

## **Therapeutic Hypothermia as a Neuroprotectant for Post ‘Out-of-Hospital’ Cardiac Arrest: a Meta-Analysis**

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Cardiac arrest (CA) is the most relevant cause of global cerebral ischaemia (GCI). With annually 30,000 people in the UK suffering an out-of-hospital CA, only 18% survive (Kendal et al, 2012). Animal and clinical studies suggest mild to moderate resuscitative hypothermia (30-35°C) might improve mortality and morbidity. A meta-analysis was carried out to assess mild-moderate hypothermia post CA, outcomes of interest being neurological outcome and survival.

RCTs were selected according to successfully resuscitated out-of-hospital adult CA (excluding traumatic) with induced mild (32-35°C) to moderate (30°C) hypothermia within 6hrs, with neurological outcome and mortality as primary and secondary endpoints. External, intravenous fluids, intravascular catheters, extra corporeal, intra-peritoneal methods were included. Outcomes were Glasgow Coma Outcome Scale, Cerebral Performance Category Scale & Overall Performance Scale. Studies were evaluated and data extracted using the tables and methodology of Berman & Parker (2002). Data bases were PubMed, BMJ journals collection, Science Direct, SpringerLink and clinicaltrials.gov to January 2013. Quantitative analysis was performed using Revman 5.2 (Copenhagen, Nordic Cochrane Centre, 2012) and two outcomes measured, favourable neurological outcome (OPC1-2), and mortality. NNT was also calculated (Bandolier).

9555 titles were reduced to 745 trials. These were screened to give 138 abstracts, of which 9 papers matched the criteria. 5 studies were included after detailed checking, totalling 568 patients (Bernard et al 2002, THACA, 2002, Hachimi-Idrissi et al, 2001, Kim et al, 2007, Laurent et al, 2005). Forest plot 95% confidence intervals showed good overlap and thus statistical homogeneity. Quantitative analysis used standard procedures, dichotomous Mantel-Haenszel analysis. Fixed effect and random effect models gave similar findings. Fixed effect model: moderate hypothermia, neurological outcome RR, 0.81 (0.71-0.92),  $I^2=32%$ , NNT 7.4; mortality rate RR, 0.80 (0.70-0.92),  $I^2=0%$ , NNT 8.1. There was heterogeneity in selection and methods of cooling. Laurent et al (2005) used haemoperfusion which could have added blood conditioning effects, however there was no significant difference in RR outcome (Fixed RR 0.8 (0.70-0.92),  $p=0.11$ ,  $I^2=50%$ ). There was no significant difference in the severe adverse events in the study and control groups.

Lack of access to patient data resulted in RRs differing to those published. During this project, a similar meta-analysis was revealed (Holzer et al, 2010). We have excluded Mori et al (2000) published as an abstract and did not fulfil their or our inclusion criteria and is no longer accessible. We included Kim et al (2007) this being of sufficient quality. Despite these and methodological differences there is broad agreement between the analyses. With therapeutic hypothermia, up to 1000 patients categorised as CPC3-5 could be potentially discharged with CPC1-2 annually in the

UK. Bernard et al N Engl J Med 346:557, 2002; Berman & Parker BMC Med Res Methodol 2:10, 2002;

Hachimi-Idrissi et al, Resuscitation 51: 275, 2001;

Holzer et al, Cochrane Database of Systematic Reviews 4, 2009. Doi 10.1002/14651858;

Kendal et al, Out of Hospital Cardiac Arrest registry 2012;

Kim et al, Circulation 115:3064, 2007;

Laurent et al, J AM Coll Cardiol 46:432, 2005; THACA, N Engl J Med 346:549, 2002.