Evidence Based Management of Intracerebral Hemorrhage

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Introduction

Definition
Intracerebral hemorrhage (ICH) results from the rupture of an intracerebral vessel leading to the development of a hematoma in the substance of the brain.

Significance
In the US ICH represents 10 percent of all strokes (approximately 70,000 new cases each year).

It is twice as common as subarachnoid hemorrhage and carries an equally poor prognosis.

Economic Cost
The estimated the lifetime cost for a new case of ICH to be on average $123,565.

This translates to 8-9 billion dollar cost to society to treat the new cases of ICH each year.
Medical Management of ICH

Is there any medical therapy which has been proven to benefit patients who suffer an ICH?

- Does treating hypertension in the acute period improve outcome?
- Is there any evidence that medical treatment of mass effect in patients with ICH improves outcome?

Hypertension in ICH

Hypertension is very common after ICH.

MAP > 140 in 34%
MAP > 120 in 78%

Typically, blood pressure returns to baseline over the course of one week, with the greatest decline occurring during the first 24 hours.

The Evidence

- Does lowering BP in acute period after ICH improve outcome?
- Does lowering of BP in acute period decrease changes of hematoma enlargement?

Lowering Blood Pressure and Outcome

Study One

- 167 patients with ICH (diagnosed by clinical suspicion, LP, and angiography) were separated into treated and untreated group.
  - 123 patients treated with hypotensive drug (Reserpine IM)
  - 44 patients untreated
- Goal BP not stated, and degree of lowering variable.
- Typically Systolic BP brought to range of 160-180 mm Hg.
- Outcome: Mortality at 6 weeks.

Results: Overall mortality rate 81%
<table>
<thead>
<tr>
<th></th>
<th># Patients</th>
<th>Mortality</th>
<th>Coma on Admission - #</th>
<th>Coma on Admission - %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequately Treated</td>
<td>40</td>
<td>63%</td>
<td>29/40</td>
<td>73%</td>
</tr>
<tr>
<td>Inadequately Treated</td>
<td>83</td>
<td>82%</td>
<td>65/83</td>
<td>78%</td>
</tr>
<tr>
<td>No treatment</td>
<td>44</td>
<td>98%</td>
<td>41/44</td>
<td>93%</td>
</tr>
</tbody>
</table>

**Study Two**


- Retrospective chart review.
- Subjects: 87 patients with hypertensive ICH in thalamus or basal ganglia who had history of HTN.
- Analysis: Mortality and severe morbidity in patients with MAP > 125 mm Hg after treatment vs. MAP < 125 mm Hg after treatment at 6 hours.

Results:

<table>
<thead>
<tr>
<th></th>
<th>Mortality Rate (30d)</th>
<th>Mortality / Severe Morbidity (30 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP &gt; 125</td>
<td>43%</td>
<td>60%</td>
</tr>
<tr>
<td>MAP &lt; 125</td>
<td>21%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Confounder:

<table>
<thead>
<tr>
<th></th>
<th>Treated MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAP &lt; 125</td>
</tr>
<tr>
<td>Initial MAP &lt; 145</td>
<td>39 patients</td>
</tr>
<tr>
<td>MAP MAP &gt; 145</td>
<td>11 patients</td>
</tr>
</tbody>
</table>

**Rate of Blood Pressure Decline**


- Design: Retrospective Chart Review
- Inclusion Criteria: 105 patients with ICH who had more than 5 blood pressure measurements over the first 24 hours were included in the analysis.
- MAP calculated as a slope (change mm Hg/hr)
• Determine effect of MAP Slope decline on mortality and functional outcome adjusted for GCS and hematoma volume.

Results:

• Rate decline patients who died -2.7 +2.1 mm Hg
• vs -1.2 + 1.1 mm Hg
• Logistic regression analysis showed that the rate of decline of BP in the first 24 hours an independent predictor of mortality but did not affect functional outcome of survivors.

Hematoma Enlargement

• 103 patients with ICH had CT done within 3 hours of onset. Repeat CT was done at 1 hour and 20 hours after baseline
• > 33% growth had occurred in 26% of patients between baseline and 1 hour CT scan
• > 33% growth had occurred in 40% of patients by 20 hour CT scan.

<table>
<thead>
<tr>
<th></th>
<th>&gt; 33% growth</th>
<th>&lt; 33% growth</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP at onset mm Hg</strong></td>
<td>200 ± 34</td>
<td>199 ± 38</td>
</tr>
<tr>
<td><strong>Diastolic BP at onset, mm Hg</strong></td>
<td>110 ± 18</td>
<td>108 ± 28</td>
</tr>
<tr>
<td><strong>History of HTN</strong></td>
<td>62%</td>
<td>68%</td>
</tr>
</tbody>
</table>

Summary of Hypertension Treatment in Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Prospective</th>
<th>Retrospective</th>
<th>Case Series</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer et al. 1962</td>
<td>Dandapani et al. 1995</td>
<td>Lower BP good</td>
<td></td>
</tr>
<tr>
<td>Qureshi et al. 1999</td>
<td>Brott T et al 1995</td>
<td>Hematoma enlargement not associated with degree of HTN</td>
<td></td>
</tr>
</tbody>
</table>
Treating Mass Effect
Is there any benefit of medically treating mass effect in ICH?

• Corticosteroids
• Glycerol
• Mannitol

Corticosteroids

• Double Blind, Randomized, Block Design.
• 93 patients with CT confirmed ICH within 48 hours of the onset were randomized.
• Treatment involved Dexamethasone 10 mg 1st day, then 5 mg every 6 hours for 5 days, then 5 mg every 12 hours for 2 days, then 5 mg for one day.
• During third interim analysis mortality rates were identical between two groups, but rate of complications ten times higher in treated group.

Result: No benefit

Glycerol

• Double-blind, randomized placebo-controlled trial.
• Patients with first stroke, with CT confirmed ICH within 24 hours of onset were recruited.
• 107 received active treatment, 109 given placebo.
• Treatment consisted of 400 cc of 10% glycerol in saline over 4 hours on 6 consecutive days.
• Outcomes (mortality, improvement in Scandinavian Stroke Study Group scores, Improvement in Barthal index) measured at 6 months.

Result: No difference between groups

Mannitol

<table>
<thead>
<tr>
<th></th>
<th>Improved</th>
<th>Worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>14/41 (34%)</td>
<td>18/41 (44%)</td>
</tr>
<tr>
<td>Mannitol</td>
<td>12/36 (33%)</td>
<td>16/36 (44%)</td>
</tr>
</tbody>
</table>
Summary of Medical Treatment of Mass Effect in ICH

- Corticosteroids = No benefit
- Glycerol = No benefit
- Mannitol = No proven benefit

There is no evidence from randomized trials that corticosteroid, glycerol, or mannitol improves patient outcome.

Hemodilution


- 164 patients with ICH within 12 hours of onset, and Hct > 35% were randomized to either hemodilution or control.
  - 83 patients treated
  - 81 patients control
- Therapy: 350 cc blood removed, and 350 cc dextran 40 in 0.9 saline infused

<table>
<thead>
<tr>
<th></th>
<th>Hemodilution</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>25/83 (30%)</td>
<td>25/81 (30%)</td>
</tr>
<tr>
<td>Dependent (Rankin 3-6)</td>
<td>32/83 (38%)</td>
<td>27/81 (33%)</td>
</tr>
<tr>
<td>Independent (Rankin 1-2)</td>
<td>26/83 (32%)</td>
<td>29/81 (37%)</td>
</tr>
</tbody>
</table>

Conclusion: No benefit

Summary of Medical Management of ICH

No acute medical treatments has been proven to improve patient outcome after ICH in a randomized trial.
Surgical Treatment of ICH

- Does open craniotomy with evacuation of supratentorial ICH improve patient outcome?
- Does endoscopic aspiration for supratentorial ICH improve patient outcome?
- Does surgical evacuation of cerebellar ICH benefit patients?
- Does ventriculostomy for hydrocephalus improve patient outcome?

Open Craniotomy with Evacuation of Supratentorial ICH: Randomized Control Trials

**Study One**

- Inclusion Criteria: Patients with clinical history, physical signs, CSF, and angiography supporting the diagnosis of supratentorial ICH were randomized to either conservative management or surgery. No time limit specified.
  - 91 patients randomized to conservative management
  - 89 patients randomized to surgery.
- Treatment was craniotomy and evacuation of the hematoma.
- Outcome was mortality and disability at 6 months.

Results:

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td>65%</td>
<td>51%</td>
</tr>
<tr>
<td><strong>Bad Outcome</strong></td>
<td>80%</td>
<td>66%</td>
</tr>
</tbody>
</table>

Odds Ratio of Death and Dependency: (95% CI) 2.00 (1.04-3.86) medical better

**Study Two**

- Inclusion Criteria: Patient with CT confirmed supratentorial ICH who were admitted within 24 hours of the onset. Patient were either unconscious or had severe hemiparesis. Surgery within 48 hours.
  - 26 in conservative management
  - 26 in surgical group
- Treatment: Craniotomy with evacuation of hematoma
- Outcome: Death or disability (Glasgow Outcome Scale) at 6 months and 12 months.
Results:

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>46%</td>
<td>38%</td>
</tr>
<tr>
<td>Bad Outcome</td>
<td>98%</td>
<td>81%</td>
</tr>
</tbody>
</table>

Odds Ratio of Death and Dependency:

4.39 (0.81-23.65) medical better

**Study Three**


- Inclusion Criteria: 21 patients with CT confirmed putaminal ICH > 3 cm and with hypertensive history who had altered consciousness or limb weakness.
  - 9 patients in best medical management
  - 4 patients with medical management and ICP monitoring
  - 8 patients with surgical evacuation
- Treatment: Craniotomy with evacuation of hematoma
- Outcome: Mortality and functional outcome at 3 and 6 months.

Results:

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>78%</td>
<td>67%</td>
</tr>
<tr>
<td>Bad Outcome</td>
<td>78%</td>
<td>83%</td>
</tr>
</tbody>
</table>

Odds Ratio of Death and Dependency:

0.86 (0.10-7.64) surgery better

**Study Four**


- Inclusion Criteria: Patients with CT confirmed supratentorial (lobar or extending out of thalamus) ICH > 9 cc, GCS 5-15 within 12 hours of onset
  - 15 patients in surgical group
  - 16 patients in medical group
- Treatment: Craniotomy with evacuation of hematoma
- Outcome: Mortality or disability at 1 month and 6 month.
Results:

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>24%</td>
<td>18%</td>
</tr>
<tr>
<td>Bad Outcome</td>
<td>50%</td>
<td>69%</td>
</tr>
</tbody>
</table>

Odds Ratio of Death and Dependency: 
0.46 (0.11 to 1.86) surgery better

Open Craniotomy with Evacuation of Supratentorial ICH: Ultra-Early Treatment

- Adult patients within 4 hours of onset of spontaneous supratentorial intracerebral hemorrhage. Comparison made to medical and surgical group treated within 12 hour time window.
  - 11 patients treated surgically within 4 hours
  - 12 patients treated surgically within 12 hours
  - 12 patients treated medically within 12 hours
- Outcome: Mortality and functional outcome at 6 months
- Study stopped because of safety concerns
- Rebleeding rate 4 HS 40%, 12 HS 12%.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>4 HS</th>
<th>12 HS</th>
<th>12 HM</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 month mortality</td>
<td>36</td>
<td>18</td>
<td>29</td>
</tr>
<tr>
<td>6 month median BI</td>
<td>75</td>
<td>65</td>
<td>55</td>
</tr>
</tbody>
</table>

Open Craniotomy with Evacuation of Supratentorial ICH: Acute Worsening

- Reviewed 26 cases of spontaneous ICH with acute worsening who had surgery for clot evacuation.
  - 56% died, 22% remained severely disabled, 22% regained independence.
  - All patients with loss of brainstem reflexes died.

[www.strokecenter.org](http://www.strokecenter.org)
Endoscopic Aspiration for Supratentorial ICH

- Inclusion Criteria: Patients with CT confirmed supratentorial ICH > 10 cc and < 48 hours from time of onset with altered level of consciousness.
  - 50 patients surgical group
  - 50 patients medical group
- Treatment: Endoscopic aspiration of clot
- Outcome: Mortality and disability at 6 months

<table>
<thead>
<tr>
<th></th>
<th>Surgical</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>42%</td>
<td>70%</td>
</tr>
<tr>
<td>Poor Outcome</td>
<td>58%</td>
<td>74%</td>
</tr>
</tbody>
</table>

Odds Ratio of Death and Dependency: \textbf{0.46} (0.20-1.04) surgery better

Meta-analysis

- Meta-analysis of all 7 randomized controlled trials of the effect of surgery after a supratentorial spontaneous ICH.
- Meta-analysis of the randomized controlled trials of the effect of surgery after a supratentorial spontaneous ICH to exclude the trial of McKissock et al.
- Meta-analysis of the randomized controlled trials of the effect of surgery after a supratentorial spontaneous ICH to exclude the trials of McKissock et al and Chen et al.

Summary of Surgical Treatment for Supratentorial ICH
Several randomized trials with low power have failed to demonstrate benefit associated with surgical evacuation of supratentorial ICH.

Surgical Evacuation of Cerebellar ICH
- No evidence from randomized trials of benefits of surgical evacuation in ICH.
- Evidence mostly in the form of case series.
Study

- Design: Non-randomized Prospective
- Patients: 75 patients with cerebellar hemorrhage were studied.
  - 45 treated medically
  - 30 treated with decompressive surgery.
- Patients with GCS < 13, and hematoma > 40 mm
- Good outcome occurred 58% with surgery while only 18% with conservative medical therapy

Ventriculostomy

- Method: Retrospective chart review.
- Inclusion: 24 patients with spontaneous supratentorial ICH who were treated with external ventricular drainage were included.
- Treatment: Ventriculostomy catheter. Best medical care.
- Results 16/22 patients died in hospital. 17/20 patients died at 3 months. 2 were lost to follow-up
- External ventricular drains did not improve hydrocephalus, and changes in ventricular volume did not correlate with changes in level of alertness.
Conclusions

- There is no medical treatment which has been proven by a randomized trial to improve patient outcome after ICH.
- No randomized trial has demonstrated benefit of surgery in patients with ICH.
- There is currently few RCT which have adequately evaluated the potential benefit of medical and surgical intervention for ICH.
- The I-STITCH trial should provide valuable insight into the efficacy of craniotomy and surgical evacuation of intracerebral hematoma.
References


www.strokecenter.org


