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ORIGINAL ARTICLE

Accidental hypothermia as an independent risk factor of poor neurological outcome in older multiply injured patients with severe traumatic brain injury: a matched pair analysis

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Abstract

Purpose Patients with multiple injuries are particularly susceptible to accidental hypothermia which is correlated with an increased risk of post-traumatic complications and mortality; however, its impact on neurological outcome in cases where there is concomitant traumatic brain injury is underexplored.

Methods We analyzed severely injured patients (ISS ≥ 16) including a moderate-to-severe traumatic brain injury ($AIS_{Head} \geq 3$). The primary endpoint was objective neurological recovery, expressed as Glasgow Outcome Scale (GOS) score at time of discharge. Secondary endpoints were mortality, systemic inflammatory response syndrome (SIRS), sepsis, acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS). Statistical analysis included logistic regression (odds ratio). The significance level in all analyses was $p = 0.05$.

Results We analyzed 278 patients (*M* age = 43 years, SD 19; *M* ISS = 32.8, SD 10.7). Mortality was 17% ($n = 14$). 102 patients (37%) were hypothermic on admission. Hypothermic patients were more severely injured (ISS 35.6 ± 11.1 vs. 31.2 ± 10.1, $p = 0.001$; APACHE II 18.1 ± 7.4 vs. 16.2 ± 7.3, $p = 0.045$) and had a higher transfusion requirement. Mortality rate in hypothermic patients was increased (23.5 vs. 13.1%, $p = 0.03$); however, hypothermia was not an independent predictor of mortality. Median GOS at discharge was 3 (IQR 3); in 47% of patients the outcome was favorable (GOS 4 or 5) and 36% it was poor (GOS 2 or 3). There were no differences in post-traumatic complications. Analysis of 73 matched pairs of hypothermic and normothermic patients could not prove hypothermia as an independent predictor of poor neurological outcome (OR 1.7, 95% CI 0.8–3.6, $p = 0.1$) in the total population. However, older patients (> 41 years) had a 4.2-times higher risk (95% CI 1.4–12.7; $p = 0.01$) of poor neurological outcome, if they were hypothermic on admission.

Conclusions Accidental hypothermia seems to have a negative impact on neurological recovery in older patients with multiple injuries including traumatic brain injury which outweighs potential benefits.

Keywords Traumatic brain injury · Polytrauma · Hypothermia · Multiply injuries · Neurological outcome

Introduction

Hypothermia is defined as a decrease in core temperature to below 35 °C or 95 °F, respectively [1–5]. Patients with multiple injuries are particularly susceptible to accidental hypothermia due to exposure to the environment, shock as a result of hypoperfusion, impaired thermoregulation, infusion of cold fluids, and therapy with anesthetics or muscle relaxants [6–8]. One has to be aware of the risk of accidental hypothermia as it is common in polytraumatized patients. Incidence of hypothermia at admission can be up to 66% in patients with multiple injuries [3, 5–7, 9–11]. Severe hypothermia induces cardiac arrhythmias, bradycardia and low cardiac output [12]. Furthermore, hypothermia is

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an inherent feature of trauma-induced coagulopathy (TIC) [13–15] and leads to immunosuppression due to reduction in levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and increased excretion of anti-inflammatory interleukin 10 (IL-10) [9, 16, 17]. Accidental hypothermia is correlated with an increased risk of post-traumatic complications such as acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS) [6, 18]. Furthermore, mortality rate in hypothermic patients is increased. Although Jurkovich et al. reported 100% mortality in polytraumatized patients with a core temperature below 32 °C, various studies have reported mortality rates of 30–80% in cases of concomitant hypothermia [9, 10, 18].

While the deleterious consequences of hypothermia are clear, its potential neuroprotective effect remains controversial. As long ago as 1950 Bigelow et al. reported an improved neurological outcome after circulatory arrests, when mild cooling was used as part of the treatment [19, 20]. Cerebral blood flow and oxygen consumption depend on core temperature [21]. Secondary brain damage is predominantly due to local ischemia and hypoxia. Thus, hypothermia might contribute to early neuroprotection [22]. Various studies have investigated the effects of induced hypothermia on neurological outcomes following traumatic brain injury and the inconsistent results are subject to discussion. Clear evidence as to whether and how hypothermia influences outcome is still lacking [23–29]. The influence of accidental hypothermia on neurological outcome in patients with multiple injuries including traumatic brain injury is underexplored [30–32].

We therefore compared the neurological outcome of normothermic and hypothermic polytraumatized patients with moderate-to-severe traumatic brain injury. We hypothesized that accidental hypothermia would not have a positive influence on neurological outcome. We analyzed incidence of post-traumatic complications as well as mortality.

Materials and methods

Following internal review board approval, a retrospective cohort and matched pair analysis was performed. Patients with multiple injuries [Injury Severity Score (ISS) ≥ 16] including moderate-to-severe traumatic brain injury [Abbreviated Injury Scale (AIS) of the head ≥ 3] admitted within 6 h of the trauma to the Hannover Medical School, a level I trauma center, between January 2005 and December 2012 were included. Participant's minimum age was 15 years. All patients with penetrating injuries, on steroid or hormone therapy, with cancer, chronic lung, liver or heart disease or diabetes were excluded.

Demographic and baseline data (age; sex; height; body weight; duration of mechanical ventilation; duration of intensive care treatment; duration of overall treatment; transfusion requirement) were extracted from the electronic patient records. Body mass index was defined as the quotient of body mass and height squared (kg/m^2). Injury pattern and severity were classified using the 2008 update of the AIS [33, 34]. Overall injury severity was described using the ISS. Hypothermia was defined as a documented temperature of less than 35 °C on admission. Body temperature was determined by bladder or esophageal probe, both representing reliable methods for the measurement of core temperature. Measurement was an integral part of initial resuscitation in the emergency room. Hypothermia was classified as mild (< 35–34 °C), moderate (< 34–32 °C) or deep (< 32 °C) [4, 35]. The primary endpoint of this study was objective neurological recovery measured at time of discharge using the Glasgow Outcome Scale (GOS) according to the procedure described by Jennett and Bond [36]. Mortality is a recognized outcome on the GOS (grade 1) and was documented accordingly. Secondary endpoints were typical post-traumatic complications, namely systemic inflammatory response syndrome (SIRS), sepsis, ARDS and MODS. Diagnoses of SIRS and sepsis were made using the 2010 revised criteria of S-2k guidelines of the German Sepsis Society and the German Interdisciplinary Association of Intensive Care and Emergency Medicine [37]. In line with standard practice SIRS or sepsis were deemed present if the criteria were met on at least 2 consecutive days [38]. ARDS was diagnosed according to the 2012 Berlin definition [39], i.e., ARDS was deemed present in cases where bilateral radiographic infiltration of the lung accompanied by reduced oxygenation (< 300 mmHg) based on Horowitz score (PaO_2/FiO_2) was present during the first week after admission. MODS was diagnosed on the basis of MODS score by Marshall et al., a generally accepted indicator: MODS was deemed present if the sum of single organ dysfunctions was > 8 on at least 1 day [40–42].

Statistical analyses were performed with IBM SPSS (Version 22, IBM, Armonk, NY, USA). Variables with a Gaussian distribution were analyzed using parametric tests (Student's t test) and other variables were analyzed using non-parametric tests (Mann–Whitney test and Kruskal–Wallis test for independent data; Wilcoxon test for dependent data). Fisher's exact test (exact χ^2 test) was used in the analysis of contingency tables. We also carried out logistic regression. Dependent variables were, if necessary, dichotomized for binomial logistic regression. Odds ratios and 95% confidence intervals were calculated. Propensity score matching was performed with a 1:1 nearest neighbor matching model with the covariates age, AIS (head, cervical spine, thorax, abdomen, extremities) and initial GCS. The significance level was set at $p = 0.05$.

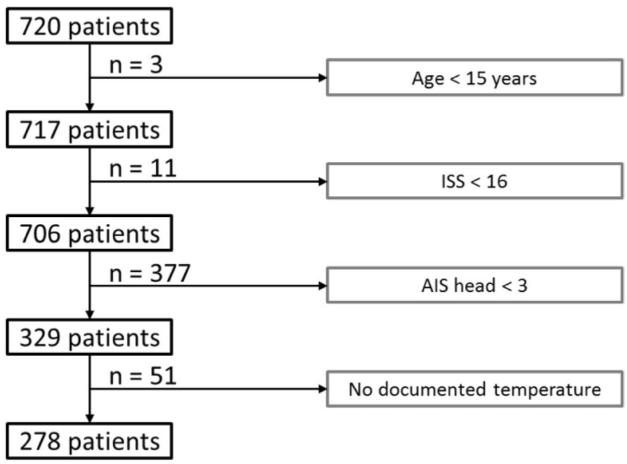

Fig. 1 Excluded patients

Results

We assessed the eligibility of 720 patients admitted between January 2005 and December 2012. 278 patients (*M* age = 43 years, SD 19; *M* ISS 32.8, SD 10.7) met the inclusion criteria. Figure 1 gives an overview of reasons for non-eligibility. Mean follow-up was 20 days (SD 15.7) with a minimum of 1 and a maximum of 121 days. One hundred and ninety-seven patients (71%) were male and 81 (29%) were female. Forty-seven patients (17%) died during treatment. Table 1 summarizes the demographic, baseline and outcome data. One hundred and two patients (37%) were hypothermic on admission. 64 patients had mild, 33 patients moderate and 3 patients severe hypothermia on admission. The hypothermic group contained a higher proportion of women (37%, 38/64) than the normothermic group (24%, 43/133; $p = 0.03$). A comparison of hypothermic and normothermic patients indicated that hypothermic patients were more severely injured (hypothermic and normothermic

Table 1 Demographic and clinical data of entire study population as well as normothermic and hypothermic subgroup; *p* value means significance level of differences between normothermic and hypothermic patients; *significant

Parameter	Total	Normothermia	Hypothermia	*p* value
Age (years), mean ± SD	42.6 ± 19.4	44.5 ± 20.2	39.3 ± 17.6	0.054
BMI (kg/m^2), mean ± SD	25.3 ± 3.9	25.6 ± 3.6	24.7 ± 4.2	*0.03
AIS_{Head}, mean ± SD	3.8 ± 0.8	3.7 ± 0.7	3.9 ± 0.8	0.25
$AIS_{Cervical\ spine}$, mean ± SD	1.4 ± 1.2	1.4 ± 1.2	1.3 ± 1.2	0.68
AIS_{Thorax}, mean ± SD	2.7 ± 1.6	2.6 ± 1.6	3.0 ± 1.6	*0.03
$AIS_{Abdomen}$, mean ± SD	0.9 ± 1.3	0.8 ± 1.3	0.9 ± 1.3	0.4
$AIS_{Extremities}$, mean ± SD	1.8 ± 1.3	1.6 ± 1.3	2.0 ± 1.4	0.06
$AIS_{External}$, mean ± SD	0.8 ± 0.9	0.7 ± 0.8	1.0 ± 1.0	*0.02
Injury severity score (ISS), mean ± SD	32.8 ± 10.7	31.2 ± 10.1	35.6 ± 11.1	*0.001
APACHE II, mean ± SD	17 ± 7.4	16.2 ± 7.3	18.1 ± 7.4	*0.045
Expected mortality (%), mean ± SD	28.8 ± 19.2	27.0 ± 18.5	31.8 ± 20.1	0.06
Initial Glasgow Coma Scale, mean ± SD	8.2 ± 4.7	8.5 ± 4.8	7.5 ± 4.6	0.06
Transfusion requirement (units), mean ± SD				
Packed red blood cells within first 48 h	5.7 ± 9.2	4.0 ± 6.9	8.7 ± 11.6	*< 0.001
Fresh frozen plasma within first 48 h	4.7 ± 7.5	3.3 ± 6.0	7.0 ± 9.0	*< 0.001
Platelet concentrate within first 48 h	0.8 ± 1.7	0.5 ± 1.2	1.3 ± 2.2	*< 0.001
Total packed red blood cells	10.0 ± 12.9	7.6 ± 10.4	14.0 ± 15.6	*< 0.001
Total fresh frozen plasma	6.7 ± 10.3	5.0 ± 8.0	9.9 ± 13.0	*< 0.001
Total platelet concentrate	0.9 ± 2.0	0.6 ± 1.5	1.5 ± 2.4	*< 0.001
Duration of mechanical ventilation (h), mean ± SD	276.3 ± 292.5	248.6 ± 271.3	323.4 ± 321.4	0.052
Duration of ICU stay (days), mean ± SD	14.8 ± 12.8	13.7 ± 11.6	16.6 ± 14.5	0.25
Duration of in-patient care (days), mean ± SD	20.0 ± 15.7	18.8 ± 12.8	22.2 ± 19.7	0.6
Glasgow Outcome Scale, median (IQR)	3 (3)	4 (3)	3 (3)	*0.01
ARDS, *n* (%)	95 (34)	58 (33)	37 (36)	0.6
SIRS, *n* (%)	161 (58)	98 (56)	63 (62)	0.4
Sepsis, *n* (%)	81 (29)	47 (27)	34 (33)	0.3
MODS, *n* (%)	20 (7)	13 (7)	7 (7)	1.0
Mortality, *n* (%)	47 (17)	23 (13)	24 (24)	*0.03

patients, respectively: *M* ISS 35.6, SD 11.1 vs. *M* ISS 31.2, SD 10.1, $p=0.001$; *M* APACHE II = 18.1, SD 7.4 vs. *M* APACHE II = 16.2, SD 7.3, $p=0.045$) and had higher early and total transfusion requirements. Mortality was higher in the hypothermic group (23.5 vs. 13.1%, $p=0.03$). Additionally, mortality was increased with increasing severity of hypothermia (mild 11 (17%); moderate 12 (35%); severe 1 (33%), $p=0.01$). However, hypothermia was not an independent predictor of mortality in a logistic regression model with age, initial GCS, AIS head, ISS and total PRBC.

The median GOS at discharge was 3 (IQR 3). Normothermic patients had a better outcome than hypothermic patients (median GOS 4, IQR 3 vs. median GOS 3, IQR 3, $p=0.01$). In addition, with increasing severity of hypothermia outcome worsened (mild: median GOS 3, IQR 3; moderate: median GOS 3, IQR 3; severe: median GOS 2, $p=0.04$). 131 patients (47%) had a favorable outcome (GOS 4 or 5) and 100 (36%) had a poor outcome (GOS 2 or 3). Thirty-eight (29%) of the patients who had a favorable outcome had been hypothermic on admission compared with 41 (41%) of those who had a poor outcome ($p=0.07$). The degree of hypothermia on admission was similar in the two outcome subgroups (good: *M* core temperature 34.1 °C, SD 0.7; poor: *M* core temperature 34.1 °C, SD 0.8, $p=0.6$). There were no gender differences in outcome distribution. Patients with a poor outcome were older ($M=46.1$ years, SD 19.7 vs. $M=38.6$ years, SD 17.2, $p=0.004$) and had more severe traumatic brain injuries (AIS head: $M=3.8$, SD 0.7 vs. $M=3.5$, SD 0.6, $p=0.004$; initial Glasgow Coma Scale (GCS): $M=7$, SD 4.5 vs. $M=9.9$, SD 4.6, $p<0.001$). Early and total transfusion requirement were also higher in patients who had a poor outcome.

73 pairs of hypothermic and normothermic patients remained after matching. In total population hypothermia was not an independent predictor of poor neurological outcome (OR 1.7, 95% CI 0.8–3.6, $p=0.1$). However, after dichotomizing patients by median age (41 years), in the older subgroup (> 41 years) hypothermia was associated with an odds ratio of 4.2 (95% CI 1.4–12.7; $p=0.01$) for a poor neurological outcome. In comparison, hypothermia was not an independent predictor of poor neurological outcome (OR 0.9, 95% CI 0.3–2.7, $p=0.9$) in the younger patients group (≤ 41 years). There were no differences in injury severity (ISS) and TBI severity (initial GCS, AIS head). Analysis of secondary endpoints revealed that 95 patients (34%) had experienced ARDS, 161 patients (58%) developed SIRS and 81 patients (29%) developed sepsis; 20 patients (7%) presented with MODS. There were no differences between hypothermic and normothermic patients with respect to secondary endpoints.

Discussion

The purpose of this study was to evaluate the effect of accidental hypothermia on neurological outcome in patients with multiple injuries including traumatic brain injury. Hypothermia was associated with poor neurological outcome and older patients had a fourfold higher risk of severe disability and lack of higher mental functions than younger patients. There were no differences in frequency of post-traumatic complications between normothermic and hypothermic patients with severe traumatic brain injury.

Thirty-seven percent of our sample was hypothermic on admission, a figure which is in line with other reports. Reported incidence of accidental hypothermia ranges between 12 and 66% in patients with multiple injuries [3, 5–7, 10, 11]. The incidence of accidental hypothermia increases with injury severity and length of pre-hospital treatment [1, 6, 7, 11, 18]. The mean ISS in our sample was 32.8. This above-average injury severity is probably the main reason for the relatively high proportion of hypothermic patients. The increased transfusion requirement of hypothermic patients can be assumed as an additional indicator of injury severity with subsequent hemorrhage. An investigation of a comparable sample corroborates this assumption [6]. In contrast, Ireland et al. reported no difference in the transfusion requirements of hypothermic and normothermic patients; however, overall injury severity and injury severity in the hypothermic and normothermic subgroups were noticeably lower in this sample than in our sample, which may account for the difference in findings [7]. As men make up the majority of severely injured patients, it is not surprising that most of our hypothermic patients were male; however, women were over-represented in the hypothermic group in our sample. Gunning et al. also reported a disproportionate number of hypothermic women [3]. On the other hand, Martin et al. reported an overproportionate number of males in a large trauma data base study of moderate and severely injured patients [1]. Our data suggest that female sex might be an independent risk factor for hypothermia in trauma, but this is not corroborated by the extant body of published evidence.

The correlation of hypothermia and mortality in severe trauma is still subject to discussion. Although in our sample mortality was higher among hypothermic patients (23.5 vs. 13.1%, $p=0.03$), we were unable to establish that hypothermia was an independent predictor of mortality. This is in line with the results of Steinemann et al., Beilman et al., and Mommsen et al. [5, 6, 43], but conflicts with several other studies which did identify pre-hospital hypothermia as an independent risk factor for mortality [1, 7, 10, 11, 30–32, 44]. Mommsen et al. attributed this, among others, to blood transfusion as a potential confounding factor, since a reduced multivariate analytic model which did not include a variable representing use of transfused blood products indicated that hypothermia was an independent contributor to mortality [3, 43]. Analyses of the influence of accidental hypothermia on mortality in patients with leading moderate-to-severe traumatic brain injury indicate that hypothermia is an independent predictor of mortality. However, the obvious differences in patient characteristics between these studies and our own (mortality from 7 to 44%, incidence from 2 to 15%, isolated vs. concomitant traumatic brain injury) limit the comparability [30–32]. Our results suggest that in patients with multiple injuries accidental hypothermia is more likely to be related to injury severity and hemorrhage than to be an independent predictor of mortality. Although mortality was increased in hypothermic patients, there was no association between accidental hypothermia and post-traumatic complications in our sample. This is in line with the results of Mommsen et al., but in contrast with those of Beilman et al., who reported that hypothermia was a predictor of MODS. However, whereas Mommsen et al. analyzed a sample comparable to our own, Beilman et al.'s analysis was limited to patients with manifest hemorrhagic shock on admission. It is reasonable to assume that impaired organ perfusion due to prolonged hypotension may be responsible for subsequent organ dysfunction [6, 43].

As well as being associated with increased mortality, hypothermia was correlated with poor neurological outcome at discharge. Comparable analyses of the influence of pre-hospital hypothermia on neurological outcome are scarce. Thome et al. reported on a multi-center trial in Switzerland involving 589 participants. Pre-hospital hypothermia was correlated with a higher risk of impaired consciousness at 14 days in the univariate model but not in the multivariate model [45]. Many more studies have analyzed the effects of therapeutic hypothermia on traumatic brain injuries and although they have limited comparative value in this context they suggest that the effects of prolonged hypothermia are debatable. Marion et al. reported that moderate hypothermia (32–33 °C) for 24 h improved neurological outcomes at 3 and 6 months in patients with GCS of 5–7 [46]. Polderman et al. reported that moderate hypothermia (32–34 °C) improved survival and neurological outcome in patients with GCS 5 and 6 who did not respond to barbiturate coma after traumatic brain injury [47]. Although there are individual studies which have demonstrated that induced hypothermia can have beneficial effects, systematic reviews and meta-analyses have been unable to conclude that hypothermia is generally beneficial in the management of severe head injury [24–29]. Depending on inclusion criteria and evaluation method it may be possible to demonstrate that prolonged hypothermia is beneficial, particularly in patients with elevated intracranial pressure which is refractory to conventional treatment [26]. Fox et al. concluded that beneficial effects were maximized by using a long-term or goal-directed cooling protocol, in which cooling was maintained for at least 72 h and/or until stable normalization of intracranial pressure for at least 24 h was achieved [24]. On the basis of the extant evidence it is not possible to recommend routine use of induced hypothermia. Data of age-dependent outcome differences in hypothermic patients are lacking. We found that the risk of poor neurological outcome was more than four times greater in older patients (> 41 years), which indicates that older patients may be a subpopulation whose neurological recovery is more strongly affected by accidental hypothermia. There are several reasons why this might be the case, including generally lower resilience leading to an incomplete, or more likely delayed, recovery. A prolonged follow-up has the potential to offer valuable information on this.

Limitations

As well as being subject to the inherent limitations of retrospective cohort studies, a parallel, balanced 1:*n*, nearest neighbor matching might have increased precision over 1:1 matching at only a small cost in bias. Additionally, our results may also be affected by bias due to missing data, since 51 patients (15.5%) had to be excluded due to missing temperature data. This missing data exclusion rate is comparable with that of other similar studies [48]. Furthermore, there was no reliable information about pre-hospital time and its correlation with hypothermia, although it seems reasonable that patients with extended pre-hospital times are at particular risk of hypothermia. Various studies demonstrated a correlation between hypothermia and coagulopathy which could independently affect neurological outcome. Nevertheless, coagulopathy was not analyzed in this study. Additionally, we did not analyze the impact of neurosurgical interventions or craniotomy on outcome and possible differences between hypothermic and normothermic patients. Although the incidence of ARDS and SIRS was lower in patients whose temperature on admission was not documented (ARDS 20 vs. 34%, $p = 0.02$; SIRS 44 vs. 58%, $p = 0.02$), there were no differences in demographic and outcome data. Moreover, outcome in cases of severe injury is related to multiple factors and cannot be predicted reliably from only a small set of factors such as injury severity or hypothermia.

This matched pair analysis focused on patients with multiple injuries including traumatic brain injury being admitted to a level I trauma center in a high-income country with a sophisticated trauma system. Outcome parameters were precisely defined and all analyses were based on validated methods. There was no loss to follow-up. For this reason, our results may be generalized to countries with comparable medical standards.

Conclusion

Accidental hypothermia seems to have a negative impact on neurological recovery in older patients with multiple injuries including traumatic brain injury. For this reason, stable maintenance of body warmth in pre-hospital care of patients with multiple injuries should be a high priority.

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Compliance with ethical standards

Conflict of interest Marcel Winkelmann, Wiebke Soechtig, Christian Macke, Christian Schroeter, Jan-Dierk Clausen, Christian Zeckey, Christian Krettek and Philipp Mommsen declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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