Research Protocol: Intravenous Access during Resuscitation: the IVAR trial

YM Smulders & PWB Nanayakkara

SUMMARY

Objective: *To compare the effects of central versus peripheral drug administration on the rate of return of organised electrical activity and/or spontaneous circulation during CPR.*

Study design: *Randomized clinical trial.*

Study population: *Hospitalized patients and patients presenting at the emergency department, older than 18 years, requiring CPR.*

Intervention: *Central venous access*

Main study parameters/endpoints: *Combined primary endpoint: rate of appearance of organised electrical activity or return of spontaneous circulation.*

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: *All patients are treated according to the guidelines of the European Resuscitation Council, which are endorsed by the local VUMC CPR-committee. Central access will be obtained by cannulation of the external or internal jugular vein. To avoid interference with initial management, central venous access will be obtained after initiation of chest compressions, first attempt at defibrillation (if applicable), securing the airway and obtaining a peripheral access.*

All resuscitated patients require vascular access and almost all successfully resuscitated patients require central venous access. Obtaining central access during CPR may be associated with a slightly higher complication rate, such as arterial puncture and pneumothorax. Possible benefits for study subjects are a higher success rate of CPR

INTRODUCTION AND RATIONALE

Introduction

During circulatory arrest, cardiopulmonary resuscitation (CPR) is performed to protect brain function and to bridge the period to return of spontaneous circulation. Administration of various drugs to facilitate return of spontaneous circulation is an essential part of CPR. Current guidelines recommend using the peripheral venous route for drug administration, as it is easy to obtain, rapidly available and safe. The intraosseous route is a generally accepted alternative when peripheral venous catheterization is difficult. Because minimizing interruptions in chest compressions is important, the placement of a central venous catheter (CVC) is not generally recommended.[1] However, the potential advantages of central venous drug administration appear to have been overlooked, and may well outweigh the potential disadvantages in terms of compression interruption, which can be minimized, and complications of insertion.

During CPR drugs must reach the heart as fast and efficiently as possible. During chest compression facilitated circulation, circulating blood is preferential directed to the heart and brain at the expense of abdominal organs and the extremities. Central delivery times and peak concentrations of drugs administered via peripheral veins are therefore expected to be severely impaired.

In our hospital we routinely obtain vascular access via the antecubital vein, the external jugular vein (central access) or via the intraosseous route, which is more or less determined at random, by pre-hospital medical personnel, or at the discretion of the individual attending anaesthetist. In the Netherlands, some hospitals routinely use the antecubital vein, some the central route, and many do not have a hospital policy for this.

Improvement in central drug delivery is likely to be clinically relevant. Here, we hypothesize that central administration of drugs during CPR is associated with signs of enhanced cardiac effects, and thus may reduce the time to return of organised electrical activity and return of spontaneous circulation.

Blood flow during CPR

Under physiological conditions, differences in peak drug levels and drug delivery times for central venous versus peripheral infusions are minimal.[2] During CPR, cardiac output falls to less than 30% during CPR and is preferentially directed to brain and heart at the expense of the peripheral circulation in the extremities.[3]

Pharmacokinetics during CPR

Animal studies

Many animal studies focused on pharmacokinetics of drugs administered during CPR. In one study, indocyanine green was injected in dogs during CPR at three sites; femoral vein, forelimb (peripheral) and proximal port of a pulmonary artery catheter (central).

PWB Nanayakkara
MD, PhD

YM Smulders
MD, PhD
Email: y.smulders@vumc.nl

Time to dye appearance in the coronary circulation was 27,6 % faster following central injection compared to femoral and 33% faster compared to peripheral injections. Coronary peak dye concentration was also 29% higher. No significant differences were observed between the femoral and peripheral access route, suggesting that femoral access, often regarded as 'central', has no advantages over peripheral access.

In another study, two different radio-isotopes were simultaneously injected in a central and peripheral vein in dogs undergoing cadiac massage.[6] Radioactivity was sampled in the femoral artery. Central injections produced a statistically significant 270% higher peak concentration and 57,9 % shorter lag time to the first appearance of tracer. More studies of essentially similar design also demonstrate that central venous administration of drugs during CPR results in more efficient central delivery compared to peripheral administration.[7,8]

To our knowledge, no animal studies have compared success rates of CPR between peripheral and central venous access sites.

Human studies

In the early eighties, a study addressed drug transit times after peripheral and central venous injection in six persons who had undergone unsuccessful CPR.[9] The protocol was initiated after the treating physicians decided that further resuscitation was futile. Cardiac compressions and mechanical ventilation were continued by the study team, and indocyanine green dye was injected via a peripheral (right antecubital) and central venous (right subclavian) access site. A high peak concentration of dye appeared in the right femoral artery after 30 seconds following central venous injection, while no dye concentration was measured at all during the first 90 seconds after peripheral injections. Moreover, the peak dye concentration obtained in the right femoral artery 30 seconds after central venous injections was more than four times higher than the maximum dye concentration observed five minutes after peripheral injections. Although this is a very small study, the pharmacokinetic differences between central and peripheral injections are impressive.

No other human studies comparing the effect of central versus peripheral drug injections during cardiopulmonary resuscitation have been published.

Intraosseous routes during CPR

The intraosseous route is increasingly used, especially in the pre-hospital setting. It provides an easy and safe intravenous access route when standard venous access cannot be rapidly achieved.[10,11] The most frequent insertion site in our region is the proximal tibia. Because these intraosseous needles drain on the popliteal vein, this should be considered as peripheral venous access.

A recent CPR study in swine showed that intraousseous drug delivery via the sternum was faster and delivered a higher central dose then intraousseous injections via the proximal tibia.[12] However, central drug concentrations were still lower than after central venous access, and the sternal route is not routinely used in our region.

Synthesis of background

During CPR, there is a significantly decreased cardiac output and preferential circulation to the brain and coronary circulation. Peripheral circulation is severely reduced. Animal studies show that drug administration via the central venous route during CPR results in substantially earlier and higher central peak concentrations. There is one small human study comparing central and peripheral venous access during CPR that confirms the results of the animal studies.

Today, there is virtually no interest in central vascular access during CPR. The reason for this is unclear. The importance of reducing interruptions of chest compression are justly emphasized, but not all techniques of obtaining central venous access require any or any meaningful interruption of compressions.

We hypothesize that central administration of drugs during CPR has positive effects on central drug delivery that could be beneficial in this setting. In this therapeutic pilot study, we aim to compare the effects of central versus peripheral drug administration on return of organised electrical activity and/or spontaneous circulation during CPR.

Objectives

Primary Objective

To study whether central venous administration of drugs during CPR is associated with:

- Higher rate of achievement of organised electrical activity.
- Higher rate of return of spontaneous circulation.

Secondary Objective(s)

- time to primary endpoints
- Complications following external jugular cannulation: arterial puncture, bleeding.
- Does central external jugular cannulation interfere with chest compressions?
- Time needed for obtaining jugular access.

Study Design

- Non-blinded randomized clinical trial.
- Duration: 12 months.
- Setting: Single Center, extension to multicenter optional.

Study Population

Population (base)

- adult patients presenting at the emergency department requiring CPR.
- adult in-hospital patients requiring CPR.

Inclusion criteria

- see population base

Exclusion criteria

- age <18 years
- Circulatory arrest following major bleeding or trauma
- central venous access in-situ at time of commencement of CPR

Treatment of Subjects

- Local VUMC CPR/ALS protocol (conforming to Guidelines of the European Resuscitation Council).
- Airway and iv access secured.
- Weekly randomisation via electronic random generator between two routinely used vascular access routes:
  - ◊ Central venous access (defined as "in close proximity to the heart")
    - external jugular vein: 18, 17 or 14 Gauge standard iv canula.
- Peripheral venous access (antecubital or lower arm vein, intraosseous)

Central access will be obtained by a physician experienced in the procedure (anesthesiologist or experienced resident).

Both peripheral and central: connected to 500 ml isotonic saline (or other volume replacement type, as decided by the CPR team), side valve for drug administration in immediate proximity of cannula.

All drugs and fluids (epinephrine, anti-arrhythmics, etc) are subsequently administered via the route determined by randomisation.

Sample size calculation

This project should be regarded as a pilot-type of study. We aim to demonstrate the feasibility and the estimated effect size of the intervention. If successful, a follow-up study will be designed with a formally estimated benefit serving as a basis for sample-size calculation.

As there are no historical/previous data available, we are not able to perform a reliable power calculation. Within the time frame of the proposed study, however, inclusion of 100 patients would be a reasonable estimate of what would be feasible. Based on personal experience as well as an informal summary of local CPR outcome data, we estimate that, under routine conditions, 30% of CPR patients reach one or both primary outcome parameters. Based on power analysis (13), the study with n=100 patients would have an 86% power to detect a Relative 'Risk' for the primary outcome of 2,0, with an alpha of 0.05. This RR may seem high, but is not unreasonable given the rather extreme differences in central peak concentrations of the drugs between peripheral and central access (see introduction).

Methods

Study parameters/endpoints

Main study parameter/endpoint

- Rate of achievement of organised electrical activity.
- Rate of return of spontaneous circulation.

Secondary study parameters/endpoints (if applicable)

- Time to achievement of organised electrical activity.
- Time to return of spontaneous circulation.
- Complications following central venous cannulation: arterial puncture, bleeding, pneumothorax.
- Time needed for obtaining vascular access.
- 1 and 7 –day survival rate.

Other study parameters (if applicable)

- Not applicable.

Randomisation, blinding and treatment allocation

- Non-blinded 1:1 randomisation via electronic random generator: weeks (Monday 08.00 to Monday 08.00) are randomised between two routinely obtained vascular access sites (central or peripheral) for all CPRs taking place in the VUMC, excluding the ICU en Cardiac Catheterisation rooms.
- Treatment allocation
  - ◊ Peripheral venous access.
  - ◊ Central access (defined as "in close proximity to the heart").

Study procedures

- Local VUMC CPR/ALS protocol (conforming to Guidelines of the European Resuscitation Council).
- Airway and peripheral access secured.
- Weekly randomisation via electronic random generator between two routinely obtained vascular access routes.
- Central venous access (defined as "in close proximity to the heart")

- 1 external jugular vein: 18, 17 or 14 Gauge standard iv canula.
- Peripheral venous access

Central access will be obtained by a physician experienced in the procedure (anesthesiologist or experienced resident).

Both peripheral and central: connected to 500 ml isotonic saline (or other volume replacement type, as decided by the CPR team), side valve for drug administration in immediate proximity of cannula.

All drugs and fluids (epinephrine, anti-arythmics, etc) are subsequently administered via the route determined by randomisation.

Recruitment and consent

The ethical implications of the study design are complex. The project team (YS) consulted legal representatives of both the CCMO and the local ethics committee prior to submission of the protocol, which led to the following conclusion:

This is a therapeutic study concerning incapacitated adults in an emergency situation. Relatives or other legal representatives are often either not present, or in a state of acute emotional shock. Hence, there is no reasonable possibility to ask patients or relatives for informed consent. All data required for adjucation of the primary and secondary endpoints will be obtained during resuscitation. The use of these data for scientific purposes does not require informed consent.

This leaves the question of whether patients or their representatives need to be informed. We decided that such information is inappropriate in case of a failed resuscitation attempt, or an adverse neurological outcome. Successfully resuscitated patients with a good clinical outcome will however be informed of the study afterwards, preferably before hospital discharge.

Benefits and risks assessment, group relatedness

The risk and burden for study subjects are small. All patients are treated according to the guidelines of the European Resuscitation Council, which are endorsed by the local VUMC CPR-committee. All resuscitated patients require vascular access and almost all successfully resuscitated patients require central venous access. Hence, the majority of survivors require central access. Obtaining central access during CPR may be associated with a slightly higher complication rate, such as arterial puncture and pneumothorax.

Possible benefits for study subjects are a higher success rate of CPR including increased rate of survival and better neurological outcome.

Declaration of competing interests

Nothing to declare.

References

1. Neumar *et al.* Part 8: Adult Advanced Cardiovascular Life Support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care *Circulation* 2010, **122**:S729-S767.
2. Barsan *et al.* differences in drug delivery with periferal en central venous injections: normal perfusion. *Am J emerg Med* 1986 jan;**4**:1-3.
3. Voorhees *et al.* Regional blood flow during cardiopulmonary resuscitation in dogs. *Crit Care Med.* 1980;**8**:134-36.
4. Goldberg. Cardiopulmonary arrest. *N Engl J Med* 1974;**290**:381-85.
5. Emerman *et al.* Effect of injection site on circulation times during cardiac arrest. *Crit Care Med.* 1988;**16**:1138-41.
6. Talit U, *et al.* Pharmacokinetic differences between peripheral and central drug administration during cardiopulmonary resuscitation. *J Am Coll Cardiol.* 1985 Nov;**6**:1073-7
7. Barsan *et al.* Lidociane levels during CPR: differences after peripheral venous, central venous and intracardiac injections. *Ann Emerg Med* 1981:**10**;73-78
8. Hedges *et al.* Central versus peripheral intravenous routes in cardiopulmonary resuscitation. *Am J Emerg Med.* 1984;**2**:385-90.
9. Kuhn *et al.* Peripheral vs central circulation times during CPR: A pilot study. *Ann Emerg Med* 1981;**10**:417-419.
10. Reades *et al.* Intraosseous Versus Intravenous Vascular Access During Out-of-Hospital Cardiac Arrest: A Randomized Controlled Trial. *Ann Emerg Med.* 2011; **58**: 509.
11. Leidel *et al.* Comparison of intraosseous versus central venous vascular access in adults under resuscitation in the emergency department with inaccessible peripheral veins. *Resuscitation*; E-pub Sep 3 2011.
12. Hoskins *et al.* Pharmacokinetics of intraosseous and central venous drug delivery during cardiopulmonary resuscitation. *Resuscitation.* 2011;**83**:107-12