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A systematic review of safety and adverse effects in the practice of therapeutic hypothermia

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ABSTRACT

Objective: To carry out a systematic review to estimate the rate and magnitude of adverse effects following therapeutic hypothermia (TH) procedure in patients resuscitated from out-of-hospital cardiac arrest (OHCA) and highlight the specific complications seen after the procedure.
Methods: A systematic review of currently published studies was performed following standard guidelines. Online database searches were performed for controlled trials for the last twenty years. Papers were examined for methodological soundness before being included. Data were independently extracted by two blinded reviewers. Studies were also assessed for bias using the Cochrane criteria. The adverse effects attributed to TH in the literature were appraised critically.
Results: The initial data search yielded 78 potentially relevant studies; of these, 59 were excluded for some reason. The main reason for exclusion (n = 43, 55.8%) was that irrelevance to adverse effects of TH. Finally, 19 underwent full-text review. Studies were of high-to-moderate (n = 12, 63%) to low-to-very low (n = 7, 37%) quality. Five studies (27.7%) were found to have high risk of bias, while 8 (42.1%) had low risk of bias.
Interpretation: Although adverse effects related to the practice of TH have been studied extensively, there is substantial heterogeneity between study populations and methodologies. There is a considerable incidence of side effects attributed to the procedure, e.g., from life-threatening ventricular arrhythmias to self-limited consequences. Most studies analyzed in this systematic review indicated that the procedure of TH has not caused severe adverse effects leading to significant alterations in the outcomes following resuscitation from OHCA.
PROSPERO, registration number is: CRD42018075026.

1. Introduction

Survival to discharge rate following resuscitation from out-of-hospital cardiac arrest (OHCA) with ventricular fibrillation (VF) was reported to be as high as 40% [1]. In the population-based 11-year study by Bunch et al., survival to admission was found to be 72%, while 42% survived to discharge and 76% of those discharged patients survived for 5 years. Neurologic injury is the most common cause of death in patients with OHCA and contributes to the mortality of in-hospital cardiac arrest [2].

Out-of-hospital cardiac arrest (OHCA) is the most common way of dying and therapeutic hypothermia (TH) is instituted to improve neurological outcome after OHCA. "Therapeutic hypothermia," is a general term to define intentional reduction of core body temperature, while it has evolved in decades into a more comprehensive control of a patient's temperature profile, a strategy now referred to as "targeted temperature management" (TTM). Recent guidelines have recommended TTM for selected patients resuscitated successfully and are still unresponsive [3]. TH is practised mainly in the treatment of adult cardiac arrest and neonatal hypoxic-ischemic encephalopathy.

Hypothermia has been historically classified into: mild (34.5–36.5 °C), moderate (34.5–32 °C), marked (28–32 °C) and profound hypothermia (<28 °C) [4-6].

In the early 2000's, researchers advocated the administration of 'mild TH' to improve neurological outcomes and to prevent severe brain damage after OHCA [5,6]. More recent evidence demonstrated that the core temperature should be maintained between 32 and 36 °C as the therapeutic range for TTM [3,7]. In this context, induced hypothermia is evaluated in three steps: induction, maintenance and rewarming, and each phase produces several changes in normal physiology.

In the post-resuscitative period, TH is thought to mitigate neurologic reperfusion injury by decreasing cerebral oxygen consumption and biochemical damage [5]. TH was postulated to offer an extended

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therapeutic window to restore the integrity of circulation, with the brain maintained in a protective, hypometabolic state.

Hypothermia induction should be started without delay to minimize neurologic damage [7]. Infusing cold fluids, e.g., Ringer's lactate >25 mL/kg at 4 °C, can be seen as the easiest method for inducing hypothermia [8]. However, The Canadian Guidelines, pointed out that although high level of evidence is lacking, most experts recommend to initiate TTM as soon as feasible after ROSC is achieved and to avoid cold IV fluids in the prehospital setting [7]. Mild cooling was shown to be beneficial without many of the feared side effects. Nonetheless, TH requires an intensive care unit setting with protocolized implementation and close monitoring [8,9]. It is likely that both survivors of arrest by itself and with the addition of TH procedure increase risk of complications from the hypothermia [9,10].

Substantial amount of literature data on adverse or side effects of TTM are available although there is a need to culminate these in a systematic and orderly fashion to guide monitoring the patients to avoid these in the procedure. This article reviews the current literature to provide systematic data regarding adverse and untoward effects attributed to the procedure of TH in the emergency setting.

2. Side/adverse effects/complications attributed to TH

Decline in body temperature has an impact on all biological processes. Many important complications of hypothermia respond to standard measures, while some may result in morbidity and mortality. MacLaren et al. compared the incidences of adverse events and predictors of good versus poor neurological recovery after TH in a review of medical records of 91 patients who received TH for ≥6 h [10,11]. They reported that common adverse events were hypoglycemia (99%), shivering (84.6%), bradycardia (58.2%), electrolyte abnormalities (up to 91.2%), acute kidney injury (52.8%), infection (48.4%), and coagulopathy (40.7%).

TH performed in most scenarios was known as “Level 2 procedure” which Australian Ministry of Health Guideline recommends “Allergy/adverse reaction check” and to be advised/informed about the “Anticipated critical events” attributed to the procedure [11]. In this context, there is also need to address safety of clinical trials and procedures pertaining to TH worldwide. Clinical trials must be conducted following established standards in order to protect the rights, safety and well-being of the subjects/participants [11,12].

To inform decision-making on the procedure of TH and attributable adverse effects, we performed a systematic review of the evidence on the probable side effects and specific subgroups predisposed to them. This article reviews the current literature to provide systematic data regarding the following questions and determine evidence-based recommendations:

1. How safe is TH in patients resuscitated from OHCA?
2. What are the specific complications seen following TH procedure?

3. Methods

A systematic review of currently published studies was carried out on the predefined subject via certain keywords. Online database searches were performed for randomized controlled trials published within twenty years before January 2018, on the comparison of the adverse and untoward effects of TH in adults and consequences in specific patient groups. Data were independently extracted by two blinded reviewers. The discrepancies, on the other hand, were resolved by the primary author.

4. Protocol and registration

This protocol is presented in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines [13]. The research protocol to answer these questions was registered in PROSPERO, the International Prospective Register of Systematic Reviews (registration number is: CRD42018075026).

4.1. Search methodology

A literature search via the Cochrane Central Register of Controlled Trials, PubMed/Medline, ClinicalKey, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and BIOSIS was carried out on the clinical trials conducted on adults published in all languages. Online searches were performed using the following search keywords and terms: ‘out of hospital cardiac arrest’ AND ‘therapeutic hypothermia’ OR ‘targeted temperature management’ AND ‘adverse effects’. The reference lists of retrieved articles were used to generate more papers related to the adverse effects attributed to the procedure.

4.2. Study selection, data screening and critical appraisal

The study included all clinical trials of any duration that examined adverse and untoward effects related to TH in humans, who underwent TTM (32–36 °C), irrespective of the presenting rhythm exclusively in adults (aged >18 years). Reference lists of relevant systematic reviews and all included studies were checked to identify additional eligible articles. Conference abstracts and proceedings were not deemed eligible for inclusion in the review. Citation titles and abstracts were independently screened and assessed regarding the methodological quality by two reviewers (H.T. and O.D.). Any disagreements between the two reviewers were then resolved by consensus or in consultation with a third reviewer (O.K.) if needed.

4.3. Assessment of quality and risk of bias

Eligible clinical studies were rated regarding the quality of evidence as per “Grading of Recommendations Assessment, Development and Evaluation” (GRADE) guidelines which scores according to risk of bias, publication bias, consistency, directness and precision [14]. In accord with the GRADE, the studies were assigned to one of four groups: High (A), moderate (B), low (C) and very low (D) quality. Table 1 summarizes this evidence; grading and levels of evidence (Sackett's original evidence based approach).

Studies that met the inclusion criteria for the review were assessed for bias using the risk of bias criteria developed by Cochrane's EPOC group [15] which is based upon Cochrane's Risk of Bias Tool [16]. Studies were assessed with regard to selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. Studies were rated as “low risk of bias (L)”, “high risk of bias (H),” or “unclear risk of bias (U)” on a general impression after evaluating all criteria (Table 2).

Table 1
Grading and levels of evidence (Sackett's original evidence based approach).

Grading of evidence
A Supported by at least two level I studies
B Supported by only one level I study
C Supported by level II studies only
D Supported by at least one level III investigation
E Supported by level IV or level V evidence
Level of evidence
Level I Large, randomized trials with clear cut results
Level II Small, randomized trials with uncertain results
Level III Non-randomized, contemporaneous controls
Level IV Non-randomized, historical controls and expert opinion
Level V Case series, uncontrolled studies and expert opinion

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