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Mild therapeutic hypothermia after cardiac arrest and the risk of bleeding in patients with acute myocardial infarction

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Abstract

Background: The aim of the study was to report the impact of our hypothermia protocol on survival and neurological outcome. Furthermore, we were interested in the risk of bleeding complications in patients with acute myocardial infarction (AMI) being treated with percutaneous coronary revascularisation (PCI) and therapeutic hypothermia.
Methods and results: In a prospective observational study we identified 31 comatose patients (25 male, age 65±13 years) admitted to our intensive care unit with out-of-hospital cardiac arrest due to AMI who were treated with hypothermia. They were compared to 31 historical age- and gender-matched controls (25 male, age 65±12 years) admitted after out-of-hospital cardiac arrest due to AMI in the era prior to hypothermia treatment. Peak creatinine kinase-MB was 118 U/L (94–248) in the hypothermia group and 131 U/L (98–257) in controls ($p=0.51$). In the hypothermia group, 19 patients were discharged with a favourable neurological outcome, whereas in controls, such outcome was observed in only six patients ($p=0.002$). In both groups, haemoglobin values and platelet counts declined during the first 48 h (all $p<0.001$). No differences regarding bleeding complications ($p=1.0$), transfusion requirements ($p=1.0$), and the number of transfusions ($p=0.9$) were observed between the groups.
Conclusions: A major improvement in neurological outcome was observed in patients treated with hypothermia. Our results indicate that the combination of reperfusion strategies and the application of hypothermia do not carry an excessive risk of bleeding complications. Patients with AMI and out-of-hospital cardiac arrest should receive the optimal therapy for both conditions, that is, either thrombolysis or PCI and therapeutic hypothermia.

Keywords: Acute coronary syndrome; Out-of-hospital cardiac arrest; Resuscitation; CPR; Percutaneous coronary intervention

1. Introduction

Acute myocardial infarction (AMI) is the most prevalent cause of sudden cardiac death. Today, there is no doubt that patients with AMI and cardiac arrest need early coronary revascularisation. This approach has been demonstrated to improve both short and long term prognosis [1,2]. Nevertheless, there is evidence to suggest that the survival of these patients is depending even more on the neurological status than on the type of specific treatment for AMI [3]. Severe hypoxic encephalopathy is a major determinant of outcome in patients after cardiac arrest. Mild therapeutic hypothermia is a neuroprotective strategy which has been shown to significantly increase both cerebral prognosis and long term outcome in this patient population [4]. In 2003, the International Liaison Committee on Resuscitation recommended such treatment for all comatose survivors of out-of-hospital cardiac arrest in case of ventricular fibrillation being the initial rhythm [5].

Hypothermia itself may result in an increased risk of bleeding as a consequence of impaired platelet function, altered clotting enzyme kinetics, and activation of the

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fibrinolysis cascade. This raises questions about the safety of therapeutic hypothermia in regard to bleeding complications in patients treated for coronary revascularisation with either thrombolysis or percutaneous coronary intervention (PCI). Major bleeding has been shown to be a strong predictor of mortality in patients after PCI [6].

Since September 2005 we use a standardised protocol for the application of mild therapeutic hypothermia in our medical intensive care unit (MICU). The aim of the study was to report the impact of this protocol on survival and neurological outcome. Furthermore, we were interested in the risk of bleeding complications in patients with acute myocardial infarction being treated with a combination of thrombolysis or PCI and therapeutic hypothermia.

2. Patients and methods

Setting: Medical intensive care unit (MICU) of a tertiary-care academic centre. The local Ethics Committee on Human Research approved the study. In a prospective observational fashion, 56 patients were identified who were admitted comatose (Glasgow Coma Scale 3–4) to our MICU after out-of-hospital cardiac arrest between December 2005 and December 2006. In 31 of these patients, myocardial infarction as the cause of cardiac arrest was diagnosed by ECG, laboratory markers and/or coronary angiography. Eleven patients received thrombolytic therapy with tissue plasminogen activator (t-PA) as a rescue measure during pre-hospital cardio-pulmonary resuscitation. In 25 patients, percutaneous coronary intervention (PCI) with stenting of the culprit lesion was performed immediately after hospital admission (in 5 patients PCI was performed after initial thrombolysis). All of these patients received a loading dose of 600 mg clopidogrel, followed by 75 mg clopidogrel per day, and unfractionated heparin adjusted to a partial thromboplastin time (PTT) of 50–60 s. In 16 PCI patients, the glycoprotein IIb/IIIa receptor inhibitor tirofiban was given for 24 h. Dose adjustment to the patients' body weight was performed. Patients were classified as having major AMI, whenever the peak serum creatinine kinase (CK)-MB was 240 U/L or higher (i.e. >10fold the upper limit of normal) during the first 24 h.

Therapeutic hypothermia was initiated immediately after admission with an infusion of cold saline and the application of circulating water blankets (CritiCool, MTRE, Yavne/Israel or ArcticSun, Medivance, Louisville, USA). A target temperature of 33°C was maintained for 24 h in all patients. All patients received the same standardised post-resuscitation care.

For comparison to the patient group treated with hypothermia, a gender- and age-matched control group ($n=31$) was identified from patients admitted after out-of-hospital cardiac arrest due to acute myocardial infarction between 2002 and 2005. During that time, therapeutic hypothermia was not applied in our MICU. Except for the application of therapeutic hypothermia, there was no change in the standard supportive intensive care treatment between the two groups. Sedation was induced in all patients by intra-venous midazolam (0.125 mg/kg/h) and fentanyl (0.002 mg/kg/h) with consecutive dose adjustment. In the hypothermia group, paralysis was induced using pancuronium (0.1 mg/kg). The respective patients received iv-injections of pancuronium every 2 h during the hypothermia treatment to prevent shivering. Bleeding complications were defined as any clinically overt blood loss. Erythrocyte transfusion was performed at the discretion of the attending intensivist without interference by the research team. All bleeding episodes and required transfusions during the first 48 h of treatment were recorded. Neurological outcome was assessed at MICU discharge according to the Pittsburgh Cerebral Performance Category (CPC) [7]. CPC scores 1 and 2 were defined as good neurological outcomes, whereas CPC scores 3, 4 and 5 showed an unfavourable neurological outcome.

The software MedCalc® (Version 9.3.2), Mariakerke, Belgium, was used for statistical analysis. Continuous data are presented as medians with 25–75% interquartile ranges (IQR), if not stated otherwise. Binary variables are presented as numbers and percentages. Fisher's exact test was used for comparison of categorical variables in both groups. For statistical calculations, Wilcoxon's test and *t*-tests for paired samples were used, as stated. For between group comparisons, Mann–Whitney *U*-tests were performed.

3. Results

Patient characteristics are listed in Table 1. First, there were no differences between the study groups with regards to the number of witnessed arrests, bystander cardio-pulmonary resuscitation efforts, or initial rhythm (all $p>0.7$). The core body temperature at hospital admission was 35.9 °C (35.3–36.4) in patients treated with hypothermia compared to 36.0 °C (35.8–36.5) in the control group ($p=0.4$). A fluid bolus of 500 ml (500–1000 ml) of cold saline was given in the hypothermia group immediately after MICU admission. The mean time to reach the target temperature (33°C) was 5 ± 3.3 h. All patients completed the hypothermia treatment for 24 h without any complications. In both patient groups we could observe a positive fluid balance after 24 and 48 h without a difference between the two study groups (both $p>0.1$, Table 1). Furthermore, there was no statistical difference between the groups in the number of patients requiring vasopressors ($p=0.3$, Table 1). Nevertheless, a trend towards an increased need of inotropic support was observed in the control cohort (Table 1). Major AMI, as indicated by an increase in creatinine kinase (CK)-MB of up to 240 U/L or higher (i.e. >10 fold the upper limit of normal), was present in 9 patients of the hypothermia group and in 11 patients of the control group. The respective peak CK-MB in the first 24 h was 118 U/L (94–248) in the hypothermia group and 131 U/L (98–257) in controls ($p=0.51$, Table 1).

In the hypothermia group, 10 patients died before ICU discharge. Overall, 19 patients had a favourable neurological outcome with either CPC 1 ($n=12$) or CPC 2 ($n=7$). One patient had moderate (CPC 3) and one patient was diagnosed

Table 1
Baseline characteristics of both study groups

	Hypothermia group (n=31)	Control group (n=31)	p value
Male	25 (80.6%)	25 (80.6%)	1.0
Age (years)	56±13	56±12	0.87
Witnessed arrest (%)	29 (94%)	29 (94%)	1.0
Bystander CPR	16 (52%)	13 (42%)	0.79
VF as initial rhythm	25 (80.6%)	25 (80.6%)	1.0
Asystole/PEA	4/2 (12.9%/6.5%)	3/3 (9.7%/9.7%)	1.0
Time from collapse to ROSC (minutes)	20 (18–45)	35 (18–49)	0.22
Core temperature at ICU admission (°C)	35.9 (35.3–36.4)	36.0 (35.8–36.5)	0.36
Thrombolysis (t-PA, ins %)	11 (35.5%)	10 (32%)	1.0
Percutaneous coronary intervention (%)	25 (80.6%)	29 (94%)	0.26
Tirofiban (%)	16 (52%)	17 (55%)	1.0
Need of dobutamine (% of patients)	14 (45%)	21 (68%)	0.06
Need of vasopressors (% of patients)	13 (42%)	18 (58%)	0.28
Cumulative fluid balance after 24 h (ml)	1900 (950–2250)	1475 (625–2100)	0.22
Cumulative fluid balance after 48 h (ml)	3600 (2500–5250)	2950 (2005–4000)	0.15
Peak serum CK-MB (first 24 h) (U/L)	118 (94–248)	131 (98–257)	0.51

CK-MB = creatinine kinase-MB. For between group comparisons, Mann–Whitney U-tests were performed.

as having severe neurological disability (CPC 4) at ICU discharge. In the control group, only two and four patients were discharged with CPC 1 or 2, respectively. Three patients had moderate, and 12 patients severe neurological disability. Ten patients died during ICU treatment. The difference in neurological outcome between the two patient cohorts was statistically significant. In patients treated with mild therapeutic hypothermia, the number of favourable neurological outcomes (as identified by CPC scores 1 and 2) was higher than in controls (p=0.002, Fig. 1).

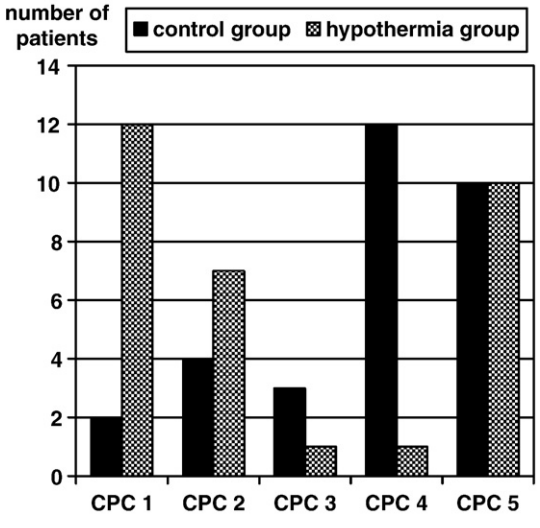

Fig. 1. Neurological outcome expressed as Pittsburgh Cerebral Performance Category (CPC) at ICU discharge for the control and hypothermia groups. Patients receiving hypothermia were more likely to be discharged with CPC scores 1 and 2 (favourable neurological outcome) when compared to controls (p=0.0019).

Table 2
Bleeding complications in the hypothermia and control groups

	Hypothermia group	Control group	p value
Patients with bleeding (n)	6	6	1.0
Patients requiring transfusion (n)	5	6	1.0
Total erythrocyte units given (n)	15	9	0.91

Between group p values were assessed using Fisher's exact test.

There were no deaths associated to haemorrhage in both patient cohorts. Bleeding was recorded in a total of 6 patients in the hypothermia group. One patient developed haematothorax related to an insertion of a central venous line. In two patients, relevant gastrointestinal haemorrhage was recorded. Furthermore, two patients had minor oropharyngeal bleeding, and one bleeding occurred at the left femoral artery, which was the angioplasty access site. Only three of these patients required erythrocyte transfusions, two of who having received pre-hospital thrombolysis with tissue plasminogen activator (t-PA). Two other patients in the hypothermia cohort were transfused due to pre-arrest anaemia in the absence of acute bleeding signs. In the control group, bleeding complications occurred in 6 patients; three patients had gastrointestinal haemorrhage; one patient had access site bleeding; in the remaining two patients, the source of the acute blood loss could not be identified. Five of the six patients with bleeding complication received erythrocyte transfusions, three of these having undergone systemic thrombolysis. One additional patient was transfused due to pre-arrest anaemia. All bleeding complications are presented in Table 2. In the hypothermia group, the patients who required transfusions needed a total of 15 erythrocyte units,

Table 3
Course of Haemoglobin (Hb) levels and platelet counts in patients not requiring transfusions (n=25, both groups)

	Hypothermia group	Control group	Between group p value
Hb (g/dl) at ICU admission	13.9 (12.4–15.1)	13.3 (12.5–14.4)	0.51
Hb (g/dl) after 24 h	12.5 (11.0–14.3) *	11.5 (12.5–14.4)$^{\#}$	0.18
Hb (g/dl) after 48 h	12.6 (11.2–13.4) **	11.3 (10.4–11.9)$^{\#\#}$	0.01
Platelet (/nl) at ICU admission	222 (160–262)	213 (161–264)	0.96
Platelet (/nl) after 24 h	165 (129–237) ***	176 (143–227)$^{\#\#\#}$	0.56
Platelet (/nl) after 48 h	164 (126–195) ****	164 (129–187) $^{\#\#\#\#}$	0.93

Hypothermia group: *p=0.01 *vs.* baseline; **p=0.01 *vs.* after 24 h.; ***p=0.0004 *vs.* baseline; ****p=0.03 *vs.* after 24 h. Control group: $^{\#}p$=0.0001 *vs.* baseline; $^{\#\#}p$=0.1 *vs.* after 24 h.; $^{\#\#\#}p$=0.003 *vs.* baseline; $^{\#\#\#\#}p$=0.0003 *vs.* after 24 h.

whereas in the control group, a total of 9 erythrocyte units were transfused ($p=0.9$). Intra-cerebral haemorrhage was observed neither in the hypothermia nor in the control group.

A statistically significant decline in both haemoglobin (Hb) levels and platelet counts occurred during the first 48 h of treatment in both study groups (Table 3). Hb levels declined in both groups within the first 48 h (both $p<0.001$). In patients receiving hypothermia, a decline in Hb levels during the first 24 h ($p=0.01$ *vs.* baseline), and 48 h ($p=0.01$ *vs.* after 24 h) was observed. In controls, Hb levels declined in the first 24 h ($p=0.0001$ *vs.* baseline), but not in the interval thereafter ($p=0.1$ *vs.* after 24 h). Platelet counts declined in both study groups within 48 h (both $p<0.0001$). In the hypothermia group, platelet counts were found to decline in the first 24 h ($p=0.0004$ *vs*. baseline), and 48 h ($p=0.03$ *vs*. after 24 h). In controls, platelet counts declined during 24 h ($p=0.003$ *vs.* baseline), and 48 h ($p=0.0003$ *vs.* after 24 h).

3. Discussion

Therapeutic hypothermia after cardiac arrest has previously been shown to significantly improve neurological outcome. In this analysis, we were able to reproduce this finding in patients with AMI surviving out-of-hospital cardiac arrest. In contrast to other investigations, however, we could not observe a reduction in ICU mortality [8]. In our opinion, this may simply be attributable to differences in end-of-life decision-making or on withdrawal of ICU-therapy between the respective ICU's. This may also explain the relatively high number of patients with persistent coma in our control group.

Since acute myocardial infarction is the most prevalent cause of sudden cardiac death, early revascularisation seems important to improve the outcome of these patients. Anticoagulants in combination with inhibitors of platelet aggregation are routinely used during and after PCI procedures, resulting in an increased risk of bleeding in these patients. The risk of bleeding might be further aggravated by therapeutic hypothermia. Our observations indicate, however, that the application of mild hypothermia following coronary reperfusion therapy – either by PCI or systemic thrombolysis – is not necessarily associated with an excessive risk of bleeding complications. This finding is in accordance with an observational study published recently reporting no serious bleeding episodes in patients with PCI and therapeutic hypothermia [9]. Another recent study has shown that the combination of PCI and therapeutic hypothermia is safe in terms of malignant arrhythmias and hemodynamic stability [10]. Apart from acute blood loss, persistent declines of both haemoglobin values and platelet counts were observed in both study groups. This may in the early phase be explained by occult bleeding, blood loss for diagnostic procedures and volume expansion. In the later stages of the disease, cytokine effects on haematopoiesis may augment such effects. Nevertheless, the observed declines in both study groups did not differ statistically.

Some limitations of our analysis deserve further discussion. First of all, the results presented here were generated in an observational fashion using historical controls. Although validation of our results using a randomised controlled approach seems preferable, some experts believe that ethical concerns will most likely prevent further randomised trials that withhold hypothermia in a control population. Secondly, the important question about the size of the respective myocardial infarction and the associated prognosis after application of mild therapeutic hypothermia could only be assessed by measurement of CK-MB levels. Major AMI, as assessed by CK-MB levels >240 U/L (i.e. >10 fold the upper limit of normal) [11], was present in 9 patients of the hypothermia group and in 11 controls. Although there were no significant differences between the respective study groups, enzyme levels and kinetics might well be influenced by therapeutic hypothermia. Third, only a limited number of study patients were investigated in this analysis.

The number needed to treat of therapeutic hypothermia to prevent persistent coma or death has previously been calculated as $n=6$ [12]. We confirm these findings in that we observed impressive improvements in neurological outcome in patients treated with hypothermia. Unfortunately, only a minority of cardiac arrest patients is currently being treated with mild therapeutic hypothermia worldwide [13]. Nevertheless, we suggest that the safety of reperfusion strategies in patients treated with mild therapeutic hypothermia should also be addressed in the large hypothermia registries, which are currently being installed.

In the present analysis, the benefit of therapeutic hypothermia clearly seemed to outweigh the risk of bleeding complications. Our data indicate that the fear of bleeding complications should not be taken as an argument to withhold controlled hypothermia. We conclude that the optimal therapy for patients with AMI and out-of-hospital cardiac arrest should include both thrombolysis or PCI and therapeutic hypothermia.

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