Meta analyses in treatment of spontaneous supratentorial intracerebral haematoma

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Published online February 9, 2006
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Summary

Background. None of the randomized controlled trials (RCT) on treatment of Intracerebral haematoma (ICH), definitely shows surgery to be beneficial over conservative treatment alone. Systematic reviews that pooled these RCTs were also inconclusive. This systematic review updates previous meta-analyses, using an alternative manner of reviewing with a criteria list constructed specifically for this type of disease and related interventions.

Methods. RCTs and quasi-RCTs (q-RCT) published in English were identified with a systematic literature search. They were evaluated with disease/intervention-specific criteria on comparability between intervention and control group concerning prognostic factors, co-interventions and effect measurement. The resulting selection of studies was compared with those of two earlier systematic reviews. In a meta-analysis selected studies were statistically pooled.

Findings. The meta-analysis of surgery versus conservative treatment failed to show a statistically significant reduction in the odds of death (OR: 0.84; 95% CI: 0.67–1.07) in surgically treated patients.

Conclusions. Like previous reviews, our disease/intervention-specific methodological evaluation showed no reduction in mortality. Sensitivity analysis demonstrates that the manner in which studies are methodologically evaluated in a systematic review has a great impact on its conclusions.

Keywords: Intracerebral haemorrhage; randomized controlled trials; stereotactic aspiration; surgical treatment; meta-analysis.

Introduction

Primary Intracerebral haematoma (ICH) has a high mortality (23–58% at 6 months) and severe disability [5, 16, 18, 20, 27, 33, 38]. There is no consensus about optimal treatment: surgical or conservative. Only a small number of randomized controlled trials (RCT) evaluated the efficacy of surgery in primary supratentorial ICH [1, 2, 6, 17, 21, 22, 26, 37, 42]. The few descriptive reviews [4, 9, 19, 31, 40, 41], systematic reviews and meta analyses [10, 29, 30, 34] were unable to demonstrate a significant treatment effect of either surgery or conservative therapy in ICH.

Most systematic reviews use predefined generic methodological criteria lists [24]. A potential weakness of this approach is that, while checking only for a methodologically adequate design of a study, it disregards whether this design results in actual good comparability of the trial groups. A second possible disadvantage is that, depending on the disease and the intervention that, some of the methodological criteria in the generic list may not be relevant. To overcome these disadvantages we carried out a systematic review on surgery for spontaneous ICH using a methodological criteria list developed/constructed specifically for this type of disease and related interventions. (For a copy of this list, please contact the first author.) The results of our systematic review were compared with other systematic reviews which used generic criteria lists [10]. In addition, this meta-analysis is an update by including new trials.

Methods and materials

Literature search

Literature selection was performed by searching MEDLINE, EMBASE-Excerpta Medica databases from 1966 to August 2005, using...
a Cochrane recommended search strategy [7] with medical subject heading (MESH) terms: intracerebral haematoma, intracerebral haemorrhage, surgery (combined with earlier MESH terms), and by citation tracking. Only RCTs and quasi-Randomized Controlled Trials (i.e. uncontrolled treatment allocation, e.g. by matching) published in English [25] were selected. Two of the authors (SE, OT) independently decided if the studies met the inclusion criteria for this review, e.g. age >15 years, altered level of consciousness, ICH-volume >10 ml, and treatment within 72 hours, surgical treatment in the experimental group and conservative medical treatment in a control group, effect parameters (mortality, functional outcome), sufficient follow-up period (>2 months).

Methodological evaluation

Selected studies were further evaluated by these authors using the disease/intervention-specific methodological criteria list to check for comparability of treatment groups for prognostic factors, co-interventions and effect measurement. Equal distribution of recognized prognostic factors, i.e. age, level of consciousness (Glasgow Coma Scale; GCS), ICH size and the presence of intraventricular blood (IVH) was checked [3, 11, 12, 23, 28, 39]. The use of pre-stratification, randomization (procedure, blinding), size of trial groups (more than 50 patients in each group), and percentage dropouts were recorded. Any co-interventions, like ventricular drainage, intracranial pressure measurement, etc. had to be regimented or at least described. Evaluation of comparability of effect measurement was done by checking if outcome was measured in mortality and/or dependency, and if the measurements were performed in a concealed fashion. The performance on these three main methodological issues (comparability of groups for prognostic factors, co-interventions and effect measurements) was graded as excellent (++++), good (+++), uncertain (++), poor (+) or unclear (?). If randomization resulted in lacking comparability, this could be corrected for by using multivariate analysis. Final inclusion in the meta-analysis was determined by these grades, (with a strong emphasis on the issue of comparability of prognostic factors (if rated less than ‘good’ on this item, than a ‘good’ rating on the other issues was necessary for inclusion). Data from included studies were entered in a meta-analysis. Statistical pooling was done by weighting the natural log of the Odds Ratio (OR) with its inverse variance. The effect of an intervention was expressed as an OR with a 95% confidence interval.

When methodological quality of a study was uncertain, a sensitivity analysis was done by in- and excluding that particular study. Furthermore, a subgroup analysis was done, comparing craniotomy with stereotactic surgery-studies to address the effect of the variability in interventions ranging from stereotactically guided endoscopic evacuation to old-fashioned craniotomy evacuation.

Results

8 RCTs [1, 2, 17, 21, 22, 26, 37, 42] and one q-RCT [36] were identified. The q-RCT of Tan et al. [36] used a non-blinded allocation method matching consecutive patients for ICH size and Glasgow Coma score (GCS) on admission, resulting in a good comparability of both intervention and control group concerning prognostic factors, co-interventions and effect-measurement (blinded).

Table 1 gives an overview containing the most important characteristics and outcome data. Four studies [1, 2, 17, 21] did not explicitly report on co-interventions. In 1 study [37] inter-group differences in side-effects were statistically analyzed, 4 studies [1, 17, 36, 42] described side effects per group (mostly concerning rebleeding), in 4 [2, 21, 22, 26] no side-effects were evaluated. No study reported blinded co-interventions. All studies had an adequate follow-up period and measured mortality and functional outcome (although not with uniform instruments). The different functional outcome scales in the studies were reclassified to a uniform outcome variable (death, dependent, independent, see Table 2).

7 studies [1, 2, 22, 26, 36, 37, 42] were included in the base-case meta-analysis, albeit most of them had some limitations. In the study of Auer et al. [1] the randomization procedure is unclear, but the study had a similar distribution of all checked prognostic factors (see Table 3). Comparability of ICH size and the presence of IVH in the study of Batjer et al. [2] was left unrevealed. In the study of Teernstra et al. [37], blinded randomization failed to achieve comparability in ICH-size between the study groups. Compensation of this possible bias with multivariate analysis, led this study to be included in the base-case meta-analysis. The presence of IVH was not mentioned in the feasibility study of Zuccarello et al. [42] and in the STICH trial (International Surgical Trial in Intracerebral Haemorrhage) of Mendelow [22]. This latest RCT with 1033 patients however achieved excellent baseline comparability between study-groups. A problem was a crossover of about 26% of patients randomised in the ‘initial conservative’ group to surgical treatment. As a worldwide multicentre trial without protocolized treatments, it is likely to have resulted in diverse patient inclusion and surgical procedures. Concealment of the outcome evaluator was absent in all trials except for the one of Tan et al. [36] and possibly the one of Zuccarello et al. [42].

Two studies [17, 21] had methodological flaws, and as a result these were included in the sensitivity analysis. Juvela et al. [17] found at baseline statistically significant differences between the trial groups for level of consciousness and the presence IVH. Multivariate analysis was not used to correct for possible confounding. The trial of McKissock et al. [21] dates from a pre CT-era, with a corresponding significant diagnostic error rate (4% in surgical patients, and in 5.5% in conservatively treated patients). Furthermore, ICH-size and IVH-presence and often ICH-localization (pre-randomization) were unknown.

Table 3 summarizes how the studies were graded and included in the base-case meta-analysis.

Statistical pooling

Figure 1a shows the ORs for the different studies and their pooled ORs for mortality. Fig. 1b is similar except