Influence of surgery on mortality of Iranian patients with subarachnoid or intracerebral hemorrhage

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Abstract
Introduction: Surgical intervention is a routine treatment in patients with Subarachnoid Hemorrhage (SAH). However, influence of aneurysm surgery in the developing counties may be different than developed countries. Decision for surgical intervention in patients with Intracerebral Hemorrhage (ICH) is a subject of controversy.

Methods and materials: Consecutive patients with SAH or ICH admitted in Ghaem hospital, Mashhad during 2005-2009 enrolled in a prospective clinical study. Diagnosis and work up of SAH and ICH was performed by neurologists. Decision for performing aneurysm surgery and evacuation of hematoma was made by neurosurgeons. All of the SAH or ICH patients received a standard conservative medical management. Frequency of complications and mortality was compared in medical and surgical groups of SAH patients.

Results: 120 SAH patients (52% females) with mean age of 50.6±7 years were evaluated and 46.6% of them underwent aneurysm surgery. The effect of therapeutic type on mortality of SAH patients was not significant; X²=1.8, df=1, p=0.17. Difference in frequency of rebleeding in two therapeutic groups of our patients was not significant; X²=0.37, df=1, p=0.54. The influence of rebleeding in mortality of our patients was significant; X²=4.50, df=1, p=0.048. 193 ICH patients (52% females) with mean age of 61±3 years enrolled the study and 62.7% of them underwent surgery. Frequency of mortality was not significantly different in two therapeutic groups of ICH patients; X²=2.34, df=1, p=0.126. The influence of surgery on mortality of the ICH patients was not significant in lobar, putaminal, cerebellar and thalamic subtypes of our patients (X²=0.16, df=1, p=0.77), (X²=2.34, df=1, p=0.126), (X²=0.01, df=1, p=1) and (X²=3.09, df=1, p=0.08) respectively.

Conclusion: Influence of aneurysm surgery in frequency of death is not significant in Iranian patients with SAH which could be due to delay in performance of surgery in Iranian neurovascular centers. Influence of surgery in frequency of death is not significant in our patients with ICH. Surgical intervention is not useful in patients with lobar, putaminal and cerebellar hemorrhage and may be harmful in patients with thalamic hemorrhage.

Keywords: Mortality, Subarachnoid, intracerebral, Surgery, Hemorrhage

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Introduction
Outcome for patients with SAH remains poor with mortality rates up to 45% and significant morbidity among survivors. Case review and prospective cohorts have shown that for untreated, ruptured aneurysms, there is at least a 3-4% risk of rebleeding in the first 24 hours and 1-2% per day in the first month. Urgent evaluation and treatment of patients with suspected SAH is therefore recommended. The major complications following SAH are ischemic deficit (27%), hydrocephalus (12%) and recurrent hemorrhage (11%). The most feared complication for the survivors of the initial hemorrhage had been recurrent bleeding, which occurred in 15-20% of the patients and was associated with a 40-78% mortality. The definitive method for prevention of rebleeding is to secure the aneurysm as soon as possible. Early surgery may not be appropriate for every patient with SAH, but every attempt like endovascular coiling should be made to secure the aneurysm as soon as possible to prevent rebleeding. Issues related to treatment of primary ICH have been dominated by two main considerations: 1- The type and intensity of medical interventions required to improve the functional and vital prognosis, and 2- The choice between medical and surgical therapy. To a great extent, these two important aspects of treatment remain unclarified, largely as a result of a remarkable paucity of prospective clinical trials. A direct surgical approach is considered frequently in patients with lobar or cerebellar hematomas, whereas patients with brainstem, caudate and thalamic hemorrhage are rarely, if ever surgical candidates. Putaminal hemorrhage occupies an intermediate position and is most controversial. ICH has a 30-day mortality rate of 35% to 52%, half of deaths occur in the first 2 days. Death at 1 year for ICH varies by location of ICH; 51% for deep hemorrhage, 57% for lobar, 42% for cerebellar and 65% for brain stem. Of all the surgical therapies described for treating ICH, craniotomy has been the most extensively studied and 7 of the 9 randomized controlled trials of ICH evaluated craniotomy. Most of these trials are small, single center studies that randomized fewer than 125 patients. None of these small studies found convincing evidence of surgical benefit. This is the first reported prospective experience of surgery on death rate and complications of Iranian SAH or ICH patients.

Patients and Methods
Part 1: Consecutive patients with Subarachnoid Hemorrhage (SAH) admitted in Ghaem hospital, Mashhad during 2005-2009 enrolled a non-blind prospective clinical study. Diagnosis of SAH was made based on brain CT. Patients suspected to SAH with normal brain CT underwent FLAIR MRI and lumbar puncture. Cerebral catheter angiography is a routine diagnostic investigation in our SAH patients. SAH patients were usually admitted for
3 weeks in either neurology or neurosurgery divisions. SAH patients who underwent aneurysmal clipping operation were categorized as surgical therapeutic group. Aneurysmal clipping is the usual type of surgical procedure in our hospital for these patients. Aneurysmal coating is not performed and endovascular coiling is not available in our hospital. Patients who underwent ventricular shunting for hydrocephalus without aneurysmal clipping were assumed as medical therapeutic group for aneurysm. Decision about performance of surgery for aneurysm was made by neurosurgeons. Patients in surgical group also received standard medical management for SAH. Principles of medical management included; analgesic, nimodipine, sedative, laxative, control of blood pressure and 3 liters of normal saline per day.7,8 Mortality and complications of SAH including rebleeding, hydrocephalus and brain infarction due to vasospasm were recorded in medical and surgical groups of our SAH patients during 3 weeks of hospitalization. Time interval between onset of SAH and death was recorded in all of the deceased SAH patients. In surgical group of the patients, mean SAH onset to surgery time and in deceased subgroup of surgically managed patients, mean surgery to death time was recorded.

Part 2: Consecutive patients with primary Intracerebral Hemorrhage (ICH) admitted in Ghaem hospital, Mashhad during 2005-2009 enrolled a prospective clinical study. Diagnosis and localization of primary ICH was made by neurologist based on brain CT.7,9 All of the ICH patients received a standard medical management including 1.5 liter of normal saline per day, control of hypertension, analgesics and other conservative managements7,9. Activated coagulation factor of seven is not available in our hospital for medical management of primary ICH patients. Selection of ICH patients for surgical evacuation was performed by neurosurgeons. Craniotomy and evacuation of hematoma is the routine surgical technique in our hospital. Shunting for hydrocephalus and drainage of intraventricular blood with or without evacuation of hematoma was performed based on the neurosurgeon decision. Stereotactic surgery with or without thrombolysis is rarely performed in our hospital and none of the reported patients with primary ICH underwent this surgical approach. Neurologists ruled out other causes of ICH based on the medical history and neuroimaging.10 ICH patients suspected to tumoral lesions underwent MRI with contrast and patients suspected to arteriovenous malformation had MRI, MRA and catheter angiography.10 In-hospital death was recorded in two therapeutic groups of primary ICH patients. Mean ICH onset to death time was recorded in whole of the deceased ICH patients. In surgical group of the patients, mean ICH onset to surgery time and in deceased subgroup of surgically managed patients, mean surgery to death time was recorded.
Chi-Square and Fisher tests served for statistical analysis and p<0.05 declared as significant.

Results
Part 1: One hundred twenty SAH patients (63 females, 57 males) with mean age of 50.6±7 years were prospectively evaluated. Medical and surgical therapeutic groups included 53.4% and 46.6% of our SAH patients respectively. Hypertension, smoking, oral contraceptive consumption, trauma and over dosage of oral anticoagulation therapy were found in 41.6%, 19.1%, 0%, 0% and 0.8% of our patients respectively. Fifty six patients underwent surgical operation, while 11 cases had ventricular shunting without aneurysmal clipping and were assumed as medical management for aneurysm and remainig 45 patients underwent craniotomy and aneurysmal clipping. Death occurred in 44.2% of whole SAH patients including 60.4% of females and 39.6% of males. 27 patients in surgical group and 34 patients in medical group deceased. The effect of therapeutic type on mortality of SAH patients was not significant; X2=1.8, df=1, p=0.17. Difference in frequency of death between two therapeutic groups of SAH patients was not significant in females and males (X2=1.54, df=1, p=0.11) and (X2=0.73, df=1, p=0.39) respectively. The mean SAH onset to death time is 14.1±2 days in all of the deceased SAH patients. In surgical group of the patients, mean SAH onset to surgery time is 8.4±3 days and in deceased subgroup of surgically managed patients, mean surgery to death time is 5.9±3 days. Rebleeding occurred in 5.4% of surgical and 3.1% of medical groups of our SAH patients. Difference in frequency of rebleeding in two therapeutic groups of our patients was not significant; X2=0.37, df=1, p=0.54. Among 5 SAH patients with rebleeding, 2 had anterior communicating artery aneurysm, 2 had normal angiogram and 1 did not underwent angiography. 75% of our SAH patients with rebleeding expired which shows prognostic effect of rebleeding on mortality of these patients. The influence of rebleeding in mortality of our patients was significant; X2=4.50, df=1, p=0.048 . Hydrocephalus was present in 14.2% of patients including 10.7% of surgical and 17.2% of medical groups. Frequency of hydrocephalus was not significantly different in two therapeutic groups of our SAH patients; X2=0.034, df=1, p=0.854. Among 17 SAH patients with hydrocephalus, 13 cases (76%) died which shows the prognostic effect of hydrocephalus in these patients. The influence of hydrocephalus in mortality of these patients was significant; X2=7.93, df=1, p=0.007. Brain infarction due to vasospasm occurred in 5.8% of patients including 3.6% of surgical and 7.8% of medical groups. The influence of aneurysmal therapeutic strategy on frequency of brain infarction due to vasospasm was not significant; X2=0.97, df=1, p=0.44. Among seven SAH patients with brain
infarction due to vasospasm, three cases died. The effect of brain infarction in mortality of SAH patients was not significant; \( X^2 = 0.005, \) \( df = 1, \) \( p = 1. \) Table 1 represents distribution of complications in two therapeutic groups of our patients. Catheter angiography was conducted in 98 SAH patients and aneurysm was found in angiography of 66 patients. Anterior communicating artery, middle cerebral artery, internal carotid artery, basilar artery, anterior cerebral artery, posterior communicating artery, vertebral artery and multiple locations consisted 42%, 24%, 15%, 5%, 5%, 3% and 3% of aneurysmal localizations respectively. Within 66 SAH patients with observed aneurysm in angiography, frequency of mortality in two therapeutic groups was not significantly different; \( X^2 = 0.65, \) \( df = 1, \) \( p = 0.537. \)

### Table 1: Distribution of complications in two therapeutic groups of our 120 SAH patients

<table>
<thead>
<tr>
<th>Therapeutic groups/Complications</th>
<th>Rebleeding</th>
<th>Vasospasm</th>
<th>Hydrocephalus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical ( (n=56) )</td>
<td>3 (5.4%)</td>
<td>2 (3.6%)</td>
<td>6 (10.7%)</td>
</tr>
<tr>
<td>Medical ( (n=64) )</td>
<td>2 (3.1%)</td>
<td>5 (7.8%)</td>
<td>11 (1.5%)</td>
</tr>
<tr>
<td>Total ( (n=120) )</td>
<td>5 (4.2%)</td>
<td>7 (5.8%)</td>
<td>17 (14.2%)</td>
</tr>
</tbody>
</table>

Part 2: One hundred ninety three ICH patients (52% females) with mean age of 61±3 years enrolled the study. In medical group 72 patients (58% females) with mean age of 62.9±4 years and in surgical group 121 patients (48% females) with mean age of 60±4 years were investigated. Table 2 represents localization of hemorrhage in two therapeutic groups of our patients. Infratentorial localization consisted 12.5% of medical and 18.2% of surgical groups of our ICH patients.

### Table 2: Localization of hemorrhage in two therapeutic groups of 193 ICH patients

<table>
<thead>
<tr>
<th>Therapeutic group/Location</th>
<th>Lobar Number(%)</th>
<th>Putaminal Number(%)</th>
<th>Thalamic Number(%)</th>
<th>Cerebellar Number(%)</th>
<th>Brainstem Number(%)</th>
<th>Isolated intraventricular hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical(72)*</td>
<td>29 (80.5%)</td>
<td>21 (27.8%)</td>
<td>11 (13.9%)</td>
<td>4 (5.5%)</td>
<td>5 (2.8%)</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td>Surgical(121)**</td>
<td>51 (81.2%)</td>
<td>14 (10.9%)</td>
<td>16 (12.5%)</td>
<td>22 (17.2%)</td>
<td>0 (0%)</td>
<td>8 (6.3%)</td>
</tr>
</tbody>
</table>

*12 patients had multiple localization of hemorrhage
**18 patients had multiple localization of hemorrhage

This difference in frequency of infratentorial localization of ICH in two therapeutic groups of our patients is due to more tendency for evacuation of cerebellar hematomas. The mean ICH onset to death time in medical and surgical groups of our deceased ICH patients is 14.8 days ranged 1-40 days and 15.4 days ranged 1-23 days respectively. In deceased subgroup of our surgically treated ICH patients mean ICH onset to surgery time and
mean surgery to death time is 2.2 days ranged 1-16 days and 14.1 days ranged 1-52 days respectively. In-hospital mortality rate for medical and surgical therapeutic groups of ICH patients was 50% and 65.6% respectively. Distribution of in-hospital mortality was not significantly different in two therapeutic groups of our ICH patients; X²=2.34, df=1, p=0.126. The influence of gender on in-hospital mortality was not significant in medical and surgical groups of our ICH patients; (X²=1.02, df=1, p=0.31) and (X²=0.201, df=1, p=0.65) respectively. Influence of surgery on mortality of ICH patients was analyzed based on ICH localization. The effect of surgery on mortality of the ICH patients was not significant in lobar, putaminal, cerebellar and thalamic subtypes of our patients (X²=0.16, df=1, p=0.77), (X²=2.34, df=1, p=0.126), (X²=0.01, df=1, p=1) and (X²=3.09, df=1, p=0.08) respectively. However surgery had a nonsignificant benefit in patients with lobar hematoma and a nonsignificant harm in patients with thalamic hematoma. Thirty seven ICH patients underwent ventricular shunting which was performed with surgical evacuation of hematoma in 13 cases. Table 3 demonstrates details of surgical approach and mortality of 37 ICH patients who underwent shunt insertion.

### Table 3: Details of surgical approach and mortality of 37 ICH patients with shunt insertion

<table>
<thead>
<tr>
<th>ICH location</th>
<th>Only Shunting</th>
<th>Shunting with hematoma evacuation</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar (n=2)</td>
<td>1</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>Putaminal(n=5)</td>
<td>5</td>
<td>-</td>
<td>75%</td>
</tr>
<tr>
<td>Thalamic(n=12)</td>
<td>8</td>
<td>4</td>
<td>80%</td>
</tr>
<tr>
<td>Cerebellar(n=10)</td>
<td>2</td>
<td>8</td>
<td>75%</td>
</tr>
<tr>
<td>Isolated IVH (n=8)</td>
<td>8</td>
<td>-</td>
<td>100%</td>
</tr>
<tr>
<td>Total (n=37)</td>
<td>24</td>
<td>13</td>
<td>86%</td>
</tr>
</tbody>
</table>

**Conclusion**

Part 1: In aneurysm surgery, increased time to treatment is associated with increased rates of preoperative rebleeding in retrospective and prospective studies and recently has been associated with higher rates of poor outcome. The International Cooperative Study on the Timing of Aneurysmal Surgery analysed management of 3521 patients and 83% of whom underwent surgical repair of the ruptured aneurysm. Timing of surgery after SAH was significantly related to the likelihood of preoperastive rebleeding. Patients who underwent early surgery had a significantly lower preoperative rebleed rate than those who underwent later surgery (3% versus 11%). Mean SAH onset to surgery time in our SAH patients was 8 days which is longer than reports of the western countries. This prominent delay in performance of aneurysm surgery in our patients could be the main reason of...
ineffectiveness of surgery in decreasing mortality of our patients. Because during this delay many complications may occur in the surgical group of our SAH patients. In recent years, there has been a trend toward early surgery for ruptured aneurysms, especially in good and moderate grade patients\textsuperscript{2,11}. In addition, early surgery facilitates the aggressive therapy of vasospasm\textsuperscript{2}. However, there were no overall differences in outcome of patients operated early (0-3 days post SAH) or late (11-14 days post SAH)\textsuperscript{11}. Surgical mortality was higher with early surgery due to brain swelling, disturbed autoregulation and hemorrhage\textsuperscript{11}. Surgery was more hazardous between days 7 and 10 due to the combined risks of rebleeding and vasospasm\textsuperscript{11}. A prospective study from three centers indicates that despite attempts at early surgery, rebleeding is still a significant problem, because only one half of the patients were operated within 72 hours, and 35% of the patients with poor outcome had suffered rebleeding\textsuperscript{13,14}. In addition, some SAH patients with acute hydrocephalus may benefit from early placement of a ventricular drain at the hospital\textsuperscript{15}. Acute hydrocephalus is more frequent in patients with poor clinical grade. The clinical significance of acute hydrocephalus after SAH is uncertain because many patients are apparently asymptomatic and do not deteriorate\textsuperscript{2}. Relationship between type of management with mortality and complications was not significant in our SAH patients. While influence of rebleeding and hydrocephalus on mortality was significant in all of our SAH patients which is congruent with results of the developed countries\textsuperscript{16}.

Part 2: This is the first reported comparison of medical and surgical management of ICH from Iran. The International Surgical Trial in Intracerebral Hemorrhage randomized 1033 patients from 107 centers over an 8-year period began in 1995\textsuperscript{12}. Patients were eligible if randomized within 72 hours and were operated within 96 hours of ictus for a clot>2 cm in diameter\textsuperscript{12}. Patients with very poor condition (GCS score <5) were excluded. Patients were randomized if the neurosurgeon was uncertain of the benefit of surgery, with 50% randomly assigned to a policy of either early surgery or initial medical management\textsuperscript{17}. Primary outcomes were the incidence of death and disability. 26% of the medical arm ultimately crossed over to surgery. This cross over was due to rebleeding or deterioration in 85% of crossover subjects and craniotomy was used in 85% of them\textsuperscript{12}. Surgery was associated with a statistically insignificant absolute benefit of 1.2% for preventing death and statistically insignificant 4.1% absolute benefit for preventing severe disability\textsuperscript{12}. Subgroup analysis identified those subjects with GCS score of 9 to 12, those with lobar clot and those with clot <1cm from the surface that may have been helped by early surgery, but this did not reach statistical significance\textsuperscript{12}. In contrast, those presenting with deep coma tend
to do better with medical management. Together, the data from this trial and other smaller trials suggests that surgery does not appear to be helpful in treating most supratentorial ICHs and is probably harmful in those presenting in coma. Surgery, particularly craniotomy, may be helpful in treating those lobar clots within 1 cm of the surface that present in patients with milder deficits (GCS score >9)\(^{17}\). Distribution of mortality was not significantly different in two therapeutic groups of our ICH patients. The effect of surgery on mortality was not significant in lobar, putaminal, cerebellar and thalamic subtypes of our ICH patients. Our results shows that surgery does not reduce in-hospital death rate in ICH patients and surgery may be harmful in patients with thalamic hematomas. Randomized trials of surgery did not include patients with cerebellar hemorrhage. Non-randomized treatment series of patients with cerebellar hemorrhage reported good outcomes for surgically treated patients who have large (>3cm) cerebellar hemorrhages or cerebellar hemorrhage with brainstem compression or hydrocephalus\(^{18}\). In these patients, medical management alone often results in bad outcomes. Smaller cerebellar hemorrhages without brain stem compression that are managed medically do reasonably well in the case series\(^{7,18}\). Overall, craniotomy and surgical evacuation of hematoma has not been better than conservative management\(^{6}\). Six randomized clinical trials compared surgical with nonsurgical treatment of ICH, and the results were generally inconclusive, mostly because of methodological issues\(^ {19}\). Our prospective case series is not a double-blind clinical trial. Well-designed, prospective multicenter clinical trial is required to answer this important clinical question and at the same time evaluate conventional craniotomy against other newer surgical approaches.
References
تأثیر جراحی بر بیماران با خونریزی زیر عنکبوتیه و یا داخل مغزی

چکیده
سابقه و هدف: اعمال جراحی یک درمان معمول در بیماران با خونریزی ساب آراکونوند است ولی تأثیر جراحی آنورسیم در کشور یک در حال توانمندی توسه همکاری می‌کند آموزه باید شاخص آموزش باشد. تصمیم گیری برای اقدام جراحی در بیماران با خونریزی داخل مغزی یک موضوع شک برانگیز است.

روش بررسی: بیماران پیوسته با بیماران با خونریزی زیر عنکبوتیه یا داخل مغزی در بیمارستان قابل مشهد در سال های 1384-1388 در این مطالعه آیین نگر باینی وارد شدند. تشخیص و اقدامات کمک تشخیصی برای خونریزی زیر عنکبوتیه و داخل مغزی توسط مختصین بیماری‌های اطفال و تصمیم گیری در مورد جراحی آنورسیم و یا تخلیه هماهنگ توسط جراح اطفال بود. تمامی بیماران فوق درمانی طبی نگهدارشده استاندارد را نیز دریافت کرده. فراوانی نسبی عوارض و مرگ و میر در دو گروه درمانی طبی و جراحی از بیماران فوق مقایسه شد.

یافته‌ها: 120 بیمار (52٪ زن) با خونریزی زیر عنکبوتیه و میانگین سنی 6/5 سال بررسی شدند و/94 در آنان تحت جراحی آنورسیم قرار گرفتند. تأثیر روش درمانی بر مرگ و میر این بیماران معنی دار نبود (X^2=1.8, df=1, p=0.17). تفاوت در توزیع فراوانی خونریزی مجدد در دو گروه درمانی از بیماران فوق نیز معنی دار نبود (X^2=0.37, df=1, p=0.54). در دو گروه درمانی طبی و جراحی از بیماران فوق تفاوت معنی‌دار نداشت (X^2=2.34, df=1, p=0.126). تأثیر نوع درمان بر مرگ و میر در گروه یک در بیماران با خونریزی داخل مغزی در انواع لیبر و بوتانیمال و X^2=2.34, df=1, p=0.16, df=1, p=0.08 و (X^2=0.01, df=1, p=0.126)

نتیجه‌گیری: تأثیر جراحی آنورسیم بر بیماران با خونریزی زیر عنکبوتیه یا داخل مغزی که می‌تواند ناشی از تأثیر در انجام جراحی در مراکز جراحی اطفال ایران باشد. تأثیر جراحی بر فراوانی مرگ در بیماران با خونریزی داخل مغزی معنی‌دار ندارست. درمان جراحی برای بیماران با خونریزی لیبر و بوتانیمال و متخیه مفید نبوده و حتی در بیماران با خونریزی تالاسوس ممکن است بشرد.

واژگان کلیدی: مرگ- زیر عنکبوتیه- داخل مغزی- خونریزی- جراحی