REVIEW

Intraosseous access in adults in cardiac arrest: a systematic review and meta-analysiss

Ignacio Morales-Cané, María del Rocío Valverde-León, María Aurora Rodríguez-Borrego, Pablo Jesús López-Soto

Objective. To evaluate the efficacy of intraosseous access versus venous access in out-of-hospital cardiac arrest in terms of return of spontaneous circulation (ROSC) and survival to hospital discharge with or without favorable neurologic status.

Methods. Systematic review and meta-analysis of articles indexed in MEDLINE (PubMed), Embase, the Web of Science, and the Cochrane Library. Other terms adapted to the language of each index were also used. We included observational studies and clinical trials published from January 1, 1950, to May 31, 2019, if the study population included adult patients in cardiac arrest outside the hospital and in whom an intraosseous or intravenous catheter was inserted. Risk of bias was evaluated with the Cochrane and GRADE (Grading of Recommendations Assessment, Development and Evaluation) tools.

Results. We identified 434 papers to include in the qualitative review and 5 studies for meta-analysis. Intraosseous access was related to a lower rate of ROSC (odds ratio [OR], 0.69; 95% CI, 0.57–0.83; *P*=.02; I^2=65%) and worse survival to discharge (OR, 0.65; 95% CI, 0.51–0.83); *P*<.01, I^2=30%).

Conclusion. Intraosseous access in out-of-hospital cardiac arrest is related to poorer outcomes in terms of ROSC and survival at hospital discharge.

Keywords: Spontaneous circulation. Intraosseous catheter. Hospital discharge.

Vía intraósea en adultos en situación de parada cardiaca: revisión sistemática y metanálisis

Objetivo. Evaluar la efectividad, en relación al retorno a circulación espontánea, la supervivencia al alta y la supervivencia al alta con buen estado neurológico, del acceso intraóseo frente al acceso venoso en la resucitación en parada cardiaca extrahospitalaria.

Método. Se realiza una revisión sistemática y metanálisis en las bases de datos Medline (PubMed), Embase, Web of Science y Cochrane Library. Se incluyeron estudios observacionales y ensayos clínicos registrados en las bases de datos mencionadas desde el 1 de enero de 1950 hasta el 31 de mayo de 2019, en los que la población incluida fueran pacientes adultos en situación de parada cardiaca extrahospitalaria y que tuvieran canalizado un acceso intraóseo o intravenoso. La evaluación del riesgo de sesgo se realizó mediante la herramienta de evaluación de sesgo de Cochrane y la herramienta GRADE.

Resultado. Se identificaron 434 referencias de las que 5 se incluyen en la síntesis cualitativa y cuantitativa. El acceso intraóseo se relaciona con una peor tasa de retorno a circulación espontánea [OR 0,69 (IC 95%: 0,57-0,83), p = 0,02, I^2 = 65%] y una peor supervivencia al alta hospitalaria [OR 0,65 (IC 95%: 0,51-0,83); p < 0,01, I^2 = 30%] en comparación con el acceso venoso.

Conclusiones. El acceso intraóseo en pacientes en situación de parada cardiaca extrahospitalaria se relaciona con peores resultados en términos de retorno a circulación espontánea y supervivencia al alta hospitalaria.

Palabras clave: Circulación espontánea. Vía intraósea. Alta hospitalaria.

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Contribution of the authors:
All authors have confirmed their authorship in the document of author's responsibilities, publication agreement and transfer of rights to EMERGENCIAS.

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Article information::
Received: 3-9-2019
Accepted: 21-10-2019
Online: 12-12-2019

Editor in charge:
Juan González del Castillo

Introduction

Out-of-hospital cardiac arrest (OHCA) has become a major global problem, since its incidence in Europe is between 28 and 244 CAs per 100,000 inhabitants per year, with an incidence of attempted resuscitation of between 19 and 104 per 100,000 inhabitants per year[1]. Guidelines on the treatment of CA exist and are published every 5 years by the European Resuscitation Council (ERC)[2] and by the American Heart Association[3], leading institutions in this field, establishing how it should be approached.

According to the ERC guidelines[2], during cardiopulmonary resuscitation (CPR), the peripheral venous line is recommended and no access preference is specified for drug administration. However, the use of the intraosseous line is recommended when there is difficulty in channelling the peripheral venous line or after three ineffective attempts at venous channeling.

Historically, the administration of drugs via the in-

traosseous route has been restricted to the paediatric population[4]. However, since 2000 there has been increasing scientific evidence on its use in out-of-hospital settings in adults, especially in critical patients[6-8]. In 2016, the results of the Resuscitation Outcomes Consortium[8] were published, among which was that the prevalence of use of the intraosseous line was 21.9% in the patients included in that study.

Previous studies[9] have shown that the intraosseous route, specifically the tibial access, has a higher success rate at first attempt and a lower time consumption for insertion, compared to peripheral intravenous access and humeral intraosseous access. There are data supporting the ease of intraosseous line placement, so its use is spreading in clinical practice[8-10]. Various authors[9,11,12] have described this fact although the clinical results do not appear to be satisfactory. The site of choice for insertion of the intraosseous line is in the proximal tibia (2-3 cm below the tibial tuberosity on the anteromedial side) and proximal humerus (in the centre of the major tuberosity of the humeral head, 1-2 cm above the surgical neck)[2,13]. On the other hand, Burget et al.[14] highlight in an experimental study carried out in animals that the sternal intraosseous access achieves plasma adrenaline concentrations similar to those when administered by central venous access, while the tibial intraosseous access has plasma adrenaline concentrations lower than the central venous access.

Based on the above, the question arises as to which of the two vascular accesses (intraosseous and venous) has the most beneficial effect on the outcome of out-of-hospital CA. The objective of this systematic review and meta-analysis was to evaluate the effectiveness, in relation to return to spontaneous circulation (ROSC), survival after hospital discharge and survival after hospital discharge with good neurological status, of intraosseous access versus venous access in out-of-hospital CA resuscitation in the adult population.

Method

A systematic review and meta-analysis was conducted according to the Cochrane Handbook (version 5.1.0)[15]. The development of the systematic review is in line with Preferred Reporting Items for Sytematic Reviews and Meta-Analysis (PRISMA)[16,17]. The review protocol was registered in PROSPERO (registry number: CRD42018112326).

PICO question

The research question was structured according to the PICO format (Population/patient, Intervention, Comparator and Outcomes). Our question was: "In adult patients with CA (P), is intraosseous vascular access (I) more beneficial than venous vascular access (C) in terms of ROSC, survival after discharge and survival after discharge with good neurological status (O)?

Databases

The search was performed in the following databases: Medline (PubMed), Embase, Web of Science and Cochrane Library. The search strategy combined the MeSH terms "Heart Arrest", "Out-of-Hospital Cardiac Arrest", "Death, Sudden, Cardiac", "Ventricular Fibrillation", "Tachycardia, ventricular" and "intraosseous Access" as keywords and free terms adapted to the language of each database. In all databases, the title/summary/keywords were included as a search field. A simple search adapted to each database was also carried out (Table 1).

Inclusion and exclusion criteria

We included studies with the following criteria: i) observational studies and clinical trials registered in the above-mentioned databases from 1 January 1950 to 31 May 2019; ii) written in Spanish or English; iii) in which the study population was adult (over 18 years of age); in a situation of cardiorespiratory arrest; iv) in which there was a comparison between intraosseous and venous drug administration; and v) that the outcome variables were ROSC, survival and neurological status.

Records involving patients under 18 years of age, pregnant women, patients with CA of traumatic etiology or in-hospital cardiac arrests were excluded. We excluded those studies in which the outcome variables did not include survival, ROSC or similar clinical variables.

The selection of studies was made by two of the authors independently (MRVL and IMC) and then a matching was done. In studies where there was disagreement, a third author (PJLS) was involved in the decision to include or exclude that article. The search was conducted between 1 April 2019 and 31 May 2019. References of included studies were also reviewed.

Quality analysis

Two researchers independently assessed the quality of evidence using the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) tool[18]. This tool determines the risk of bias, imprecision, directionality, inconsistency and suspected publication bias. Based on the above variables, the evidence is stratified into very low, low, moderate and high. In relation to the risk of bias, the Cochrane risk assessment tool[15,19] was used to determine the existence of selection bias, performance bias, attrition bias, reporting bias and other biases. Cochrane RevMan software version 5.3. was used for the development of the funnel plot[15].

Data extraction and analysis

The information in the articles was extracted according to the PICO strategy, using a form designed by

Table 1. Search strategy

Database	Search strategy
Medline	("Infusions, Intraosseous"[MeSH Terms]) OR "Infusions, Intraosseous"[Title/Abstract]) OR "Infusion, Intraosseous"[Title/Abstract]) OR "Intraosseous Infusion"[Title/Abstract]) OR "Intraosseous Infusions"[Title/Abstract]) OR "Infusions, Intra-Osseous"[Title/Abstract]) OR "Infusion, Intra-Osseous"[Title/Abstract]) OR "Infusions, Intra Osseous"[Title/Abstract]) OR "Intra-Osseous Infusion"[Title/Abstract]) OR "Intra-Osseous Infusions"[Title/Abstract]) OR "Intraosseous access"[Title/Abstract]) OR "Intraosseous"[Title/Abstract]) AND (“Heart Arrest”[Title/Abstract]) OR “Heart Arrest”[MeSH Terms]) OR “Arrest, Heart”[Title/Abstract]) OR “Out-of-Hospital Cardiac Arrest”[MeSH Terms]) OR “Out-of-Hospital Cardiac Arrest”[Title/Abstract]) OR “Asystoles”[Title/Abstract]) OR “Asystole”[Title/Abstract]) OR “Cardiopulmonary Arrest”[Title/Abstract]) OR “Arrest, Cardiopulmonary”[Title/Abstract]) OR “Arrest, Cardiac”[Title/Abstract]) OR “Cardiac Arrest”[Title/Abstract]) OR “Cardiac Arrest, Out-of-Hospital”[Title/Abstract]) OR “Out-of-Hospital Heart Arrests”[Title/Abstract]) OR “Cardiac Arrests, Out-of-Hospital”[Title/Abstract]) OR “Out of Hospital Cardiac Arrest”[Title/Abstract]) OR “Out-of-Hospital Heart Arrest”[Title/Abstract]) OR “Heart Arrest, Out-of-Hospital”[Title/Abstract]) OR “Heart Arrests, Out-of-Hospital”[Title/Abstract]) OR “Out of Hospital, Heart Arrest”[Title/Abstract]) OR “Death, Sudden, Cardiac”[Title/Abstract]) OR “Death, Sudden, Cardiac”[MeSH Terms]) OR “Sudden Cardiac Death”) OR “Cardiac Death, Sudden”[Title/Abstract]) OR “Death, Sudden Cardiac”[Title/Abstract]) OR “Cardiac Sudden Death”[Title/Abstract]) OR “Death, Cardiac Sudden”[Title/Abstract]) OR “Sudden Death, Cardiac”[Title/Abstract]) OR “Sudden Cardiac Arrest”[Title/Abstract]) OR “Arrest, Sudden Cardiac”[Title/Abstract]) OR “Cardiac Arrests, Sudden”[Title/Abstract]) OR “Cardiac Arrest, Sudden”[Title/Abstract] OR "Fibrillation, Ventricular"[Title/Abstract]) OR "Fibrillations, Ventricular"[Title/Abstract]) OR "Ventricular Fibrillations"[Title/Abstract]) OR "Ventricular Fibrillation"[Title/Abstract]) OR "Ventricular Fibrillation"[MeSH Terms]) OR "Tachycardias, Ventricular"[Title/Abstract]) OR "Ventricular Tachycardias"[Title/Abstract]) OR "Ventricular Tachycardia"[Title/Abstract]) OR "Tachycardia, Ventricular"[Title/Abstract]) OR "Tachycardia, Ventricular"[MeSH Terms]) OR "pulseless electrical activity"[Title/Abstract]) OR "PEA"[Title/Abstract])
Embase	(“bone infusion” OR “bone injection” OR “drug administration, intraosseous” OR “drug administration, bone” OR “infusions, intraosseous” OR “intra-bone drug administration” OR “intra-bone marrow injection” OR “intra-osseous administration” OR “intra-osseous infusion” OR “intra-osseous injection” OR “intrabone injection” OR “intrabone marrow injection” OR “intraosseous administration” OR “intraosseous application” OR “intraosseous infusion” OR “intraosseous injection” OR “IO administration” OR “IO drug administration” OR “IO infusion” OR “IO injection” OR “intraosseous drug administration” OR “intraosseous drug administration”/exp OR “Route of drug administration” OR “Route of drug administration”/exp) AND ("heart arrest"/exp OR "heart arrest" OR "arrest, heart" OR "asystole" OR "asystolia" OR "asystoly" OR "cardiac arrest" OR "circulation arrest" OR "circulatory arrest" OR "heart arrest, induced" OR "heart asystole" OR "heart standstill" OR "OHCA" OR "out of hospital cardiac arrests" OR "out of hospital cardiopulmonary arrest" OR "out of hospital cardiopulmonary arrests" OR "; out of hospital heart arrest" OR "out-of-hospital cardiac arrest” OR “cardiac death, sudden" OR "cardiac sudden death" OR "death, sudden, cardiac" OR "sudden cardiac arrest" OR "sudden heart death" OR "cardiopulmonary arrest" OR "experimental heart arrest" OR "out of hospital cardiac arrest" OR "sudden cardiac death" OR "cardiac ventricle fibrillation" OR "cardiac ventricular fibrillation" OR "fibrillation, heart ventricle" OR "heart ventricular fibrillation" OR "ventricle fibrillation" OR "ventricle fibrillation, heart" OR "ventricular fibrillation" OR "heart ventricle fibrillation"/exp OR "heart ventricle tachycardia"/exp OR "heart ventricle tachycardia" OR "ventricle* tachycardia" OR "pulseless electric* activity" OR "pulseless ventricle* tachycardia")
Cochrane	("Infusions, Intraosseous"[MeSH Terms]) OR "Infusions, Intraosseous"[Title/Abstract]) OR "Infusion, Intraosseous"[Title/Abstract]) OR "Intraosseous Infusion"[Title/Abstract]) OR "Intraosseous Infusions"[Title/Abstract]) OR "Infusions, Intra-Osseous"[Title/Abstract]) OR "Infusion, Intra-Osseous"[Title/Abstract]) OR "Infusions, Intra Osseous"[Title/Abstract]) OR "Intra-Osseous Infusion"[Title/Abstract]) OR "Intra-Osseous Infusions"[Title/Abstract]) OR "Intraosseous access"[Title/Abstract]) OR "Intraosseous"[Title/Abstract]) AND (“Heart Arrest”[Title/Abstract]) OR “Heart Arrest”[MeSH Terms]) OR “Arrest, Heart”[Title/Abstract]) OR “Out-of-Hospital Cardiac Arrest”[MeSH Terms]) OR “Out-of-Hospital Cardiac Arrest”[Title/Abstract]) OR “Asystoles”[Title/Abstract]) OR “Asystole”[Title/Abstract]) OR “Cardiopulmonary Arrest”[Title/Abstract]) OR “Arrest, Cardiopulmonary”[Title/Abstract]) OR “Arrest, Cardiac”[Title/Abstract]) OR “Cardiac Arrest”[Title/Abstract]) OR “Cardiac Arrest, Out-of-Hospital”[Title/Abstract]) OR “Out-of-Hospital Heart Arrests”[Title/Abstract]) OR “Cardiac Arrests, Out-of-Hospital”[Title/Abstract]) OR “Out of Hospital Cardiac Arrest”[Title/Abstract]) OR “Out-of-Hospital Heart Arrest”[Title/Abstract]) OR “Heart Arrest, Out-of-Hospital”[Title/Abstract]) OR “Heart Arrests, Out-of-Hospital”[Title/Abstract]) OR “Out of Hospital, Heart Arrest”[Title/Abstract]) OR “Death, Sudden, Cardiac”[Title/Abstract]) OR “Death, Sudden, Cardiac”[MeSH Terms]) OR “Sudden Cardiac Death”) OR “Cardiac Death, Sudden”[Title/Abstract]) OR “Death, Sudden Cardiac”[Title/Abstract]) OR “Cardiac Sudden Death”[Title/Abstract]) OR “Death, Cardiac Sudden”[Title/Abstract]) OR “Sudden Death, Cardiac”[Title/Abstract]) OR “Sudden Cardiac Arrest”[Title/Abstract]) OR “Arrest, Sudden Cardiac”[Title/Abstract]) OR “Cardiac Arrests, Sudden”[Title/Abstract]) OR “Cardiac Arrest, Sudden”[Title/Abstract] OR "Fibrillation, Ventricular"[Title/Abstract]) OR "Fibrillations, Ventricular"[Title/Abstract]) OR "Ventricular Fibrillations"[Title/Abstract]) OR "Ventricular Fibrillation"[Title/Abstract]) OR "Ventricular Fibrillation"[MeSH Terms]) OR "Tachycardias, Ventricular"[Title/Abstract]) OR "Ventricular Tachycardias"[Title/Abstract]) OR "Ventricular Tachycardia"[Title/Abstract]) OR "Tachycardia, Ventricular"[Title/Abstract]) OR "Tachycardia, Ventricular"[MeSH Terms]) OR "pulseless electrical activity"[Title/Abstract]) OR "PEA"[Title/Abstract])
Web of Science	TS=("cardiac arrest" OR "out-of-hospital cardiac arrest" OR "heart arrest") AND TS=(intraosseous) *Databases= WOS, CCC, DIIDW, KJD, MEDLINE, RSCI, SCIELO Timespan=All yearsSearch language=Auto*

the authors. Specifically, clinical characteristics of the participants and characteristics of the intervention (administration of drugs by venous versus intraosseous route) were extracted. Outcome variables included were: ROSC, survival after discharge from hospital and survival after discharge from hospital with good neurological status.

Regarding quantitative analysis (meta-analysis), dichotomous variables were analysed using the Mantel-Hansen random effects method with a 95% confidence interval. For continuous variables the inverse variance method of random effects was used. The I2 statistic was used to assess heterogeneity, considering values of less than 25% as low heterogeneity. Values in the I2 statistic of 26-50% and > 75% were considered to be of moderate and high heterogeneity, respectively[16]. A sensitivity analysis of the meta-analyses was performed in which more than two studies were included to study the influence of each of the studies on the overall estimate of effect.

Results

A total of 746 references were identified, of which 312 were removed because they were duplicated. After reading the title and abstract of the remaining 434 references, 62 were chosen for full text review, the rest were excluded because they did not meet the inclusion criteria. The reasons for exclusion of the studies in subsequent reading of the full text were: 20 for the study design (communications to congresses, editorials, protocols, etc.); 14 for the study population; 3 for the language of publication; and 20 for not addressing the subject matter of the study. Finally, five studies were subjected to a qualitative and quantitative analysis[4,10,20-22] (Figure 1). The design of the study, the characteristics of the participants, the type of vascular access established and the outcome variables have been summarized in Table 2. No clinical trials were found.

The study population, in all the documents analyzed, was adults in a situation of out-of-hospital CA of non-traumatic etiology. The studies were carried out between 2007 and 2017 and published between 2016 and 2019. In total, 35,339 patients were analyzed (9,398 according to data obtained from propensity analyses), divided into two groups according to the type of study intervention. The number of patients in whom interosseous access was obtained for drug administration was 4,747 (868 according to propensity analysis) and the patients in whom venous access was obtained was 30,592 (1,877 according to propensity analysis). The mean age of patients was about 66 years for both groups. Overall, males predominated.

There are no differences between the groups regarding confounding variables such as presence of initial defibrillable rhythm, witnessed CA or witnessed resuscitation. To avoid some of the observed differences in confounding variables such as initial heart rate, witnessed CA, data from the paired propensity analysis were used in the studies by Mody et al.[10] and Kawano et al.[22].

Return to spontaneous circulation

The five analysed studies[4,10,20-22] included data on the success of ROSC. A total of 2,745 (29.2%) of 9,398 patients obtained ROSC, of which 868 (22%) fell into the intraosseous access group and 1,877 (34.4%) into the intravenous access group.

A higher success rate appeared in the group of patients where a venous access was obtained for drug administration compared to patients receiving an intraosseous access, [odds ratio OR 0.69 (95% CI 0.57-0.83)]. Statistical heterogeneity was moderate (I2 = 65%, P = 0.02) (Figure 2). Sensitivity analyses were performed in which no changes were observed by eliminating, one by one, each study from the meta-analysis (Table 3).

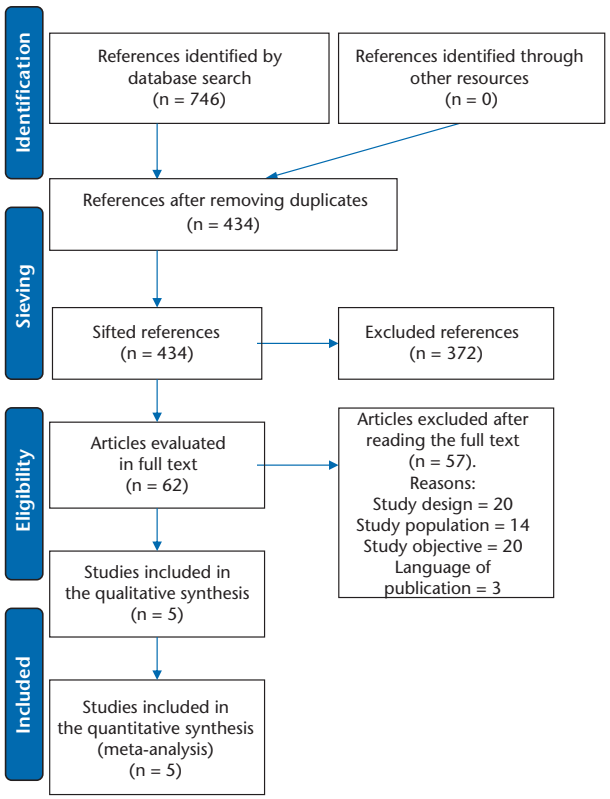

Figure 1. Flow chart of study selection according to PRISMA[16,17].

Table 2. Characteristics of the studies included in the meta-analysis

Study	Year	Country	Period	N	Design	Population	Intervention vs Comparator	Outcome variable
Clemency[20]	2017	USA	2013-2015	1,340	Retrospective cohort	≥ 18 years, non-traumatic OHCA	Venous Access vs. Intraosseous Access	ROSC
Feinstein[21]	2017	USA	2012-2014	1,800	Retrospective cohort	≥ 18 years, non-traumatic OHCA	Venous Access vs. Intraosseous Access	Survival after discharge from hospital, ROSC, survival on admission to hospital
Mody[10]	2019	USA	2011-2015	19,731	Retrospective cohort	≥ 18 years, non-traumatic OHCA	Venous Access vs. Intraosseous Access	SSurvival after discharge, ROSC, survival with good neurological status (Modified Rankin ≤ 3)
Kawano[22]	2018	USA, Canada	2007-2009	13,155	Retrospective cohort	≥ 18 years, non-traumatic OHCA	Venous Access vs. Intraosseous Access	Survival after discharge, ROSC, survival with good neurological status (Modified Rankin ≤ 3)
Nguyen[4]	2019	USA.	2013-2017	795	Retrospective cohort	≥ 18 years, non-traumatic OHCA	Venous Access vs. Intraosseous Access	ROSC

N: sample size; USA: United States; OHCA: out-of-hospital cardiorespiratory arrest; ROSC: return of spontaneous circulation.

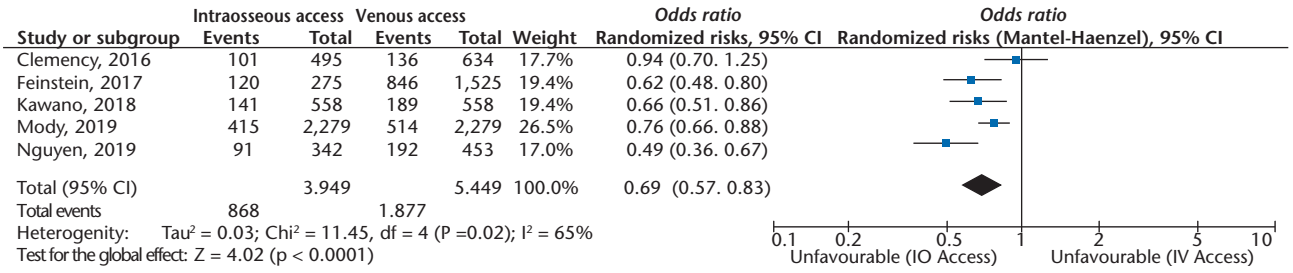

Figure 2. Return to spontaneous circulation.

Survival after discharge from hospital

Three[10,21-22] of the five studies analysed included data on survival after discharge from hospital. A total of 702 (9.4%) of 7,474 patients obtained ROSC, of which 171 (5.5%) belonged to the intraosseous access group and 531 (12.2%) to the intravenous access group. A better survival rate to hospital discharge was found in the group of patients in whom a venous access was channelled versus patients in whom an intraosseous access was obtained [OR 0.65 (95% CI 0.51-0.83)]. We also found moderate statistical heterogeneity (I2 = 30%, P < 0.01) (Figure 3). A sensitivity analysis was performed in which 0% heterogeneity was observed by eliminating the study by Mody et al.[10] from the meta-analysis (Table 3).

Survival after discharge from hospital with good neurological status

Two of the five included studies[17,18] provided data on survival after discharge with good neurological status. A total of 702 (9.4%) of 7474 patients obtained ROSC, of which 171 (5.5%) were in the intraosseous access group and 531 (12.2%) in the intravenous access group. Both studies considered good neurological status when patients were discharged with a value less than or equal to 3 on the modified Rankin scale[23]. A higher survival rate with good neurological status was found in the group of patients in whom a venous access was obtained versus those in whom an intraosseous access was obtained, although without statistically significant differences, [OR 0.52 (95% CI 0.18-1.46)], with high statistical heterogeneity (I2 = 86%, P = 0.21) (Figure 4).

Table 3. Sensitivity analysis

Study excluded from the meta-analysis	OR	95% CI (min-max)
Sensitivity analysis: Return to spontaneous circulation		
Clemency, 2016[20]	0.65	0.54-0.78
Feinstein, 2017[21]	0.70	0.56-0.88
Kawano, 2018[22]	0.69	0.55-0.87
Mody, 2019[10]	0.66	0.52-0.84
Nguyen, 2019[4]	0.74	0.63-0.86
Global	0.69	0.57-0.83
Sensitivity Analysis: Survival after discharge from hospital		
Feinstein, 2017[21]	0.65	0.43-0.98
Kawano, 2018[22]	0.69	0.54-0.89
Mody, 2019[10]	0.56	0.42-0.75
Global	0.65	0.51-0.83
Sensitivity analysis: Survival at discharge with good neurological status (Modified Rankin Scale[23] ≤ 3)		
Mody, 2019[10]	0.29	0.14-0.59
Kawano, 2018[22]	0.84	0.60-1.16
Global	0.52	0.18-1.46

Analysis of the quality of studies

The assessment of the risk of bias is summarised in Table 4 and Figure 5. The presence of confounding variables that have not been taken into account in the survival analysis, such as witness resuscitation and the initial rhythm of defibrillable CA, has been detected. On the other hand, the design of the studies analyzed is observational so there is no randomization or blinding. In addition, the size of both groups is quite unequal. According to the analysis of the risk of bias performed with GRADE[18], the quality of the results is very low due to the type of design of the studies included (observational), the presence of confounding variables that could not be controlled in the analyses and moderate-high heterogeneity.

Discussion

In this systematic review and meta-analysis we have analysed the available evidence to determine the benefit of intraosseous versus intravenous route[4,10,20-22]. The results obtained suggest that in patients in whom an intraosseous access was inserted, a lower rate of ROSC and a lower survival rate after hospital discharge were achieved. This could be due to the fact that patients in whom a venous access was obtained may have had better hemodynamic status, since interosseous access is considered a second option, and could therefore be associated with patients with a worse hemodynamic status[21], although in the studies analysed no significant differences are found in the time from recognition of CA or from the call to the emergency system to vascular access, whether this is intraosseous or venous. CPR guidelines for adults[2,3] indicate that it is advisable to perform an intraosseous route after three unsuccessful attempts at venous canalisation[2,3].

On the other hand, some authors such as Voelckel et al.[24] have stated, through animal research, that in a situation of shock the bone blood flow decreases consi-

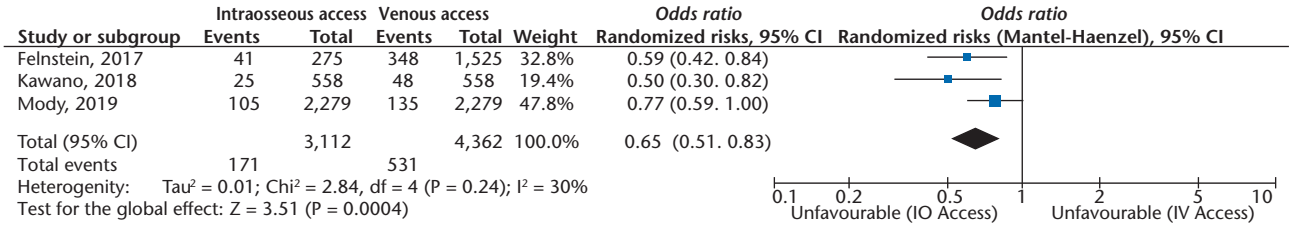

Figure 3. Survival after discharge from hospital.

derably, which may favour this worse prognosis. The place of choice for intraosseous access in the studies analysed was the tibial access[4,10,20-22]. It has been shown in animal tests[14,25] that serum epinephrine concentrations administered by the tibial route are lower than those administered by intravenous route or other intraosseous accesses such as sternal. Similarly, Zuercher et al.[26] showed, in an animal experimental study, that the maximum serum adrenaline concentration was reached 17 seconds later when administered by the intraosseous route than when administered by the intravenous route.

In addition, the decrease in the rate of ROSC is also associated with a delay in the administration of the first dose of adrenaline[27-32], especially in the initial rhythms of non-defibrillable CA such as asystole and pulseless electrical activity where, according to the recommendation guidelines[27], the administration of adrenaline is indicated at the first moment after insertion of the venous or intraosseous line.

Regarding the results obtained concerning survival after discharge from hospital, patients with intraosseous access showed less survival than patients where an intravenous access was inserted. Survival after discharge with good neurological status, with 3 or less on the modified Rankin scale[23], was worse in patients with an intraosseous access than in patients with an intravenous access.

Regarding the success of intraosseous access device placement, the influence of the type of device used for this purpose has been described, with a better result in terms of first attempt placement success rate and faster with automatic intraosseous devices, such as the EZ-IO® type device, than with manual devices such as the Cook needle[33-35]. A study in the United States[9] compared intraosseous access (humeral and tibial) and venous access in order to determine the success rate at the first attempt, and concluded that intraosseous access is faster to perform than intravenous access. These conclusions are similar to those reported by other authors, who state that the intraosseous route is a fast and safe alternative to venous access, especially in the pre-hospital setting, although it should not replace venous access, especially central access[36].

Considering the ease with which intraosseous access can be achieved, it would seem logical that it should be done as the first option for early adrenaline administration[29]. However, the above results would contradict that recommendation. However, the lower rate of ROSC could be associated with delayed adrenaline administration, as the intraosseous route is used as an alternative access after failed attempts to obtain a venous access[21,36].

The present systematic review and meta-analysis has limitations. Firstly, the small number of studies obtained, which limits the possibility of adequately interpreting the comparisons made, in addition to not being able to correctly analyse the publication bias that may exist. Secondly, we found high statistical heterogeneity. Finally, there are a number of confounding variables that may influence the results and which were not available in the studies analyzed. These include the lack of clinical records indicating the reason for choosing a venous or bone access channel, or certain characteristics of CA that may influence therapeutic success, such as whether it has been witnessed, whether witness resuscitation was initiated, or the arrival time of the emergency teams.

Based on the results obtained, we can conclude that there is a lower rate of ROSC and a lower survival rate after hospital discharge in those patients receiving an intraosseous route compared to the venous route. This study highlights the need to record the type of vascular access and the reason for channeling one or another device, as well as the need for more controlled studies to analyze the effectiveness of the intraosseous route for critical patients in a pre-hospital setting, especially in patients with CA, in order to clarify clinical aspects related to intraosseous access.

Conflicting interests: The authors declare no conflict of interest in relation to this article.

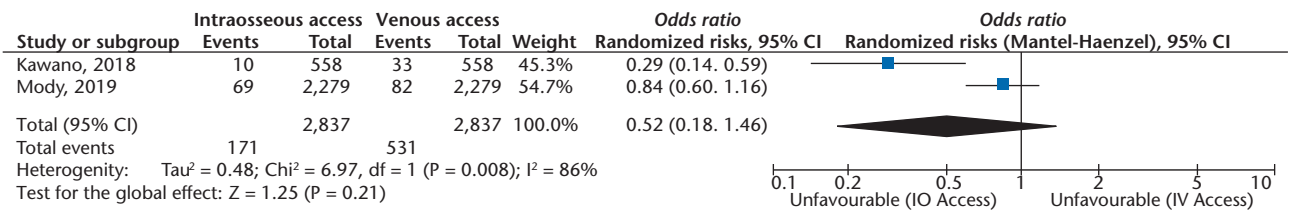

Figure 4. Survival after discharge from hospital with good neurological status (Modified Rankin Scale[23] ≤ 3).

Table 4. Evaluation of biases according to GRADE[18]

Question: Intraosseous access compared to venous access in cardiac arrest as first choice								
Certainty analysis				Number of patients		Effect		
Number of studies	Study design	Risk of bias/ Inconsistency/ Indirect evidence/ Imprecision	Other considerations	Intraosseous access	Venous access	Relative 95% CI)	Absolute (95% CI)	Certainty
Return to spontaneous circulation								
5	Observational studies	Serious[a]/Serious[b]/ Serious[c]/Serious[d]	All possible residual confounding factors could reduce the demonstrated effect	868/3.949 (22.0%)	1.877/5.449 (34.4%)	OR 0.69 (0.59 a 0.83)	78 less for 1,000 (from 108 less to 41 less)	⨁◯◯◯ VERY LOW
Survival after discharge from hospital								
3	Observational studies	Serious[a]/Serious[b]/ Serious[c]/Serious[d]	All possible residual confounding factors could reduce the demonstrated effect	171/3.112 (5.5%)	531/4.362 (12.2%)	OR 0.65 (0.51 a 0.83)	39 less for 1,000 (from 56 less to 19 less)	⨁◯◯◯ VERY LOW
Survival after discharge from hospital with good neurological status (assessed with: Modified Rankin Scale[19])								
2	Observational studies	Serious[a]/Serious[b]/ Serious[c]/Serious[d]	All possible residual confounding factors could reduce the demonstrated effect	79/2.837 (2.8%)	115/2.837 (4.1%)	OR 0.52 (0.18 a 1.46)	19 less for 1,000 (from 33 less to 18 more)	⨁◯◯◯ VERY LOW

CI: Confidence interval; OR: Odds ratio.
[a]Retrospective observational designs without randomization or blinding. [b]Heterogeneity (I2) high. [c]There are confounding variables that may benefit the Venous Access group. [d]There is a great difference between the size of the intraosseous access group and the venous access group.

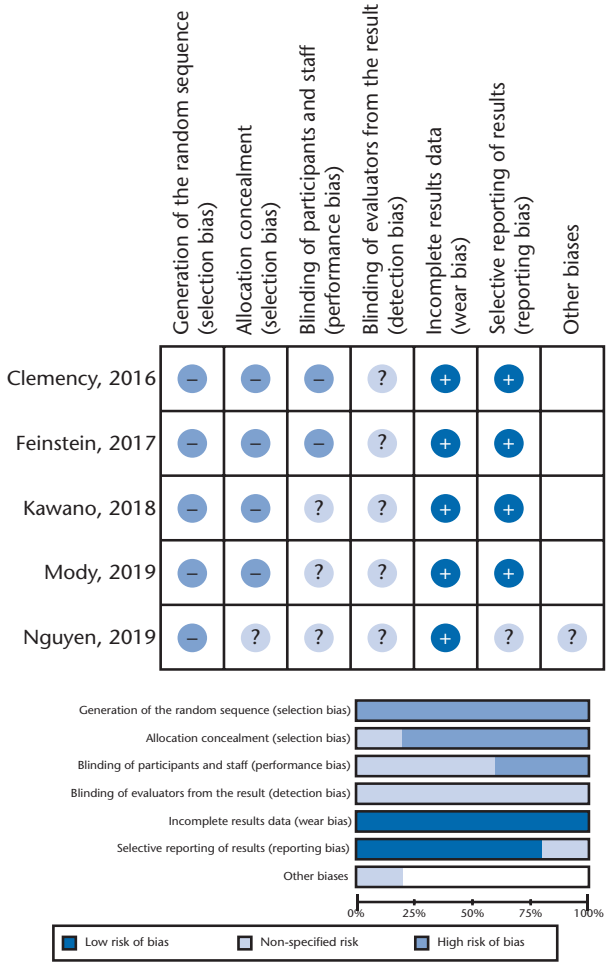

Figure 5 Analysis of the risk of bias.

Financing: The authors declare the non-existence of funding in relation to this article.

Ethical responsibilities: All authors have confirmed the maintenance of confidentiality and respect for patients' rights in the author's responsibilities document, publication agreement, and assignment of rights to EMERGENCIAS.

Article not commissioned by the Editorial Committee and with external peer review.

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