Cochrane Report

A Systematic Review of Mannitol Therapy for Acute Ischemic Stroke and Cerebral Parenchymal Hemorrhage

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**Background**—Mannitol was reported to decrease cerebral edema associated with tissue damage and is used to treat acute stroke in many countries.

**Summary of Review**—We tested whether there is any evidence from unconfounded randomized clinical trials that treatment with mannitol reduces short- and long-term case fatality and dependency if administered after ischemic stroke or cerebral parenchymal hemorrhage. Trials were identified by the standard search strategy of the Cochrane Collaboration Stroke Review Group. A supplementary MEDLINE search was performed, and the Chinese Stroke Trials Register and the Latin-American databank LILACS were checked. A search was performed of master’s and PhD degree theses in the databank of Sao Paulo University and in abstracts of medical congresses on neurology and neurosurgery during 1965–1997 in Brazil. Investigators were contacted for unpublished information. Only truly randomized unconfounded clinical trials were eligible for inclusion. Two of the reviewers independently extracted data from the trials. Data synthesis and analysis was performed with the use of the Cochrane Review Manager software (RevMan version 4.0.4).

**Conclusions**—Only 1 trial fulfilled the inclusion criteria. The number of included patients was small, and the follow-up was short. Case fatality, the proportion of dependent patients, and side effects were not reported and were not available from the investigators. As a result of lack of appropriate randomized trials, currently no conclusion can be drawn on the effects of mannitol in acute stroke. The routine use of mannitol in all patients with acute stroke is not supported by evidence from randomized controlled clinical trials. (*Stroke*. 2000;31:2719-2722.)

**Key Words:** mannitol ■ randomized controlled trials ■ stroke, acute ■ treatment outcome

There is no specific medical therapy that can be recommended for routine use in patients with acute ischemic stroke, except for aspirin.1,2 Thrombolysis with tissue plasminogen activator is recommended in selected patients,3 but there is insufficient evidence to recommend the use of thrombolytic drugs in general to treat acute ischemic stroke.4 The few randomized trials that exist for cerebral parenchymal hemorrhage cannot prove a beneficial effect of medical5,6 or surgical7 interventions.

Cytotoxic edema develops in the first hours after the onset of ischemic stroke and can be detected as a decrease in the apparent diffusion coefficient (ADC) of water. This reduction in ADC lasts for 3 to 4 days and then increases as vasogenic edema develops.8,9 A decrease in ADC was also shown in acute hemorrhagic stroke,10 but in contrast to ischemic strokes, ADC in hemorrhagic stroke remains decreased even 100 days after stroke onset. Continuous monitoring of intracranial pressure (ICP) shows that the pronounced brain edema that develops during days 4 to 14 of an intracerebral hemorrhage could lead to an increase in ICP, requiring treatment.11

Corticosteroids, although frequently used to treat cerebral edema, did not increase survival after stroke.12 Osmotic diuretics, especially mannitol, are among the agents that are widely used in the treatment of cerebral edema.13–16 Mannitol is thought to decrease ICP by decreasing overall water content and cerebrospinal fluid volume and by reducing blood volume due to vasoconstriction.17–19 Mannitol may also improve cerebral perfusion by decreasing viscosity or by altering red blood cell rheology.20 As a free radical scavenger, mannitol may exert a protective effect against biochemical injury.21

Mannitol is reported to decrease cerebral edema, infarct size, and neurological deficit in several experimental models of ischemic stroke,22–26 although primarily when administered within 6 hours after stroke onset. The results of some animal studies do not prove the beneficial effects of mannitol in rodent27 or monkey28 models of ischemic stroke. The worsening of
cerebral edema by multiple-dose mannitol was also reported in cats,29 and a harmful effect of a single very large dose was assumed although not found in complete middle cerebral artery infarcts in humans.30

Mannitol has been used in human ischemic brain damage for >30 years.31 Cerebral edema in humans is regularly treated with mannitol, which is known to decrease ICP in several diseases32 and was found to decrease case fatality in cerebral edema due to hepatic failure.33 In a study of middle cerebral artery territory stroke, treatment modalities for elevated ICP, including osmotherapy, were initially effective, but ICP control could only be sustained in a minority of patients.34

The most common complications of mannitol therapy are fluid and electrolyte imbalances, cardiopulmonary edema, and rebound cerebral edema.18,35 Mannitol might cause kidney failure46–38 in therapeutic doses, and hypersensitivity reactions may also occur.39

Although there are several reports that could not prove the beneficial effects of mannitol in ischemic or hemorrhagic strokes in humans,40–43 the guidelines of the American Heart Association currently recommend the use of mannitol in certain clinical conditions in selected cases of acute stroke.44 Mannitol is widely used in acute stroke throughout the world. Almost 70% of physicians in China use mannitol or glycerol routinely in acute stroke,45 and mannitol is used routinely in acute stroke in several European countries as well. For example, mannitol is listed among recommended therapeutic interventions by the consensus statement of the Hungarian Stroke Society for cases when elevated ICP is proven in stroke.46 Although treatment with osmotic diuretics seems logical from a physiological point of view, and mannitol has some effect on the brain in ischemic stroke,47 it is presently not clear whether the routine use of mannitol results in increased survival and decreased dependency in stroke patients.48

In this systematic review, we sought to test whether treatment with mannitol reduces short- and long-term case fatality and dependency after ischemic stroke or cerebral parenchymal hemorrhage. A more detailed review will be published and updated in the Cochrane Database of Systematic Reviews.49

Methods

Criteria for Considering Studies for This Review

Truly randomized, unconfounded, clinical trials comparing the effect of mannitol with placebo or open control in patients with acute ischemic stroke or parenchymal hemorrhage were eligible for inclusion. Mannitol alone compared with standard therapy was considered confounded, whereas mannitol added to standard therapy compared with standard therapy was acceptable.

We planned to evaluate the effects of mannitol in patients within 2 weeks of onset of ischemic stroke or cerebral parenchymal hemorrhage. Trials with intravenous, oral, or rectal treatment schedules were planned to be included in the review. The analysis was to be stratified by treatment route.

Outcome Measures

We planned to extract information on the following outcomes: (1) deaths from all causes within the scheduled treatment period; (2) deaths from all causes at the end of the scheduled follow-up period; and (3) the number of patients dead or dependent in activities of daily living. Patients dependent in daily living are those who are unable to care for themselves and need daily help from others, which corresponds to a score of 3 to 5 on the modified Rankin Scale.50

Since it is likely that a number of outcome scales will have been used, we planned to extract data using the reported results to estimate the number of patients dead or dependent in activities of daily living. If the same continuous outcome scales were used in the studies, these data would also be analyzed. Data for length of hospital stay and quality of life at final follow-up were to be analyzed if available.

In regard to safety parameters, we planned to determine the rate of kidney failure, pulmonary edema, and pulmonary embolism and the frequency of other fatal and nonfatal adverse events in each treatment group.

Search Strategy for Identification of Studies

Trials were identified by the standard search strategy of the Cochrane Collaboration Stroke Review Group. In addition to this, MEDLINE searches were performed with the search terms (stroke OR cerebrovascular) AND (mannitol OR mannit) and (cerebral OR brain) AND (mannitol OR mannit) to look for further possible trials of mannitol therapy in acute stroke. One of the reviewers (M.L.) searched for studies in the Chinese language in the Chinese Stroke Trials Register. Another reviewer (G.F.P.) searched in Spanish and Portuguese languages in the Latin-American databank LILACS51 with the search term mannitol and its variations in the Portuguese and Spanish languages using the strategy suggested by Castro et al52 and performed a search of master’s and PhD degree theses in the databank of Sao Paolo University (BIREME/PAHO-WHO [Biblioteca Regionale Medicina/Panamerican Health Organization of the World Health Organization]) and in abstracts of medical congresses on neurology and neurosurgery during 1965–1997 in Brazil. We attempted to obtain missing data from the published trials by correspondence with the trialists.

Methods Used to Select Trials for Inclusion

At least 2 of the 4 reviewers independently judged each identified trial to determine whether it should be included in the review. For studies reported in non-English languages, one of the reviewers had to know the language, and the other reviewer made his/her decision on the basis of the “data extract form” used by the Cochrane Stroke Review Group. For trials reported in languages not familiar for the reviewers, consultations were arranged to obtain a reliable translation. Disagreements were solved by discussion among reviewers. Before data analysis, all reviewers agreed on each trial to be included.

Assessment of Methodological Quality of Included Trials

We planned to evaluate the trials for methodological quality, including method of randomization and blinding, concealment of randomization, balance in baseline prognostic factors between treatment and control groups, whether CT scanning was performed, patient follow-up, and whether an intention-to-treat analysis was performed.

Data Collection From Included Trials

After reaching an agreement on which trials to include, 2 of the reviewers (D.B. and I.F.) independently extracted data from the trials and performed the data analysis. Accuracy of data extraction was checked by comparing the 2 results.

Methods Used to Synthesize Data

Data synthesis and analysis were performed with the use of the Cochrane Review Manager software, RevMan version 4.0.4. The Peto odds ratio was used for calculating relative treatment effects. We also planned to report the absolute risk difference for each of the primary outcome measures (death and dependency).

The primary analysis was planned to include all trials irrespective of whether the trials primarily intended to include patients only with ischemic stroke or only hemorrhagic stroke. Separate subgroup analyses on outcome in patients with confirmed ischemic stroke and in patients with hemorrhagic stroke confirmed by CT scan or cerebrospinal fluid examination were planned to be completed. A sensitivity analysis was to
be performed to compare the overall results when all trials were included with the results when the analysis was restricted to trials in which patients had a CT scan.

Since mannitol might be more effective in patients with more severe brain edema, we planned to perform a subgroup analysis for those patients who had a decreased level of consciousness. A further subgroup analysis was planned for studies with intravenous administration of mannitol. Trials would be analyzed separately if a dose of $\geq 1$ g/kg of mannitol was given because it was found that administration of $\geq 1.0$ g/kg per dose consistently reduced ICP from control values, but dosages $<1$ g/kg per dose did not always reduce ICP. A separate analysis was planned for studies in which the total daily dose was divided into $\geq 3$ doses because the edema-reducing effect of mannitol lasts for a few hours. An additional analysis was planned for studies in which mannitol was given for $>7$ days because edema around the ischemic or hemorrhagic region might persist for longer periods of time.

Results

Description of Studies
The searches resulted in 5 randomized, controlled trials for possible inclusion. Three of these studies were published in Chinese language journals. All of them were found to be confounded trials, and therefore these trials were excluded. In the fourth excluded study of Freeman and coworkers, dexamethasone was coadministered with mannitol, and therefore no clear conclusion could be made for mannitol from this trial. The only study that fulfilled the inclusion criteria randomized 300 patients to 1 control and 3 treatment groups: a mixture of ergot alkaloids, dexamethasone, or mannitol. Of the 300 patients in the only included trial, 241 had presumed ischemic stroke based on clinical and cerebrospinal fluid examination, but only 166 were included in data analysis. Since clinical and cerebrospinal fluid examinations are not reliable methods to exclude cerebral hemorrhage, some of those considered to have ischemic strokes might have had hemorrhagic stroke. Of the 166 patients for whom data were reported, 41 belonged to the control and 36 to the mannitol groups. Mannitol was administered intravenously once a day in a dose of 0.8 to 0.9 g/kg for 10 days.

Methodological Quality of Included Studies
The method of randomization was not reported, and no information about the concealment of randomization was available. The initial number of patients randomized to the control and mannitol groups was not reported, and no intention-to-treat analysis was performed. Follow-up was not performed after 10 days. Case fatality and the proportion of those who were dependent were not reported, and data could not be obtained from the investigators.

Results of Studies
The reported outcome of the only included study was the change in clinical condition, categorized as improved, unchanged, or worsened. Fourteen of 41 controls (34%) and 12 of 36 mannitol-treated patients (33%) improved, whereas the number of those whose condition worsened was 18 of 41 (44%) and 16 of 36 (44%). With the use of the Peto odds ratio method, neither beneficial nor harmful effects of mannitol could be found. Case fatality, the proportion of dependent patients at the end of the follow-up, and side effects were not reported and were not available from the investigators. The planned outcome analyses and sensitivity analyses could not be performed because of lack of appropriate trials.

Discussion
Despite the facts that mannitol has been widely used to decrease elevated ICP and that both ischemic and hemorrhagic strokes are associated with some cerebral edema, very few randomized trials were performed to study the effects of mannitol in acute stroke. Four of the 5 randomized trials were confounded and therefore were excluded from analysis. In the only unconfounded randomized trial on mannitol in acute stroke, the method of randomization was not stated, information on concealment of randomization was not available, CT was not performed, no intention-to-treat analysis was performed, the number of included patients was small, the follow-up period was very short, and no data could be obtained on case fatality and dependency. On the basis of this single trial, no conclusion can be drawn, and currently there is not enough evidence to decide whether the routine use of mannitol in acute stroke would result in any beneficial or harmful effect. Therefore, the routine use of mannitol in all patients with acute stroke is not supported by any evidence from existing randomized clinical trials.

Although the beneficial effect of mannitol in acute stroke cannot be excluded, and the use of mannitol in certain clinical conditions in selected cases of acute stroke might be appropriate, the routine use of mannitol in all patients with acute stroke cannot be recommended at this time. The clinical efficacy of mannitol in acute stroke has not yet been properly evaluated. On the basis of some animal experiments and clinical observations, mannitol has effects that might be beneficial in acute stroke. To prove this hypothesis, placebo-controlled, unconfounded, properly randomized clinical studies should be designed and performed. In these studies, the registration of early and late case fatality and of valid and reliable measures of dependency and disability is recommended. Brain CT should be part of the study protocol, long-term follow-up (eg, 3 and 6 months) is mandatory, and intention-to-treat analysis should be performed.

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References
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