IPDMA PROTOCOL

The effect of fever control of survival duration in Intensive Care Unit (ICU) patients: an individual patient data meta-analysis

Protocol Version: Version 1.0

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ADMINISTRATIVE INFORMATION

1.1 Title

The effect of fever control of survival duration in Intensive Care Unit (ICU) patients: an individual patient data meta-analysis.

1.2 Protocol version

Version 1.0

1.3 Roles and responsibilities

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2 INTRODUCTION

More than 20M people globally are admitted to an ICU annually[1]. Fundamentally, if an illness is reversible, ICU therapy allows patients to survive if they can be supported long enough to recover. Fever occurs commonly in ICU patients and increases metabolic demand[2]. Increasing metabolic demand has important physiological consequences including increasing oxygen consumption and cardiac output[2].

One potential way to protect patients from the physiological demands associated with fever is to aim to prevent it and treat it assiduously[3]. This strategy is an attractive candidate intervention to reduce mortality risk in the ICU because patients with a range of critical illnesses including those admitted to ICU following major surgery, trauma, infection, acute myocardial infarction, and pancreatitis develop fever[4-6] and many have limited functional reserve that means they may be unable to respond to the physiological demands created by fever.

Body temperature can be manipulated in ICU patients with medicines[7,8] and physical cooling devices[9] allowing for *more* or *less* assiduous approaches to fever control. We have recently published a systematic review and aggregate data meta-analysis evaluating the effect of active temperature management on on-cause mortality in ICU patients[10]. We found that active temperature management (*more* assiduous treatment of fever) neither increased nor decreased mortality in critically ill adults compared with control (*less* assiduous treatment of fever) [10]. Despite these findings, it is plausible that the balance of risks and benefits of fever control in ICU patients varies based on specific patient factors including the physiological reserves of such patients and the nature of their critical illness (see Figure 1)[11].

Thus, we hypothesise that *more* assiduous fever control will improve survival among patients with limited physiological reserves. We further hypothesis that *more* assiduous fever control will improve survival when infection is not present and when high fever is present.

Accordingly, we plan to perform an individual level patient data meta-analysis using data, where available, from RCTs identified in our previous systematic review and aggregate meta-analysis[10]. We aim to determine if, with adjustment for important co-variates, available at individual level, among adult ICU patients, treating fever *more* assiduously alters survival, and other secondary outcomes, compared with treating fever *less* assiduously. We specifically wish to explore evidence for differences in survival, and other relevant secondary outcome variables, of those where fever is treated *more* assiduously and those where fever is treated *less* assiduously, in the following sub-groups:

1. Mechanical ventilation vs. those not receiving this therapy;
2. Vasopressor and/or inotrope use vs. those not receiving these treatments;
3. Mechanically ventilation use and vasopressor and/or inotrope use vs. not receiving either therapy;
4. Infection vs. no infection;

5. A fever of at least 39.5°C vs. a lower temperature;
6. Median age or older vs. less median age;
7. APACHE score ≥25 vs. <25;
8. Enrolled in a study using physical cooling vs. enrolled in a study that did not use physical cooling as a component of the intervention.

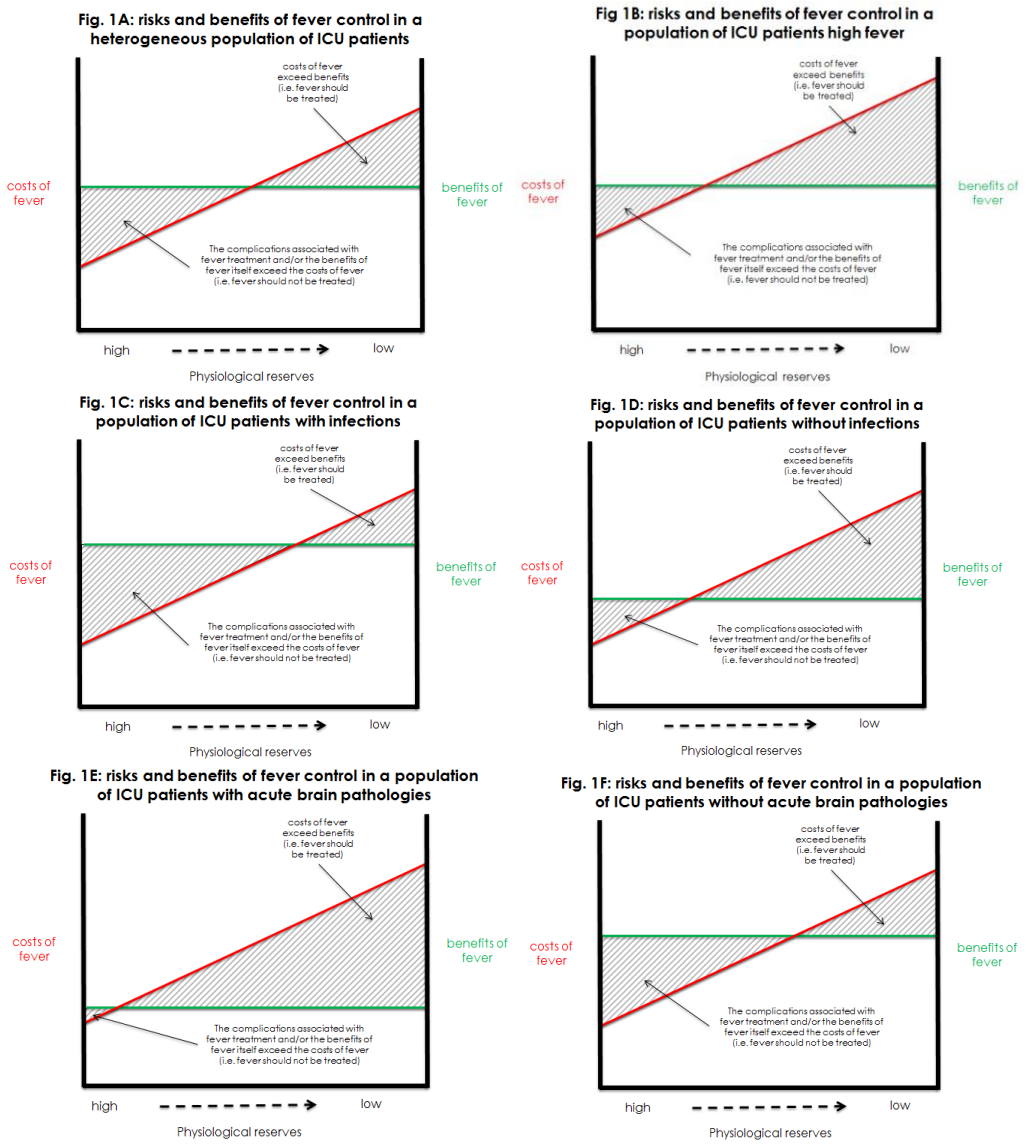

Figure 1. Hypothetical framework for evaluation of the risks and benefits of fever control in critically ill patients (adapted from Young et al[11])

On each graph the green line represents the potential benefits of fever while the red line represents the potential harms of fever; shaded areas above each green line represent circumstances in which treatment of fever may be beneficial and shaded areas below each green line represent circumstances in which treatment of fever may be harmful. The physiological reserves represented on the horizontal axis will depend on both the physiological demands and the patients' capacity to meet those demands. Demands will typically increase with increasing illness acuity and a patient's capacity to meet demand will fall with increasing age and in the presence of comorbidities.

3 METHODS: INCLUDED STUDIES

3.1 Systematic review

3.1.1 Condition being studied

Fever control in Intensive Care Unit (ICU) adult patients.

3.1.2 Eligible trials

Inclusion criteria:
Randomised controlled trials evaluating treatments commonly used to treat fever, e.g. physical cooling, NSAIDs, or paracetamol; or evaluating different temperature thresholds for treating fever in adult patients admitted to an ICU

Exclusion criteria:
Trials conducted solely in a Paediatric ICU, Coronary Care Unit, Respiratory Care Unit, or Burns Unit; trials of therapeutic hypothermia (with the intention to cool patients below 36°C).

3.1.3 Intervention

Interventions will be any treatment commonly administered to febrile patients in order to reduce body temperature. Our pre-specified list, for the aggregate meta-analysis, was physical cooling, NSAIDs, paracetamol, or any combination of these. Any method of external cooling was however included, as was any dose of NSAID or paracetamol, delivered by any route. For studies that compared different thresholds of temperature treatment, the arm of the study that targeted the lowest body temperature will be defined as the intervention.

3.1.4 Control

For studies that compared interventions that can be used to treat fever with placebo, the placebo will be defined as the control. For studies that compared different thresholds of temperature treatment, the arm of the study that targeted the highest body temperature was be defined as the control arm.

3.1.5 Search strategy

The results of our systematic review and aggregate data meta-analysis have been published previously[10]. In brief, we searched the following databases: MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials, PubMed, and CINAHL.

Our search terms were as follows:
1. Theme of ‘intensive care’:
Exploded Medical Subject Headings terms – ‘critical care’ (includes intensive care on MEDLINE) or ‘intensive care units’
OR
Keywords - “critical care” or “intensive care” or “ICU” or “high dependency” or “HDU” or “level three care” or “level 3 care”
AND

2. Theme of 'antipyretic therapy and cooling'
Exploded Medical Subject Headings terms – "antipyretics" or "anti-inflammatory agents, non-steroidal" or "acetaminophen" or "ibuprofen" or "aspirin"
OR
Keywords – "cooling" or "fever control" or "fever reduction" or "temperature control" or "temperature reduction" or "normotherm*" or "anti-pyre*" or "paracetamol" or "acetaminophen" or "non-steroidal anti-inflammatory" or "NSAID" or "cyclo-oxygenase inhibitor*" or "COX inhibitor*" or "salicyl*" or "aspirin" or "ibuprofen" or "diclofenac" or "naproxen" or "indomethacin" or "acemetacin" or "aceclofenac" or "fenoprofen" or "fenbufen" or "dexibuprofen" or "dexketoprofen" or "ketoprofen" or "flurbiprofen" or "oxaprozin" or "sulindac" or "etodolac" or "ketorolac" or "nabumetone" or "azapropazone" or "phenylbutazone" or "piroxicam" or "meloxicam" or "tenoxicam" or "droxicam" or "lornoxicam" or "isoxicam" or "mefenamic acid" or "meclofenamic acid" or "flufenamic acid" or "tolfenamic acid" or "tiaprofenic acid" or "valdecoxib" or "parecoxib" or "metamizole" or "nimesulide" or "etoricoxib" or "lumiracoxib" or "firocoxib" or "celecoxib" or "rofecoxib"

The systematic review was originally performed in March 2016. We will update the systematic review in June 2018.

3.2 Studies included in the IPDMA

We will contact the authors of all studies identified in the systematic review to request individual, anonymised patient level data, for IPDMA.

3.3 Outcomes

3.3.1 Primary outcome

- The primary outcome variable will be the unadjusted time to death after randomisation.

3.3.2 Secondary outcomes

- Mortality at ICU discharge
- ICU length of stay
- Hospital length of stay
- Body temperature at each of 6, 12, 48, and 72 hours, after randomisation

4 METHODS: DATA EXTRACTION FOR IPDMA

4.1 Baseline data

Pre-randomisation (baseline) data points will be extracted from individual study databases (where available) and pooled into an IPDMA database:
1. Study name
2. Age (years)
3. Gender (M/F)
4. Invasive ventilation at baseline (Y/N)
5. Inotropes and/or vasopressors at baseline (Y/N)

6. Suspected infection at baseline (Y/N)
7. Acute Physiology And Chronic Health Evaluation (APACHE) II score
8. Mean Arterial Pressure (mmHg)
9. Heart Rate (beats per minute)
10. Serum creatinine (µmol/L)
11. Temperature (°C)

4.2 Treatment group data

Patients will be allocated into *more* vs. *less* assiduous fever control groups as outlined in sections 3.1.4 and 3.1.5.

4.3 Outcome data

4.3.1 Survival

Time to death after randomisation will be defined as the difference between time zero (T0) and the date and time of death.

T0 will be defined as the date and time of randomisation. Where the date and time of randomisation is not available, the date and time of administration of the first dose of study medication will define T0.

Where no time, only a date, is available to define either T0 or the time of death, the time(s) will be assumed to be 12:00pm.

The time for censored participants (those who do not die) will be the last time of observation in relation to the time of randomisation as described above.

4.3.2 Mortality at ICU discharge

All patients who die on or before the date of ICU discharge will defined as dead for the purposes of evaluating the end point ‘mortality at ICU discharge’.

4.3.3 ICU length of stay and hospital length of stay

ICU and hospital length of stay will be defined as the difference between T0 as defined in section 4.3.1 and ICU and hospital discharge respectively. Where no time, only a date, is available to define either T0 or the time of death, the time(s) will be assumed to be 12:00pm.

4.3.4 Body temperature

Body temperature at each of: 6, 12, 48, and 72 hours after randomisation, will be included in the IDPMA database. One study reported temperature data at 4 hours and 8 hours after randomisation[8]. For this study, the 6-hour temperature data point will be calculated by averaging the values from the 4 hour and 8 hour time points, i.e. linear interpolation.

5 METHODS: DATA ANALYSIS

5.1 Statistical methods

For all baseline variables appropriate data summaries; *n* with percentages for categorical variables, and means, standard deviations, median (interquartile range [IQR], and minimum to maximum values, for continuous variables; by treatment group and sub-groups defined in the introduction, will be calculated.

Although it is not of direct interest for this study we plan to compare the baseline variables between randomised groups by X^2 tests for equal proportions for categorical variables, Student *t* test for variables where normality assumptions for analysis are reasonable and Wilcoxon rank sum tests otherwise, for continuous variables. As discussed below we have pre-specified important possible confounders and effect modifiers.

Some general features of the analyses are that individual participants will be analysed as randomised (rather than as treatment received) in accordance with the 'Intention to Treat' principle. Except as outlined section 4 for nomination of a time where no time was given in relation to date data, no imputation of missing data will be performed. A two sided p-value of 0.05 will be used to indicate statistical significance. No adjustment will be made for multiple comparisons.

The general strategy for analysis for the main effect of treatment is to estimate differences between randomised groups for all the variables nominated in section 3.3; with and without important possible confounding variables of: age, gender, and APACHE-II score, with the addition of ‘individual study’ treated as a fixed effect.

The general strategy for the sub-group analyses, which is relevant to the variables in section 3.3 other than the serial temperature measurements, is to fit interaction terms in the statistical models and estimate whether the strength of evidence that the effect of treatment is different within sub-groups. The nominated sub-groups are as discussed in the introduction: Mechanical ventilation vs. those not receiving this therapy; Vasopressor and/or inotrope use vs. those not receiving these treatments; Mechanically ventilation use and vasopressor and/or inotrope use vs. not receiving either therapy; Infection vs. no infection; A fever of at least 39.5°C vs. a lower temperature; median age or older vs. less than median age; APACHE score ≥25 vs. <25; and enrolled in a study using physical cooling vs. enrolled in a study that did not use physical cooling a component of the intervention.

Survival time from randomisation, according to treatment group, will be displayed as Kaplan–Meier curves, as well as in relation to sub-groups within treatment groups. Estimates of hazard ratios for survival, with corresponding 95% CI and will be obtained from the Cox proportional hazards models incorporating treatment group, the potential confounding variables for the main effect of treatment, and the interaction with the particular sub-groups.

The risk of mortality at ICU discharge, according to treatment group, will be evaluated by logistic regression, the potential confounding variables for the main effect of treatment, and the interaction with the particular sub-groups.

Length of stay variables, such as ICU and hospital length of stay, are often right-skew and statistical assumptions of normality of residuals are often better met on the logarithm-transformed scale. Back-transformation of the coefficients in a logarithm-transformed linear model (ANOVA) can be interpreted as the ratio of geometric means. In a similar approach to already described main effects models for treatment will be fitted with and without the nominated confounding variables and interaction models fitted for the nominated sub-groups.

Comparisons of body temperature over time will be performed using mixed linear modelling, fitting main effects for treatment and time and an interaction between the two to determine if treatments differed over time. Estimates of the differences in body temperature and associated confidence intervals will be reported comparing treatment groups within each time point.

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) will be used for analyses.

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