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a randomised, controlled, open-label trial

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Induced Hypothermia in Patients with Septic Shock and Respiratory Failure: an international, parallel-group, open-label, randomised controlled trial

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SUMMARY

BACKGROUND

Animal models of serious infection suggest that 24 hours of induced hypothermia improves circulatory and respiratory characteristics, and reduces mortality. We tested the hypothesis that reducing core temperature to 32-34°C attenuates organ dysfunction and reduces mortality in ventilator-dependent patients with septic shock.

METHODS

In this parallel group, open-label, randomized controlled trial, patients were enrolled within six hours after onset of septic shock with respiratory failure from participating intensive care units. They were randomized 1:1, to routine thermal management or 24 hours of induced hypothermia (target 32-34°C) followed by 48 hours of normothermia. Other aspects of care were per routine. Patients and care givers were not blinded to the treatment allocation; the assessors of the primary outcome were blinded to the treatment allocation. The primary endpoint was 30-day all-cause mortality. Clinicaltrials.gov number: NCT01455116.

FINDINGS

The CASS trial recruited patients from November 1st 2011 to November 4th 2016. At the 3rd scheduled interim analysis, after recruitment of 432 of the planned 560 participants, the Monitoring Board recommended that the trial be terminated for futility. The hypothermic target temperature was reached in a median of 3·2 hours [Interquartile range (IQR): 2·2, 4·8]. In the hypothermia group, 96/217, 44·2% died within 30 days vs. 77/215, 35·8% in the routine thermal management group, (absolute difference 8·4 percentage points; 95% CI -0·8 to 17·6; relative risk 1·24 [95% CI: 0·98, 1·56, p=0·074]). At 72 hours after inclusion, 165/191 (86·4%) were still on mechanical ventilation in the hypothermia group vs. 144/192 (75·0%), absolute difference 11·4 percentage points; 95% CI 3·1 to 18·9, p=0·0071; 132/191 (69·1%) vs. 102/192 (53·1%) still received vasoactive medication, absolute difference 15·9 percentage points; 95% CI 6·8 to 26·4, p=0·0019.

INTERPRETATION

Among patients with septic shock and ventilator-dependent respiratory failure, induced hypothermia did not reduce mortality, and instead prolonged the duration of acute respiratory failure and shock. Induced hypothermia should not be used in patients with septic shock.

FUNDING

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INTRODUCTION

Septic shock is an acute life-threatening condition caused by a deleterious non-resolving host response to pathogenic microorganisms that leads to organ dysfunction .[1] Key aspects of the pathophysiology include endothelial dysfunction, vasodilation, coagulopathy, mitochondrial breakdown, and consequent organ function loss.[2] Respiratory failure requiring mechanical ventilation is a feared complication of septic shock and carries high mortality.[3] Sepsis remains a leading cause of death in hospitals[4], and multiple attempts to improve the prognosis have failed in recent decades. [5-8]

In rodents, induced hypothermia for sepsis, in the range of 31-34^{o}C maintained for 24-72 hours, has been associated with a substantial mortality reduction.[9-11] The benefit of induced hypothermia appears consequent to reduced sepsis-related damage to the lungs[12], heart[12,13], and liver.[14] In reptiles, bacteraemia challenge studies have shown that body temperatures as high as 42 ^{o}C were associated with a higher survival rate.[15]

On a cellular level, improved intracellular metabolism was observed in a pneumococcal challenge model, along with reduced dissemination of the infection to other organs in cooled animals.[16] In rabbits challenged with bacteraemia, pyrexia has been associated with improved survival.[17] Paradoxically, physical cooling to reduce fever in a similar experiment improved survival.[18] Spontaneous hypothermia in sepsis is associated with persistent lymphopenia and a worse prognosis.[19]

In humans, pharmaceutical fever prevention does not improve organ function or survival in patients with severe infections.[20] However, in a trial of 200 febrile patients in septic shock, external cooling to normothermia reduced the need for vasoactive therapy and non-significantly improved mortality.[21] Data from a small uncontrolled study of induced hypothermia in patients with sepsis and respiratory failure also suggested improved cardiac physiology and survival.[22] Based on animal evidence and limited human data, induced hypothermia has been used as a treatment for serious infections for decades[23,24] — although there is currently no convincing evidence that induced hypothermia improves survival in human septic shock. We decided only to recruit patients of 50 years or above for power concerns, since we noted a low mortality rate among the younger septic shock patients in a previous trial.[25] When the intervention was designed, several members of the steering committee with experience in this field, mentioned the challenge with “rebound” fever after therapeutic hypothermia. This phenomenon was estimated to be rather frequent and far from negligible, and the potential harm from severe hyperthermia was considered as a possible limitation in the intervention: if some patients would have benefit from the intervention and the same or other patients be harmed from rebound fever, the interpretation of the trial results may eventually be compromised. The notion from the steering committee was to decide for a two-phased intervention to avoid rebound fever: 24 hours of induced

hypothermia followed by 48 hours fever-control/normothermia. During our trial, it has been published that in cardiac arrest patients, rebound fever is frequent, approx. 30%-40%.[26,27] Normothermia was defined as temperature in the range 36·0 °C – 37·5 °C as defined by others.[28] The question of whether to aim for a hypothermia intervention or a fever control (normothermia) intervention was discussed in the steering committee: All members agreed that the rationale for induced hypothermia in this patient group was strong, as summarized by others also[29], and since this intervention had never been tested in a trial setting, all members of the steering committee wanted to test this. However, the steering committee also agreed that the rationale for testing fever control was present. Some members weighted that the effect on intracellular functions seemed to be more pronounced in hypothermia in animal studies. A possibility of a three armed trial was discussed (fever respect, fever control, induced hypothermia). However, this would increase the needed sample substantially and would not be feasible in the planned setting. We were aware that a trial of fever control was already ongoing. In summary, we decided to test the induced hypothermia intervention.

We therefore tested the hypothesis that reducing core temperature to 32-34°C for 24 hours followed by slow rewarming and normothermia for 48 hours (fever control) attenuates organ dysfunction and reduces mortality in patients with septic shock and accompanying acute respiratory failure. Secondary endpoints included duration of shock and respiratory failure, alive without need for organ support, inflammation control, and 180-day mortality.

METHODS

STUDY DESIGN

The Cooling And Surviving Septic shock study (CASS) was a parallel-group, 1:1, open-label superiority randomized trial recruiting patients from ten intensive care units in Europe and North America. For the interim analyses, a group-sequential design was used. The original and final protocol versions with a complete list of changes (adding of additional sites) is available in the supplementary appendix. The protocol was approved by the ethics committees at each institution. The steering committee of the trial (see supplementary appendix) vouches for the accuracy and completeness of the data and analysis, and that data reporting adheres to the trial protocol.
The trial was registered at Clinicaltrials.gov: NCT01455116

PARTICIPANTS

Patients with severe sepsis or septic shock were considered for enrollment when they *i)* had a mean arterial pressure <70 mmHg, *ii)* were on mechanical ventilation in an intensive care unit (ICU), *iii)* were ≥50 years, *iv)* were expected

to stay in the ICU for ≥24 hours, and *v)* could be recruited within six hours after fulfilling all inclusion criteria. Exclusion criteria were uncontrolled bleeding, clinically important bleeding disorder (acute or chronic), recent open surgery, pregnancy or breast feeding, or involuntary psychiatric admission. Written informed consent was obtained from patients or next-of-kin when possible or from two independent medical legal representatives (see supplementary appendix), except in the Netherlands and United States where the ethics board required informed consent from patients or next-of-kin in all cases. Data management and analysis were performed by Centre of Excellence for Health, Immunity and Infections (CHIP), Rigshospitalet, Denmark and University College of London.

RANDOMISATION AND MASKING

Enrolment, randomization, and data entry were performed via a locally developed online system. Patients were randomized 1:1 to induced hypothermia for 24 hours and subsequent normothermia (36·0-38·05^{o}C) or to no thermal management (control group). Randomization was based on computer-generated variable block sizes stratified for validated predictors of mortality, age (≥65 years vs. <65 year), APACHE II score (≥25 vs. <25), and for study site. Stratification limits for APACHE II and age were chosen according to the expected medians, this based on a previous trial we conducted[25]. The randomization sequence was prepared by the study statistician who did not take part in randomization. Allocation was concealed by our web-based system until qualifying patients were consented and ready for thermal management.

Health care professionals taking part in the intervention were aware of the treatment assignment because they were responsible for implementing the designated thermal management. However, assessors of the primary endpoint were fully blinded to treatment. Investigators and steering committee members were unaware of all data until the trial concluded. Since safety of the patients was our primary concern, the Data and Safety Monitoring Board (DSMB), which was independent of the steering committee, was unblinded throughout the trial.

PROCEDURES

In all aspects of treatment, except regarding temperature management, all patients in both groups of the trial, were treated according to the most recent surviving sepsis campaign guidelines at the time.[30] In the control arm, no physical or pharmacological thermal interventions were permitted during the initial 24 hours, unless a specific indication for hypothermia treatment emerged such as cardiac arrest. Thereafter, antipyretic drugs were allowed as a part of the standard treatment. In patients assigned to hypothermia, the thermal intervention started immediately after randomization. The target was to reduce core body temperature to 32-34^{o}C within 2 hours. Two types of induced

hypothermia intervention were used: 1) external pad-based (n=202 = 93·1%), either using the Artic Sun® device, Medivance, Inc., Louiseville, CO, USA, or the Flex.Pads.™ , Emcools, Traiskirchen, Austria or 2) intravenous catheter (n=15 = 6·9%) using the IVTM™, Zoll, Chelmsford, MA, USA) The latter method was used as a "backup" method, when other hypothermia devices were used for other purposes at two sites. Mild hypothermia was maintained for 24 hours. Thereafter, patients were rewarmed to 37°C at a rate of 0·5°C per hour. And for the next 48 hours, patients in the induced hypothermia group were kept normothermic (36-38^{o}C) with additional cooling if necessary to prevent fever (see supplementary appendix for additional details of thermal management).

Antibiotics were initiated within an hour after severe sepsis or septic shock was diagnosed, with drug selection based on the relevant national guidelines and accounting for differences in distribution and susceptibility of the suspected causative microorganisms.

OUTCOMES

Our primary outcome was 30-day all-cause mortality. Secondary endpoints were defined as: i) all-cause mortality at 180 days, ii) "days alive and without mechanical ventilation within 30 days", iii) "days alive and without vasopressors/inotropics within 30 days", iv) "days alive and without dialysis within 30 days", in the latter three, patients who died within 30 days were given the score "0"[31]. v) ICU length of stay (total and separated between survivors and non-survivors). Specific organ failures were all assessed at the end of two-phased intervention, at 72 hours: i) acute respiratory failure: on mechanical ventilation (yes vs. no), ii) PaO_2/Fi O_2 ratio (median, interquartile range (IQR)). Circulatory failure / shock: i) Mean Arterial Pressure (median, IQR), ii) on any vasoactive support (yes vs. no), iii) vasoactive-inotropic score (VIS), actual (median, IQR), iv) vasoactive-inotropic score, accumulated (median, IQR), v) achieved min. 50% decrease in vasoactive-inotropic score (yes vs. no). VIS was estimated according to Gaies et al.[32] Renal failure: i) diuresis pr. kg pr. hour (median, IQR), ii) creatinine, µmol/L (median, IQR), iii) any renal replacement therapy (yes vs. no), iv) acute kidney injury according to RIFLE criteria: R (yes vs. no), I (yes vs. no), F (yes vs. no), Any (yes vs. no).[33] Coagulation: i) International Normalized Ratio (INR, median, IQR), ii) platelet count (median, IQR), iii) platelet count<150 x 10^6/L (yes vs. no), iv) platelet decrease >25% from baseline. Liver: i) bilirubin (median, IQR), ii) bilirubin >21 mmol/L. C-reactive protein normalization: i) C-reactive protein (median, IQR), ii) CRP decrease>30% from baseline. Cerebral function and sedation: i) receives sedatives (yes vs. no), ii) Richmond Agitation Sedation Score (median, IQR), Delirium diagnosed (yes vs. no). Sequential Organ Failure Assessment (SOFA) was estimated as defined, except that the data were collected at 06.00 a.m. daily (and not

as "worst value last 24 hours").[34] Patients discharged from the ICU were considered not to need vasopressor/inotropics nor mechanical ventilation.

STATISTICAL ANALYSIS

Mortality in qualifying patients in the participating centres was estimated to be 40-56%, based on a data draw from participating sites, and on the available literature.[35,36] We thus performed two sample size calculations to cover this range of presumed control group event rate: i) Estimated 560 patients would provide 80% power at a two-sided alpha level of 0·05 to detect a relative 21% change in the primary endpoint, corresponding to a change in the absolute risk from 56% to 44%, ii)This sample size, with equal power and alpha, also allowed us to detect a relative 28% change in the primary endpoint, corresponding to a change in the absolute risk from 40% to 29%. No loss to follow up was included in the sample-size estimate.

Since no trials in humans had previously explored hypothermia for severe sepsis or septic shock, safety was a special concern, especially the risk of coagulopathy.[37] Ongoing safety was evaluated at three levels: *i)* ordinary, full-data interim analyses were planned after recruitment of 140, 280, and 420 patients. These included data on the primary outcome, on the safety endpoints defined in the protocol, on the intervention (time to target temperature, temperature maintenance) and recruitment rates; *ii)* complications with focus on bleeding and coagulopathy were evaluated after the initial 10 and 24 patients were recruited; *iii)* seven organ-related outcomes were evaluated on a patient-by-patient basis by a database manager. The DSMB requested an additional interim analysis at 337 patients, but this evaluation was not disclosed to the Steering Committee until after study closure. For the interim analyses, a group-sequential design for normally distributed data, based on the approach of O´Brien & Fleming was used.[38] For the ordinary, full data interim analyses, the following terms were employed regarding efficacy and harm: If the z-value for mortality analysis was larger than the upper boundary value (efficacy) or smaller than the lower boundary (harm) at the specified interim analysis, the trial may be prematurely stopped. The Z-values used for stopping for efficacy or harm at 140, 280 and 420 patients, as displayed in the protocol, were: 3·359, 2·760, 2·359 (efficacy) and -2·241, -2·125, -2·019 (harm).

Regarding the planned futility analysis, the following was employed: At 3rd ordinary interim analysis, the DSMB formally conducted a futility analysis referring to the protocol. Two distinct assumptions to demonstrate benefit were made about unobserved future data: i) that the underlying effect of the intervention was going to remain the same in the remaining 140 patients as the rate seen up to stage 6 and ii) that the underlying effect of induced hypothermia was as hypothesised when planning the trial. At the actual analysis at 420 patients, the conditional power to demonstrate a

benefit from induced hypothermia was effectively zero whatever was assumed about the underlying effect of the intervention in the remaining 140 patients. All analyses were done in the modified intention-to-treat population, defined as all randomized patients except those in whom the patient or relatives withdrew consent and demanded data deleted and those where pre-existing fulfilment of exclusion criteria were discovered after randomization and who never received the trial intervention. Patients who had at least one major protocol violation were considered as not fulfilling the protocol and additional per-protocol analyses were performed when excluding these patients. A list of protocol violations is available in the supplementary appendix.

All comparisons were between the randomized arms. The primary endpoint was analysed with 1) Kaplan-Meier survival curves and corresponding log-rank tests, 2) Cox proportional hazards models, adjusted for pre-stratification variables according to published principles for this[39], 3) subgroup analysis utilizing Cox proportional hazards models with interactions tested across stratification layers.

Secondary endpoints were analysed regarding categorical variables using chi-square for equal proportions (or Fisher´s exact test when events were seldom), and continuous outcome measures were compared with Mann-Whitney U-tests (non-normally distributed) or Student´s t-test (normally distributed data. All analyses were conducted with R software version 3·02 and SAS version 9·4. Tests were two-sided and p values <0·05 were considered statistically significant. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

ROLE OF THE FUNDING SOURCE

The trial was funded by *TrygFonden (App. No. 7-10-1301), Lundbeckfonden (application no. R54-A5342)* and *Danish National Research Foundation [Grant No. DNRF126] (CHIP & PERSIMUNE).* Initially, the sites financed the cooling equipment. During the trial, C. R. Bard, Inc. (NJ, USA), Emcools, GmbH (Vienna, Austria), and Zoll (Chelmsford, MA, USA) agreed to donate cooling equipment. None of the funders had any role in designing the trial, collecting or analyzing the data, data interpretation, writing the manuscript, or decisions related to submission for publication.

RESULTS

The CASS trial recruited patients from November 1st 2011 to November 4th 2016. At the third scheduled interim analysis, the independent Data and Safety Monitoring Board recommended the trial to be closed for futility. At that point, 432 of a planned 560 patients had been enrolled and the conditional power for showing a positive effect of the

intervention on the primary outcome was zero. The recommendation to close the trial prematurely after the third interim analysis was per protocol. Interim analysis data regarding the primary endpoint are available in the supplementary appendix.

A total 220 patients were allocated to receive mild induced hyperthermia and 216 to the control arm. The next-of-kin withdrew consent for three patients. Another patient proved to have a severe bleeding disorder that was considered a contraindication to hypothermia. The latter was included in the intention-to-treat analysis (see trial profile, Figure 1). The intervention and control groups were fairly balanced at baseline, although acute renal failure seemed more frequent in the mild induced hypothermia group and this group also had a median lower platelet count (table 1). Hypothermia was induced in 217 patients. The median time to target temperature was 3·2 hours (IQR 2·2 to 4·7), and all but 23 patients reached the target temperature within 6 hours. Twenty-six patients did not complete 24 hours of induced hypothermia and 48 hours of normothermia, as detailed in the supplementary appendix. These patients were included in the intention-to-treat analysis. Figure 2 shows the temperature in the control and intervention groups during the initial 72 hours after randomization. Temperatures differed significantly the treatment groups at all times except baseline ($P < 0·001$)

Follow-up on the primary outcome was complete in all patients. After 30 days, 96/217 patients (44·2%) died in the induced hypothermia group compared to 77/215 (35·8%) in the control group (absolute difference 8·4 percentage points; 95% CI -0·8 to 18; $P = 0·074$), relative risk 1·24 [95% CI: 0·98, 1·56] favouring no thermal management, figure 3. Patients in the induced hypothermia group, within the first 30 days, had fewer days alive and without mechanical ventilation, alive without vasoactive treatment and alive without renal replacement therapy (table 2). The duration of critical care was similar in each group (table 2).

Seventy-two hours after randomization, patients in the induced hypothermia group were more often given vasoactive medications: 132/191 (69·1%) vs. 102/192 (53·1%, absolute difference 15·9 percentage points; 6·8 to 26·4; $P = 0·0019$). Fewer hypothermic patients had at least 50% reductions in vasoactive medications: 104/187 (55·6%) vs. 128/184 (69·6%, absolute difference -14·0; 95% CI -23·7 to – 4·2; $P = 0·0055$). Fewer hypothermic patients had >30% decrease in CRP from baseline: 60/180 (33·3%) vs. 88/175 (50·3%, absolute difference -17·0; 95%-CI -27·1 to -6·8; p=0·0012). More hypothermic patients still required sedation: 150/191 (78·5%) vs. 130/192 (67·7%, absolute difference 10·8 percentage points; 95% CI 2·0 to 19·6; $p = 0·017$). And more hypothermic patients were still mechanically ventilated: 165/191 (86·4%) vs. 144/192 (75·0%, absolute difference 11·4 percentage points; 95% CI 3·1 to 18·9; $p = 0·0071$), table 2.

There were no detectable differences in renal outcome variables. Platelet counts were lower in the induced hypothermia arm, but were also lower at baseline. The need for blood transfusions and surgery was similar in each group (see supplementary appendix).

Per protocol, the effects of hypothermia were in pre-planned subgroups, as displayed in figure 4; no subgroup seemed to benefit from the intervention. Based on request from the trial Steering Committee, additional exploratory subgroups were added: platelets count ($\geq 150 \times 10^6$/L vs. $<150 \times 10^6$/L, PaO_2/FiO_2-ratio (($\geq$20 KPa vs. <20 KPa and temperature ($\geq 38\,^{o}C$ vs. $<38\,^{o}C$). None of the exploratory subgroups of patients had a favourable effect of the intervention (negative interaction test), figure 4. Patients with higher eGFR (>60 mL/kg/min), higher platelets ($>150 \times 10^6$/L), lower APACHE II score (<25), lower age (<65 years), higher PaO_2-ratio ($\geq$20) and female gender non-significantly appeared to develop more harm from the intervention (figure 4). Patients cooled with intravenous catheters had similar mortality to those cooled with external pads: 7/15 (46·7%) vs. 89/202 (44·1%, p=0·84, Fisher´s exact).

DISCUSSION

This international randomized trial evaluated patients with sepsis, circulatory failure, and ventilator-dependent respiratory failure and who were at least 50 years old. Induced hypothermia to a target temperature of 32°C-34°C for 24 hours, slow rewarming, and 48 subsequent hours of fever suppression was not superior to routine thermal management. Specifically, the primary outcome, 30-day all-cause mortality, was not improved by hypothermia — and possibly worsened. Furthermore, hypothermia aggravated circulatory collapse, respiratory failure, and delayed the decrease in C-reactive protein.

We selected a target temperature range of 32°C-34°C based on experimental animal studies showing: *i)* pronounced immunomodulatory effects[40]; *ii)* reduced sepsis-related liver damage[14,41] and lung damage[12]; and, *iii)* improved survival in studies where mammals were cooled to 32-34°C (90-93F) for 24-72 hours.[9-11] In contrast, shorter durations of the hypothermia, especially combined with rapid rewarming, appear detrimental.[42] During the course of the trial, additional studies were published showing hypothermia-induced reversion of sepsis-related mitochondrial dysfunction in rats[16] and marked improvements in respiratory physiology in septic pigs.[12]

Perhaps the most striking aspect of our negative results is the extent to which they contrast with the positive findings in mammals.. Similar divergence in studies of therapeutic hypothermia has been demonstrated in the recent years for several clinical entities, including (but not restricted to) : brain trauma[43,44] and out-of-hospital cardiac arrest in adults,[45] The most obvious explanation is that hypothermia usually takes several hours to induce in humans by which

time tissue damage may already have occurred. Tissue damage consequent to sepsis presumably develops over a far longer period than the roughly three hours our patients required to reach the hypothermic target, making sepsis an attractive target for therapeutic hypothermia. Since hypothermia was not beneficial, it seems likely that the effects of hypothermia on sepsis differ between elderly humans on one hand and young rodents and pigs on the other hand. Whether this is a true difference between these animals and humans or rather an age phenomenon remains undetermined.

The most relevant previous human study reported that fever control in patients with septic shock reduced the need for vasoactive medications and non-significantly improved mortality (N=200).[21] Our study combined therapeutic hypothermia for 24 hours with fever control from 24 to 72 hours without improving mortality and worsening of other outcomes. Thus while fever control appears beneficial in septic patients, the combination of therapeutic hypothermia and subsequent fever control is not. A possible explanation for this pronounced difference is suggested to be hypothermia-induced tryptophan catabolism and lymphocytopenia, leading to immune paresis.[19,46]

Since we wanted to explore the effect of induced hypothermia, not fever control, we decided not to restrict the inclusion to febrile patients. However, we are aware that febrile patients may be different in many ways, compared to normothermic and spontaneously hypothermic patients. To explore whether the effect of the intervention seemed to be different in febrile patients compared to others, we did a subgroup analysis and a corresponding interaction test: none of these groups seemed to benefit from the intervention.

We also included patients with spontaneous hypothermia, since the steering committee agreed that spontaneous hypothermia is often transient. This has recently been confirmed.[47]

Two different methods were used for the temperature intervention: external, pad-based or intravenous. The latter was used in only few patients as a backup system and the observed mortality in patients cooled with these modalities seemed similar and thus, it seems unlikely that different harm profiles from the methods could have driven the harm, we noted.

Pre-defined and post hoc analyses did not identify any subgroups in which hypothermia was especially beneficial or harmful, although hypothermia non-significantly caused most harm in the younger, healthier women. This observation suggests that potential harm from induced hypothermia may be readily identifiable in those patients, in whom co-morbidities were not a competing risk for death, reflecting that the signal-to-noise ratio to identify harm was higher in this subgroup. Two subgroup analyses showed positive interactions, however none of the subgroups had a significant benefit signal, and thus we interpret the positive interactions as a signal that the harm effect was more pronounced among certain patient groups, than in others. Since our trial was conducted at ten intensive care units scattered across

Europe and North America, the results seem likely to apply broadly. Furthermore, the results were clear: mild hypothermia worsened organ function and tended to worsen mortality.

A limitation of our trial is that investigators and other health care professionals treating the participants were aware of the study group allocation; this is an inherent challenge in temperature interventions and other physical interventions. However, bias was reduced by using a robust primary endpoint (mortality) assessed by blinded investigators. At one site, a surgical intensive care unit, most patients who met other criteria were excluded (before randomization) because of recent major surgery; the steering committee nonetheless included this site to enhance accrual and increase generalizability. Additionally, we observed a higher use of sedation in the hypothermia group in the intervention period, and since substantial harm has been demonstrated from sedation in patients like these[48], this may, independently of the physiological effects of induced hypothermia, have resulted in some harm. And finally, we tested a specific amount and duration of hypothermia; results may have differed with other degrees and lengths of hypothermia.

In summary, we did not find a benefit of inducing hypothermia to 32-34^{o}C followed by slow rewarming and 48 hours of fever prevention in septic patients who required vasopressors and were ventilator-dependent acute lung injury. In fact, hypothermia delayed recovery of several key organ functions.Our findings do not support the use of induced hypothermia in patients with septic shock.

CONTRIBUTORS

JUJ, JDL, MB generated the hypothesis for the study. All authors contributed to study design, data collection, data interpretation and critical revision of the manuscript (writing phase). MB, KT, LH, LG, AL, HC, SE, HPP, MH, UKS, SPP, NW, US, JAP, TM, TW, LMP, DS, OC, NJ, ET, KM recruited and followed up patients. MEJ, TSI and JUJ coordinated the trial and were responsible for monitoring. TSI, JUJ, JDL and ACL analysed the data. JUJ, JDL, TSI and DIS prepared the manuscript. All authors read, revised and approved the final manuscript.

DECLARATION OF INTERESTS

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