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ORIGINAL RESEARCH

Effect of prehospital intraosseous combined with in-hospital intravenous access in out-of-hospital cardiac arrest

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Abstract

Objective: Obtaining vascular access during out-of-hospital cardiac arrest (OHCA) is challenging. The aim of this study was to compare the effectiveness of prehospital intraosseous infusion (IO) combined with in-hospital intravenous (IV) (pre-IO + in-IV) access versus the simple IV (pre-IV + in-IV) access in adult OHCA patients who do not achieve prehospital return of spontaneous circulation (ROSC).
Methods: This retrospective observational study included adults with OHCA of presumed cardiac etiology between October 1, 2017-October 1, 2020 at an academic emergency department in China. All of the OHCA patients included within the study had Emergency Medical Services cardiopulmonary resuscitation and received prehospital epinephrine administration, but did not achieve prehospital ROSC. The study population were classified as either pre-IO + in-IV or IV (pre-IV + in-IV) based on their epinephrine administration route. The prehospital epinephrine routes were the first and only attempted route. The primary outcome investigated was sustained ROSC following arrival at the emergency department. The secondary outcome considered was the time from dispatch to the first epinephrine dose.
Results: Of 193 included adult OHCA subjects who did not have prehospital ROSC, 128 received IV access only. The 65 pre-IO + in-IV-treated patients received epinephrine faster compared to IV-treated patients in terms of the median time from dispatch to the first injection of epinephrine (14.5 *vs.* 16.0 min, $P = 0.001$). In the pre-IO + in-IV group, 34 of 65 patients (52.3%) achieved sustained ROSC compared with 65 of 128 (50.8%) patients in the IV group ($\chi^2 = 0.031$, $P = 0.841$). There was no significant difference in sustained ROSC (adjusted OR1.049, 95% CI: 0.425-2.591, $P = 0.918$) between the two groups.
Conclusion: A similar sustained ROSC rate was achieved for both the pre-IO + in-IV access group and the simple IV access group. Our results suggested that an IV route should be established quickly for prehospital IO-treated OHCA patients who do not achieve prehospital ROSC.

Keywords

Out-of-hospital cardiac arrest; Intraosseous; Intravenous; Epinephrine; Return of spontaneous circulation

1. Introduction

Out of hospital cardiac arrest (OHCA) is a global problem with high mortality and morbidity worldwide [1]. Annually, more than 347,000 adults and in excess of 7,000 children experience Emergency Medical Service (EMS)-assessed OHCA in the United States [2]. It is well known that obtaining vascular access to administer resuscitation medications is associated with an increased chance of return of spontaneous circulation (ROSC) and survival to hospital discharge for OHCA patients [3–5]. However, obtaining intravenous (IV) access under emergent conditions, especially in OHCA, can prove to be challenging based on patient characteristics and operator experience, leading to delays in pharmacological treatments.

Given the relative ease and speed with which it can be achieved, a higher successful placement rate compared with IV cannulation, and the relatively low procedural risk, intraosseous (IO) access has grown in popularity and is increasingly implemented as a first-line approach for drug administration during cardiac arrest [6, 7]. However, recent observational studies support the theory that IV access appears to be the optimal route for epinephrine administration during resuscitation [8–12]. In a 2020 study by Zhang *et al.* [13], where the IV or IO routes of OHCA patients were the first and only attempted route, IO treatment was associated with worse outcomes in comparison to an IV approach. Outcomes for IO patients included a lower likelihood of prehospital ROSC achieved, lower survival to hospital discharge rates and less favorable neurological outcomes at discharge. As a result, the latest resuscitation guidelines favor IV rather than IO access [14]. However, the subgroup analyses of two randomized clinical trials observed no statistically significant interactions between the route of access and the study drug on outcomes [15, 16]. At present, EMS always initially attempts to establish IO access to shorten the time to first epinephrine dose during prehospital resuscitation. For these OHCA patients who do not achieve prehospital ROSC, an IV route is rapidly established for subsequent epinephrine management after arriving at the emergency department (ED). Meanwhile, IO cannulation is only used for fluid replacement. However, data regarding the effects of the approach of prehospital IO combined with in-hospital IV (pre-IO + in-IV) administration versus the simple IV (pre-IV + in-IV) administration are scarce.

The objective of this retrospective observational study was to compare the effectiveness of pre-IO + in-IV versus the simple IV administration of epinephrine in adults who suffered from OHCA of presumed cardiac etiology and did not have prehospital ROSC.

2. Methods

2.1 Study design and setting

This was a retrospective observational study. Data were collected from our hospital, which is a tertiary academic medical center with about 5000 beds. Our EMS respond to nearly service 5000 requests each year which are activated by central dispatch via a call to the '120' emergency telephone number. It should be noted that a mature prehospital EMS in China consists of at least two ED paramedics who generally have substantial experience with basic and advanced life support. The current cardiac arrest protocol for our EMS allows for either IV or IO access to be placed at the discretion of the on-scene paramedic, this was also during the study dates of October 1^{st} 2017-October 1^{st} 2020. IV access is usually established at standard sites, such as the hand, forearm as well as the antecubital fossa. The approved IO insertion site was the proximal tibia. A standard 1 mg dose of epinephrine 1:1000 was administrated. For the OHCA patients who received IO route treatment but did not achieve prehospital ROSC, the IV route was established by an experienced senior paramedic for subsequent epinephrine administration after arriving at ED. In this study, this access type is termed 'prehospital IO combined with in-hospital IV access' (pre-IO + in-IV). The present study was approved by the Henan Provincial People's Hospital Institutional Review Board (reference number: 2015, 08).

2.2 Study population

All OHCA patients who received EMS treatment and prehospital epinephrine administration over a 3-year period from October 1, 2017 to October 1, 2020 were retrospectively screened. Patients were excluded if they were younger than 18 years old, pregnant, had a trauma-related cardiac arrest, dead on arrival at hospital or on-scene, or if essential data was not available about the patient/treatment or if family members asked for resuscitation to be stopped during the rescue process. Patients whose epinephrine administration route was unclear were also excluded from this study, as were patients who achieved prehospital ROSC. To ensure that the epinephrine routes of the included patients were the first and only attempted route before the transporting vehicle arrived at ED, patients who experienced failed administration attempts through another route were further excluded. The included population was divided into two study cohorts, OHCA patients with the simple IV route of epinephrine administration (IV group) and those with prehospital IO combined with in-hospital IV route (pre-IO + in-IV group).

2.3 Outcome

The primary outcome investigated was sustained ROSC after arriving at ED. The sustained ROSC was defined as patients with a persistent circulation for at least 20 consecutive minutes not requiring chest compressions. The secondary outcome assessed was the time from dispatch to the first dose of epinephrine.

2.4 Data extraction

Patient information was collected from dispatch, EMS, and hospital records without the requirement for patient consent. The study contains information pertaining to patient demographics (age and gender), witness status (none, bystander, or EMS), bystander cardiopulmonary resuscitation (CPR), episode location (public or non-public), EMS response interval, initial EMS-recorded rhythm (shockable or non-shockable), prehospital and in-hospital cumulative epinephrine dosages. A senior resident checked all data to ensure accuracy and check that data had been anonymized.

2.5 Statistical analysis

Descriptive statistics were performed to summarize the demographics and relevant characteristics of the entire study population including each study cohort individually. Continuous data were expressed as mean $\pm$ standard deviation or median and inter-quarter range, whereas categorical data were presented as an absolute number and percentage. The Kolmogorov-Smirnov test was used to assess normality distributions of continuous variables. Normally distributed continuous variables (age) were compared using Student t test, while the continuous variables that were not normally distributed (EMS response interval, cumulative epinephrine dosages) were compared using Mann-Whitney U tests. Categorical data were analyzed with Chi-square tests. Univariate and multivariate logistic regression analyses were performed to calculate odds ratios (OR), while adjusted outcome estimates were used for covariables such as age, gender, witnessed status, bystander CPR, public location, EMS response interval, initial cardiac rhythm and cumulative adrenaline dosage. All analyses were conducted using SPSS statistical software version 24.0 (IBM Corporation, Armonk, NY).

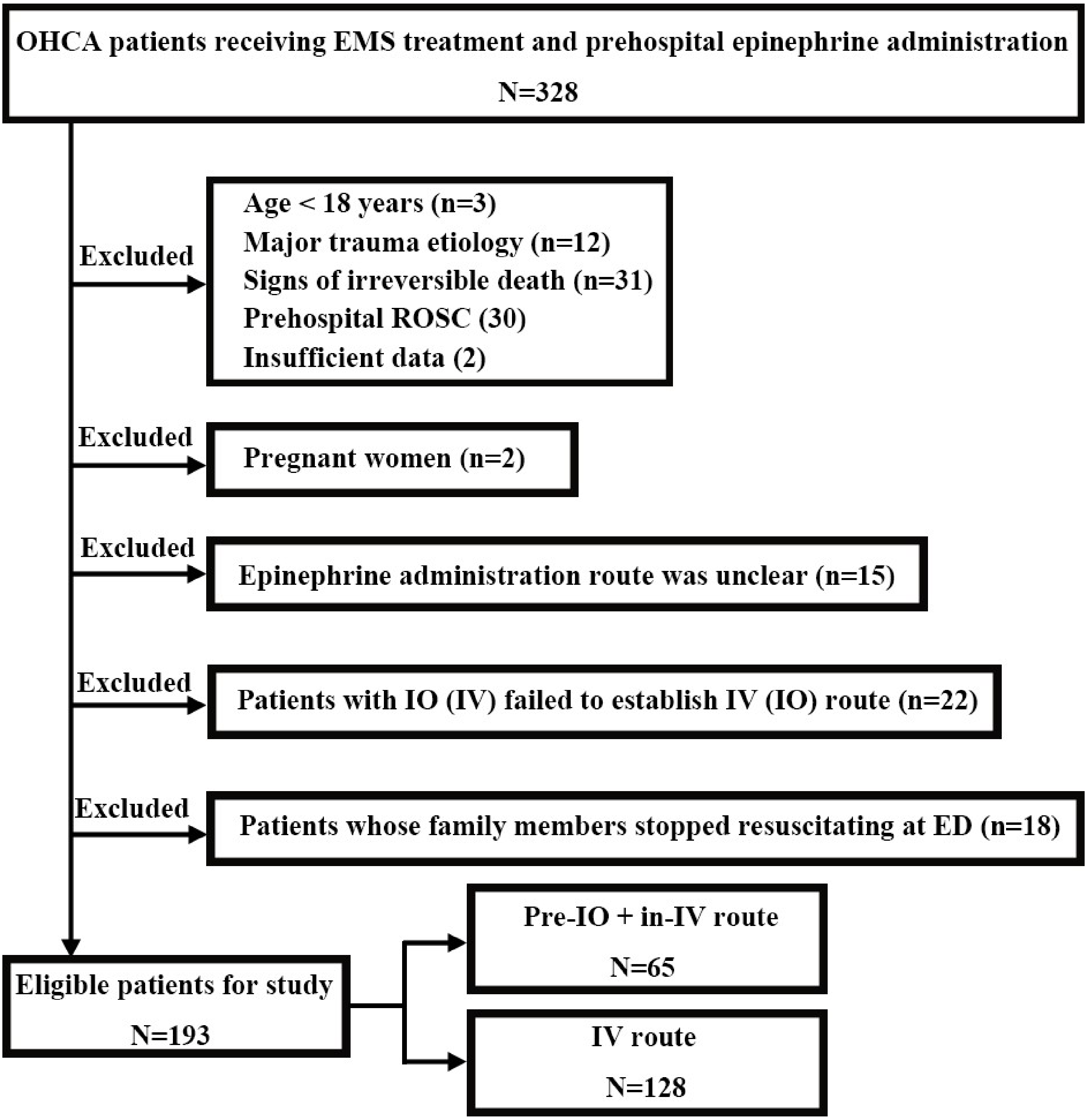

FIGURE 1. Study Flow Diagram.

3. Results

Fig. 1 shows the flowchart of our study. From October 1, 2017 to October 1, 2020, a total of 328 OHCA patients receiving EMS treatment and prehospital epinephrine administration were screened. Of these, 78 patients were excluded due to various combinations of age (< 18 years), major trauma etiology, presenting with signs of irreversible death (e.g. lividity or rigor) on arrival at hospital or on-scene, achieving prehospital ROSC, and/or insufficient data. Two pregnant women with OHCA were also excluded. 15 patients whose epinephrine administration route was unclear and 22 patients who experienced failed administration attempts through another route were further excluded. Notably, 18 patients were excluded as their family members stopped the resuscitation process. After exclusions, 193 patients remained in the study and their outcomes were analyzed, 65 in pre-IO + in-IV group and 128 in IV group.

The baseline characteristics from both groups (IV only or pre-IO + in-IV) did not show any significant differences. The two groups were similar in terms of age, gender, bystander witnessed arrest, bystander CPR, episode location and EMS response interval, as shown in Table 1. However, it should be noted that both groups had a large number of patients that presented with a non-shockable initial rhythm, but there were no significant differences between the groups.

TABLE 1. Baseline characteristics of the study population

	Overall (N = 193)	Pre-IO + In-IV (N = 65)	IV (N = 128)	*P* Vaule
Male, n (%)	132 (68.4)	44 (67.7)	88 (68.8)	0.947
Age, years, mean (SD)	65.5 (14.1)	63.6 (15.7)	66.4 (13.2)	0.207
Witness status, n (%)				0.988
None witnessed	107 (55.4)	35 (53.8)	72 (56.3)	
Bystander witnessed	77 (39.9)	27 (41.6)	50 (39.0)	
EMS witnessed	9 (4.7)	3 (4.6)	6 (4.7)	
Bystander CPR, n (%)	46 (23.8)	16 (24.6)	30 (23.4)	0.776
Episode location, n (%)				0.972
Public	21 (10.9)	7 (10.8)	14 (10.9)	
Non-public	172 (89.1)	58 (90.2)	114 (90.1)	
EMS response interval, min, median (IQR)	12 (11, 14)	12 (10, 14)	12 (11, 14)	0.175
Initial EMS-recorded rhythm, n (%)				0.974
Shockable	18 (9.3)	6 (9.2)	12 (9.4)	
Non-shockable	175 (90.7)	59 (90.8)	116 (90.6)	
Prehospital cumulative epinephrine dosage, mg, median (IQR)	3 (3, 4)	3 (3, 4)	3 (3, 4)	0.894
In-hospital cumulative epinephrine dosage, mg, median (IQR)	7 (5, 11)	7 (4.5, 11)	7.5 (5, 11)	0.647

CPR, cardiopulmonary resuscitation; EMS, Emergency Medical Services; IQR, inter-quarter range; mg, milligram; min, minute; Pre-IO + in-IV, prehospital intraosseous combined with in-hospital intravenous; SD, standard deviation.

TABLE 2. Pre-IO + in-IV versus IV placement

	Pre-IO + In-IV, n (%)	IV, n (%)	*P* Vaule
Sustained ROSC, n (%)	34 (52.4)	65 (50.8)	0.841
Time from dispatch to the first epinephrine dose, min, median (IQR)	14.2 (13.2, 17.0)	15.1 (13.8, 18.3)	0.001

min, minute; IQR, inter-quarter range; Pre-IO + In-IV, prehospital intraosseous combined with in-hospital intravenous; ROSC, return of spontaneous circulation.

A total of 65 (50.9%) out of 128 IV-treated OHCA patients achieved sustained ROSC. A total of 34 (52.3%) out of 65 pre-IO + in-IV-treated OHCA patients achieved. There was no significant difference in sustained ROSC figures reported between the two groups (χ^2= 0.031, P = 0.841), although pre-IO + in-IV-treated patients received epinephrine faster compared to the IV-treated patients in terms of the time from dispatch to first epinephrine dose (median 14.5 *vs.* 16.0 min, P = 0.001) (Table 2). In the multivariable adjusted analysis, the sustained ROSC outcome were also not significantly different between the pre-IO + in-IV group in comparison to the IV group (adjusted OR1.049, 95% CI: 0.425-2.591, P = 0.918) (Table 3). It seems reasonable to conclude that, compared with the simple IV access, similar sustained ROSC rates were achieved when using pre-IO + in-IV access.

TABLE 3. Logistic regression for sustained ROSC with odds ratio

Sustained ROSC	OR†	95% CI	*P* Vaule
Unadjusted model	0.941	0.518-1.710	0.841
Adjusted model*	1.049	0.425-2.591	0.918

CI, confidence interval; OR, odds ratio; ROSC, return of spontaneous circulation.
† Pre-IO + In-IV access in relation to IV access.
**The multivariable model was adjusted for age, gender, witnessed status, bystander CPR, public location, EMS response interval, initial cardiac rhythm and cumulative adrenaline dosage.*

4. Discussion

It is common knowledge in medical settings for every minute that epinephrine administration is delayed, there is an associated decrease in ROSC and survival outcomes in cardiac arrest patients. The perceived means by which IO epinephrine could be superior to IV is based upon the time taken for administration, by allowing earlier access for more prompt drug delivery the patient outcomes could be enhanced [6, 17]. Thus, IO access had been increasingly implemented as a first-line approach for emergent vascular access. Surprisingly, recent clinical studies documented an association between use of the IO route and a lower likelihood of ROSC, survival to hospital discharge, and favorable neurological outcomes, whilst the studies also showed that IO epinephrine was indeed administered earlier. The presumed reason that may contribute to the worse clinical outcomes of OHCA patients, despite the increased speed of administration, was the pharmacologic disadvantage of the epinephrine sedimentation effect at IO insertion sites [13, 18, 19]. In addition, several studies have verified that bone marrow blood flow was significantly decreased in cardiac arrest patients receiving CPR, leading to a prolonged time to reach the maximum concentration of epinephrine when administered by IO versus IV [7, 20, 21]. However, Nolan *et al*. [16] could not detect any differences in treatment effects between the IV and IO routes on ROSC, this was despite longer delays in time to first epinephrine delivery between the IV and IO routes (median 12.7 *vs.* 17 min respectively). Accordingly, it is currently believed that IV access is superior to IO access when it is associated with only minor delays in epinephrine administration [22].

During prehospital resuscitation, more and more paramedics prefer IO access in order to shorten the time to first epinephrine dose, followed by IV access being established. Due to the difficulties in establishing IV cannulation in a moving ambulance, the procedure have always been performed once the transporting vehicle has arrived at the ED. In this retrospective study, we explored whether the approach of pre-IO + in-IV administration can compensate for the presumed pharmacologic disadvantage caused by the first-attempt IO administration. We first found that IO access had a slight advantage over the IV route in relation to the initial time to first prehospital epinephrine dose (median 14.2 *vs.* 15.1 min respectively), which was similar to the slight delay time (median 15.6 min for IO *vs.* 16.7 min for IV) shown in Zhang's study [13]. Their results suggested that patients in the pre-IO + in-IV group probably showed a lower rate of ROSC. Whereas we found that pre-IO + in-IV epinephrine administration for OHCA patients who did not achieve prehospital ROSC showed a similar rate of sustained ROSC after arriving at ED, compared to the IV administration group. Our results also indicated that an IV route should also be established quickly for OHCA patients who have received a first-attempt and successful prehospital IO access. Additionally, our results indirectly supported some currently published evidence that the IV approach appears to be the optimal route for epinephrine administration in advanced life support for OHCA during resuscitation [8–13].

The limitations of this study are as follows: Firstly, given the retrospective, observational nature of our study, our results regarding the associations between pre-IO + in-IV access and sustained ROSC need to be interpreted with caution. Secondly, we lacked other variables that could affect the resuscitation outcomes in OHCA patients, such as patient factors (e.g. body mass index or comorbidities), socioeconomic factors, and resuscitation effort. Thirdly, due to various reasons (e.g. patients going into unwitnessed cardiac arrest), the lengths of times for each OHCA patient were often inaccurate or unknown. In addition, the number of survivors at hospital discharge and number with a favorable neurological outcome who received drug via IO route were small. Therefore, this study only assessed the primary outcome of sustained ROSC. However, to our best knowledge, this is the first study that has demonstrated the association between pre-IO + in-IV access and ROSC for OHCA.

5. Conclusions

Similar sustained ROSC rates were achieved with a prehospital IO combined with in-hospital IV access versus a simple IV access. Our results suggest that an IV route should be established quickly for prehospital IO-treated OHCA patients who do not achieve prehospital ROSC. Future randomized studies are needed to confirm the findings and elucidate the optimal route(s) of access for administration of drugs in OHCA patients.

AUTHOR CONTRIBUTIONS

YC and JZ wrote the first draft of this article and designed the figure, tables. XC, JZ and LQ critically revised the manuscript for important intellectual content. All authors approved the final version.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The present study was approved by the Henan Provincial People's Hospital Institutional Review Board (reference number: 2015, 08).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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