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Hypertonic saline versus other intracranial pressure–lowering agents for people with acute traumatic brain injury: a Cochrane Review

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Background

Increased intracranial pressure has been shown to be strongly associated with poor neurological outcomes and mortality for patients with acute traumatic brain injury. Currently, most efforts to treat these injuries focus on controlling the intracranial pressure. Hypertonic saline is a hyperosmolar therapy that is used in traumatic brain injury to reduce intracranial pressure. The effectiveness of hypertonic saline compared with other intracranial pressure-lowering agents in the management of acute traumatic brain injury is still debated, both in the short and the long term.

Objectives

To assess the comparative efficacy and safety of hypertonic saline versus other intracranial pressure-lowering agents in the management of acute traumatic brain injury.

Search methods

ISI Web of Science: Science Citation Index and Conference Proceedings Citation Index-Science, as well as trials registers, on 11 December 2019. We supplemented these searches with searches of four major Chinese databases on 19 September 2018. We also checked bibliographies, and contacted trial authors to identify additional trials.

Selection criteria

We sought to identify all randomised controlled trials (RCTs) of hypertonic saline versus other intracranial pressure-lowering agents for people with acute traumatic brain injury of any severity. We excluded cross-over trials as incompatible with assessing long-term outcomes.

Data collection and analysis

Two review authors independently screened search results to identify potentially eligible trials and extracted data using a standard data extraction form. Outcome measures included: mortality at end of follow-up (all-cause); death or disability (as measured by the Glasgow Outcome Scale (GOS)); uncontrolled intracranial pressure (defined as failure to decrease the intracranial pressure to target and/or requiring additional intervention); and adverse events e.g. rebound phenomena; pulmonary oedema; acute renal failure during treatment).

Main results

Six trials, involving data from 287 people, met the inclusion criteria. The majority of participants (91%) had a diagnosis of severe traumatic brain injury. We had concerns about particular domains of risk of bias in each trial, as physicians were not reliably blinded to allocation, two trials contained participants with conditions other than traumatic brain injury and in one trial, we had concerns about missing data for important outcomes. The original protocol was available for only one trial and other trials (where registered) were registered retrospectively.

Meta-analysis for both the primary outcome (mortality at final follow-up) and for 'poor outcome' as per conventionally dichotomised GOS criteria, was only possible for two trials. Synthesis of long-term outcomes was inhibited by the fact that two trials ceased data collection within two hours of a single

JBMEDE 2021;1(1):e21008

bolus dose of an intracranial pressure-lowering agent and one at discharge from the intensive care unit (ICU). Only three trials collected data after participants were released from hospital, one of which did not report mortality and reported a 'poor outcome' by GOS criteria in an unconventional way. Substantial missing data in a key trial meant that in meta-analysis we report 'best-case' and 'worst-case' estimates alongside available case analysis. In no scenario did we discern a clear difference between treatments for either mortality or poor neurological outcome.

Due to variation in modes of drug administration (including whether it followed or did not follow cerebrospinal fluid (CSF) drainage, as well as different follow-up times and ways of reporting changes in intracranial pressure, as well as no uniform definition of 'uncontrolled intracranial pressure', we did not perform meta-analysis for this outcome and report results narratively, by individual trial. Trials tended to report both treatments to be effective in reducing elevated intracranial pressure but that hypertonic saline had increased benefits, usually adding that pretreatment factors need to be considered (e.g. serum sodium and both system and brain haemodynamics). No trial provided data for our other outcomes of interest. We consider evidence quality for all outcomes to be very low, as assessed by GRADE; we downgraded all conclusions due to imprecision (small sample size), indirectness (due to choice of measurement and/or selection of participants without traumatic brain injury), and in some cases, risk of bias and inconsistency.

Only one of the included trials reported data on adverse effects; a rebound phenomenon, which was present only in the comparator group (mannitol). None of the trials reported data on pulmonary oedema or acute renal failure during treatment. On the whole, trial authors do not seem to have rigorously sought to collect data on adverse events.

Authors' conclusions

This review set out to find trials comparing hypertonic saline to a potential range of other intracranial pressure-lowering agents, but only identified trials comparing it with mannitol or mannitol in combination with glycerol. Based on limited data, there is weak evidence to suggest that hypertonic saline is no better than mannitol in efficacy and safety in the long-term management of acute traumatic brain injury. Future research should be comprised of large, multi-site trials, prospectively registered, reported in accordance with current best practice. Trials should investigate issues such as the type of traumatic brain injury suffered by participants and concentration of infusion and length of time over which the infusion is given.

Section Info

This section reproduces articles previously published by Cochrane Database of Systematic Reviews and is carried out in coordination with Patricia Jabre, Yannick Auffret, Sebastien Beroud, Julie Dumouchel, Virginie-Eve Lvovschi, Kirk Magee, Daniel Meyran, Patrick Miroux, Nordine Nekhili and Youri Yourdanov from the Cochrane Pre-hospital and Emergency Care group.