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Targeting out-of-hospital cardiac arrest: the effect of heparin administered during cardiopulmonary resuscitation (T-ARREST)

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ABSTRACT

Introduction. Heparin administration during cardiopulmonary resuscitation (CPR) may prevent activation of coagulation after successful resuscitation for out-of-hospital cardiac arrest (OHCA). We hypothesize that such an approach is not associated with an increased rate of bleeding, but it has not been evaluated. We performed a pilot randomized clinical study assessing the safety of intra-arrest heparin administration in OHCA patients with suspected acute myocardial infarction (AMI) and its impact on their prognosis.

Materials and Methods. OHCA patients were randomized during CPR to 10 000 units of intra-arrest intravenous heparin (Group H) or to treatment without heparin (Group C). The occurrence of major bleeding and the presence of a favourable neurological result 3 months after OHCA, were analyzed.

Results. Out of 88 randomized patients, AMI was subsequently confirmed in 63 of them (71.6 %). There were 30 patients in group H and 33 in group C. No major bleeding event was observed in either group. Return of spontaneous circulation (ROSC), Group H: 40.0%, Group C: 45.4%, $p=0.662$) and a good neurological result 3 months after OHCA (Group H: 6.7 %, Group C: 9.1 %, $p=0.921$) did not differ between groups.

Conclusions. Intravenous administration of 10 000 units of heparin during CPR for OHCA in patients with supposed AMI was safe. We did not find any improvement in prognosis for our sample of limited size. Though the procedure proved safe, we recommend postponing the administration of heparin until ROSC, assessment of clinical state and recording of a twelve-lead ECG.

Key words: out-of-hospital cardiac arrest, heparin, major bleeding

Introduction

Out-of-hospital cardiac arrest (OHCA) is a critical condition with an uncertain prognosis. Even if effective cardiopulmonary resuscitation (CPR) is started, a number of complex pathophysiological mechanisms are activated during the arrest and after it, resulting in the development of ischemia-reperfusion injury and post-cardiac arrest syndrome. (1) One of these processes is systemic coagulation activation with subsequent fibrin formation. In conjunction with other processes, such as activation of leucocytes, endothelial dysfunction and increased blood viscosity, this can lead to microcirculatory dysfunction and no-reflow phenomenon. (2-4) One of the theoretical possibilities of how to stop the spiral of ischemia-reperfusion injuries is the preventive administration of a thrombolytic and/or anticoagulant agent during CPR. Moreover, in the case of a cardiac aetiology of OHCA, the primary thrombotic episode in the coronary or pulmonary artery may also be a potential target of this therapy.

While systemic thrombolysis during OHCA has been studied, to the best of our knowledge, there has been no published clinical trial evaluating the preventive impact of sole heparin administration during CPR. (3,5) We hypothesize that such an approach is safe and not associated with an increased rate of bleeding. However, this treatment has not been included in the CPR guidelines. (6,7) Thus, it should be assessed by a clinical study.

Therefore, we decided to perform a pilot randomized clinical study to assess the safety of administering non-fractionated heparin during CPR for OHCA to patients presumed to have acute myocardial infarction (AMI) and also to analyze its impact on their prognosis.

Materials and Methods

The clinical study was carried out in accordance with the Declaration of Helsinki and its realization was approved by the ethics committee. Informed

consent was waived for the clinical condition of the patients with cardiac arrest. The study was the first part of the project T-ARREST working group (Targeting Out-of-Hospital Cardiac Arrest). Patients treated by the City of Prague Emergency Medical Service were included. The protocol of the study was carried out during emergency pre-hospital care and contained two decision-making moments (figure 1). In the first stage, the attending physician of the Emergency Medical Service decided, usually immediately upon arrival, if the patient having an OHCA is a suitable prospective candidate for randomization. The criteria for including or not including the patients for randomisation are summarized in table 1. The diagnosis of acute myocardial infarction, as a supposed cause of OHCA, was done on the basis of the following conditions: 1. the absence of signs of bleeding and trauma and 2. the collapse was preceded by the sudden onset of chest pain (or another type of sudden pain as left or right arm, abdominal or neck pain) and/or with dyspnoea or 3. the patient exhibited any prodromal symptoms before collapse and/or 4. known history of coronary artery disease.

CPR was always performed in accordance with European resuscitation council guidelines. After completing all routine procedures specified by standard protocols (continuous ECG monitoring, endotracheal intubation, venous access, initial defibrillation if indicated, continuous monitoring of peripheral oxygen saturation SpO₂ and end tidal CO₂ (EtCO₂), the patients were randomized (by random numbers generator) during ongoing CPR to a intravenous bolus administration of non-fractionated heparin (Heparin, Leciva, inj. sol.) in a dose of 10 000 units (Group H) or to continuing standard resuscitation without the administration of heparin during the procedure (Group C). For both groups, CPR was performed for at least 30 minutes or until return of spontaneous circulation (ROSC). In the case of ROSC, patients were transported to hospitals where the method of direct percutaneous coronary

intervention was available. Subsequent in-hospital therapy was standard and not influenced by the study protocol. Clinical course was followed up according to the Utstein protocol. Finally, the diagnosis of acute myocardial infarction was reassessed for all patients (clinically during hospitalization or by post-mortem examination).

The patients whose spontaneous circulation returned before completing all monitoring and therapeutic procedures and the patients who failed to undergo all the above mentioned procedures were not randomized. These patients were not followed up.

Artificial ventilation during and after CPR was carried out in a routine way with the respiration rate approximately 14/min, the tidal volumes 7-10 ml.kg⁻¹ and oxygen inspiratory fraction 1.0 (MEDUMAT Standard, Weinmann medical technology, Hamburg, Deutschland). Monitoring of EtCO₂ was performed using the mainstream technique (Zoll's M Series defibrillator, Zoll Medical Corporation, Chelmsford, MA, USA). Monitoring of ECG and electric impulse therapy was also ensured by the Zoll apparatus and all measurements were saved on the memory card of the apparatus providing precise feedback and assessment of the resuscitation. Midazolam combined with fentanyl or sufentanyl were used for analgesia and sedation of patients. Pipecuronium was used for muscle relaxation, if needed. All patients who achieved ROSC were subsequently administered lysine salicylate intravenously. Patients in Group C were not given heparin in the pre-hospital stage of treatment even after achieving ROSC.

Endpoints

The primary endpoint was the presence of major bleeding in the pre-hospital stage of treatment or during the first 48 hours of hospitalization, as a safety measure. Major bleeding was defined as a decrease in haemoglobin levels of >20 g.l⁻¹, need for transfusion of >2 units of blood, need for corrective surgery, intracranial or retroperitoneal haemorrhage, or any combination of

Table 1. Inclusion and exclusion criteria for randomization.

INCLUSION CRITERIA FOR RANDOMIZATION*
■ out-of-hospital cardiac arrest
■ supposed aetiology of acute myocardial infarction
■ starting cardiopulmonary resuscitation
EXCLUSION CRITERIA FOR RANDOMIZATION**
■ possible or certain traumatic, bleeding or other non-infarction aetiology of cardiac arrest
■ absence of a physician at the emergency medical service at the start of cardiopulmonary resuscitation
■ pre-defined status not to intubate and/or resuscitate

Note: *...must meet all criteria, **...must not meet any of the criteria

Table 2. Clinical causes of OHCA, ROSC rate, three-month mortality and the neurological result in patients with other aetiology of OHCA, other than AMI. OHCA, out-of-hospital cardiac arrest; AMI, acute myocardial infarction; ROSC, return of spontaneous circulation; CPC, cerebral performance category.

	GROUP H	GROUP C	p
Number of patients (n)	11	14	
Clinical cause of the arrest			
Pulmonary oedema (n (%))	4 (36.4)	4 (28.6)	0.987
Pulmonary embolism (n (%))	4 (36.4)	3 (21.4)	0.704
Pulmonary disease (n (%))	3 (27.2)	5 (35.7)	0.984
Other (n (%))	0	2 (14.3)	0.572
Achieved ROSC (n (%))	6 (54.5)	6 (42.3)	0.839
Three-month mortality (n (%))	6 (54.5)	10 (71.4)	0.650
CPC 1 or 2 after 3 months (n (%))	2 (18.2)	1 (7.1)	0.820
CPC 3 or 4 after 3 months (n (%))	3 (27.3)	3 (21.4)	0.897

OHCA, out-of-hospital cardiac arrest; AMI, acute myocardial infarction; ROSC, return of spontaneous circulation; CPC, cerebral performance category.

these events diagnosed clinically or by post-mortem examination. (8) The secondary endpoints were mortality rate and recovering with a favourable

neurological result 3 months after cardiac arrest. The neurological result was assessed according to the Cerebral Performance Category (CPC) marking

system. (9) Categories 1 and 2 were considered a favourable result.

Statistical analysis

The values of monitored parameters were expressed as average values \pm standard deviation (SD) or as median (minimal – maximal value) or by percentage. The differences between unpaired groups in case of alternative variables were compared by Pearson's chi-square test and in case of continual variables by Student's t-test. The differences between groups with non-normal data distribution were compared by Wilcoxon rank sum test. The statistics were processed using Microsoft Excel 2007 programme (Microsoft, Redmond, WA, USA) and JMP 3.2 statistical software (SAS Institute, Cary, NC, USA). P value < 0.05 was considered statistically significant.

Results

From January 2004 till December 2006 there were 141 prospective candidates chosen for randomization. 88 of them (62.4 %) were randomized. The remaining 53 patients either achieved ROSC before meeting technical conditions for randomization or it was not possible to ensure reliably all monitoring procedures required by the protocol and preceding the randomization (most often reliable monitoring of EtCO₂ or oxygen saturation).

AMI was subsequently confirmed in 63 out of 88 randomized patients (71.6 %). In the group of randomized patients who had another cause of OHCA other than AMI (as confirmed afterwards), 11 were given heparin during CPR and 14 patients were not. Major bleeding (gastrointestinal) was observed at post-mortem examination in one patient who had been given heparin. Clinical causes of arrest, the primary success rate of CPR and the neurological result and mortality during the three months after the arrest are presented in table 2.

In the group of randomized patients with confirmed AMI, 30 were randomized to Group H and 33 patients to Group C. These patients were subject to detailed analysis. Basic demographic data, the

Table 3. Demographic data, initial rhythm and characteristics of CPR.

	GROUP H	GROUP C	p
Number of patients in the group (n)	30	33	
Men in the group (n (%))	25 (83.3)	30 (90.1)	0.367
Age (median (min-max))	65.0 (27-85)	64.0 (20-82)	0.934*
Estimated body weight (kg±SD)	84 ± 13	89 ± 16	0.181
Any bystander CPR attempt (n (%))	12 (40.0)	13 (39.4)	0.961
Any symptoms preceding OHCA (median (min-max))	12 (40.0)	14 (42.4)	0.845
VF as the initial rhythm (n (%))	27 (90.0)	30 (90.1)	0.902
Time from collapse to any resuscitation attempt (min±SD)	4.3±3.1	4.5±3.4	0.807
Time from collapse to ROSC/end of CPR (min±SD)	38 ± 22	29 ± 12	0.046
Cumulative defibrillation energy in ventricular fibrillation patients (J, median (min-max))	560 (0-2520)	560 (0-2880)	0.590*
Cumulative epinephrine dose (mg, median (min.max))	4.0 (0-14)	4.0 (0-13)	0.787*
Achieved ROSC (n (%))	12 (40.0)	15 (45.4)	0.662
Recurrence of cardiac arrest during transport (n (%))	2 (6.7)	3 (6.1)	0.722
Ongoing CPR on arrival at hospital (n (%))	1 (7.5)	1 (12.5)	0.945

CPR, cardiopulmonary resuscitation; max, maximal value; min, minimal value; ROSC, return of spontaneous circulation; OHCA, out-of-hospital cardiac arrest; SD, standard deviation; VF, ventricular fibrillation.

Table 4. Three-month mortality and patients' neurological results. CPC, cerebral performance category.

	GROUP H	GROUP C	p
Three-month mortality (n (%))	26 (86.6)	26 (78.8)	0.411
Achieved CPC 1 or 2 after 3 months (n (%))	2 (6.7)	3 (9.1)	0.921
Achieved CPC 3 or 4 after 3 months (n (%))	2 (6.7)	4 (12.1)	0.885

initial rhythm and parameters describing cardiopulmonary resuscitation are presented in table 3. Ventricular fibrillation, as an initial rhythm, was found in the majority of patients in both groups, all remaining patients had asystole. Only a minority of patients presented prodromal pre-arrest symptoms, namely chest pain (group H: 20.0 %, group C: 21.2 %, p=0.905), nausea (group H: 13.3 %, group C: 12.1 %, p=0.885) and dyspnoea (group H: 6.7 %, group C: 9.1 %, p=0.722). AMI was diagnosed in most of them as a probable cause (in Group H: 60.0 %, in Group C: 57.6 %, p=0.735).

Major bleeding was not observed in any patient in Group H and in Group C.

There were no statistical differences between groups in regard to having a favourable neurological result and mortality 3 months after the OHCA (table 4). In the subgroup of patients who achieved ROSC in the pre-hospital stage of treatment, a favourable neurological result 3 months after the OHCA was reached with comparable frequency as well (Group H: 16.7 %, Group C: 20.0 %, p=0.825).

Discussion

The main finding of our study is that the administration of heparin during cardiopulmonary resuscitation for OHCA as a consequence of acute myocardial infarction is a safe procedure, not associated with an increased number of major bleeding events. Its impact on long-term prognosis is not clear. Out-of-hospital cardiac arrest is an extremely serious medical event. Only approximately 11% of patients survive to be discharged from hospital. (10,11) One of the procedures that may possibly improve the clinical results of resuscitated OHCA patients is very early pharmacological intervention during CPR, potentially having an influence on the cause of OHCA and also on subsequent post-resuscitation processes. Some mechanisms of ischemia-reperfusion injury are activated as early as during CPR. Significant activation of thrombocytes and coagulation cascades without corresponding increase

of fibrinolytic activity are also among them. (12) This considerable imbalance favouring blood clotting may lead to microcirculation dysfunction based both on the vasoactive basis and microthrombi formation in tissues. This was described especially in the brain and the impairment of coagulation activity in the microvascular compartment has been considered to be one of the main conditions leading to the cerebral no-reflow phenomenon. (3) The degree of no-reflow probably translates into the neurological outcome. A decreased possibility of spontaneous reperfusion of the thrombotic closure of the coronary artery may also play a role. Observational studies assessing the importance of echocardiography during prolonged resuscitation showed that the presence of a spontaneous echo contrast during CPR was connected with a worse prognosis. (13-15) All of these lead to the reduction of oxygen supplies in tissues and contribute to the development of the post-cardiac arrest syndrome and subsequent organ dysfunctions. (2,16) In theory, this unfavourable state may be positively modified by antithrombotic treatment.

The isolated effect of the antiaggregant treatment on the processes during and after cardiac arrest has been studied only to a very limited extent. (17-22) In general, these are experimental receptor studies. No trials evaluating the safety and/or clinical effectiveness of antiaggregants administered during cardiac arrest have been published. With regards to the boom of new and very effective antiaggregants, with the possibility of intravenous administration, there is much space left for research into their effect in patients with cardiac arrest. (23)

The attention of researches has been recently focused on the study of the effect of systemic thrombolysis given during CPR on patients' prognosis. (24-30) Bottiger et al. have carried out an extensive multicentric clinical trial TROICA (Thrombolysis Using Tenecteplase in Cardiac Arrest). They randomized 1050 patients with OHCA of supposed cardiac aetiology to the adminis-

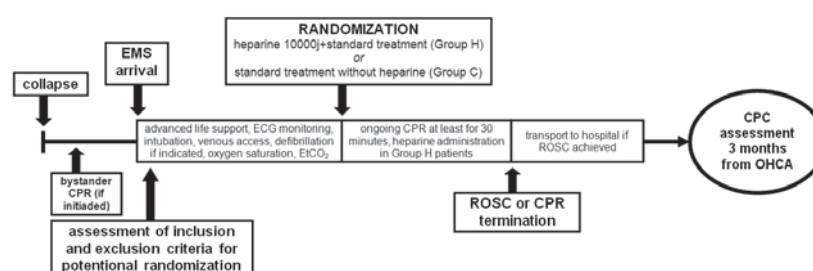


Figure 1. Study protocol schedule.

CPR, cardiopulmonary resuscitation; EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation

tration of tenecteplase bolus or placebo during CPR. The authors did not find any difference in thirty-day survival (14.7 versus 17.0 %, $p=0.36$). (27)

The only bleeding event found in the study was an incidence of intracranial bleeding. It was increased in the tenecteplase group (2.7 versus 0.4 %, $p=0.006$). However, in some patients the bleeding was a cause of cardiac arrest and most of the patients were asymptomatic. Since indications for cranial computer scanning were not predefined, detection bias cannot be ruled out. A metaanalysis of small studies and case reports revealed data about the safety of the administration of a thrombolytic agent during CPR. (31) We decided to evaluate the safety and effect of heparin administered during CPR for several reasons. Firstly, the influence of heparin on the success rate of CPR has been studied insufficiently in a similar way as the effect of antiaggregant treatment. Only certain positive results were observed in animal experiments. (32,33) In clinical practice, there are only studies combining heparin with system thrombolysis and a case report concerning the administration of heparin. (27,34) Secondly, it is important that ambiguous results of thrombolytic studies do not automatically disqualify a possible profit from the administration of heparin. The effect of heparin on the coagulation and fibrinolytic system is different from the effect of thrombolysis and from the point of view of pathophysiology it may be used especially as intracardiac thrombosis prevention

during arrest and microcirculation dysfunction. (34) Thirdly, the administration of heparin is very simple and it is an inexpensive drug. Being a pilot study, we mainly focused on the safety of such an approach, expressed by the incidence of major bleeding events.

The first important point is the diagnosis of a possible cardiac cause of OHCA itself. It is necessary to disqualify any traumatic cause and/or bleeding. The information about the medical history of the patients and about any prodromal symptoms that directly preceded OHCA (if there were any at all) is not always available. Usually, it is necessary to make a diagnosis based on the result of a rapid examination of an unconscious patient with cardiac arrest and to use the process of elimination. Acute myocardial infarction is the cause of OHCA in one half to two thirds of all cases of OHCA after eliminating apparently non-cardiac causes, that is traumatic causes and/or bleeding etc. (35,36) The number of patients with AMI would be probably even higher after eliminating patients supposed to have pulmonary embolism. In our group, respecting the inclusion criteria, the diagnosis of acute myocardial infarction was confirmed later in 71.6 % of cases. This relatively high confidence level of the initial diagnosis confirms the above mentioned observations and at the same time makes it possible in a relatively reliable way to identify the most suitable target group of patients with OHCA for anti-thrombotic intervention during CPR.

The key finding of our study is that the use of heparin during CPR was not associated with an increase in major bleeding events during the pre-hospital and early in-hospital period. Even in those patients who did not reach ROSC in the field, no bleeding events, potentially worsening the chance to achieve ROSC, were found. Therefore, we consider the administration of unfractionated heparin during CPR in OHCA patients with presumed AMI safe. We did not observe any impact of heparin administration on the three-month mortality and on the incidence of a good neurological outcome in our study. There are several possible reasons for this finding: Is it a small number of patients in the study? Is it the absence of any effect of heparin, an unsuitable study design, an incorrect dosage of heparin or a choice of unsuitable endpoints? All of the above

mentioned elements may influence the result. We are sure that more patients included would be beneficial, however, the outcome was not the primary endpoint. An optimal way would be to perform a double-blinded clinical study with a high number of randomized patients and thoroughly defined pre-hospital and hospital care, with heparin dosages in units/kg of body weight and a technical primary endpoint directly assessing the coagulation activity and the state of microcirculation. Nevertheless, such a study would be extremely demanding in regard to financing, time and organization, especially in view of the fact that the study concerns a pre-hospital intervention in patients with OHCA during CPR.

The major limitation of the study is the sample size. It is not large enough to evaluate the impact of the study intervention on the neurological prognosis.

However, the primary endpoint was a safety issue and because of absence of previous data about this topic, sample size was not possible to calculate.

In conclusion, the intravenous administration of non-fractionated heparin in a dose of 10 000 units during CPR for out-of-hospital cardiac arrest in patients with supposed AMI was a safe procedure. We did not observe any improvement in patients' prognosis. Though the procedure proved safe, we recommend postponing the administration of heparin until the return of spontaneous circulation, the assessment of clinical state and the recording of a twelve-lead ECG and until further specification of the diagnosis or of acute coronary syndrome or pulmonary embolism. Our pilot study presents more questions than answers. However, it is important from our point of view that the study proved the safety and simplicity of the procedure.

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