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Pharmacological versus non-pharmacological antipyretic treatments in febrile critically ill adult patients: A systematic review and meta-analysis

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Summary
Objectives: Fever is common in critically ill patients and there are myriad of antipyretic and cooling treatments used. A systematic review was undertaken of the safety and efficacy of methods used to reduce fever.
Methods: Medline, EMBASE, CINAHL and Cochrane Database of Systematic Reviews were searched for randomised control trials (RCTs) of head-to-head and versus placebo/no treatment comparisons of pharmacological and/or non-pharmacological treatments for reducing fever in critically ill adult patients. Primary outcomes were reduction of fever and haemodynamic effects of treatments.
Results: 11 of 48 trials reviewed were included. The studies analysed were separated into common antipyretic treatment groups for comparison. Our main findings include, newer versus conventional external cooling therapies where newer external cooling methods (intravascular cooling and hydrogel cooling system) were better at reducing the fever burden than conventional methods (surface cooling) (MD, −8.00, 95% CI = −12.54, −3.47, $P < 0.001$), with a trend for higher mortality for newer methods (RR, 1.42; 95% CI, 0.99—2.03; $P = 0.06$). In the group comparison of the effectiveness of pharmacological antipyretic treatments, reduction on core body temperature favoured continuous antipyretic infusions rather than bolus doses (MD, 0.30, 95% CI 0.09, 0.51, $P = 0.005$). For aggressive versus permissive antipyretic treatments, a reduction in mean daily temperatures favoured the aggressive group (MD, −1.09, 95% CI −1.37, −0.81, $P < 0.001$) with a trend towards higher mortality for aggressive treatment (RR, 6.05, 95% CI 0.78, 46.95, $P = 0.09$).

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Conclusion: Additional studies are needed to explore and clarify the role of antipyretic treatments in febrile critically ill adult patients.

Introduction

Fever occurs frequently in critically ill patients with reports of an incidence of 70% in general intensive care unit (ICU) patients.[1] Fever is caused by an elevation in the thermoregulatory set-point and may result from infectious and non-infectious causes. Fever is thought to be an adaptive and beneficial response to infection and stress.[2] Treatments to reduce body temperature may be utilised to reduce metabolic rate and hence oxygen demand or to reduce further brain cell death after brain injury or haemorrhage.[3,4]

Thermoregulation maintains core body temperature within a narrow normal range despite considerable extremes in environmental conditions. This is achieved by balancing heat production and heat loss to the environment. Heat loss to the environment is primarily controlled by behavioural responses and controlling heat loss from skin.[5–7] Heat dissipation can either be increased or decreased as required by respectively increasing or decreasing skin blood flow (skBF).[5–7] Heat dissipation can also be increased dramatically through sweating and the heat loss associated with the latent heat of evaporation. A rise in body temperature is effected by increased heat production (shivering, increased metabolic rate) coupled with a decrease in heat loss that occurs with vasoconstriction of cutaneous blood vessels and a reduction in skBF.[5–7] Antipyretic treatments either increase heat loss through various cooling methods or involve pharmacological agents that reset hypothalamic temperature set point.

The primary purpose of this review is to clarify what single or combination antipyretic therapy best reduces fever without adverse effects in febrile critically ill adult patients. The current literature reports that therapeutic hypothermia results in significant physiological change and has well known side effects including immunosuppression.[8] Suppression of the febrile response and the maintenance of normothermia may also result in immunosupression.[8] Other adverse responses also reported when administering antipyretic pharmacological drugs to febrile critically ill adult patients are adverse haemodynamic responses, such as hypotension, impaired hepatic and renal function, oliguria and sodium and water retention.[9–12] furthermore, when external cooling aids are used the reported adverse effects include shivering, vasoconstriction and patient discomfort.[13,14]

The most common treatments used for fever are antipyretic drugs, external cooling methods such as specialised cooling blankets, sponging and ice packs or a combination of these therapies.[15] Even though fever is common, there is controversy surrounding reducing fever as fever is a natural body response and yet in some instances, such as traumatic brain injury, ineffective control of hyperthermia may result in harm.[16] If and when it is decided to treat fever, there are a range of treatment methods available with no established clinical or gold standard. In view of the uncertainty regarding the comparative safety and efficacy of the current methods of temperature control a systematic review of the current evidence was undertaken.

Objectives

This systematic review aimed to compare randomised control trials of head-to-head and versus placebo/no treatment comparisons of pharmacological and non-pharmacological antipyretic methods to, firstly; assess the effectiveness of core body temperature reduction and maintenance amongst antipyretic therapies and, secondly; to see if adverse haemodynamic outcomes are reported. Based upon the review findings further objectives were to make clinical recommendations for the use of antipyretic treatments in febrile critically ill adult patients and to identify areas for further investigation.

Methods

Study types

All randomised controlled trials of head-to-head and versus placebo/no treatment comparisons of pharmacological, and non-pharmacological antipyretic therapies in critically ill adult patients were included in the review. To be included, the