No-flow and low-flow in TTM

Research · January 2016

DOI: 10.13140/RG.2.1.1453.5766

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Resuscitation 99 (2016) 44–49

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Clinical paper

Time to start of cardiopulmonary resuscitation and the effect of target temperature management at 33 °C and 36 °C☆

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ARTICLE INFO

Article history:
Received 5 August 2015
Received in revised form 17 October 2015
Accepted 22 October 2015

Keywords:
Cardiac arrest
Targeted temperature management
Neurological function

ABSTRACT

Introduction: The optimal temperature during targeted temperature management (TTM) for comatose patients resuscitated from out-of-hospital cardiac arrest is unknown. It has been hypothesized that patients with long no-flow times, for example those without bystander CPR would have the most to gain from temperature management at lower temperatures.
Methods: We analysed data from an international clinical trial randomizing cardiac arrest patients to targeted temperature management at 33 °C and 36 °C for an interaction between no-flow time and intervention group, with neurological function at six months after cardiac arrest as the primary outcome. A cerebral performance category (CPC) score of 1 or 2 was considered a good outcome.
Results: No-flow time (min) was associated with poor neurological outcome (OR 1.13, 95% confidence interval 1.06–1.20, $p < 0.001$). There was no statistically significant interaction between no flow-time and intervention group ($p = 0.11$), which may imply that the non-superior effect of 33 °C was consistent for all no-flow times. Bystander CPR was not independently associated with neurological function.
Conclusions: TTM at 33 °C compared to 36 °C was not associated with an increased probability of a good neurological function for patients with longer no-flow times.

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2015.10.013.
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http://dx.doi.org/10.1016/j.resuscitation.2015.10.013
0300-9572/

Introduction

Targeted temperature management (TTM) after cardiac arrest is currently recommended by international guidelines for both shockable and non-shockable rhythms based on two trials from 2002.[1–3] Following the publication of the TTM-trial, which showed no difference in survival or neurological outcome between 33 °C and 36 °C,[4] an update from the International Liaison Committee on Resuscitation (ILCOR) preceding a formal consensus statement stressed that target temperature management remains an important aspect of post-resuscitation care, and stated that target temperatures of 33 °C and 36 °C were both acceptable options. [5]

Since the adoption of TTM more than a decade ago efforts have been made to elucidate which patients gain most benefit from TTM. Subgroups that have been investigated include different age groups, shockable and non-shockable rhythms as well as patients with in-hospital cardiac arrest.[3,6–8] Based on the classification of cardiac arrest into three stages by Weisfeld and Becker it has been suggested that patients in the metabolic phase of arrest, which include those with more than 10 min of no-flow time (time from cardiac arrest to start of cardiopulmonary resuscitation (CPR) would be particularly responsive to TTM.[9,10] This hypothesis is to some extent supported by animal studies showing that ischemia persisting beyond 8 min is progressively associated with worse neurological outcomes.

There have been concerns regarding the generalizability of the results of the TTM-trial because a high proportion of patients received bystander-CPR (73%) and a median time to start of basic life support (for patients with bystander-CPR) of 1 min (interquartile range (IQR) 0–2 min, range: 0–25 min).[11,12]

The aim of this study was to explore any potential interaction between temperature and no-flow time to investigate whether patients with longer periods of cerebral ischemia had a better response to the lower target temperature of 33 °C in the TTM-trial.

Methods

Patients

This study is a post hoc analysis of the TTM-trial, an investigator-initiated, multicentre, randomized, parallel group, and assessor-blinded clinical trial (NCT01020916).[3] The TTM-trial included adult patients (≥18 years) resuscitated from OHCA of presumed cardiac cause, irrespective of the initial rhythm, who remained unconscious (Glasgow coma scale <8) after sustained (>20 min) return of spontaneous circulation (ROSC). The main exclusion criteria were unwitnessed arrest with asystole as the primary rhythm, an interval from ROSC to screening of >240 min and a state of refractory shock, defined as a systolic blood pressure (SBP) of <80 mm Hg despite fluid loading, vasopressors, inotropes and/or treatment with mechanical assist devices that could not be reversed within the inclusion time window.[3]

This post hoc analysis included all patients in the trial with available data on no-flow time. No-flow time was defined as the reported time from cardiac arrest to the start of bystander CPR. For patients who did not receive bystander CPR, no-flow time was defined as time between the cardiac arrest and initiation of CPR by a medical provider. Low-flow time was defined as time with active CPR by a bystander and/or a medical provider. Therefore, low-flow time equalled time to ROSC minus no-flow time.

Outcome

Primary outcome was the neurological function at six months assessed by the cerebral performance category (CPC) scale.[13] A CPC of 1–2 was considered a good neurological outcome and a CPC of 3–5 was considered a poor neurological outcome. As an additional outcome, mortality at six months was assessed.

Table 1
Characteristics of the study population.

Characteristic	TTM 33 (n = 473)	TTM 36 (n = 464)
Bystander CPR	344 (73)	339 (73)
Age–median (IQR)	65 (57–73)	65 (56–73)
Male sex–no (%)	393 (83)	367 (79)
Shockable rhythm–no (%)	375 (79)	376 (81)
No-flow time–median (IQR)	1 (0–6)	1 (0–5)
Low-flow time–median (IQR)	23 (14–35)	21 (13–35)
Shock on admission–no (%)	70 (15)	67 (14)
Site[a]–no (%)	110 (23)	108 (23)

TTM: target temperature management; IQR: inter-quartile range.
[a] Patients from the two sites with the highest number of randomized patients. All other sites comprise the reference category.

Statistical analysis

Comparisons between groups were assessed by the Mann–Whitney U test for continuous variables and the chi-squared test for categorical variables. Logistic regression was used to analyse six-month neurological outcome and mortality at six months providing odds ratios (OR) with 95% confidence intervals (CI). Variables included in the models were bystander CPR and the design variables from the TTM-trial (age, gender, initial rhythm, time to ROSC, circulatory shock at admission and site) with time to ROSC subdivided into no-flow and low-flow time.[14] To avoid multicollinearity, continuous variables were centred. The low-flow variable was also included as a squared variable. No-flow time was studied as a continuous variable and in a separate model as a categorical variable. The categories used were the same as those proposed by Testori et al.[9] An interaction between no-flow time and the intervention group (36 °C) was included in both models. To study the effect of temperature at different no-flow times, adjusted predictions at representative values were made using the STATA command margins. These calculations were performed, as the interpretation of the odds ratio of an interaction can be misleading. Variables other than treatment group were left at their actual values while the effect of managing the entire study population at 33 °C and 36 °C was studied. Average probability of a poor neurological function and mortality was calculated at 2-min intervals from 0 min of no-flow time to 20 min of no-flow time. In the categorical analysis the average probability of a poor outcome was calculated for each category. To test the statistical significance of the difference between the estimated average probabilities at different no-flow times we used the STATA command margins (dydx), as overlapping confidence intervals can be too conservative.[15] p-values < 0.05 were considered significant. STATA 13.1 (StataCorp, College Station, Texas, USA) was used for all analyses.

Results

Study population

The modified intention to treat population of the TTM-trial included 939 patients with 473 patients randomized to targeted temperature management at 33 °C and 466 at 36 °C. Exclusions and withdrawals of patients before and after randomization, as well as the main results of the trial have been reported previously.[4] Patient characteristics are shown in Table 1. There were no significant differences in baseline variables between intervention groups.

Table 2
Adjusted multivariate analysis—all patients.

Poor neurological function or death at 180 days after cardiac arrest.			
Characteristic	OR	95%CI	*p*
No-flow time (min)	1.13	1.06–1.20	<0.001
TTM 36 °C	1.03	0.75–1.41	0.86
Interaction term:TTM36 °C and no-flow time			0.11
Low-flow time (min)	1.05	1.04–1.06	<0.001
Low-flow time (quadratic)	0.99	0.99–0.99	<0.001
Bystander CPR	1.09	0.66–1.82	0.73

Model obtained from multivariate logistic regression. In addition to the presented variables adjustments were made for design variables (age, sex, site, initial shockable rhythm and shock on admission). OR: odds ratio. $n = 910$.

Bystander CPR

In the analysis of bystander CPR, 937 (99.8%) patients were included; data on bystander CPR were missing in two cases. A majority of patients had bystander CPR performed ($n = 683$, 73%). Patients who received bystander CPR were younger (64, IQR (56–72) vs. 67, IQR (59–74), $p < 0.01$) and more often had a shockable initial rhythm (86% vs. 66%, $p < 0.01$). A good neurological outcome was more common for patients who received bystander CPR (51% vs. 37%, $p < 0.001$), but bystander CPR was not independently associated with neurological outcome (OR 1.09, 95%CI 0.66–1.82, $p = 0.73$) or mortality (OR 0.89, 95%CI 0.54–1.47, $p = 0.64$), (Table 2).

Time to start of cardiopulmonary resuscitation

Data on no-flow times were available for 915 (97%) patients (Fig. 1). Median no-flow time was 1 min (IQR 0–5 min; range 0–33 min). There was no statistically significant difference in no-flow time between temperature groups ($p = 0.78$). The median low-flow time was 22 min (IQR 14–35 min; range 0–169 min) with no statistically significant difference between intervention groups ($p = 0.41$, Table 1). Patients with bystander CPR had shorter no-flow time, 1 min (IQR 0–2 min) vs. 8 min (IQR 5–12 min) ($p < 0.001$) in patients without bystander CPR. The median low-flow time was longer for patients with bystander CPR (24 min, IQR 16–35 min) compared to patients without (18 min (IQR 10–30 min), $p < 0.001$). Time to ALS (advanced life support) was 10 min (IQR 6–13 min) in the 33 °C-group and 9 min (IQR 5–13 min) in the 36 °C-group ($p = 0.06$). Patients with bystander CPR had longer times to ALS than those without bystander CPR, 10 min (IQR 6–13 min) vs. 8 min (IQR 5–12 min) ($p < 0.001$). In multivariate analysis a 1-min increase in no-flow time was significantly associated with a poor outcome (OR 1.13, 95%CI 1.06–1.20, $p < 0.001$). The average marginal effect of no-flow time was 0.016 ($p < 0.001$). For every 1-min increase in no flow

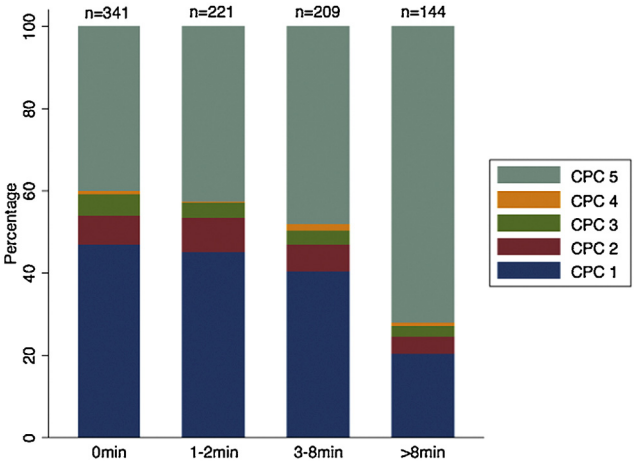

Fig. 1. *No-flow time and survival.* Number of patients categorized by no-flow time and neurological outcome at 6 months.

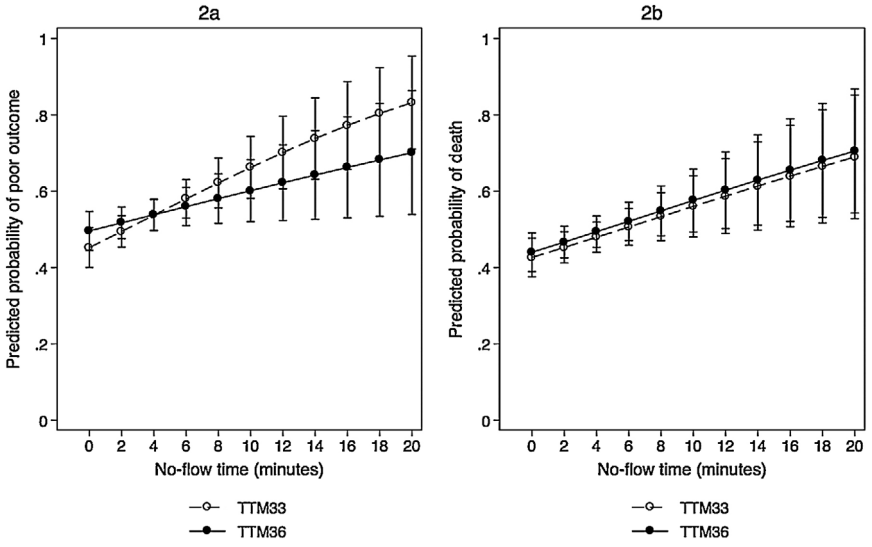

Fig. 2. *Adjusted predictions by no-flow time.* Adjusted predictions for TTM at 33 °C or 36 °C for different values of no-flow time. (a) Predicted probability of poor neurological outcome. (b) Predicted probability of death at six moths. Derived from logistic regression models adjusting for covariates. No marginal increase (2 min) in no-flow time was associated with a significant benefit of 33 °C or 36 °C. TTM: Target temperature management.

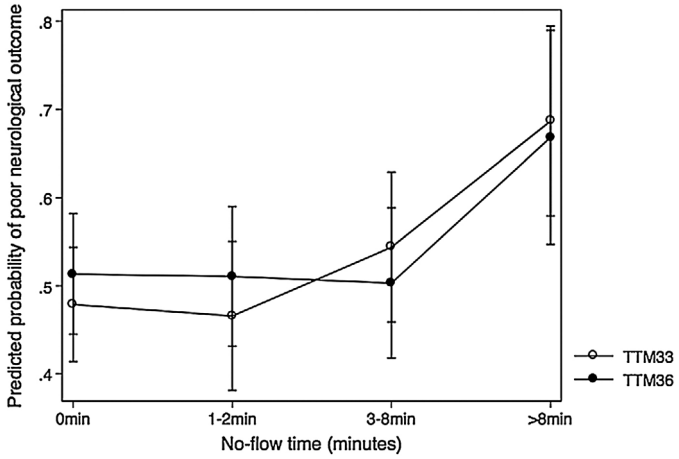

Fig. 3. *Adjusted predictions of poor neurological function (Categorical).* Adjusted predictions of poor neurological function by TTM at 33 °C or 36 °C at different no-flow times. Derived from logistic regression model adjusting for covariates. No shift from the reference category was associated with a significant benefit of 33 °C or 36 °C. TTM: target temperature management.

time the average predicted probability of a poor outcome increased by 1.6% ($p < 0.001$).

Intervention effect in all patients

In multivariate analysis, there was no significant difference in poor neurological function (OR 1.03; 95%CI 0.75–1.41; $p = 0.86$) or mortality (OR 1.09; 95%CI 0.79–1.49; $p = 0.61$; Table 2) between the 36 °C group and the 33 °C group. The interaction between no-flow time and treatment group was not statistically significant in terms of a poor neurological function ($p = 0.11$) or mortality ($p = 0.98$). Incremental increases in no-flow time (2 min intervals, 0–20 min) were not associated with a statistically significant difference between treatment groups in the predicted probability of a poor neurological function or death (Fig. 2a and b). When no-flow times were grouped into four categories (0 min, 1–2 min, 3–8 min, and >8 min) (Fig. 3) the OR for a poor neurological outcome was 3.29 95%CI (1.48–7.32) in the group with the longest no-flow time (9–33 min) compared to the reference category of 0 min of no-flow time ($p = 0.003$). There were no statistically significant interactions between any of the four no-flow categories and temperature group (all p values > 0.31).

Adjusted predictions

There were no statistically significant differences in the average marginal effect of TTM at 36 °C compared to 33 °C on the probability of a poor neurological outcome (0.011, 95%CI −0.04–0.065, $p = 0.7$). Adjusted predictions using no-flow time as a continuous variable showed no statistically significant differences in the predicted probability of poor neurological function, or death at six months at any of the values that were studied (Fig. 2a and b). In the categorical analysis, the adjusted predictions of poor neurological function did not show any significant differences between TTM at 33 °C and TTM at 36 °C (Fig. 3). For patients with 3–8 min of no-flow time there was no statistically significant difference in the average predicted probability of a poor outcome between TTM at 36 °C compared to 33 °C (−0.041, 95%CI −0.16–0.076, $p = 0.49$). In the group of patients with more than 8 min of no-flow time there was no statistically significant difference in the average predicted probability of a poor outcome between TTM at 36 °C compared to 33 °C (−0.019, 95%CI −0.17–0.13, $p = 0.81$) (Fig. 3).

Discussion

In this post hoc study of a large randomized trial of out-of-hospital cardiac arrest we investigated the time to start of resuscitation attempts on the efficacy of two target temperature levels, 33 °C and 36 °C. This study has two main findings. First, we found no statistically significant interaction between no-flow times and intervention group, which may imply that the non-superior effect of TTM at 33 °C was consistent for all no-flow times. The adjusted average predictions also supported this finding. Second, we found bystander CPR not to be significantly associated with neurological function or survival after multivariate adjustment.

In light of the main results of the TTM-trial these findings may not be unexpected, although prior observational studies seem to suggest an increased benefit of targeted temperature management at 33 °C with longer no-flow times.[9] Adverse neurological outcomes occur from 5 min of global cerebral ischemia, and include death.[16–18] Despite this subsequent poor outcome is common in patients with shorter no-flow times due to inadequate or prolonged CPR with low-flow.[19,20] Median no-flow time in this study was one minute, but a large number of patients in the primary analysis had comparatively long durations of no-flow; 144 patients had no-flow times longer than 8 min. These patients approximate the third, or metabolic, phase of cardiac arrest as proposed by Weisfeld and Becker [10] in which hypothermia is hypothesized to have its best effect. Importantly, the low-flow time reported in this study comprised both time when bystanders performed CPR and the time when medical personnel provided ALS.

In this study, the average adjusted predictions showed no difference between target temperatures at 36 °C vs. 33 °C for increasing times of no-flow when analysed as a continuous variable over the whole time span. In the categories of 3–8 min and >8 min of no-flow time there was also no difference. Contrary to this, in a retrospective observational study from 2011 Testori et al. found statistically significant effects of hypothermia only in the longer time-intervals of no-flow while no associations with outcome were detected when no-flow was short (0–2 min). In the Testori study, the adjusted odds ratio for a good neurological function for patients treated with hypothermia was 2.72 in the time interval 3–8 min. For the patients with no-flow times longer than 8 min the adjusted OR was 6.15, roughly equating a number needed to treat of between 3 and 4, which seems rather optimistic. As the Testori study was not randomized it is prone to a high risk of selection bias, which might be one likely explanation for the discrepant results compared with the TTM-trial. Differences might also be explained by the lack of a control group with active temperature management.

Our findings challenge the hypothesis of an increased effect of TTM at 33° for patients with longer periods of cerebral ischemia. However confidence intervals were large due to comparatively fewer patients with no-flow times >8 min, and a possible benefit of TTM at 33 °C for this subgroup of patients cannot be excluded on the basis of this study. Though, to detect or reject even a rather optimistic intervention effect of a relative risk reduction (RRR) of 20% with a power of 80% in this end of the time span of no-flow, the TTM-trial would have needed to include over 20,000 patients in total based on the same distribution of no-flow times. Regarding the adjusted predictions in this study, it is important to emphasise that they are only valid in patients who have achieved ROSC and therefore cannot be extrapolated to a general cardiac arrest population.

Despite recruiting consecutive patients from 32 sites in Europe and Australia one of the main concerns regarding the TTM-trial has been the purported lack of generalizability due to high rates of bystander CPR and short no-flow times.[12] Bystander CPR was indeed more common in the TTM-trial than in the original trials on

hypothermia for OHCA.[3,21] Rates of bystander CPR have been rising over recent years, which might account for the difference.[22–24] Another possible explanation is regional differences in rates of bystander CPR, which are well described.[25] Crucially, similar rates of bystander CPR have been described in other large studies.[26,27] It is also important to note that rates of bystander CPR in pre-hospital studies should not be compared with bystander rates in studies of patients who have achieved sustained ROSC and are admitted to intensive care, such as those in the TTM-trial. No-flow times are rarely reported in cardiac arrest studies or trials, but times identical to those of the TTM-trial (median 1 min with IQR 0–2 min for patients with bystander-CPR) were reported by Zeiner et al. as early as 2001.[28] The focus on the no-flow time of the TTM-trial should also be considered in the context of a time to ROSC of 25 min and an overall mortality of 49% indicating a substantial total ischemic insult. As expected, no-flow times were shorter for patients who received bystander CPR but low-flow times were longer probably because bystander CPR prevented ventricular fibrillation from deteriorating to asystole making it more likely to achieve ROSC after longer resuscitation efforts. Similar findings were described in a recent publication by Hasselqvist et al.[29] Patients with bystander CPR had a lower mortality than patients without, but bystander CPR was not independently associated with mortality or neurological outcome. This is likely due to the fact that adjustments were made for no-flow and low-flow time, and suggests that bystander CPR should be viewed as a proxy for no-flow time rather than a prognostic factor in its own right. The fact that bystander CPR added little value to a multivariate model containing no-flow and low-flow times is perhaps unsurprising, but raises the question of what information this variable contains. It is our interpretation that in this case bystander CPR represents the difference between BLS and ALS during part of the low-flow time, which as might be expected does not contribute much weight to the predictive power of the model.

Limitations

This study has several limitations. Although it is based on prospectively retrieved data from a randomized trial, this analysis was not predefined. Moreover, the study was not powered to detect differences in outcome at different no-flow times as indicated above. Data on times to ROSC and ALS were monitored, but time to BLS was not. Considering the stressful situation of cardiac arrest, bystanders might have difficulty recalling exact times. However the vast majority of patients who received bystander CPR did so within one or two minutes suggesting a small margin of error.

Conclusion

In this post hoc analysis of the TTM-trial, the effect of a target temperature at 33 °C or 36 °C after cardiac arrest does not appear to be influenced by the time to initiation of CPR. A target temperature of 33 °C compared to 36 °C did not confer a survival benefit for patients who had longer durations of no-flow time. The hypothesis that the efficacy of target temperature at 33 °C vs. 36 °C is influenced by no-flow time could not be supported.

Conflict of interest statement

Dr Erlinge reports receiving speaker fees from Philips and Zoll. Drs Friberg, Nielsen, Pellis, and Wise have received lecture fees from Bard Medical.

We report no other conflicts of interest.

Acknowledgements

Support was provided by independent research grants from the Swedish Heart–Lung Foundation, Arbetsmarknadens Försäkringsaktiebolag Insurance Foundation, Swedish Research Council, Region Skåne (Sweden), National Health Service (Sweden), Thelma Zoegas Foundation, Krapperup Foundation, Thure Carlsson Foundation, Hans-Gabriel and Alice Trolle-Wachtmeister Foundation for Medical Research, Skåne University Hospital, TrygFonden (Denmark), European Clinical Research Infrastructures Network, European Union Interreg programme IV A.

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