Early Mortality Following Stroke: A Prospective Review

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SUMMARY Analysis of early deaths after stroke is important, since some deaths may be preventable. Previous studies have relied on retrospective and often incomplete clinical data, for comparison with pathological findings.

The present study is based on 1073 consecutive stroke patients admitted to an intensive care stroke unit from a well-defined population. There were 212 deaths within the first 30 days, yielding a mortality rate of 20%. Clinical, radiological, and laboratory data were collected prospectively according to a standardized protocol. Autopsies were performed on 90 of the 212 patients, and CT scanning on a further 27.

Early mortality after stroke exhibits a bimodal distribution. One peak occurs during the first week, and a second during the second and third weeks. The majority of deaths in the first week are due to transtentorial herniation. Of these, deaths due to hemorrhage usually occur within the first three days, whilst deaths due to infarction peak between the third and sixth day post ictus. After the first week, deaths due to relative immobility (pneumonia, pulmonary embolism and sepsis) predominate, peaking towards the end of the second week. Cardiac deaths occur throughout the first month, and unfortunately account for many deaths in patients with small functional deficits.

STROKE is the third leading cause of death in adults, and many stroke-related deaths occur shortly after the onset of symptoms. Available data suggest a 30-day mortality ranging from 40 to 84% in cerebral hemorrhage, and from 15 to 33% in cerebral infarction.1-3 To date only a few studies have attempted to determine the timing and pathogenesis of early stroke deaths,4-7 but their results may not be representative of the early mortality of all types of stroke. Thus, three studies concerned only patients with carotid territory infarcts, and none included patients with brainstem infarcts. All were reviews of autopsied cases, and so may not accurately reflect clinical experience.

Planning treatment strategies, and assessing prognosis, in acute stroke requires as complete as possible an understanding of the mechanisms culminating in death. Therefore, a prospective combined and pathological evaluation of early deaths, from consecutive patients admitted to a hospital stroke unit, was undertaken.

Methods

The study population consisted of all patients admitted consecutively to the MacLachlan Stroke Unit of Sunnybrook Medical Centre, between January 1, 1975 and March 31, 1980, with a diagnosis of completed stroke. All patients presenting to the hospital with suspected acute stroke, other than those requiring urgent neurosurgical intervention, were admitted to this unit.

The hospital services a primarily middle-class residential area in Metropolitan Toronto. Fewer than 10% of the patients admitted to the unit were referred from other centres, so that the study population is representative of the community.

Prospective data were collected according to a standardized stroke unit protocol. All patients, whilst in the Stroke Unit, had continuous ECG monitoring, serial cardiac enzymes and 12-lead ECG's; Lumbar puncture, isotope brain scans and angiography were performed when indicated. CT scanning became available after September 1978. Autopsies were requested on all patients who died and obtained in 42% of cases.

"Completed stroke" was defined as cerebral infarction or intracerebral hemorrhage, associated with a focal neurological deficit which persisted longer than 24 hours. Patients were divided into four "stroke types" by the pathology of the lesion (infarct or hemorrhage) and the site of lesion (supratentorial or infratentorial). Embolic cerebral infarction cannot be reliably distinguished from non-embolic even at autopsy, let alone by clinical or radiological examination. Hence such distinction could not be used as a prognostic guide, and was not attempted. When there were multiple lesions, patients were classified according to the clinically presenting lesion. Infarction secondary to migraine, arteritis or profound hypotension (eg post-cardiac arrest), and hemorrhage secondary to trauma, tumor, aneurysm or arteriovenous malformation, was classified as "secondary stroke" and excluded from further analysis.

The definitive diagnosis was based on autopsy findings and/or CT scan, or on the combination of clinical, radiological and laboratory findings.

"Stroke onset" to the nearest hour was obtained from the patient when possible, or from relatives or witnesses at the time of admission. Survival time was defined as the interval from stroke onset (not the date of admission) to death. Assessment of functional status

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Received July 21, 1983; revision #1 accepted October 28, 1983.

Stroke Vol. 15, No 3, 1984
was based on the patient's best performance in activities of daily living. It was classified as Grade I (fully independent), Grade II (independent but requiring assistance or supervision), Grade III (fully dependent and usually bed ridden), and Grade IV (comatose or chronic vegetative state).

Cause of death

The following criteria were used to determine the cause of death:

Transventorial Herniation
Autopsy findings of caudal axial shift including caudal thalamic and subthalamic shift, secondary (Dur-et's) hemorrhages, midline compression of thalamus, subthalamus and/or midbrain, or distinct uncal herniation and its sequelae. Clinical picture of progressive rostrocaudal brainstem deterioration just prior to death.

Pneumonia
Autopsy findings of bilateral acute confluent bronchopneumonia associated with markedly increased lung weights. Clinical and radiological findings of fever, positive sputum cultures and pulmonary consolidation.

Pulmonary embolus
Autopsy findings of a saddle pulmonary embolus or bilateral multiple large pulmonary emboli. Clinical picture, confirmed by arterial blood gas determinations, chest x-ray and lung scan.

Cardiac
Autopsy findings of pulmonary edema with excessive lung weights, supported by evidence of underlying significant heart disease (recent MI, myocardial fibrosis, dilated ventricles). Clinical evidence of severe pulmonary edema or documented life-threatening arrhythmias. (The presence of transventorial herniation excludes a patient from this category).

Septicemia
Autopsy demonstration of a source or multiple sites of infection with positive ante-mortem blood cultures. Clinical evidence of infection, positive cultures and hypotension.

Sudden death
Sudden, unexpected death in a patient who was neurologically and medically stable, and in whom the autopsy and clinical data provided no apparent cause for death.

Unknown
Cases in which death was neither sudden nor unexpected, but in whom neither clinical, radiological nor autopsy findings explicitly indicated a cause of death. Many brainstem infarcts fall into this group (see Discussion).

Results

From January 1975 to April 1980, 1705 patients were admitted with a suspected stroke, and the final diagnosis in 1073 patients was completed stroke. There were 583 men and 490 women. Diagnosis was infarction in 967 (538 men, 429 women) and hemorrhage in 106 (45 men, 61 women). The mean age in both groups was the same (71 years).

212 patients died within 30 days of stroke onset (table 1). The diagnosis was confirmed by autopsy alone in 67 patients, by CT scan alone in 27, and by autopsy and CT scan in 23. In the remaining 95 patients diagnosis was based on a combination of clinical, laboratory and radiological findings.

Supratentorial Infarction
All 125 patients had cerebral infarction in a carotid distribution. Of the 67 cases with autopsy or CT scan data, twelve had bilateral or multiple infarcts. Only six patients arriving in hospital within 6 hours of onset were comatose. Three of these patients were postictal, and one at autopsy had multiple bilateral infarcts.

Transventorial herniation (TTH) accounted for 36 of 46 (78%) deaths during the first week (table 2). No patient died of TTH in the first 24 hours, and only four TTH deaths occurred after the tenth day (fig. 1). One of these four patients died of hemorrhage into an infarct while on heparin therapy, and in the other three, a sudden change in neurological condition just prior to death suggested a second episode of infarction. This was confirmed in the two autopsied cases, both of which revealed areas of infarction of different ages, one corresponding to the onset of symptoms, and one recent. Deaths from pneumonia were spread over the last three weeks, whereas cardiac deaths occurred throughout the period.

The functional status of the 83 patients dying of non-cerebral causes was grade III or IV in 59 (71%). Of the 24 grade I or II patients, 13 suffered cardiac or sudden death (table 3).

Supratentorial Hemorrhages
There were 55 patients with hemispheric hemorrhages (see fig. 2). 18 were located in the basal ganglia, 10 were lobar and 6 thalamic. In 21 the location was not documented (CT scan or autopsy not done). Of the 48 patients examined within 6 hours of stroke on-
TABLE 2  Comparison between Mechanisms of Death during the First Week and the 2nd to 4th Week in 180 Patients with Supratentorial Lesions

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Infarction</th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First week</td>
<td>2-4th week</td>
</tr>
<tr>
<td>Transtentorial herniation</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Cardiac</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Sudden death</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Septicemia</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Brain stem extension (of hematoma)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Totals</td>
<td>46</td>
<td>79</td>
</tr>
</tbody>
</table>

set, 32 were stuporous or comatose, and twenty-two of these patients survived less than 72 hours.

In the first week TTH accounted for 42 of the deaths (see table 2) (37 occurring within the first 72 hours). Of six TTH deaths between the fourth and the ninth days, three were clinically attributed to rebleeding and three to edema. Marked edema was seen pathologically in two, but none of the autopsies revealed separate hemorrhages of different ages. Two patients with thalamic hemorrhages died because of direct extension of blood into the brainstem. One occurred on the twelfth day and autopsy disclosed only fresh hemorrhage, suggesting that a second recent hemorrhage must have obliterated the original hematoma. Intraparenchymal hemorrhage was present in 26 of 36 patients.

Only one patient was functionally independent prior to death (table 3). This patient had a small thalamic hemorrhage and died from pulmonary embolism on day 22.

Infratentorial Infarction

This group included 28 patients with vertebrobasilar infarction. All had clinical or pathological evidence of brainstem lesions, except one patient with a massive cerebellar infarct. Some had multiple areas of infarction including the occipital lobes and cerebellar hemispheres.

Of the 13 deaths occurring in the first week, one was secondary to brainstem compression from a massive cerebellar infarct, 2 were secondary to pneumonia, 2 were cardiac, and 8 were classified as unknown. Over the whole 30 days there were 13 of these “unknown” deaths, with survival times varying from 12 hours up to 21 days.

Only two patients were classified as functional grade I or II (table 3). One had a lateral medullary infarct and died suddenly, and the other had dysarthria and dysphagia which lead to death from aspiration pneumonia.

Infratentorial Hemorrhage

There were four deaths from brainstem hemorrhage. All four patients were comatose during their entire stay in hospital, and the longest survival was 8 days. One case was confirmed by autopsy as a massive pontine hemorrhage.

TABLE 3  Functional Status Prior to Death (in 123 Patients Dying of Non-cerebral Causes)

<table>
<thead>
<tr>
<th></th>
<th>Supratentorial</th>
<th>Infratentorial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>Infarction</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Infarction</td>
<td>Hemorrhage</td>
</tr>
<tr>
<td>I</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>37</td>
<td>5</td>
</tr>
<tr>
<td>IV</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Totals</td>
<td>83</td>
<td>9</td>
</tr>
</tbody>
</table>

FIGURE 1.  Causes of death in the 125 patients with supratentorial infarction. The top histogram shows all patients with the lower two histograms represent the non-cerebral deaths.

FIGURE 2.  Causes of death in the 55 patients with supratentorial hemorrhage.
Discusssion

In this study, we have attempted to achieve an accurate perspective of the mechanisms and timing of death in acute stroke patients by combining autopsy, CT and prospective clinical data. Therefore all patients admitted to our stroke unit have been included in the analysis. Autopsy series have an inherent bias, in that they tend to include the most dramatic deaths where consent for autopsy is more successfully obtained. Clinical information in published series was obtained retrospectively, and data as to the exact onset of ictus is usually lacking. These factors may account for some of the differences in results between the present study and previously published studies.

A known selection bias in our series was, that patients requiring urgent neurosurgical intervention were not included in our stroke unit admissions. This explains the lack of cerebellar hemorrhages, and suggests that intracerebral hemorrhage may be slightly underestimated. Also, in order to determine the "true" number of early stroke deaths, the number of patients dying before reaching hospital would have to be known.

The overall 30 day case fatality rate for patients with completed stroke was 20%. Mortality was highest in patients with hemispheric hemorrhage (58%) and lowest with hemispheric infarction (15%). These 30 day case fatality rates are in close agreement with the Framingham study, except for the patients with intracerebral hemorrhage, where the Framingham rate (82%) was considerably higher than in our series (52%). This can be explained in part by the smaller number of CT scanned patients in the Framingham series (CT scanning will detect small hemorrhages which have a better prognosis) and the fewer total number of patients in that study, 17 as compared to 55 in our study. Douglas and Haerer reviewed 70 patients with CT-proven intracerebral hemorrhage, and found an in-hospital mortality of only 40%.

Shaw, Alvord and Berry suggested in 1959 that deaths during the first week following cerebral infarction were directly related to brain swelling. Similarly in this series, deaths from transtentorial herniation accounted for 82% of deaths during the first week in those patients with supratentorial infarction or hemorrhage. Most late deaths from transtentorial herniation occurred after a second event, implying again that death had occurred within one week of the latest cerebral infarction.

It is not clear from the literature when brain swelling is maximal following cerebral infarction. Shaw et al concluded, after looking at midline brain shifts at autopsy, that swelling is maximal at 3 to 5 days. This has also been supported by angiographic, CT, and other autopsy studies. Experimental models of cerebral infarction show an increase in water content beginning within hours and peaking at 48 hours, which is reasonably consonant with the clinical and autopsy evidence. Our results would favor brain swelling being maximal from 2 to 6 days following hemispheric infarction. Thirty of 37 deaths (80%) due to TTH occurred during this period and no TTH deaths occurred in the first 24 hours. In fact, coma shortly after the onset of symptoms tends to exclude the diagnosis of hemispheric infarction.

The time course for patients with TTH secondary to hemorrhage is different. Unlike patients with cerebral infarction, most of these deaths occurred in the first 72 hours. The principle early cause of brain swelling in intracerebral hemorrhage is the space-occupying effect of the hematoma. Although the number of patients is small, there is a suggestion of a second peak of deaths at the end of the first week, perhaps attributable to edema formation around the hematoma. However, Classen et al demonstrated that edema increases only during the initial 3 days and then declines. Rebleeding, although probably rare, could account for some late TTH deaths. Douglas and Haerer had no examples of rebleeding in their series of 70 patients with intracerebral hemorrhage.

Seven of the 15 early deaths following brain stem infarction were classified as "cause unknown." Logi-
cally, if the initial area of infarction included medul-
ary cardiopulmonary centres, death would occur
instantaneously, the patients would be dead on admis-
sion, and no structural changes could be seen at autops.
Patients who survive long enough to be admitted to
hospital must die from such causes as extension of
their infarct, edema formation with secondary compro-
mise of nearby vital centres, or non-neurological prob-
lems. The first two mechanisms may be responsible for
many of the "unknown" early deaths, but since they
are not explicit at autopsy we prefer to term them
"cause unknown" pending a more detailed study.

Although patients with brainstem hemorrhage had a
high early mortality, they seem to be rare and account-
ed for only 1.5% of the completed strokes in this
series.

After the first week, most stroke deaths are non-
neurological in nature (fig. 4). The high frequency of
pneumonia and pulmonary embolism between the sec-
ond and fourth weeks reflects the complications of
relative immobilization, secondary to the patients' de-
pressed levels of consciousness and motor deficits.
Brown and Glassenberg6 suggested that these non-neu-
rological deaths were preventable. However, the ma-
jority of patients who survived longer than one week in
our series, and died of non-cerebral, therefore poten-
tially preventable, causes, had poor functional grades.
Their neurological deficit left them totally dependent
for only 1.5% of the completed strokes in this
series.

The results of this study suggest that controlling
brain swelling in the first week, and reducing periods
of immobilization in the subsequent weeks, could po-
tentially prevent many early stroke-related deaths.
However, these strategies do little to reduce the size of
the primary brain lesion, and therefore would prolong
the lives of some patients with enormous functional
deficits. Until methods are available to minimize or
reverse ischemic tissue damage, and to reduce the size
of infarcts and hemorrhages, perhaps the emphasis of
stroke units should be to admit patients with small
neurological deficits, or with transient ischemic
events, in the attempt to prevent future strokes. Table 4
indicates the non-neurological causes of death in 27
patients of functional grades I or II, and underlines
attention necessary to preempt cardiovascular and re-
spiratory complications in this type of patient.

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distribution of water in brains of cats after occlusion of the middle

<table>
<thead>
<tr>
<th>Functional grade</th>
<th>Cardiac</th>
<th>Sudden</th>
<th>Pneumonia</th>
<th>Pulmonary embolism</th>
<th>Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>6</td>
<td>2</td>
<td>nil</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>2</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4: Non-neurological Causes of Death in 27 Patients of Good Functional Status
Early mortality following stroke: a prospective review.
F L Silver, J W Norris, A J Lewis and V C Hachinski

Stroke. 1984;15:492-496
doi: 10.1161/01.STR.15.3.492

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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