TITLE (SHORT, 200 CHARACTERS MAX.):

DOES MILD INDUCED HYPOTHERMIA INCREASE BLEEDING RISK?

MAIN HYPOTHESES TESTED (2 MAX)

Does mild induced hypothermia after cardiac arrest in comatose survivors of assumed cardiac cause increase bleeding risk?

SINGLE CENTER [ ] , MULTICENTER [ ]

All sites

PICO

Patients: All patients in TTM2

Comparison: 33°C and normothermia groups

Outcome: All bleeding events during the first 72 hours after inclusion

DATA NEEDED FOR THE ANALYSIS (SPECIFY VARIABLES AND MOTIVATE ANY PROPOSED ADDITIONS TO THE ECRF)

Background. There is a paucity of data regarding effects of mild hypothermia on platelet function and coagulation. Many studies have focused on results of assays monitoring platelet function and coagulation in vitro in hypothermic conditions with conflicting results. Furthermore, it is not obvious that platelet function and coagulation disturbances demonstrated in-vitro are clinically significant and also present in-vivo causing bleeding events. There is no high quality prospective randomized controlled study other than TTM1, that evaluates bleeding events in mild induced hypothermia compared to normothermia .In TTM1 there were no difference in the number of bleeding events between the groups, however a signal towards more bleedings from insertion sites in the 33°C group. Two problems with the bleeding outcomes in TTM1 was that the bleeding outcome variables were a mixture of severity grade and location and that the bleeding events were registered day 1- 7 in the ICU and not only during the intervention.

If coagulation and platelet function are significantly affected by mild induced hypothermia the effects are most likely small and not possible to demonstrate with differences in events of moderate and severe bleedings between the groups but rather with differences in events of mild bleedings. To increase clarity and reduce the risk for missing events of mild bleeding **we propose that the question concerning bleeding (any bleed/ moderate/severe) in the daily ICU form to be replaced by the following questions**:

1. Did the patient have any bleeding graded as GUSTO 1 (eg bleeding from insertion site, nose bleeding, genital bleeding or other mild bleedings)? Y/N

2. Did the patient have any bleeding graded as GUSTO 2 (moderate bleeding requiring blood transfusion)? Y/N

3. Did the patient have any bleeding graded as GUSTO 3 (severe bleeding with substantial hemodynamic compromise requiring treatment)? Y/N

Based on the above we argue that, it is of great interest to study if the total number of bleeding events during the first 72 hours differs between the groups, since the result would be indicative of how induced mild hypothermia affects platelet function and coagulation in vivo. **The hypothesis in this sub-study would be that mild induced hypothermia to 33 degrees C for 24 hours after OHCA does not increase bleeding risk.**

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LOGISTICS – HOW WILL ADDITIONAL DATA BE GATHERED?

We are not planning on gathering additional data due to the risk of low quality retrospective data

BRIEF STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE ESTIMATE

The sample size is determined by how many patients that are included in the TTM2 study.

The differences in number of bleeding events between the groups during the intervention period will be compared using univariate Chi2 test or Fischer´s exact test. Furthermore, independent risk factors for bleeding events during the intervention period will be tested using age, gender, eGFR, coronary intervention (y/n), coronary angiography (y/n), PT-INR at admission, platelet count at admission, chock at admission (y/n) and cooling device as independent variables in a multiple logistic regression model.

FUNDING (IF APPLICBABLE)

No funding

CORRESPONDING AUTHORS NAME, INSTITUTION & E-MAIL ADDRESS:

Thomas Kander. Dept of Intensive and Peri-Operative Care, Skåne University Hospital, Lund, Sweden.
thomas.kander@med.lu.se

CO-WORKERS:

Malin Rundgren[1]

Josef Dankiewicz[1]

Ulf Schött[1]

Sigurdur Benediktsson[1]

[1] Dept of Intensive and Peri-Operative Care, Skåne University Hospital, Lund and Malmö, Sweden

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