Meta-analysis of randomized studies of surgery for supratentorial intracerebral hemorrhage

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Summary Objective: The efficacy of surgical treatments on supratentorial intracerebral hemorrhage (STICH) is not conclusive although many studies have been performed. Relevant factors, such as the injury inflicted to the brain by different kinds of surgery, degrees of severity, and locations of intracerebral hemorrhage (ICH), should be taken into consideration for a better appraisal of the efficacy of surgery on STICH.
Methods: Randomized controlled trials to evaluate the efficacy of surgery on STICH were included for this meta-analysis. The appraised primary outcome was death, and the secondary outcome was death or dependence.
Results: Eighteen studies with 3616 patients were included in this meta-analysis. Surgery and minimal invasive surgery (MIS) showed a significant reduction in mortality as the primary outcome, and mortality or dependence as the secondary outcome, for all the intracerebral hemorrhage (ICH) patients and of the subgroup of deep-located ICH patients. MIS also showed a significant reduction both in mortality and dependence of the subgroup of putaminal ICH patients. In contrast, craniotomy showed no significantly better outcome than medical treatment. However, we found the mortality rate of the medical treatment group in the studies of craniotomy and MIS was different: 39% versus 20% for all cases of ICH, 50% versus 16% for putaminal ICH, and 51% versus 15% for deep ICH.
Conclusion: In terms of mortality and dependence, MIS had significantly better results than medical treatment for STICH, deep ICH, and putaminal ICH. In the present review, craniotomy showed no significantly better outcome than medical treatment.

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1. Introduction

Many studies conducting meta-analyses on randomized controlled trials to evaluate the efficacy of surgical treatments for supratentorial intracerebral hemorrhage (STICH) have shown diverse results. However, many factors that are relevant to the treatment outcomes in these studies, such as degrees of the severity, intracerebral hemorrhage (ICH) location, types of surgery, the definition of dependence in the study method, and the management of the cases lost to follow-up, were different in these studies. Because the treatment of STICH is still controversial, the review procedure should be more carefully designed, and an evidence-based methodology is necessary.

To date, various studies and guidelines for managing ICH are still not conclusive about the effects of surgery on STICH. One potential factor is the additional injury inflicted by surgery to the brain. For example, the additional injury of surgery for putaminal ICH would be different from that for lobar ICH, and so the injury of craniotomy would be different from that of the minimal invasive surgery (MIS, including stereotactic aspiration of ICH or endoscopic evacuation of ICH). Therefore, instead of comparing the results by pooling together all types of surgery against those of conservative medical treatment, different surgical methods should be viewed as independent factors for comparison. In addition, the results of putaminal ICH and deep-located ICH should be reviewed separately. By doing so, effects of different modes of surgery in these randomized studies can be delineated.

2. Methods

We followed the PRISMA statement to identify relevant studies, and two review authors independently identified the articles according to inclusion and exclusion criteria. Studies published in PubMed (1966–2012), Medline (1966–2012), and the Cochrane library regarding CT-confirmed STICH were included. The types of intervention included surgery (craniotomy, endoscopic evacuation or stereotactic aspiration) supplemented with medical treatment, and medical treatment alone. Exclusion criteria were hemorrhage caused by brain injury, brain tumor bleeding, intracranial aneurysm, or arteriovenous malformation rupture. Papers that were irrelevant to the surgical results of ICH were excluded, and so were all retrospective reviews. We did not include the reports that only compared the results of different types of surgery without a control medical treatment group.

The locations of STICH were differentiated into putaminal and deep-located ICH, if mentioned. In the present study, the primary outcome was death, and the secondary outcome was death or dependence. For assessment of “dependence”, the definition of the primary outcome from the original studies was adopted. Comparisons were drawn on groups of surgery for STICH versus medical treatment, craniotomy for STICH versus medical treatment, MIS for STICH versus medical treatment, surgery for deep ICH versus medical treatment, craniotomy for deep ICH versus medical treatment, MIS for deep ICH versus medical treatment, surgery for putaminal ICH versus medical treatment, craniotomy for putaminal ICH versus medical treatment, and MIS for putaminal ICH versus medical treatment. The data were also calculated separately with and without the cases lost to follow-up. Pooled estimates of the effects of surgery on STICH were acquired by the Mantel–Haenszel method. The 95% confidence interval (CI) of the results, and the odds ratio (OR) for surgical effects, were calculated by the dichotomous random-effects model was used for the possibility of heterogeneity across studies. We assessed heterogeneity among the trial results using the chi-square test and I² square index (I²). A p value of 0.05 or less was taken as statistically significant and I² values of 25%, 50%, and 75% were considered as low, moderate, and high heterogeneity, respectively. Because the severity in the studies of MIS may be different from that of craniotomy, the experimental event rate (EER, surgical treatment group), control event rate (CER, medical treatment group), absolute risk reduction (ARR) and the number needed to treat to benefit (NNTB) were calculated to evaluate if there were any differences between these two groups.

3. Results

The 3678 studies from PubMed (1966–2012), and 3890 studies from Ovid Medline (1966–2012) on spontaneous STICH were retrieved, including 125 randomized studies and meta-analyses. The original studies from references of meta-analyses were also reviewed, and several additional papers were included. In the end, 18 studies with 3616 patients were included for this meta-analysis (Fig. 1). All these studies had data of mortality about surgery and medical treatment, and 17 of them also had data regarding dependence. Criteria for evaluating “dependence” included Auer’s Grade 5 (totally dependent on others for activities of the day), Batjer’s Level 1 (dead or vegetative) and Level 2 (dependent at home or institution), extended Glasgow Outcome Scale, ≤3 on the 5-point Glasgow Outcome Scale on the modified Rankin Scale score, and ≤60 of the Barthel Index (Table 1).

The reported duration of follow up was 30 days in one study, 3 months in four studies, 6 months in 10 studies and 1
3678 publications from PubMed

3890 publications from Ovid Medline

Excluded criteria:
1. Irrelevant to the surgical results.
2. Retrospective studies.

125 randomized studies and meta-analyses were fully reviewed

Excluded studies:
1. No medical treatment group as control.
2. No clear data of surgical results.
3. Duplicated studies.

Additional studies:
Eligible original randomized studies from reference of qualified meta-analyses.

18 eligible studies

Figure 1 Flow charts of all studies included.

Table 1 All included studies for meta-analysis.

<table>
<thead>
<tr>
<th>Case number (surgery versus medical)</th>
<th>Follow-up duration</th>
<th>Primary outcome and definition of dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auer 1989 (E)</td>
<td>6 months</td>
<td>Grade 5¹</td>
</tr>
<tr>
<td>Juvela 1989 (C)</td>
<td>6 months</td>
<td>GOS &lt; 3</td>
</tr>
<tr>
<td>Batjer 1990 (C)</td>
<td>6 months</td>
<td>Level 1 and 2²</td>
</tr>
<tr>
<td>Chen 1992 (C or S)</td>
<td>3 months</td>
<td>中, 差³</td>
</tr>
<tr>
<td>Morgenstern 1998 (C)</td>
<td>6 months</td>
<td>Bl &lt; 60</td>
</tr>
<tr>
<td>Zuccarello 1999 (C or S)</td>
<td>3 months</td>
<td>GOS &lt; 3</td>
</tr>
<tr>
<td>Cheng 2001 (S)</td>
<td>3 to 6 months⁴</td>
<td>中, 差⁴</td>
</tr>
<tr>
<td>Kurtsoy 2001 (C)</td>
<td>30 days</td>
<td>GOS III and GCS IV⁵</td>
</tr>
<tr>
<td>Hosseini 2003 (S)</td>
<td>1 year</td>
<td>Average Karnofski’s score⁶</td>
</tr>
<tr>
<td>Teernstra 2003 (S)</td>
<td>6 months</td>
<td>mRS ≥ 3</td>
</tr>
<tr>
<td>Sun 2004 (C or S)</td>
<td>6 months</td>
<td>Dependent⁷</td>
</tr>
<tr>
<td>Hattori 2004 (S)</td>
<td>1 year</td>
<td>mRS ≥ 3</td>
</tr>
<tr>
<td>Mendelow 2005 (C, E or S)</td>
<td>6 months</td>
<td>Extended GOS⁸</td>
</tr>
<tr>
<td>Pantazis 2006 (C)</td>
<td>1 year</td>
<td>GOS &lt; 3</td>
</tr>
<tr>
<td>Wang 2008 (C, E, or S)</td>
<td>6 months</td>
<td>mRS ≥ 3 or Bl &lt; 60</td>
</tr>
<tr>
<td>Miller 2008 (E)</td>
<td>3 months</td>
<td>mRS ≥ 3</td>
</tr>
<tr>
<td>Wang 2009 (S)</td>
<td>3 months</td>
<td>mRS ≥ 3</td>
</tr>
<tr>
<td>Kim 2009 (S)</td>
<td>6 months</td>
<td>mRS ≥ 3</td>
</tr>
</tbody>
</table>

E = endoscopic surgery; C = craniotomy; S = stereotactic surgery.

¹ Grade 5: conscious patients totally dependent on others for activities of the day.
² Level 1: dead or vegetative; level 2: dependent at home or institution.
³ 中, 差: no definition in papers.
⁴ 中, 差: Barthel Index was used to evaluate the results 3 to 6 months after intervention, without further definition.
⁵ GOS III: severe disability, same as GOS 3; GOS IV: vegetative state, same as GOS 2.
⁶ Only average Karnofski’s score were compared between the studied groups.
⁷ No definition of “dependent”.
⁸ Extended GOS: favourable and unfavourable outcomes were defined a little different on the basis of the original clinical status at randomization.
⁹ One patient who had been excluded due to brain tumor found during autopsy was added back to the medical treatment group.
¹⁰ Four patients assigned to BMM (best medical management) plus ICP (Intracranial pressure) monitoring were excluded due to ventriculostomy received.
¹¹ Same author used different last name in English; two different studies in different periods and hospitals.
¹² Only “ultra-early” and “early” groups were included because there were no clear data about dependency in “late” groups.
year in three studies. Data on death at the end of follow up were available for all the 18 studies. At the end of the follow up, it was found that surgery was associated with a statistically significant reduction in mortality of all ICH patients (OR 0.65, 95% CI 0.50 to 0.85, \( p = 0.002 \), Fig. 2A), and of the subgroup of deep ICH patients (OR 0.60, 95% CI 0.39 to 0.92, \( p = 0.02 \), Fig. 2B). MIS showed significant reduction in mortality of all ICH patients (OR 0.55, 95% CI 0.35 to 0.87, \( p = 0.01 \), Fig. 3A), of the subgroup of putaminal ICH patients (OR 0.52, 95% CI 0.31 to 0.86, \( p = 0.01 \), Fig. 3B) and of the deep ICH patients (OR 0.57, 95% CI 0.34 to 0.96, \( p = 0.04 \), Fig. 3C).

A total of 17 studies reported the outcome of death or dependence at the end of follow up. Surgery was associated with a statistically significant reduction in mortality or dependence of all the ICH patients (OR 0.62, 95% CI 0.46–0.84, \( p = 0.002 \), Fig. 4A), and of the subgroup of deep ICH patients (OR 0.6, 95% CI 0.37–0.96, \( p = 0.04 \), Fig. 4A). MIS was found to be associated with a significant reduction in mortality or dependence of all the ICH patients (OR 0.52, 95% CI 0.33–0.80, \( p = 0.003 \), Fig. 5A), of the subgroup of putaminal ICH patients (OR 0.44, 95% CI 0.32–0.61, \( p < 0.001 \), Fig. 5B), and of the deep ICH patients (OR 0.39, 95% CI 0.30–0.52, \( p < 0.001 \), Fig. 5C).

Craniotomy showed no significantly better outcome than medical treatment in mortality of all the ICH patients (OR 0.72, 95% CI 0.42–1.22, \( p = 0.22 \), of the subgroup of putaminal ICH patients (OR 0.9, 95% CI 0.39–2.07, \( p = 0.8 \)) and of the deep ICH patients (OR 0.57, 95% CI 0.23–1.40, \( p = 0.22 \)). Craniotomy also showed no significantly better outcome than medical treatment in mortality or dependence of all the ICH patients (OR 0.83, 95% CI

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**Figure 2** Mortality rate of surgery versus medical treatment. Significant results were found for (A) all included patients and (B) the subgroup of deep intracranial hemorrhage patients.
CI 0.41–1.67, \( p = 0.6 \)), of the subgroup of putaminal ICH patients (OR 0.77, 95% CI 0.18–3.28, \( p = 0.73 \)) and of the deep ICH patients (OR 0.62, 95% CI 0.22–1.78, \( p = 0.38 \), Table 2).

Upon further inspection, it was found that the event rate of the medical treatment group was different between the studies of craniotomy and MIS. The mortality rate of the medical treatment group in the studies of craniotomy and MIS was 39% (74/188) and 20% (126/646), respectively. When the outcome event was death or dependence for analysis, the event rate of the medical treatment group in the studies of craniotomy and MIS was 77% (404/524) and 67% (475/713), respectively (Table 2).

For putaminal ICH, MIS was adopted much more than craniotomy, and thus the sample sizes were quite different between these two groups (124 cases for craniotomy and 665 cases for MIS). When death was taken as the outcome for comparison between the medical treatment groups in craniotomy versus MIS studies, it was found that the event rate was 50% in craniotomy studies (34/68) versus 16% of MIS studies (52/329). When the outcome was death or dependence, the event rate for the medical treatment group in craniotomy studies was 81% (55/68) whereas that in the MIS studies was 67% (221/328) (Table 2).

For deep ICH, MIS was also adopted much more than craniotomy, and thus the sample sizes were quite different between these two groups (172 cases for craniotomy and 1115 cases for MIS). When death was taken as the outcome for comparison between the medical treatment groups in craniotomy versus MIS studies, it was found that the event rate was 51% in craniotomy studies (48/95) versus 15% of MIS studies (89/582). When the outcome was death or...
dependence, the event rate for the medical treatment group in craniotomy studies was 83% (79/95) whereas that in MIS studies was 65% (367/564) (Table 2).

4. Discussion

Many reported randomized studies and their meta-analyses showed different results about the effects of surgery on STICH. The beneficial effects of surgery on STICH included removing the mass, reducing the toxicity of ICH, and preserving the penumbra area around the ICH.28 However, surgery itself unavoidably inflicted certain brain damage. Therefore, the clinical outcome of surgery-treated ICH is related to the degree of brain damage brought about by the procedure. For example, less injury caused by operation on lobar ICH, especially for ICH 1 cm near the brain surface, is correlated to a better outcome as compared to that for deep-located ICH, including putaminal ICH. Additionally, the minimal invasive surgery, including the stereotactic aspiration and endoscopic removal of hematoma, usually has better clinical results due to less harm to the brain tissue. This is consistent with our finding in the current study that minimal invasive surgery had better results than medical treatment for all STICH, deep ICH and putaminal ICH. However, the less favorable results of craniotomy may also be due to other factors. For example, the lower death rate in the medical treatment group for MIS studies than that for craniotomy studies (20% and 39%, respectively as shown in Table 2) suggests that the overall severity was different from the beginning. Therefore, various outcomes from different surgeries may be due to different degrees of injury to brain by surgical methods (craniotomy versus MIS), different ICH locations (putaminal or deep-located ICH versus lobar ICH) as well as the severity of the patients’ conditions.

For meta-analysis of studies, intent-to-treat should be considered to minimize the bias. Some reports analyzed the results including the number of cases lost to follow up, but...
not in others. Several studies reviewed in the current study had cases lost to follow up. However, no great differences were observed when data with or without cases lost to follow-up were compared.

In the present study, several different data from other previous reviews were used with careful consideration. We included one patient in Juvela’s study who was assigned to the medical treatment group initially and was excluded later due to the brain tumor found at autopsy. Four patients assigned to the best medical treatment (BMM) plus ICP monitoring in Batjer’s study were excluded because they underwent ventriculostomy for drainage. In Wang’s (2008) study, only surgical data in “ultra-early” and “early” stages were included since no clear data of dependence were reported in the group of surgery in the “late” stages. Additionally, the number of deaths or that of dependence cases in Kim’s study was derived by subtracting the cases with a modified Rankin Scale (MRS) score of ≤2 at 6-month follow ups from the total studied cases, that was 56 in the stereotactic-guided surgical group and 102 in the medical treatment group. With such calculations, the case numbers were different from those reported by Zhou.

For comparison the outcome of death or dependence, many reports used different methods for definition of dependence, and we used the primary outcome reported. In some reports, where they included different data by different definition of dependence, and if we compared the studies using these different data, we found that the difference became small.

Our review revealed that in terms of mortality and dependence, minimal invasive surgery had better results than medical treatment for all supratentorial intracerebral hemorrhage, deep-located ICH and putaminal ICH. Craniotomy showed no significant better outcome than medical treatment for all supratentorial intracerebral hemorrhage, deep-located ICH and putaminal ICH.
Acknowledgments

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References


