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Clinical paper

Prolonged targeted temperature management reduces memory retrieval deficits six months post-cardiac arrest: A randomised controlled trial

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Abstract

Background: Cognitive sequelae, most frequently memory, attention, and executive dysfunctions, occur commonly in out-of-hospital cardiac arrest (OHCA) survivors. Targeted temperature management (TTM) following OHCA is associated with improved cognitive function. However, the relationship between the duration of TTM and cognitive outcome remains unclear. We hypothesised that OHCA survivors that were subjected to prolonged TTM of 48 h (TTM48) would exhibit better cognitive functions compared to those subjected to standard TTM of 24 h (TTM24) six months post-OHCA.

Methods: A predefined, cognitive post-hoc sub-study was conducted on the multicentre clinical trial: "Target Temperature Management for 48 vs. 24 h and Neurologic Outcome after out-of-hospital cardiac arrest: A Randomised Clinical Trial" (the TTH48 trial). OHCA survivors with perceived good cognitive outcome (CPC score ≤ 2) were invited to a neuropsychological assessment of memory, attention, and executive functions six months post-OHCA.

Results: In total, 79 patients were included in the study. Multivariate regression analysis revealed that TTM48 was associated with a significant better performance on three of 13 cognitive tests specific to memory retrieval after adjusting for age at follow-up and time to return of spontaneous circulation. Overall, patients in the TTM24 group were almost three times more likely (RR = 2.9 (95% CI 1.1–7.4)), p = 0.02) to be cognitively impaired.

Conclusions: This study reports an association between the duration of TTM and cognitive outcome. In OHCA survivors with perceived good cognitive outcome (CPC ≤ 2), TTM48 was associated with reduced memory retrieval deficits and lower relative risk of cognitive impairment six months after OHCA compared to standard TTM24.

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Introduction

Cognitive sequelae are, on average, documented in about half of all out-of-hospital cardiac arrest (OHCA) survivors with a reported prevalence that ranges from 6% to 100%[1] depending on the cognitive outcome measures that are used. Memory is the most common cognitive domain that is impaired in OHCA survivors, and this is followed by deficiencies in attention and executive functions. In severe cases, most cognitive domains have been shown to be affected.[1]

Targeted temperature management (TTM) is associated with decreased mortality and improved cognitive functions, as measured by Cerebral Performance Category (CPC) scores, in OHCA survivors ever since the two original landmark studies in 2002.[2,3] TTM is also a recommended practice of current clinical guidelines.[4] However, the relationship between the targeted temperature and duration of TTM with cognitive outcome remains unclear.[5,6]

Results from the temperature-differentiated TTM clinical trial (33 °C versus 36 °C) revealed no significant difference between the temperature groups on overall mortality[7] or cognitive functions[8] six months post-OHCA. Similarly, the time-differentiated TTH48 trial (24 versus 48 h at 33 °C) did not show significant effects on cerebral outcome and mortality six months post-OHCA[9], although there was a trend towards a more favourable neurological outcome for patients in the TTM48 group. Moreover, TTM48 was not effective in lowering the biomarker levels in OHCA survivors, even though biomarkers were in fact a predictor of poor neurological outcome.[10]

TTM trials often apply crude assessment measures of cognitive outcome, such as the Cerebral Performance Category (CPC) score.[11] As a result, subtle differences in cognitive outcome between treatment groups of temperature and time-differentiated TTM trials might not be recognised. Thus, a detailed, comprehensive assessment of milder cognitive impairments is needed to evaluate the potential subtle dose-dependent treatment differential effects that might occur in such TTM trials among patients with perceived good cognitive outcome.

In this study, we conducted a comprehensive neuropsychological assessment of OHCA survivors from the aforementioned time-differentiated TTH48 trial at six months follow-up.[9] The objective of the study was to evaluate the effect of TTM duration on cognitive outcome six months post-OHCA among patients with perceived good cognitive outcome (CPC score $\leq$2). Prolonged TTM at 33 ± 1 °C for 48 h (TTM48) was hypothesised to reduce cognitive impairment on memory, attention, and executive functions at six months follow-up compared to standard TTM at 33 ± 1 °C for 24 h (TTM24).

Methods

This study was a predefined cognitive post-hoc study of the multicentre clinical trial: "Target Temperature Management for 48 vs. 24 h and Neurologic Outcome after Out-of-Hospital Cardiac Arrest: A Randomised Clinical Trial" (the TTH48 trial). This trial investigated the effect of TTM48 at 33 ± 1 °C on cerebral outcome and mortality.[12] Patients with perceived good cognitive outcome, as suggested by their Cerebral Performance Category scores (CPC score $\leq$2), were invited to a follow-up neuropsychological assessment of memory, attention, and executive functions six months after OHCA.

Patients

In the original TTH48 trial, a total of 355 patients were enrolled; of which, 159 patients were enrolled in this subsequent study from participating intensive care units (ICUs) at the Aarhus University Hospital in Denmark and the Stavanger University Hospital in Norway. All unconscious OHCA patients were screened for eligibility when they entered the ICU. Written informed consent was obtained from a legal surrogate before patients were randomised to one of two intervention groups, standard TTM for 24 h (TTM24) or prolonged TTM for 48 h (TTM48). Patients had to meet the following inclusion criteria: an OHCA of presumed cardiac cause, an age between 17 and 80 years, a sustained return of spontaneous circulation (>20 consecutive minutes), and a Glasgow Coma Scale (GCS) score of <8 on admission. Detailed inclusion and exclusion criteria were previously described in the original study protocol.[12] Patients that met the inclusion criteria were invited to participate in a neuropsychological assessment six months post-OHCA if they met the following inclusion criteria: pre-OHCA CPC $\leq$ 2 and six months post-OHCA CPC $\leq$ 2.

The study was approved by the Danish Data Protection Agency and the Central Denmark Region Committees on Health Research Ethics (case number 20110022) and the Regional Ethics Committee of Western Norway (ref 2013/1486). The original TTH48 trial was registered at clinicaltrials.gov (identifier: NCT01689077).

Outcome measures

Cognitive outcome at six months follow-up was assessed by neuropsychological tests of memory, attention, and executive functions that are known to be sensitive to cognitive sequelae following OHCA. The assessment was performed by a trained, assessor-blinded research assistant. The cognitive tests included Rey Auditory-Verbal Learning Test (RAVLT)[13] and Rey–Osterreith Complex Figure Test (ROCFT)[14–16] for learning and memory; WAIS-IV Digit Span[17] and Trail Making Test A & B (TMT-A & B)[18,19] for attention; and D-KEFS Verbal Fluency[20] for executive functions. Finally, an estimate of premorbid intelligence by the WAIS-IV Vocabulary[17] test was conducted to control for the premorbid level of cognitive functions. Normative data for the WAIS-IV and D-KEFS subscales were obtained from their scoring manuals. Pooled normative data for TMT-A & B, RAVLT and ROCFT was obtained from Mitrushina[21] using regression equations derived from meta-analysis of multiple normative datasets.

Statistical methods

The baseline characteristics were presented as medians and interquartile ranges for continuous data and as count and percentages for categorical data. The baseline characteristics of the TTM24 and the TTM48 treatment groups were compared using *t*-test for continuous data and Fisher's Exact test for categorical data. The same analyses were conducted to compare the baseline characteristics of eligible patients who participated in this study and invited eligible patients who were lost to follow-up.

An unadjusted multivariate regression analysis and a multivariate regression analysis adjusted for age and time from cardiac arrest to return of spontaneous circulation (ROSC) were used to test the effects of TTM48 on cognitive test raw scores at 6 months follow-up. An alpha value less than 5% ($p < 0.05$) was considered statistically significant.

To control for the false discovery rate that result from multiple comparisons while assuming independence of cognitive tests[22], we assessed the likelihood of the number of significant findings occurring by chance. In other words, we determined the probability of one or more significant findings in 13 comparisons ($p = 0.49$), two or more findings ($p = 0.14$), three or more ($p = 0.03$), and so forth.

Cognitive test raw scores were converted to age-adjusted standardised z-scores based on the normative data. The cut-off value for z-scores was set at $z = -1.67$ because the standardised scaled scores of the WAIS-IV and D-KEFS subscales increased in increments of one-third of the standard deviation (SD) and this z-value closely resembled the one-tailed 5th percentile (4.75%). The ROCFT recognition trial was only administered at the Aarhus University Hospital site, and hence had too many missing values (n = 16 missing). Thus, ROCFT recognition trial was not included in the impairment criterion (described below).

A cognitive impairment criterion that was based on the remaining twelve cognitive tests was defined. In this study with 12 cognitive tests, patients were considered cognitively impaired if their performance were below the cut-off score for three or more cognitive tests ($p = 0.02$). Patients with performance below the cut-off score on two or less cognitive test were considered cognitively non-impaired.

Effect sizes for continuous data were calculated using Cohen's *d*[23] and converted to numbers needed to treat (NNT) as described by Furukawa and Leucht[24] with the assumption of a favourable control event rate (CER) of 50%. Effect sizes for categorical data were calculated using relative risk ratios (RR) and numbers needed to treat (NNT).[25]

Statistical analysis was conducted on a blinded dataset. All data were analysed using SPSS® Version 20 for Windows® (IBM Corp (2011). SPSS Statistics for Windows. IBM Corp., Armonk, NY) and *R* statistics (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

Sample characteristics

All patients with a CPC score ≤2 in the TTH48 trial in Aarhus, Denmark (N = 135) and Stavanger, Norway (N = 24) were invited to participate in a follow-up neuropsychological assessment six months post-OHCA between October 2013 and December 2016. A total of 159 patients were enrolled at the two participating facilities. However, 46 patients had died (CPC = 5) and two patients had a CPC score of 3 six months post-OHCA. Thus, these patients were excluded and a total of 111 eligible patients were invited to the follow-up study. Of the eligible patients, 32 were lost to follow-up (Fig. 1).

The baseline characteristics were comparable and not significantly different between the TTM24 and TTM48 treatment groups. Similarly, no significant differences in baseline characteristics were noted between study participants and eligible patients who were lost to follow-up. However, we noted a discrete trend towards older patients being less likely to participate in this study. Furthermore, patients assigned to the TTM24 group were less likely to be included in this study (Table 1). Specifically, 64% of the patients assigned to the TTM24 group participated in this study whereas 78% of the patients in the TTM48 group participated (Fig. 1), although, this difference was not significant ($p = 0.14$).

Treatment effects of TTM48 on cognitive raw scores six months post-OHCA

Unadjusted multivariate regression analysis revealed that the raw scores for the TTM48 group were significantly different ($p < 0.05$) from the TTM24 group on the three cognitive tests that were specific for memory retrieval (Table 2). Specifically, these tests were the auditory verbal memory retrieval of 15 words (RAVLT), immediate and delayed visual memory retrieval of a complex figure (ROCFT). The discovery of three significant findings in 13 comparisons of cognitive test results between treatment groups corresponded to a false discovery rate of less than 5% ($p = 0.03$), suggesting that these results were unlikely to occur by chance (type 1 error).

Performance on the cognitive tests included in this study is known to be affected by age and severity of hypoxic brain injury. Thus, a multivariate regression analysis that was adjusted for age at follow-up and duration of hypoxia (time to ROSC) was also conducted. The adjusted analysis revealed a slightly stronger association of TTM48 with significant differences in the results of the same three memory retrieval tests relative to the unadjusted analysis (Table 2).

Treatment effect sizes of TTM48 on memory retrieval raw scores six months post-OHCA

The association of TTM48 with improved cognitive outcome were specific to the memory retrieval tests, namely the RAVLT and immediate and delayed ROCFT tests (Fig. 2). On average, the TTM48 group remembered almost two (1.9) words more than the TTM24 group in the RAVLT test, which corresponded to a moderate effect size (Cohen's $d = 0.66$ (95% CI 0.21–1.11)) or a number needed to treat of approximately four patients (NNT = 4.1 (95% CI 2.7–12.0)). The TTM48 group also performed nearly three raw score points better than the TTM24 group on the immediate and delayed ROCFT tests (3.1 and 2.9, respectively), which corresponded to a small-moderate effect size (Cohen's $d = 0.44$ (95% CI 0.01–0.90) and Cohen's $d = 0.41$ (95% CI −0.04 to 0.87), respectively) or a number needed to treat of approximately six patients (NNT = 5.9 (95% CI 3.2–∞) and NNT = 6.3 (95% CI 3.2–∞), respectively).

Treatment effect of TTM48 on cognitive impairment six months post-OHCA

Neuropsychological raw scores were converted to standardised z-scores that were adjusted for age, and patients were categorised as being impaired or non-impaired based on the number of deviant performances on twelve cognitive tests. There were significantly fewer cognitively impaired patients in the TTM48 group compared to the TTM24 group ($p = 0.02$), and it corresponded to a moderate effect size (Cohen's $d = 0.61$). Specifically, 5 of the 43 patients (12%) in the TTM48 group were classified as being impaired compared to 12 of the 36 patients (33%) in the TTM24 group (Fig. 3). This difference corresponded to a relative risk ratio (RR) of 2.9 (95% CI 1.1–7.4) or a number needed to treat of approximately five patients (NNT = 4.6).

Discussion

This study suggests a specific association between TTM48 and improved memory retrieval six months post-OHCA (Table 2). Effect size estimates indicate that four patients need to be treated with

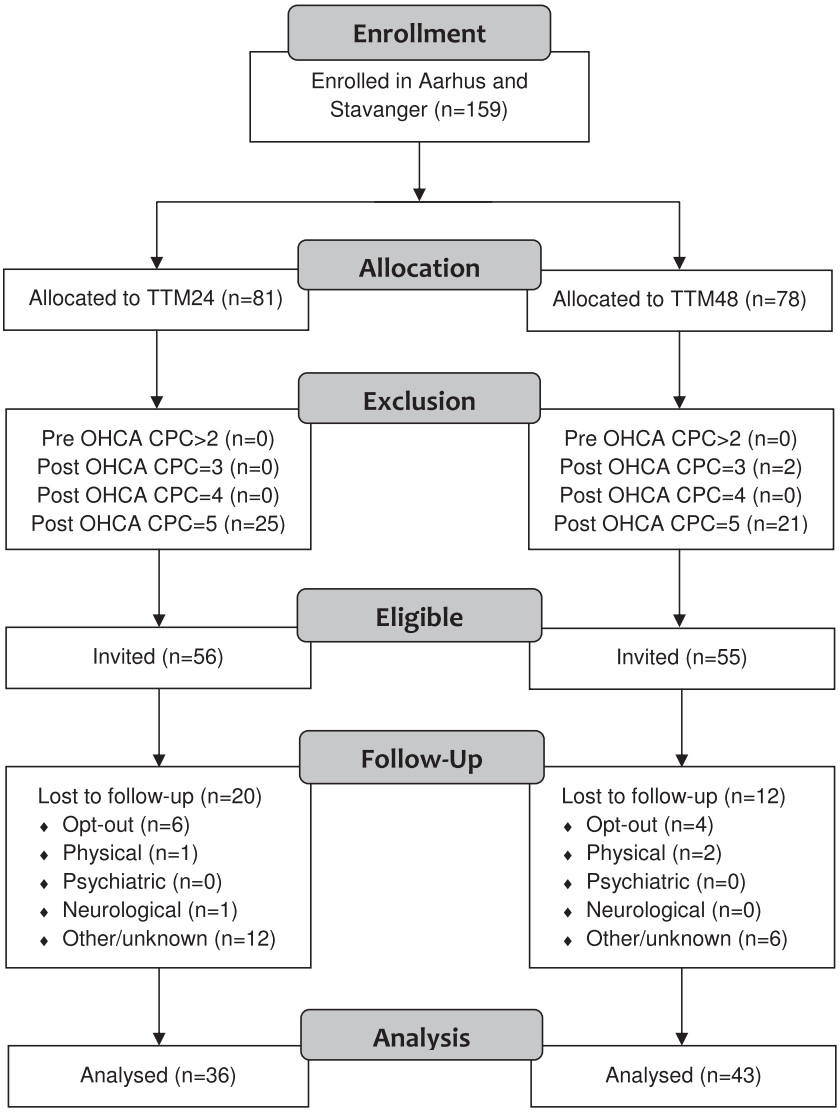

Fig. 1 – Recruitment flow-chart. CPC = Cerebral Performance Category.

TTM48 to have one more patient with favourable memory retrieval outcome in the TTM48 group compared to the TTM24 group. Although no significant associations were evident between TTM48 and other cognitive domains (attention and executive function), participants in the TTM48 group performed numerically better on most cognitive tests. Consequently, patients in the TTM24 group were almost three times more likely (RR = 2.9) to be cognitively impaired compared to patients in the TTM48 group (Fig. 3).

The results imply that the treatment effects of TTM on cognitive outcome six months post-OHCA might be time dependent (24 h versus 48 h), as opposed to being temperature-dependent as shown in a previous TTM study that compared the effects of TTM at 33 °C and 36 °C on cognitive outcome six months post-OHCA.[8] However, these studies are difficult to compare directly because different cognitive outcome measures were applied. For instance, the temperature-differentiated TTM trial included a memory sum-score and it did not analyse different theoretical aspects of episodic memory such as learning, recall, and recognition. Consequently, such specific treatment effects might have been overlooked.

Crude clinical outcome measures, such as mortality and good/poor cognitive outcome measures (CPC scores), might underestimate the subtle treatment effects of TTM. Specifically, they may fail to capture more specific, yet unneglectable, treatment effects that greatly impact everyday life, such as memory retrieval. Memory problems are well-known cognitive sequelae following OHCA.[1] and have a significant impact on the quality of life of survivors.[26] If the severity of memory deficits is in fact reduced by TTM48, the independence, work capacity, and quality of life of OHCA survivors and their informal caregivers might in turn be improved.

The present study leaves certain critical questions unanswered. It does not give definite evidence whether the treatment effects of TTM are truly specific to memory retrieval or whether it can affect other cognitive domains as well. In other words, it is uncertain if the underlying treatment effects of TTM affect the central nervous system focally or in a more global manner.

We hypothesise that TTM might have a neuroprotective treatment effect on the neurons that are located in the hippocampal circuit of OHCA patients with perceived good cognitive outcome. The medial

Table 1 – Baseline characteristics of eligible patients. P-values indicate significant differences that were found between the TTM groups and between study participants and eligible patients who were lost to follow-up. P-values were generated by conducting Fisher's exact test on categorical variables and independent t-test on continuous variables in comparisons between groups. TTM24 = Targeted Temperature Management for 24 h. TTM48 = Targeted Temperature Management for 48 h. IQR = inter-quartile range. ROSC = return of spontaneous circulation. OHCA = out-of-hospital cardiac arrest.

	Included			Eligible		
	TTM24 n = 36 (%)	TTM48 n = 43 (%)	p-value	Included n = 79 (%)	Missed inclusion n = 32 (%)	p-value
Male	34 (94.4)	37 (86.0)	0.28	71 (89.9)	28 (87.5)	0.74
CPC 1	29 (80.6)	30 (69.8)	0.31	59 (74.7)	23 (71.9)	0.81
Basic CPR (yes)	31 (86.1)	39 (90.7)	0.72	70 (88.6)	30 (93.8)	0.51
Shockable rhythm (yes)	34 (94.4)	41 (95.3)	1.00	75 (94.9)	28 (90.3)	0.40
	Median (IQR)	Median (IQR)		Median (IQR)	Median (IQR)	
Age at inclusion	58 (50–66)	57 (53–67)	0.73	58 (51–66)	65 (51–70)	0.33
Minutes to ROSC	18 (12–27)	17 (14–25)	0.65	17 (13–25)	19 (13–26)	0.71
Days since OHCA	187 (181–204)	188 (181–198)	0.64	187 (181–201)	–	–
Vocabulary (WAIS-IV)	27 (22–33)	31 (27–34)	0.24	30 (25–34)	–	–

temporal lobe and the hippocampus are known to be crucial parts of the memory circuit, and they are critical in the processes of encoding and retrieval of memory, specifically, subiculum and CA1 of cornu ammonis are known be involved in retrieval of episodic memory.[27,28] Hippocampus has been reported to have its volume reduced by 10–20% even after brief (<7 min to CPR) episode of hypoxia.[29] Neurons in CA1 have been shown to be selectively vulnerable to anoxia.[30] as well as CA3 and subiculum.[31] These particular sub segments of hippocampus are known to cause severe amnesia if damaged.[32] Thus, the memory retrieval deficits of OHCA survivors might have been reduced by TTM48 if it decreased the neurodegenerative effects of OHCA that occurred as a result of hypoxia.

Additionally, the focal effects of TTM on memory retrieval processes could be due to specific neuroprotective effects on the cells in the dentate gyrus that are responsible for neurogenesis. Studies in rodents have shown that acute brain insults initiate the proliferation of neural stem cells.[33] One study demonstrated that rodents exposed to ischemia showed increased neurogenesis in the dentate gyrus following mild hypothermia.[34] However, another study showed hypothermia had no effect on neurogenesis in rats exposed to ischemia.[35] Though it has been shown that, unlike other mammals, the neurogenesis in humans does not carry on into adulthood at a detectable level,[36] it is still unknown whether this observation holds true upon exposure to hypoxia and hypothermia.

Alternatively, the seemingly focal treatment effects of TTM on memory retrieval among patients with good cognitive outcome might be due to an attenuation of the neurodegenerative effects of OHCA progressing from focal to global with increasing severity of hypoxia. OHCA might affect neurons more locally in OHCA patients with good outcome and more globally in OHCA patients with poorer cognitive outcome due to them having experienced hypoxia at a greater severity. Hence, the treatment effect of TTM might also have less specific cognitive effects on OHCA survivors with poorer cognitive outcome.

Consequently, it would be of interest to investigate if TTM acts on the hippocampus at the cellular and anatomical level, specifically the cornu ammonis (CA1-4), subiculum and the dentate gurys, to determine if they are involved in the mediating the focal effects of TTM on memory functions using various methods, such as MRI volumetric sub segmentation.[37] Moreover, future studies should investigate whether the possible treatment effects are truly specific to memory retrieval or whether other cognitive domains are also significantly affected by the treatment. Memory retrieval processes other than episodic memory such as autobiographical or semantic memory functions could also be included as possible outcome measures.

A limitation of this cognitive sub-study was that only OHCA survivors with perceived good cognitive outcome (CPC ≤ 2) were included. It remains unclear whether TTM48 also has specific treatment effects on memory retrieval in OHCA survivors with poorer cognitive outcome (CPC ≥ 3). However, in this study, the CPC scores of OHCA survivors at six months follow-up were dichotomously distributed. Most patients were assigned scores in either the good cognitive outcome categories (CPC ≤ 2) or in the very poor outcome category (CPC = 5). Only two patients were assigned a CPC score of three and none were assigned a CPC score of four. Thus, almost all of the OHCA survivors from the two participating facilities were invited for the follow-up assessment, even though some were lost to follow-up.

While no statistically significant differences in baseline characteristics were observed between study participants in the TTM treatment groups and the invited OHCA patients that were lost to follow-up, we noted the discrete trends of older patients and patients in the TTM24 group being less likely to participate in this sub study. These trends could introduce a systematic bias against the beneficial effects of TTM48. Namely, if TTM48 had a beneficial effect on cognitive outcome of OHCA patients and patients with poorer cognitive outcome were less likely to participate, then more patients in the TTM24 group would be expected to have poor cognitive outcome. Thus, fewer patients assigned to the TTM24 group would be included in the analysis. As a result, the performance of the TTM24 group might be inflated and the true treatment effects of TTM48 might be underestimated (type 2 error). Conversely, although statistically insignificant, the percentage of patients in the TTM24 group with a CPC score of one appeared to be higher than that in the TTM48 group (80.6% compared to 69.8%).

Table 2 – Multivariate regression models of the effects of TTM treatments that were unadjusted and adjusted for age and time to ROSC. Positive B-values indicate favourable treatment effects for the TTM48 group in cognitive tests, except for the Trail Making A & B tests in which negative values indicate positive treatment effects for TTM48. * denotes a statistical difference between TTM groups at $p < 0.05$. RAVLT = Rey Auditory Verbal Learning test. ROCFT = Rey-Osterrieth Complex Figure Test.

	Unadjusted multivariate regression									Multivariate regression adjusted for age and ROSC time								
	Constant				Treatment group					Constant					Treatment group			
Attention	B	SE B	t	p	B	SE B	ß	t	p	B	SE B	t	p	B	SE B	ß	t	p
Trail making A	49.24	11.57	4.26	<0.001	−3.85	7.13	−0.06	−0.54	0.590	13.22	20.42	0.65	0.519	−4.92	6.96	−0.08	−0.71	0.481
Trail making B	120.15	16.79	7.15	<0.001	−12.75	10.31	−0.14	−1.24	0.220	33.95	28.12	1.21	0.231	−14.65	9.62	−0.16	−1.52	0.132
Digit span	22.89	2.17	10.56	<0.001	0.20	1.34	0.02	0.15	0.884	30.60	3.77	8.11	<0.001	0.43	1.29	0.04	0.33	0.741
Executive function																		
Fluency phonemic	28.06	4.28	6.55	<0.001	2.13	2.64	0.09	0.81	0.422	39.75	7.68	5.17	<0.001	2.32	2.62	0.10	0.89	0.379
Fluency semantic	35.23	3.49	10.08	<0.001	1.91	2.15	0.10	0.89	0.378	45.44	6.20	7.32	<0.001	2.21	2.11	0.12	1.04	0.300
Fluency categoric	11.17	1.02	11.00	<0.001	0.92	0.63	0.16	1.46	0.147	18.01	1.61	11.22	<0.001	1.05	0.55	0.19	1.93	0.058
Verbal memory																		
RAVLT learning	34.63	3.20	10.83	<0.001	2.01	1.97	0.12	1.02	0.310	50.47	5.43	9.29	<0.001	2.38	1.85	0.14	1.29	0.202
RAVLT recall 30 min	4.83	1.07	4.50	<0.001	1.94	0.66	0.32	2.94	*0.004	9.87	1.84	5.36	<0.001	2.03	0.63	0.33	3.24	*0.002
RAVLT recognition	10.70	1.15	9.27	<0.001	0.92	0.71	0.15	1.30	0.198	12.31	2.06	5.99	<0.001	0.88	0.70	0.14	1.26	0.213
Visual memory																		
ROCFT copy	32.91	1.33	24.65	<0.001	−0.15	0.82	−0.02	−0.18	0.858	36.03	2.39	15.07	<0.001	−0.05	0.81	−0.01	−0.06	0.953
ROCFT recall 3 min	13.78	2.35	5.86	<0.001	3.16	1.45	0.24	2.18	*0.032	25.61	4.00	6.40	<0.001	3.40	1.36	0.26	2.49	*0.015
ROCFT recall 30 min	13.81	2.34	5.91	<0.001	2.90	1.44	0.22	2.01	*0.048	26.19	3.93	6.66	<0.001	3.13	1.34	0.24	2.34	*0.022
ROCFT recognition	19.83	0.99	20.08	<0.001	0.10	0.60	0.02	0.17	0.869	21.70	1.87	11.60	<0.001	0.20	0.60	0.04	0.34	0.738

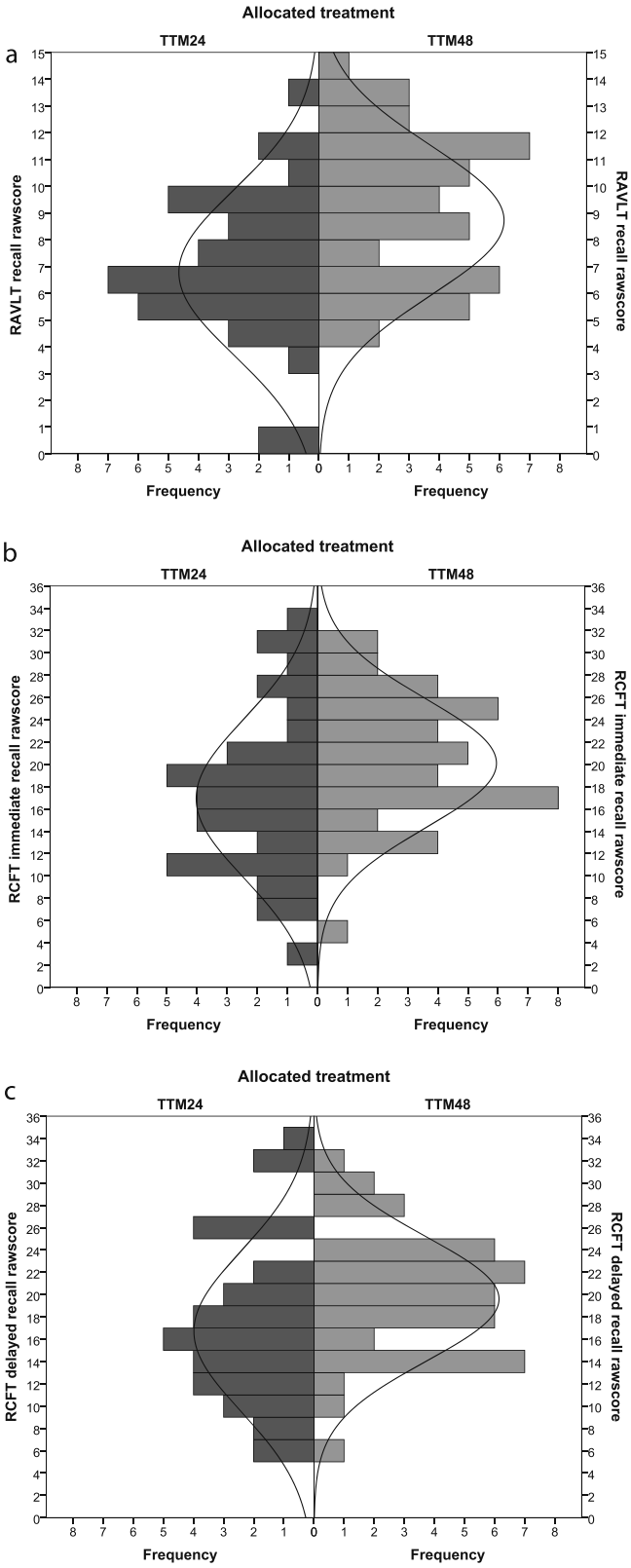

Fig. 2 – a–c Histograms of retrieval raw score frequencies for memory retrieval tests with superimposed normal curves split by the treatment groups. The histograms of theTTM24 group are found on the left in dark grey, while the histograms of the TTM48 group are found on the right in bright grey. Fig. 2a depicts the results of the delayed (30 min) retrieval of auditory memory (RAVLT) of 15 words. The scores range from 0 to 15. Fig. 2b and 2c depicts the results of the immediate (3 min) and delayed (30 min) retrieval of a visual complex figure (RCFT) with 18 elements, respectively. Each element was assigned 0–2 point. The scores range from 0 to 36.

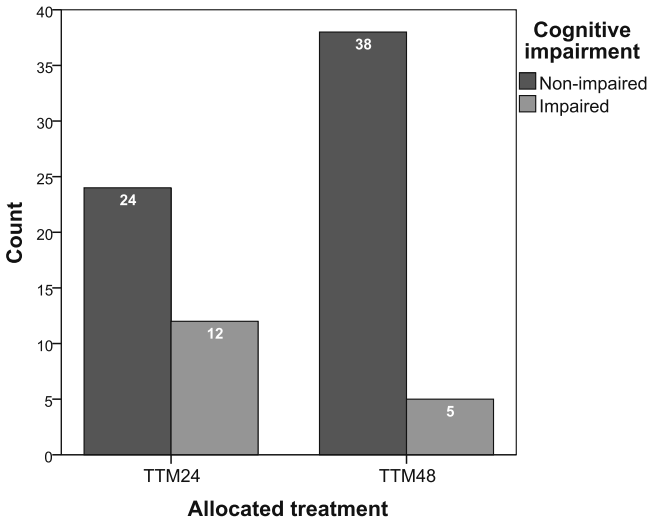

Fig. 3 – Bar graphs for the number of cognitively impaired and non-impaired patients in the TTM24 and TTM48 groups. Participants in the TTM24 group were almost three times more likely to be considered cognitively impaired. Non-impaired: ≤2 test scores below cut-off. Impaired: ≥3 test scores below cut-off. A cutoff of z = −1.67 was used.

This study used multiple cognitive tests to assess study participants because little was known about the mechanisms by which TTM could improve cognitive functions and, by extension, the specific cognitive domains that TTM affected. As a result, this study had a potential risk of false positive findings (type 1 errors). We controlled for this risk by estimating the false discovery rate and found that the probability of false positive results was negligible.

The statistical power in the present study was sufficient to detect moderate treatment effect sizes. However, a larger sample size would be able to detect smaller effect sizes, e.g. of other cognitive domains, and demonstrate the generalizability of this study's findings to other OHCA survivors. Thus, it is essential to demonstrate that the findings here for prolonged TTM of 48 h can be reproduced by others and at a larger scale before it can be considered for general use in clinical practice. Moreover, previous studies have demonstrated that prolonged TTM at 72 h improves clinical outcome of neonates with hypoxic-ischemic encephalopathy.[38] Thus, prolonged TTM at 72 h might also improve subtle cognitive outcomes of adults that experienced OHCA, such as memory retrieval. Additional studies would have to be conducted to assess the duration of TTM that would maximise the effects of TTM on the cognitive outcome of OHCA survivors, e.g. by including three treatment groups randomly assigned to 24, 48 or 72 h of TTM.

Conclusion

This study suggests an association between the duration of TTM and cognitive outcome six months post-OHCA. In cardiac arrest survivors with perceived good cognitive outcome (CPC ≤ 2), prolonged TTM at 33 °C for 48 h is associated with a lower relative risk of overall cognitive impairment and specifically with a decrease in memory retrieval deficits compared with the standard protocol of 24 h TTM at 33 °C.

Conflict of interest

The authors declare that they have no conflict of interest with the contents of this article. The sub study received no external funding.

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