Intraosseous versus intravenous vascular access in upper extremity among adults with out-of-hospital cardiac arrest: cluster randomised clinical trial (VICTOR trial)

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ABSTRACT

OBJECTIVE

To compare the effectiveness of intraosseous versus intravenous vascular access in the treatment of adult patients with out-of-hospital cardiac arrest.

DESIGN

Cluster randomised controlled trial.

SETTING

The VICTOR (Venous Injection Compared To intraOsseous injection during resuscitation of patients with out-of-hospital cardiac arrest) trial involved emergency medical service agencies with all four advanced life support ambulance teams in Taipei City, Taiwan. The enrolment period spanned 6 July 2020 to 30 June 2023 and was temporarily suspended between 20 May 2021 and 31 July 2021 owing to the covid-19 pandemic.

PARTICIPANTS

Adult (age 20-80 years) patients with non-traumatic out-of-hospital cardiac arrest.

INTERVENTIONS

Biweekly randomised clusters of four participating advanced life support ambulance teams were assigned to insert either intravenous or intraosseous access.

MAIN OUTCOME MEASURES

The primary outcome was survival to hospital discharge. Secondary outcomes included return of spontaneous circulation, sustained return of spontaneous circulation (≥2 hours), and survival with favourable neurological outcomes (cerebral performance category score ≤2) at hospital discharge.

RESULTS

Among 1771 enrolled patients, 1732 (741 in the intraosseous group and 991 in the intravenous group) were included in the primary analysis (median age 65.0 years; 1234 (71.2%) men). In the intraosseous group, 79 (10.7%) patients were discharged alive, compared with 102 (10.3%) patients in the intravenous group (odds ratio 1.04, 95% confidence interval 0.76 to 1.42; P=0.81). The odds ratio of intraosseous versus intravenous access was 1.23 (0.89 to 1.69; P=0.21) for pre-hospital return of spontaneous circulation, 0.92 (0.75 to 1.13; P=0.44) for sustained return of spontaneous circulation, and 1.17 (0.82 to 1.66; P=0.39) for survival with favourable neurological outcomes.

CONCLUSIONS

Among adults with non-traumatic out-of-hospital cardiac arrest, initial attempts to establish vascular access through the intraosseous route did not result in different outcomes compared with intravenous access in terms of the proportion of patients surviving to hospital discharge, pre-hospital return of spontaneous circulation, sustained return of spontaneous circulation, and favourable neurological outcomes.

TRIAL REGISTRATION

ClinicalTrials.gov NCT04135547.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Out-of-hospital cardiac arrest affects millions of people worldwide annually

Peripheral intravenous and intraosseous access are two of the most commonly used types of vascular access in resuscitation after out-of-hospital cardiac arrest

Resuscitation guidelines suggest the deferred use of intraosseous access in resuscitation after out-of-hospital cardiac arrest, based on evidence from retrospective studies

WHAT THIS STUDY ADDS

This clinical trial found no difference in the proportion of patients surviving to hospital discharge between initial vascular access strategies of intraosseous and intravenous insertion in the upper extremity

The intraosseous route could be considered as a first line choice of vascular access rather than being secondary to intravenous access in resuscitation after out-of-hospital cardiac arrest

Introduction

Out-of-hospital cardiac arrest affects millions of people worldwide annually.[1] Bystander cardiopulmonary resuscitation and early defibrillation have been shown to improve outcomes, especially for patients with a shockable rhythm.[2 3] However, a larger proportion of patients worldwide have non-shockable rhythms. Despite the expected lower impact, timely vascular access is also vital to facilitate the prompt administration of drugs, fluid resuscitation, and other interventions, all of which play a crucial role in resuscitation. Peripheral intravenous and intraosseous access are two of the most common types of vascular access in pre-hospital settings, and both have been an integral part of advanced life support.[4 5] Guidelines for resuscitation suggest prioritising the intravenous route for administering drugs during out-of-hospital cardiac arrest and using the intraosseous route as a back-up when intravenous access is not possible.[4 5]

Previous retrospective studies have attempted to compare outcomes between intraosseous and peripheral intravenous vascular access in adult patients with out-of-hospital cardiac arrest.[6-18] None

of these studies has reported a statistically significant association between intraosseous access and improved patient outcomes after resuscitation, and some studies have further indicated that intravenous access leads to better survival outcomes.[7 11 12 14 16-18] However, all these studies have common limitations; hence, objective interpretation of the results and drawing definitive conclusions are challenging. In some studies, the choice of vascular access was at the discretion of the healthcare providers,[7-9] whereas intraosseous access was applied only when the intravenous route was unsuccessful in other studies.[10 17] Under these circumstances, the patients who received intraosseous access possibly had worse conditions and inherited resuscitation time bias.[19] Furthermore, the anatomical sites for intraosseous access placement varied. Although the humeral intraosseous route provides more rapid drug delivery to the right ventricle,[20 21] its use may be less prevalent in some health systems.[9 22] A recent meta-analysis of nine observational studies found no significant association between intraosseous versus intravenous access and clinical outcomes.[23] Moreover, reviews have highlighted the heterogeneity across the observational studies and emphasised significant concerns about selection bias and confounding.[23 24]

Compared with the intravenous route, the intraosseous route offers quicker and more reliable access in cardiac arrest situations with collapsed peripheral veins,[25] resulting in a higher first attempt success rate and significantly shorter time to medication than conventional intravenous access.[26 27] However, the clinical significance of variation in vascular access remains uncertain, underscoring the need for further high quality prospective studies. In this study, we hypothesised that adult patients with out-of-hospital cardiac arrest who underwent intraosseous vascular access attempts would have higher rates of survival at hospital discharge than those who underwent intravenous access.

Methods

Trial design

The multicentre, clustered, pragmatic, randomised controlled VICTOR (Venous Injection Compared To intraOsseous injection during Resuscitation of patients with out-of-hospital cardiac arrest) trial was conducted in four advanced life support ambulance service teams in Taipei City from 6 July 2020 to 30 June 2023. Owing to the covid-19 pandemic, recruitment was temporarily suspended between 20 May 2021 and 31 July 2021. We recruited all emergency medical technicians-paramedics in the four participating advanced life support ambulance service teams belonging to Taipei City Fire Department, and all emergency responsibility hospitals in Taipei City (supplementary appendix 1). Each paramedic had completed 1280 hours of training that was regulated by the Taiwan Ministry of Health and Welfare.[28] They were trained and authorised to perform both intravenous and intraosseous procedures in pre-hospital settings. All paramedics in the trial took at least a four hour course comprising one hour of lectures and three hours of hands-on practice sessions on intraosseous insertion. The emergency medical service configuration in Taiwan and Taipei city was briefly described in supplementary appendix 2. Eligible patients were enrolled automatically under the waiver of informed consent at the time of the study. Informed consent was obtained from the survivors or their legal representatives after enrolment.

Patient population

Adult (age ≥20 years) patients with out-of-hospital cardiac arrest treated by participating emergency medical service agencies were eligible for inclusion. The exclusion criteria were signs of obvious death (presence of rigor mortis or livor mortis); family's do-not-resuscitate order at the scene; contraindications for intravenous access (presence of local infection, burns, compromised skin, or arteriovenous fistula formation at the intended entry site) or intraosseous access (signs of infection at the intended entry site, possible fracture of the extremity, or prosthesis or orthopaedic procedure near the insertion site); return of spontaneous circulation achieved before the intervention; cardiac arrest during transportation to the hospital; vascular access established before the arrival of the trial trained paramedic; and other reasons for exclusion: traumatic out-of-hospital cardiac arrest, known or suspected pregnancy, known or suspected age <20 or >80 years, cancelled ambulance call, and patient transported to the hospital before the arrival of emergency medical technicians-paramedics.

Randomisation and intervention

The trial used cluster randomisation based on biweekly periods from 6 July 2020 to 30 June 2023. Four participating advanced life support ambulance service teams were assigned to either intravenous or intraosseous interventions biweekly, as illustrated in supplementary figure A. The allocation sequence was generated by a computer using code created by a research statistician, and the study centre instructed the clusters to change to either the intraosseous or intravenous intervention according to the sequence of random allocation. To balance the cases that received successful vascular access, the clusters were randomised in a 1:2 allocation ratio to intervention (intraosseous) versus control (intravenous), as intraosseous attempts were considered twice as likely to be successful in a previous study.[29]

Patients in the intervention group received a mechanical intraosseous puncture (EZ-IO, Teleflex), and the control group received an intravenous puncture. The protocol in the intraosseous group was limited to an attempt at the humeral bone; patients in the control group received intravenous puncture in the upper extremities. Trained paramedics were limited to a maximum of one attempt at intraosseous insertion or two attempts at intravenous procedures. Before the trial, emergency medical technicians in Taiwan were not authorised to perform intraosseous insertion. Given

that intraosseous insertion is in its pilot phase, and scenes of out-of-hospital cardiac arrest and hospitals in Taiwan are not far apart, the protocol required that if the initial access attempt failed, the patient would be promptly transported to the hospital without attempting alternative access methods, mirroring the standard practice before the trial.

After vascular access was established, 1 mg of adrenaline (epinephrine), followed by 10 mL of normal saline, was rapidly pushed through the access. Except for vascular access, all resuscitations performed at the scene, including delivery of shocks and administration of anti-arrhythmic drugs, followed the local standard protocol (supplementary appendix 3).

Clinical outcomes

The primary outcome was survival to hospital discharge. The secondary outcomes were return of spontaneous circulation; survival to hospital admission, surrogated by sustained return of spontaneous circulation in some overcrowded hospitals where admission might be delayed[30-32]; and favourable neurological outcomes at hospital discharge. We defined sustained return of spontaneous circulation as return of spontaneous circulation for at least two hours and survival with a favourable neurological outcome as a Cerebral Performance Category score ≤2.[33] The initial care providers, including paramedics and emergency physicians, could not be blinded to the study intervention because the interventions were clearly visible, whereas the substantial in-hospital caregivers were unaware of the pre-hospital interventions after the removal of the initial intraosseous access.

Statistical analysis

We estimated the required study sample size on the basis of an assumed differences of 5% of the primary outcome in the two arms, with a power of 80% at a 5% significance level on a two sided test to detect the difference from 10% survival to 15% (expected survival).[34 35] With a 1:2 randomisation ratio, we needed 1506 patients (502 in the intraosseous group and 1004 in the intravenous group). Assuming that 5% of the patients would have incomplete data or missing outcomes, we estimated that we needed a final sample size of 1581 patients. Taking a conservative estimation of the intracluster correlation coefficient of 0.03, the required total sample size was 1680 patients. We used the Pocock boundary for determining whether to prematurely stop the clinical trial, and two interim analyses were planned.[36]

The primary and secondary outcomes were analysed and reported on an intention-to-treat basis, including all patients who underwent assigned randomisation, and cases with missing outcomes were excluded from the analysis. We also present the results of the per protocol analysis, which included patients who strictly adhered to the study intervention according to their allocation (successful intravenous or intraosseous access). We summarised the trial data by using different statistical measures based on variable distributions. We calculated means and standard deviations for normally distributed variables, and we used medians and interquartile ranges for non-normally distributed variables. We summarised categorical variables by using sample size and percentage. We analysed continuous variables by using Student's t test or a Wilcoxon rank sum test; we used a χ^2 or Fisher's exact test to analyse categorical variables. We analysed primary and secondary outcomes by using regression models with and without adjustment for covariates, including age, sex, arrest characteristics, location, initial rhythm, and time intervals between key events and initial response.

We used fixed effects logistic regression models to obtain unadjusted and adjusted odds ratios, and we calculated 95% confidence intervals. We also did pre-specified subgroup analyses according to age, initial presenting rhythm (shockable versus non-shockable), witnessed versus not witnessed arrest, bystander cardiopulmonary resuscitation versus non-bystander cardiopulmonary resuscitation, response intervals, region, time to vascular access, time to administration of first dose drug, and total pre-hospital drug dose. We used post hoc generalised estimating equations in the intention-to-treat and per protocol populations to assess within cluster correlation. We did supplementary analyses to evaluate the effectiveness of pre-hospital medications. Statistical significance was set at a P value of <0.05. We used SAS software, version 9.2, for statistical analyses.

Patient and public involvement

Several conferences involving the research team, Taipei City Fire Department, Taipei City Government's Department of Health, and relevant stakeholders were held to establish a consensus on trial management, before the study was implemented. Our research encountered a distinctive barrier in involving patients experiencing out-of-hospital cardiac arrest owing to the immediate and critical nature of their condition. The unpredictable and abrupt onset of out-of-hospital cardiac arrest made participation of or feedback from patients before the start of the trial practically impossible. The involvement of patients in the early phase of the trial was hindered by the outbreak of the covid-19 pandemic.

Results

Patient characteristics and study intervention

From 6 July 2020 to 30 June 2023, a total of 276 clusters with 7780 patients were assessed for eligibility and were randomised to either the intraosseous or intravenous group. Owing to a lower than expected enrolment rate and the additional challenges posed by the covid-19 pandemic, the trial was extended to a third year. Two interim analyses were conducted and the trial continued, as neither result reached the stopping threshold. After the exclusion of 6009 patients who met the pre-defined exclusion criteria, 1771 patients with out-of-hospital cardiac arrest were enrolled, and outcomes were available for 1732

(97.8%) patients: 741 in the intraosseous group and 991 in the intravenous group. Figure 1 shows the reasons for exclusion, which were similar in the two groups. Table 1 shows the baseline characteristics of the patients. Twelve cases of protocol violation occurred: 10 cases in which intravenous access was inserted after failed intraosseous attempts and two cases in which intraosseous access was inserted after failed intravenous attempts.

Primary outcome and secondary outcomes

Primary outcome data were available for 741 (97.6%) patients in the intraosseous group and 991 (97.9%) patients in the intravenous group. We did not apply multiple imputations owing to the low number of missing cases (2.2%; 39 of 1771 enrolled patients). In the intraosseous group, 79 (10.7%) patients were discharged alive, compared with 102 (10.3%) patients in the intravenous group (odds ratio for survival to hospital discharge 1.04, 95% confidence interval 0.76 to 1.42; P=0.81). For the secondary outcomes, the proportion of patients achieving pre-hospital return of spontaneous circulation (odds ratio 1.23, 0.89 to 1.69; P=0.21), sustained return of spontaneous circulation (0.92, 0.75 to 1.13; P=0.44), and favourable neurological outcome (Cerebral Performance Category score 1 or 2) (1.17, 0.82 to 1.66; P=0.39) was not significantly different between the two groups (table 2). The results of the per protocol analyses, presented in supplementary tables A and B, showed no difference between the two groups after adjustment. The intracluster coefficient correlation calculated by using generalised estimating equations was 0.01, and the post hoc generalised estimating equations analysis to evaluate the effect of clusters showed no significant differences (supplementary table C)

Subgroup analysis

We did several pre-specified subgroup analyses based on the intention-to-treat principle and found that the absence of significant differences in the proportion of patients surviving to hospital discharge between the two study groups was consistent across all subgroups (fig 2). Subgroup analyses of secondary outcomes are shown in supplementary figures B-D.

Discussion

In this pragmatic trial of 1771 adult patients with out-of-hospital cardiac arrest, the proportion of patients surviving to hospital discharge did not differ significantly between the groups with initial intraosseous and intravenous vascular access. In addition, we observed no statistically significant associations with the proportion of patients with pre-hospital return of spontaneous circulation, sustained return of spontaneous circulation, and favourable neurological outcomes. Although not achieving statistical significance, the results of our study showed that for every 100 patients assigned to intraosseous rather than intravenous access, approximately two

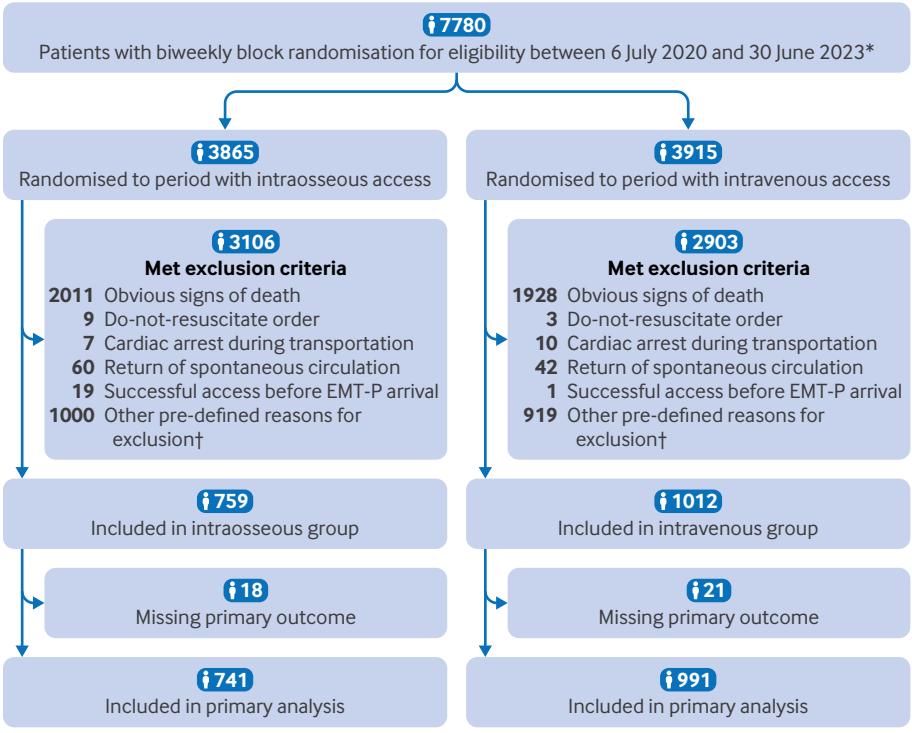

Fig 1 | Flowchart of patients through trial. *Recruitment was temporarily suspended between 20 May 2021 and 31 July 2021 owing to covid-19 pandemic. †Other pre-defined exclusion criteria include traumatic cardiac arrest, known or suspected pregnancy, age <20 or >80 years, cancelled ambulance call, or patient being transported to hospital before arrival of emergency medical technician-paramedic (EMT-P)

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Table 1 | Baseline characteristics of patients. Values are numbers (percentages) unless stated otherwise

Characteristic	Total (n=1732)	Intraosseous (n=741)	Intravenous (n=991)
Median (IQR) age, years	65.0 (55.0-73.0)	64.0 (54.0-72.0)	66.0 (56.0-74.0)
Male sex	1234 (71.2)	521 (70.3)	713 (71.9)
Location:			
Home	1238 (71.5)	536 (72.3)	702 (70.8)
Nursing home	33 (1.9)	18 (2.4)	15 (1.5)
Public	461 (26.6)	187 (25.2)	274 (27.6)
Witnessed arrest	762 (44.0)	326 (44.0)	436 (44.0)
Bystander CPR	1232 (71.1)	531 (71.7)	701 (70.7)
EMS treatment:			
Shockable rhythm	502 (29.0)	217 (29.3)	285 (28.8)
PAD use before EMS arrival	92 (5.3)	37 (5.0)	55 (5.5)
Successful access*	1270 (73.3)	694 (93.7)	576 (58.1)
Drug†:			
Adrenaline	1184 (68.4)	669 (90.3)	515 (52.0)
Mean (SD) dose, mg	2.6 (0.9)	2.6 (0.9)	2.6 (1.0)
Amiodarone	104 (6.0)	48 (6.5)	56 (5.7)
Advanced airway	1517 (87.6)	658 (88.8)	859 (86.7)
Mean (SD) time interval:			
Between dispatch and arrival of EMS at scene	7.2 (3.0)	7.0 (2.8)	7.4 (3.1)
Between EMS arrival at scene and departure	20.6 (6.4)	21.7 (5.8)	19.8 (6.7)
Between EMS departure from scene and hospital arrival	5.4 (2.7)	5.3 (2.6)	5.5 (2.8)
Between EMS arrival at scene and first drug administration	15.6 (6.2)	15.9 (6.1)	15.3 (6.3)

EMS=emergency medical services; IQR=interquartile range; PAD=public access defibrillator; SD=standard deviation.
*Successful access establishment followed allocation, excluding 12 cases of protocol violation: 10 cases received intravenous access after failed intraosseous access attempt; 2 cases received intraosseous access after failed intravenous access attempt.
†Drugs administered via crossover route (violated protocol) were not included (intraosseous group: 7 epinephrine and 2 amiodarone via intravenous route; IV group: 2 epinephrine and 2 amiodarone via intraosseous route).

extra returns of spontaneous circulation and one extra neurologically favourable survival (Cerebral Performance Category score ≤2) occurred, without extra patients having severe disability (fig 3). The current resuscitation guidelines suggest deferring the use of intraosseous access in resuscitation after out-of-hospital cardiac arrest, but our study offers a different insight that could inform pre-hospital vascular practices and serve as a basis for future research.

Possible explanations for findings

Although we observed a trend towards a higher proportion of patients with pre-hospital return of spontaneous circulation after intraosseous access, these differences were not statistically significant. Two potential reasons for this finding exist. Firstly, although we observed higher success rates in the intraosseous group, the intraosseous intervention was not as fast as expected in real scenarios. Notably, establishing humeral intraosseous access is time consuming, including removing clothing to expose the humeral head, using specialised equipment, and securing access placement without impeding cardiopulmonary resuscitation. In a randomised trial comparing tibial intraosseous, humeral intraosseous, and peripheral intravenous access, the time to achieve initial success in humeral intraosseous placement was the longest.[37] However, the paramedics were more familiar with tibial intraosseous access, and the patients in the humeral intraosseous group had a higher average weight. Despite practising with intraosseous needles in the training arm, time was needed for paramedics to become comfortable with the procedure and shorten the insertion time in real clinical situations. Secondly, we observed an extended overall pre-hospital stay; in our study, the overall pre-hospital time increased by about 4 min on average compared with the previous study in the same region two years earlier.[30] The most likely contributing factor would be the influence of covid-19, which was also seen in another area in Taiwan.[38] During the

Table 2 | Primary and secondary outcomes. Values are numbers (percentages) unless stated otherwise

Outcome	Total (n=1732)	Intraosseous (n=741)	Intravenous (n=991)	Odds ratio* (95% CI); P value
Primary				
Survival to hospital discharge	181 (10.5)	79 (10.7)	102 (10.3)	1.04 (0.76 to 1.42); 0.81
Secondary				
Pre-hospital return of spontaneous circulation	169 (9.8)	80 (10.8)	89 (9.0)	1.23 (0.89 to 1.69); 0.21
Sustained return of spontaneous circulation	562 (32.4)	233 (31.4)	329 (33.2)	0.92 (0.75 to 1.13); 0.44
Survival with favourable neurological outcomes (CPC ≤2)	136 (7.9)	63 (8.5)	73 (7.4)	1.17 (0.82 to 1.66); 0.39

CI=confidence interval; CPC=Cerebral Performance Category.
*Odds ratios are unadjusted, with intravenous serving as reference.

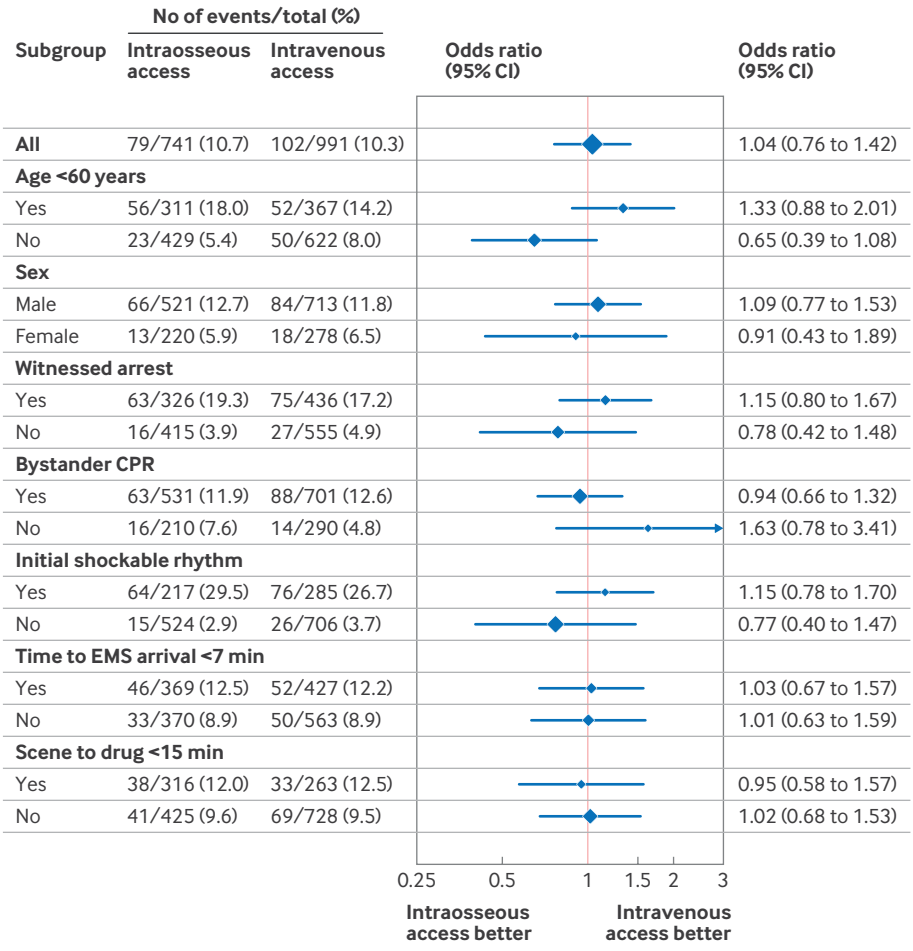

Fig 2 | Subgroup analyses of primary outcome. CPR=cardiopulmonary resuscitation; EMS=emergency medical service

pandemic, adjustments were made to the resuscitation protocol. For every case of out-of-hospital cardiac arrest, emergency medical technicians-paramedics had to be equipped with N95 masks, fluid resistant gowns, hair caps, goggles, full face shields, and gloves, potentially leading to clumsiness during performance. Despite the temporary suspension of the trial during the recruitment period due to the covid-19 outbreak, the ongoing impact persisted.

In the per protocol analysis, patients who received successful intraosseous access showed a notably lower rate of sustained return of spontaneous circulation and a trend towards poorer outcomes before adjustment, compared with intravenous access (supplementary tables A and B). However, the outcomes reversed after adjustment. Comparing the two groups, patients who successfully received intravenous access had a higher proportion of witnessed arrests and presence of shockable rhythms, which are indicators of better outcomes. This result can be explained by the assumption that the success rate of intraosseous access is less affected by the patient's condition, whereas attempting an intravenous route is a selective process. The possible mechanism behind the equal effect observed between the two interventions in our trial suggests that patients with successfully established intravenous access have the best condition, followed by those with successful intraosseous access, with the poorest condition being in those with failed intravenous access (supplementary table D). The findings highlight the importance of our prospective randomised controlled trial, whereas previous retrospective studies were largely affected by inherent biases in the selection of studied patients.

Comparison with other studies

To clarify the effect of pre-hospital medication, we compared patients receiving adrenaline as per the study protocol and those with no adrenaline administration owing to failure to establish a route (supplementary tables E and F). The results showed that patients who received adrenaline had a higher proportion of short term outcomes such as pre-hospital return of spontaneous circulation, and the effect was more prominent in patients with non-shockable rhythms. However, the use of adrenaline was not associated with survival to hospital discharge. These findings are comparable to those of a recent network meta-

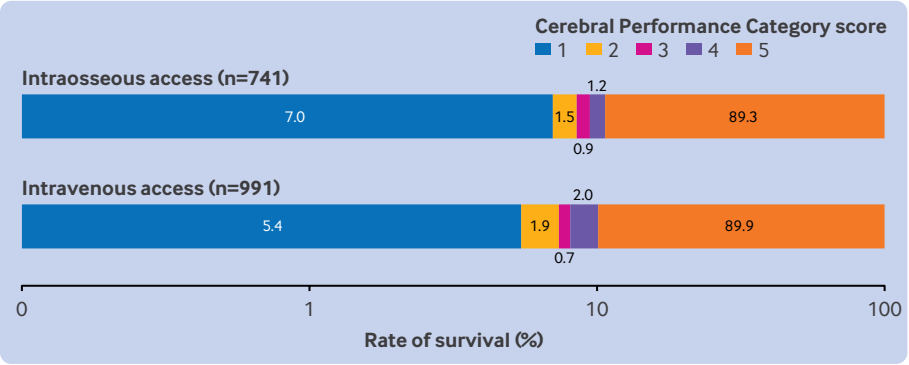

Fig 3 | Survival with favourable neurological outcomes at hospital discharge. Patients' Cerebral Performance Category scores ranged from 1 (good cerebral performance) to 5 (brain death). Data are presented on log10 scale as percentage of patients in each group. IO=intraosseous; IV=intravenous

analysis.[39] Furthermore, for patients with shockable rhythm who received amiodarone, we did not find a significant difference in survival between intravenous and intraosseous routes (supplementary table G). In a post hoc analysis of the ALPS randomised controlled trial, comparison of two routes of administration for ventricular tachycardia/ventricular fibrillation found that intravenous administration of amiodarone resulted in better survival than did intraosseous administration.[9] This difference in outcomes may be attributed to the drug's lipophilicity and its local interaction with bone marrow.[40] However, in our study, we included all non-traumatic patients with out-of-hospital cardiac arrest, both non-shockable and shockable. Given that only a small portion of patients in our trial had a refractory shockable rhythm, the result was inconclusive. Future studies to answer these complex clinical questions are warranted.

Recent resuscitation guidelines recommend that healthcare providers initially establishing intravenous access for drug administration during cardiac arrest is reasonable and that intraosseous access is appropriate if the intravenous route fails or is not feasible.[4 5] However, all previous studies supporting the practice were retrospective in design, lacked a meticulously defined intervention protocol, and could potentially introduce significant selection bias into the results.[24] Moreover, site specificity would also be a problem that might affect outcomes with intraosseous administration.[4] In a study involving 10 cases of out-of-hospital cardiac arrest, the mean time from humeral intraosseous access to the right ventricle was 5.6 s, and it was theoretically quicker than tibial access.[20] Therefore, our study followed a strictly defined protocol to control the comparability of insertion sites in which intraosseous access was limited to the humeral head, whereas intravenous access was directed to the upper extremities to reduce the concerns about different distances from the insertion site to the heart. Also, a recent retrospective study found that upper extremity intraosseous access was associated with slightly better outcomes than lower extremity intraosseous access.[41]

Implications of findings

To the best of our knowledge, this is the first randomised clinical study completed to compare two different methods of vascular access. The pragmatic trial design of the study mirrors real world scenarios, thereby offering invaluable insights into how interventions are performed under everyday conditions and increasing the practical relevance of its findings. When applying resuscitation guidelines worldwide, the global evidence should be modified for local solutions. In Taipei, as the average transport time from the scene to the destination hospital is less than six minutes, making additional attempts may only increase the overall pre-hospital time without providing actual benefits to patients. Hence, the trial emergency medical technicians-paramedics made only limited attempts at establishment of vascular access and patients were promptly transferred to hospital after initial failure to minimise unnecessary delays.

On the basis of the results of our study, indicating that intraosseous access did not lead to worse outcomes, the intraosseous route may be regarded as a potential first line option for vascular access rather than being seen as secondary to the intravenous route. However, the costs related to intraosseous access were higher than those for intravenous access, and the level of specific intravenous training among pre-hospital personnel varied across different emergency medical service systems. Therefore, the decision between intravenous and intraosseous access should be tailored to the specific characteristics and needs of each local emergency medical service system.

Limitations of study

This study has some limitations. Firstly, we did not include patients aged >80 years, who account for approximately 40% of patients with out-of-hospital cardiac arrest according to previous experience, and the effects of the two different interventions are not known in this population. As this represents the initiation of intraosseous use in Taiwan, our primary concern was to minimise complications, considering the increased

susceptibility of the older population to osteoporosis. Secondly, the study is at risk of being underpowered owing to an overoptimistic expectation of the difference in survival between the two groups, and it did not account for the outcomes of patients who did not receive medication owing to failed access. The assumption was based on the correlation between delayed drug administration and unfavourable outcomes.[35] Furthermore, the time required for intraosseous insertion exceeded expectations and could potentially offset the overall benefits in patients receiving intraosseous access. However, if we re-estimated the sample size from the true effect obtained by the study result, more than 184 000 patients would be needed to detect the difference. Enrolling such a large sample size in a pre-hospital clinical trial on patients with out-of-hospital cardiac arrest would be impracticable. Thirdly, despite the study being planned with a 2:1 randomisation ratio, the number of participants evaluated included in each group unexpectedly ended up being similar. After reviewing details with on-site emergency medical technicians-paramedics, we considered that two possible factors may have contributed to the uneven distribution. The trial was greatly affected by the covid-19 pandemic and was temporarily suspended. Uncontrollable modifications included single tier dispatch and advanced life support teams specialising in transfers of patients with covid-19. In addition, the intravenous group experienced a higher proportion of prolonged pre-hospital time, potentially leading to lower turnover and fewer overall emergency medical service dispatches. Fourthly, in-hospital management was unavailable in our trial, which may have influenced the results. Actual overcrowding in healthcare facilities during or after the pandemic and its effects on patient outcomes could not be clearly quantified. However, the level of hospital transfer was similar between the two groups. Therefore, we believe that in-hospital management would not be directionally biased by this factor. Finally, the patient and public involvement in our study was not fully aligned with contemporary expectations, representing a limitation in the research design that may affect the applicability of the findings.

Conclusions

We found that initial establishment of vascular access through the intraosseous route in patients with out-of-hospital cardiac arrest did not yield a different outcome in terms of survival to hospital discharge, pre-hospital return of spontaneous circulation, sustained return of spontaneous circulation, and favourable neurological outcomes, compared with intravenous access. Intraosseous vascular access may not be a deferred choice for resuscitation in patients with out-of-hospital cardiac arrest. The optimal decision making process for vascular access based on various characteristics of patients and emergency medical service systems should be explored.

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Contributors: WCC designed the study and supervised the project. HYL, AFL, MJH, WSY, BCL, and CWY curated the data. YCK and WCC did the formal analysis. EPCH, JTS, and WCC developed the methods. YCW, YCC, and WCC administered the project. MHMM and WCC provided resources. MHMM and WCC supervised the project. YCK wrote the original draft, and WCC reviewed and edited the manuscript. All authors contributed to interpreting the data, revising the article for important intellectual content, and giving final approval of the manuscript. WCC is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data sharing: The data will be available to other researchers on request, with information shared after approval by the corresponding author (WCC).

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The research findings will be shared across various social media platforms to reach a wider audience, thus enhancing visibility and engagement. The research will be presented at upcoming international conferences, including the International Conference of Emergency Medicine, Asia Association of Emergency Medical

Service, European Resuscitation Congress, and Taiwan Associations of Emergency Medical Service Physician. These conferences provide an excellent platform to share insights, exchange ideas, and collaborate with experts in the field. The results will also be presented at the medical director meeting of the Taipei Fire Department, which allows direct communication with stakeholders and policy makers, ensuring that the findings inform decision making. Research staff and medical students will be informed about the study's design and the processes to communicate the experience of conducting a good pragmatic trial.

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Web appendix: Supplementary materials