided to the patients who achieved ROSC as per the unit protocol (from PALS-2015 guidelines) [2]. All patients were followed up until death or 90 day post-discharge. The functional status of the survivor was assessed by using the pediatric cerebral performance category (PCPC) scale and pediatric overall performance category (POPC) scale (lower the score, better the neurological outcome) [7]. Data regarding the cardiac arrest events and their outcomes were collected as per the Utstein style template and in the predesigned proforma [8-10].

The primary outcome was the proportion of patients who achieved ROSC. The secondary outcomes were (*i*) survival rate (at 24 hours, PICU, hospital, and 90-day of discharge), (*ii*) functional status (at PICU, hospital, and 90-day of discharge), (*iii*) need for organ support(s), (*iv*) length of stay in PICU and hospital, and (*v*) adverse effect(s) of the study drugs if any. ROSC was defined as the restoration of a spontaneous perfusing rhythm that results

in more than an occasional gasp, fleeting palpable pulse, or arterial waveform [2,3,10]. Sustained ROSC was defined as not requiring chest compressions for 20 consecutive minutes after obtaining ROSC and signs of perfusion [2,3,10]. The probability of adverse trial drug reaction was assessed by Naranjo algorithm [11].

The ROSC rate varies between 47% and 64.6%, as reported by previous studies [12,13]. We assumed that the primary outcome of interest in the control group was 50%. We calculated the sample size based upon the assumption of 30% improvement in the primary outcome by the intervention with 80% power at the 5% significance (two-sided) and 1:1 allocation. Thirty-nine patients were required in each group by calculation. With a 10% attrition rate, the final sample size was estimated as 86 [12-14]. The sample size was calculated using the software nQuery version 4.0.

Statistical analysis: Data were analyzed according to their assigned groups (intention to treat analysis). The distribution of data was checked with the Kolmogorov-Smirnov Z test. Continuous variables were compared between the two groups by Student's *t*-test for normally distributed or by the Mann-Whitney *U* test for skewed data. Proportions were compared by the Chi-square test (or Fisher's exact test if expected cell frequencies were less than five). Kaplan-Meier curve and log-rank test were used to analyze 'time to event' data followed by Cox proportional hazard regression analysis to adjust for the prespecified baseline factors (age, sex, and PRISM-III score). The relative risk and hazard ratio, with a 95% confidence interval, was calculated as appropriate. All tests were two-tailed, and a *P* value of less than 0.05 was considered statistically significant. IBM SPSS software 20.0 (IBM Corp) and Epi Info 7 (7.0.9.7, CDC) were used for data analysis.

RESULTS

The study flow is depicted in **Fig. 1**. Ninety patients were enrolled (epinephrine plus vasopressin, *n*=45, and epinephrine plus placebo *n*=45) after the screening of 118 patients. The baseline characteristics and clinical variables are described in **Table I**. The median (IQR) time to first cardiac arrest since admission was similar between groups [2 (1-7) vs 2 (1-5) day; *P*=0.75]. The most common (80%) arrest rhythm was pulseless electrical activity (PEA). Hemodynamic abnormality (67.8%) was the most common event that led to arrest, followed by respiratory events (23.3%). Respiratory failure was an underlying illness in 76 (84.4%) patients and sepsis in 60 (66.7%) patients. The median (IQR) duration of CPR was similar between groups [18 (10-30) vs 15 (6–30) minutes; *P*=0.96].

The proportion of patients who achieved ROSC was similar in epinephrine plus vasopressin group and epinephrine plus placebo group [RR (95% CI) 1.04 (0.71-1.52); *P*=0.83]. The time to achieve ROSC and the proportion of patients requiring ongoing CPR was similar between two groups during the first 30 minutes of CPR [Log rank *P*=0.99] **(Fig. 2)**. Among ROSC achieved patients (*n*=49), the median (IQR) time taken to ROSC was similar between two groups [10 (4-14) vs 6 (5-10) minutes, *P*=0.21]. The proportion of patients who underwent CPR beyond 30 minutes was also similar between two groups [RR (95% CI) 0.50 (0.19-1.35); *P*=0.16] and none achieved ROSC. There was no significant difference in the proportion of patients who achieved sustained ROSC in the study groups [44.4% vs 53.3%; *P*=0.40]. The survival to hospital discharge was similar in both groups [*n*=1 each]. Mean (SD) diastolic blood pressure (DBP) was similar in epinephrine plus vasopressin group as compared to epinephrine plus placebo group during CPR (38.1 (11.5) mm Hg vs 37.1 (13.4) mm Hg, *P*=0.77). There was no significant difference in the other secondary outcomes between study groups **(Table II)**. In epinephrine plus vasopressin group, one patient developed pulseless ventricular tachycardia which converted into asystole

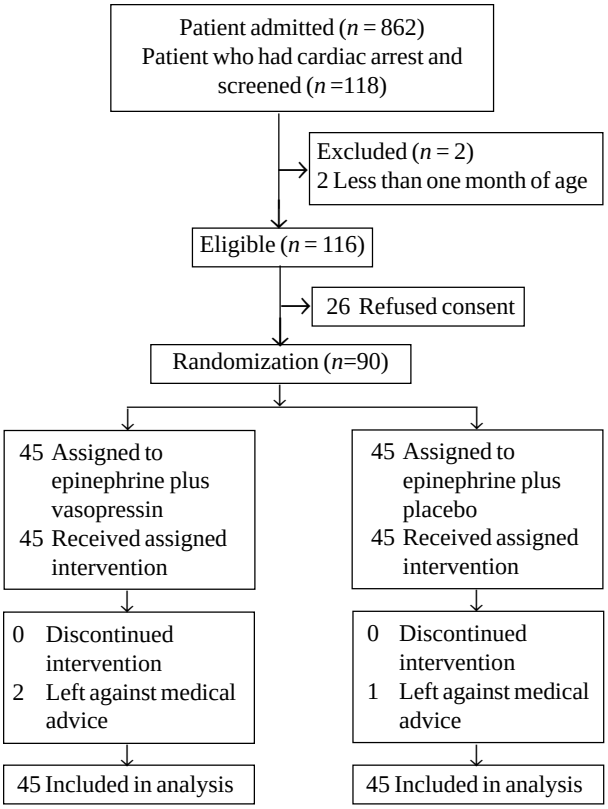

Fig. 1 Study flow chart.

Table I Baseline Characteristics and Clinical Variables of the Two Study Groups

Variables	*Epinephrine plus vasopressin group (n = 45)*	*Epinephrine plus placebo group (n = 45)*
Age, y[a]	2.5 (3.3)	3 (4.4)
Male: female	25:20	28:17
Body mass index[a]	– 2 (1.9)	– 1.9 (2.0)
Pediatric risk of mortality - III score[a]	19.6 (9.6)	18 (8.6)
Arrest rhythm		
Pulseless electrical activity	38 (84.5)	34 (75.6)
Asystole	6 (13.3)	10 (22.2)
Pulseless ventricular tachycardia	1 (2.2)	1 (2.2)
Events leading to arrest		
Hemodynamic abnormality	31 (68.9)	30 (66.7)
Respiratory events	11 (24.4)	10 (22.2)
Rhythm disturbance	3 (6.7)	5 (11.1)
Illness category		
Medical condition	40 (89)	42 (93.3)
Surgical condition	5 (11)	3 (6.7)
Diagnosis and underlying illness[b]		
Respiratory failure	38 (84.4)	38 (84.4)
Sepsis and shock[d]	37 (82.2)	23 (51.1)
CNS illness	19 (42.2)	22 (49)
Pneumonia	24 (53.3)	17 (37.8)
Congenital heart disease	7 (15.6)	10 (22.2)
Renal insufficiency	21 (46.7)	16 (35.6)
Hepatic insufficiency	21 (46.7)	14 (31.1)
Malignancy	5 (11)	4 (9)
Intervention in place at the time of event[c]		
Mechanical ventilation	44 (97.8)	43 (95.6)
$EtCO_2$ monitoring	44 (97.8)	43 (95.6)
Arterial line	37 (82.2)	34 (75.6)
Central venous access	43 (95.6)	42 (93.3)
Vasoactive drug infusion	40 (89)	39 (86.7)
Renal replacement therapy	8 (17.8)	6 (13.3)
Intervention done during CPR		
Sodium bicarbonate	14 (31.1)	23 (51.1)
Calcium gluconate	8 (17.8)	14 (31.1)
Atropine	1 (2.2)	2 (4.4)
Defibrillation	1 (2.2)	1 (2.2)
Doses of study drug[a]	3.6 (1.6)	3.5 (1.6)

Data in no. (%) or [a]mean (SD). CNS: central nervous system; SD: standard deviation; $EtCO_2$: end-tidal carbon dioxide; CPR: cardiopulmonary resuscitation; [b]Patient had one or more conditions; [c]had one or more interventions. Hence, the cumulative totals do not necessarily equal. Three patients also received EtCO2 monitoring after placement of endotracheal tube during CPR; [d]P=0.002.

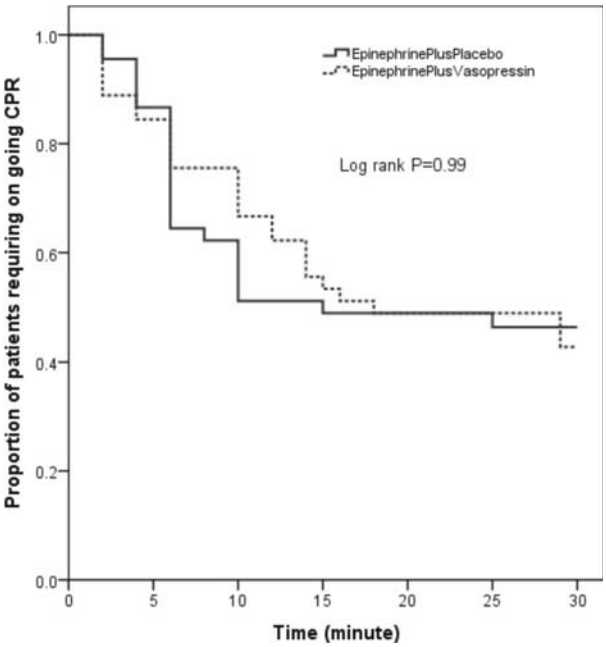

Fig. 2 Kaplan Meier curves showing time to return of spontaneous circulation (ROSC) and the proportion of patients requiring on-going cardio pulmonary resuscitation (CPR) between the two study groups.

during the third cycle of CPR. There were no serious trial drug-related adverse events observed.

DISCUSSION

This randomized controlled trial enrolled 90 patients who underwent CPR in PICU. We found no significant difference in the proportion of patients who achieved ROSC and survival rate between the Epinephrine plus Vasopressin group and Epinephrine plus Placebo group. In our study, the overall rate of achieving ROSC was 54.4%, and survival to hospital discharge was 2.2%. This observation contrasts with the data from high-income countries, where the rates were more than 80% and 40%, respectively [15]. The potential reasons could be the uniform reporting registries, universal healthcare programs, training of health care workers, and accessibility to extracorporeal membrane oxygenation (ECMO).

The outcome of a pediatric cardiac arrest depends upon many factors, including the initial presenting rhythm, the place of cardiac arrest, early recognition of the arrest, and the underlying conditions. In the previous studies done in high-income countries, asystole (55%) was the initial arrest rhythm, and respiratory failure was the common precipitating factor [1,9]. Nevertheless, they enrolled patients not only from PICU but also from the emergency department and general ward [1,9]. In contrast, this study

Table II Primary and Secondary Outcomes of the Study Groups

Variables	*Epinephrine plus vasopressin group (n = 45)*	*Epinephrine plus placebo group (n =45)*	*Relative risk (95% CI)*	*P value*
Primary outcome				
Proportion of patients achieved ROSC	25 (55.5)	24 (53.3)	1.04 (0.71-1.52)	0.83[a]
Proportion of patients achieved sustained ROSC	20 (44.4)	24 (53.3)	0.83 (0.54-1.28)	0.40[a]
Secondary outcomes				
Survival rate at 24 – hour	7 (15.6)	8 (17.8)	0.88 (0.35-2.21)	0.78[a]
At PICU discharge	1 (2.2)	1 (2.2)	1.00 (0.06-15.50)	1.00[c]
At Hospital discharge	1 (2.2)	1 (2.2)	1.00 (0.06-15.50)	1.00[c]
At 90-day post-discharge	1 (2.2)	1 (2.2)	1.00 (0.06-15.50)	1.00[c]
Functional status				
PCPC score – 1 (mild)	-	1 (2.2)	-	-
POPC score – 4 (severe)	1 (2.2)	-	-	-
Organ support therapy among patients achieved ROSC[a,b]				
Mechanical ventilation, h	1.5 (0.5-12)	5 (1.3-33)	-	0.07[b]
Vasoactive therapy, h	1.5 (0.4-8)	4 (1.3-19)	-	0.07[b]
RRT, h[c]	1 (1-14.3)	50 (1-137)	-	0.13[b]
PICU stay, h	1.5 (0.5-12)	5 (1.3-33)	-	0.08[b]
Hospital stay, h	1.5 (0.5-12)	5 (1.3-33)	-	0.08[b]

Data are presented as no.(%) except [a]median (IQR). ROSC: return of spontaneous circulation; CI: confidence interval; IQR: interquartile range; RRT: renal replacement therapy; PCPC: pediatric cerebral performance category; POPC: pediatric overall performance category. [b]25 in epinephrine plus vasopressin group and 24 in epinephrine plus placebo group; [c]seven in epinephrine plus vasopressin and six in epinephrine plus placebo group received RRT support after ROSC.

enrolled patients only from PICU, where stringent monitoring helped identify the arrest much earlier, before progressing to asystole. Similar to our study setting, Rathore, et al. [12] reported bradycardia (52.2%) and sepsis (71%) as the initial arrest rhythm and underlying diagnosis, respectively. They reported a higher ROSC rate (64.6%) and survival to hospital discharge (14%). However, only 21% of CPR occurred in PICU in that study. In our study, patients were enrolled only from PICU. So, the study population was different. Generally, PICU patients are sicker and the majority of them have multiple organ dysfunction requiring organ support. Also, the initial rhythm is an important factor in predicting the outcome; bradycardia rhythm with a pulse is more likely to recover than pulseless non-shockable rhythms [12].

At present, only a limited number of vasopressors are available for use in pediatric CPR, and insufficient data supporting their use [2]. The pediatric guidelines were extrapolated from adult clinical trials and animal studies. Vasopressin acts via the V-1 receptor in the arterial wall and increases the aortic diastolic pressure, thereby improving coronary perfusion pressure. In contrast to epinephrine, there are no β_1 mediated chronotropic and inotropic actions; hence it enhances the myocardial oxygen delivery and reduces the myocardial oxygen consumption during CPR and in the post-resuscitation period [1,16]. Another advantage of vasopressin includes the continuation of vasoconstrictive effects, even in severe acidosis, accompanying cardiac arrest. Hence, vasopressin can act as a better vasopressor during CPR, particularly in patients with sepsis-associated myocardial dysfunction and severe acidosis [16]. However, vasopressin has a longer duration of action than epinephrine, where the persistent vasoconstriction may worsen the myocardial dysfunction in the immediate post-resuscitation period. Post cardiac arrest myocardial dysfunction can be caused by various factors, including the underlying pre-arrest cardiac status, duration and quality of CPR, and the presence of other organ dysfunction(s). So, it is difficult to establish the causal relationship between post-cardiac arrest myocardial dysfunction and vasopressin use. However, no probable serious adverse event due to the trial drug was observed in this study.

The feasibility pilot study in pediatric cardiac arrest by Carroll, et al. [6] reported no significant difference in ROSC, survival to hospital discharge, and neurological

WHAT IS ALREADY KNOWN?

- Few studies have shown promising results of vasopressin use in pediatric in-hospital cardiopulmonary resuscitation.

WHAT THIS STUDY ADDS?

- The combination of cpinephrine and vasopressin did not improve the rate of return of spontaneous circulation, survival, and favorable neurological outcome as compared to Epinephrine alone.

outcome at discharge between vasopressin and control groups (who did not receive vasopressin). Nevertheless, they reported a higher survival rate at 24 hours in the vasopressin group. Their study was limited by non-randomization, small sample size, and addition of vasopressin only after non-response to epinephrine.

Similarly, Duncan, et al. [1] explored the use of vasopressin in pediatric in-hospital arrest from the American Heart Association National Registry of CPR data [1]. Patients who received vasopressin had a longer median arrest duration as compared to those who did not. They also noted that, on multivariate analysis, those who received vasopressin had a reduced ROSC; however, there was no difference in survival at 24 hours. Vasopressin was used as a "drug of last resort" for many of their patients [1], in contrast to our study, where it was used from the time CPR was initiated.

In comparison with an adult, children often present with a non-shockable rhythm, which requires high-quality chest compressions [15]. A systematic review that included 26 RCTs and 21704 participants found that vasopressin did not improve the ROSC rate but improved the survival to hospital admission compared to epinephrine [17]. However, the combination of epinephrine and vasopressin did not show any significant outcome benefits as compared to epinephrine alone [17]. However, most of the included studies were conducted over two decades back. Hence, these findings may not reflect the current practice in the growing era of extracorporeal life support (ECLS) availability.

Though all healthcare providers in our study have been trained in CPR, the intra- and inter-personal variations in chest compression were not monitored objectively. The temporal profiles of end-tidal carbon dioxide and DBP were not analyzed with the outcome of the study. Though our study found similar DBP in both the groups, the pediatric-specific target DBP during CPR is yet to be studied. However, evidence suggests that those who achieve DBP of 25 to 30 mm Hg during CPR have a higher chance of ROSC and survival [15]. Hence, goal-directed CPR targeting the end-tidal carbon dioxide and DBP needs to be considered in future study design. The availability of ECMO service during CPR or after achieving ROSC could have improved the survival to discharge. Recent studies showed that extracorporeal CPR (E-CPR) in pediatric cardiac arrest was associated with shorter resuscitation time and higher survival rate, ranging from 33-64% [18-20]. The AHA recommends considering E-CPR during in-hospital pediatric cardiac arrest, when standard resuscitation has failed, especially in a potentially reversible cause of cardiac arrest [2].

The study concludes that a combination of epinephrine and vasopressin did not improve the rate of return of spontaneous circulation, survival, and favorable neurological outcomes in pediatric intensive care unit cardiac arrest resuscitation as compared to epinephrine and placebo.

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Contributors: RR: had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis; RR: Study concept and design; AS, MC, KM, RSK, AJ, RB: acquisition, analysis, or interpretation of data and drafting of the first manuscript; MC, RB, NB, SM: protocol development and revision of the manuscript; RR, SM: critical revision of the manuscript for important intellectual content; RR, NB: study supervision. RR: is the guarantor of the paper. All authors approved the final version of the manuscript.

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