STROKE STUDY GROUP

PRELIMINARY RESULTS
EARLY INTENSIVE CARE IMPROVES FUNCTIONAL OUTCOME

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SUMMARY - Early and intensive care seems to positively affect outcome in stroke patients. A standardized protocol, costly adjusted to our reality and suitable for application by non-specialist at Emergency Room, proved effective, reflecting in diagnosis reliability, reducing time for beginning therapy, leading to low mortality rates and better functional outcomes at discharge.

KEY WORDS: stroke, treatment, functional outcome, mortality.

Rather than mortality, recovery from stroke is hallmarked by functional improvement. Recent evidences pointing to a trend in mortality reduction need, to have greater social impact, be followed by a parallel decline in stroke morbidity. There is no concern about proper management in acute phase of stroke: despite these controversies, early intensive care seems to result in better outcomes, whether consequence of some specific therapeutic measure or of the whole rational treatment. Experimental data points to a "therapeutic window", a time-related interval in which neurons functionally inactive might be restored if adequate conditions are provided. Precise duration of this interval remains speculative but, it seems reasonable to suppose with some confidence, from animal data, that it is not far from 6 to 8 hours. In our country, first aid for stroke sufferers are provided usually by a non-specialist, an internist; and he is the fortunate "therapeutic window guest". Delay in time-to-start therapy must account, at least partially, for some deterioration in cellular condition, spreading damage to adjacent "ischemically threatened neurons", rendering their potentially recovering state to a irreversible one, with necrosis and worsening functional outcome. So, functional outcome serves as a sensitive marker to estimate extension and progression of ischemic process.

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Since September 1992, patients entering our hospital with presumed diagnosis of stroke are submitted to a standard protocol including clinical, laboratory and neuroimaging evaluation, with early and rational therapeutic measures, in order to shorten time for beginning treatment. This study, Stroke Study Group, was designed to be readily accessible to the internist and costly adjusted to our reality. Despite still low number of cases, some preliminary considerations about functional outcome after first year of protocol can be done.

**METHODS**

**Demographic Data.** Between September 1992 and August 1993, 157 consecutive patients were admitted with presumed diagnosis of “clinically probable non-categorized stroke”, involving the carotid artery distribution territory. After admission form (Appendix 1), all them were submitted to the same protocol including clinical and laboratorial evaluation, besides with therapeutic measures (Appendix 2), as early as possible, at Emergency Room. Patients were examined by the same neurologist on first 24 hours interval from beginning of symptoms; a CT scan was done between 24-48 hours and repeated if necessary. Additional investigation, e.g. echocardiography, carotid ultrasound and aortic arch angiography, was performed, if indicated case by case.

A control group, matched for age and sex distribution, was composed by retrospective hospital charts analysis of 113 consecutive non-selected patients admitted 1 year just prior to standardization, with final diagnosis of stroke in carotid artery territory.


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<th>Date:</th>
<th>Hour:</th>
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1. **DEMOGRAPHIC DATA**

Patient initials: Age: years Sex: 

File: Race: Manual dexterity: Educational grade: years 

2. **MEDICAL HISTORY**

Tabagismo: cigarettes/day years Alcohol abuse: Coffee: cups/day 

Hipertension: Regular treatment: Diabetes mellitus: Insulin dependent: 

Medications (dose):

Major surgery (with dates):

3. **CLINICAL EXAMINATION**

(\textit{Glasgow Coma Scale})

3.1. **Level of consciousness:** 

Ocular: Verbal: Motor: Total GCS score:

3.2. **Signs and symptoms at Entry:**

Headache Vomiting Seizures Speech deficit 

Focal deficit: motor sensitive visual 

specify 

Time from onset of symptoms: hours 

Blood pressure (decubitus): / mmHg Pulse rate bpm Temperature:

Cardiovascular examination: 

Respiratory examination: 

Presumed diagnosis:

1. ACUTE PHASE:

   Early care, after presumed diagnosis, performed at Emergency Room.

1.1 - VENOUS ACCESS:

   * Routine blood analyses
     - complete haematology with platelet count
     - erythrocyte sedimentation rate and aPTT
     - serum glucose, urea, creatine and electrolytes
     - V.D.R.L.
   * Ringer lactate 1500 ml/24h IV
   * Pentoxiphyline 100 mg 8/8h IV
   * GM1 100 mg 12/12h IV

1.2 - HAEMOGLUCOTEST, each 6 hour

   Correct with regular insulin SC according to below:
   - 160-200 mg % = 4 unit
   - 300 mg % = 8 unit
   - 500 mg % = 12 unit

1.3 - BLOOD PRESSURE CONTROL, each 4 hour

   Nifedipine 100 mg SL if systolic > 200 mmHg or diastolic > 110 mmHg

1.4 - ORAL FEEDING = 0

2. SUBACUTE PHASE

2.1 - BEFORE final diagnosis:

   2.1.a - VENOUS ACCESS
   * Ringer lactate 1500 ml/24h IV
   * Pentoxifiline 100 mg 8/8h IV
   * GM1 100 mg/24h IV for 15 days

2.1.b - HAEMOGLUCOTEST, each 6 hour, with regular insulin as in 1.2

2.1.c - BLOOD PRESSURE CONTROL, each 6 hour, as stated in 1.3

2.1.d - Low-volume non-glycosylated oral diet

   Consider nasoenteral feeding (Doob-Hoof), if one of the following:
   - Glasgow Coma Scale score 15 points
   - Objective evidence of bronchoaspiration
   - Marked cough after swallowing

2.2 - AFTER definitive diagnosis:

2.2.1 - Clinically probable cardiogenic embolism

   Measures outlined in 2.1, plus:
   - Massive infarction or severe hypertension ⚫ Repeat CAT scan after 7 days
   - Non-massive infarction ⚫ Heparin IV (continuous infusion)
   - (aPTT 1.5 - 2 times baseline)

2.2.2 - Ischemic stroke with no clinical evidence for embolism

   Heparin 5000 U 12/12h SC

3. OTHER MEASURES

   Supportive medical and nursing care:
   1. Rehabilitation program, since acute phase
   2. Nursing attention to pressure points as well as foam rubber mattress
   3. Positional and respiratory care to reduce risk for bronchoaspiration
   4. Nutritional evaluation and supportive care.
**Diagnostic Criteria.** After neurological and neuroimaging evaluation, cases were classified according to NINCDS Stroke Data Bank criteria, adapted10,11,14,16.

**Ischemic stroke with clinical evidence of probable cardiogenic embolism**

Acute onset of a cortical infarction plus one of the following:

- a potential source of cardiac embolism:
  - non-valvular atrial fibrillation
  - myocardial infarction within previous 6 weeks
  - rheumatic heart disease
  - prosthetic heart valves
  - other sources (atrial myxoma, PFO)

- echocardiographic evidence of:
  - intracavitary vegetation
  - global or segmental left ventricle akinesia

**Ischemic stroke without evidence of probable cardiogenic embolism**

- Large-vessel atherosclerotic disease: cortical infarction with appropriate angiographic or ultrasound evidence of > 50% stenosis
- Small-vessel disease: small, deep lacunar infarction

**Ischemic stroke of undetermined etiology**

- Other causes (uncommon but determined, as migraine stroke, arteritis)

**Functional Evaluation.** A complete examination was done at days 1, 2, 3, 7, 10, 15 and at discharge. Impairment was evolutively quantified by Canadian Neurological Scale Score (CNSS)7, and patients classified after first 3 days serial examinations - worsening stroke: with a progressive deterioration of 1 or more points in CNSS; stable stroke: improvement or no evidence of deterioration in CNSS8. Disability was evaluated at discharge considering - no sequelae; mild disability: minor sequelae, returning to previous activities; moderate disability: limited for previous activities but independent; severe disability: dependent.

**RESULTS**

**Sample Profile.** After proper investigation, presumed diagnosis was confirmed in all but 7 cases: 4 non-hypertensive lobar hemorrhage in elderly patients, probably related to amyloid angiopathy, and 3 cases of hypertensive cerebral hemorrhage. There was a reliability of 94.69% in entry diagnosis. Final sample rested composed by 150 patients, 92 male (61.3%) and 58 female (38.6%), mean age 69.8 years (SD= 12.04). Patients were divided in 3 groups according to estimates of time from first symptoms to therapeutic measures: first 6 hours, 38 patients (25.3%); 6 to 12 hours, 87 patients (58.0%); more than 12 hours, 25 patients (16.6%). Overall mean time for beginning therapy was 8.34 hours, whereas in control group this time interval was 14.79 hours10.

There were 29 cases of ischemic stroke with clinical evidences for probable cardiogenic embolism and 121 cases without such evidences: of these, 24 met criteria for lacunar infarction while 97 were diagnosed as large-vessel atherosclerotic disease.

**Early Mortality Rates.** Seventeen patients died during hospitalization, a mortality rate of 11.3%. Mortality rate of control group was 16.8%.

During first week, 6 patients died from primary complication of stroke (progressive worsening by mass effect with transtentorial herniation - see below). After second week of admission, there were other 11 deaths: 9 related to secondary complications (6 cases from bronchoaspirative pneumonia, 1 case of pulmonary embolism, 1 case of sepsis secondary to urinary tract infection and 1 sudden death, probably related to myocardial infarction) whereas 2 patients died from transtentorial herniation due to progressive worsening of stroke.

**Functional Outcome Scores.** Baseline and evolutive numbers of CNSS varied among groups (Table 1). Despite still compromised by low number of cases in each subpopulation, overall scores clearly demonstrate a
trend toward better results in earlier treatment patients, when compared with control group (p<.05, Fisher exact test) (Figl).

Isolated evaluation of cortical infarcts by large vessel atherosclerotic disease patients, the worst CNSS baseline group, revealed the same trend to better outcomes in early onset treatment patients (Fig. 2), here including progressive and stable stroke cases.

There were 28 cases diagnosed as “worsening stroke”, corresponding to 17.8% of total sample, 24 of them from large vessel disease group. Acute persistent hyperglycaemia was found in 12 cases, positive antecedents of diabetes in 7 and abnormally elevated baseline glycosylated haemoglobin in another 2 cases: no other clinical features distinguished these patients. A progressive pattern of evolution in first phase of stroke carried a poor prognosis on follow-up: early mortality was elevated in these patients and survivors were left with high grade impairment and disability (Table 2).

Table 1. Baseline and evolutive impairment scores: CNSS results with standart deviation between bars (*p<.05, Fisher exact test).

<table>
<thead>
<tr>
<th></th>
<th>Entry</th>
<th>7th day</th>
<th>15th day</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;12h</td>
<td>4.25</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>&gt;12h</td>
<td>5.54 [2,71]</td>
<td>5.64 [2,79]</td>
<td>5.72 [2,86]</td>
</tr>
<tr>
<td>small vessel disease</td>
<td>&lt; 6h</td>
<td>6.40 [1,23]</td>
<td>6.91 [1,33]</td>
<td>7.97 [1,38]</td>
</tr>
<tr>
<td></td>
<td>6-12h</td>
<td>6.33 [1,53]</td>
<td>6.94 [1,21]</td>
<td>7.32 [1,42]</td>
</tr>
<tr>
<td></td>
<td>&gt;12h</td>
<td>6.25</td>
<td>7.0</td>
<td>7.0</td>
</tr>
</tbody>
</table>

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Table 2. Morbidity and mortality rates according to patterns of evolution.

<table>
<thead>
<tr>
<th>impairment</th>
<th>entry</th>
<th>discharge</th>
<th>disability state</th>
<th>mortality rate (number)</th>
<th>days of hospitalization mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>worsening pattern</td>
<td>5.48</td>
<td>5.93</td>
<td>moderate=6</td>
<td>39.2% [N=11]</td>
<td>21.54 [9.37]</td>
</tr>
<tr>
<td>[N=28]</td>
<td>[2,27]</td>
<td>[3,48]</td>
<td>severe=11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>stable pattern</td>
<td>5.71</td>
<td>6.88</td>
<td>no+mild=73</td>
<td>4.91% [N=6]</td>
<td>17.16 [7.39]</td>
</tr>
<tr>
<td>[N=122]</td>
<td>[3,80]</td>
<td>[3,91]</td>
<td>moderate=37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall</td>
<td>5.64</td>
<td>6.84</td>
<td>no+mild=73</td>
<td>11.3% N=17</td>
<td>17.87 [7.47]</td>
</tr>
<tr>
<td>SSG</td>
<td>[3,76]</td>
<td>[3,87]</td>
<td>moderate=43</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>severe=17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Most patients with small vessel disease, deep lacunar infarcts, had good recovery. Exceptions were 5 cases of massive pure motor hemiplegia with proportionate distribution ("FUL pattern"), with CAT scan evidence of a corresponding capsular lacune, each one improving no more than 1.5 points in CNSS at discharge. Leucoaraiosis, a controversial neuroimaging finding of uncertain significance, was much more frequent in small vessel disease patients, as well as the concomitant association of diabetes, retinal and renal hypertensive disease.

Disability Scores. As expected, disability grade at discharge correlated well with impairment scores, measured by CNSS; mild language dysfunction accounted for some disproportionately higher disability degree. Nevertheless, functional outcome measured by disability scores reveals a clear trend for better results in early care groups when compared with controls (Table 3), reflecting impact of recovery on social skills and quality of life.

### Table 3. Disability degrees at discharge.

<table>
<thead>
<tr>
<th></th>
<th>no sequelae</th>
<th>mild sequelae</th>
<th>moderate sequelae</th>
<th>severe sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td>cerebral embolism</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>[N=6]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12h</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>[N=21]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 12h</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>[N=2]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>large vessel disease</td>
<td>4</td>
<td>9</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>[N=25]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12h</td>
<td>6</td>
<td>16</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>[N=51]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 12h</td>
<td>1</td>
<td>7</td>
<td>8</td>
<td>5</td>
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<tr>
<td>[N=21]</td>
<td></td>
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<tr>
<td>small vessel disease</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
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<tr>
<td>[N=7]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12h</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>[N=15]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 12h</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>[N=2]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSG overall</td>
<td>29 [19,3%]</td>
<td>44 [29,3%]</td>
<td>43 [28,6%]</td>
<td>17 [11,3%]</td>
</tr>
<tr>
<td>[N=150]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>control group</td>
<td>15 [13,2%]</td>
<td>33 [29,2%]</td>
<td>44 [38,9%]</td>
<td>21 [18,5%]</td>
</tr>
<tr>
<td>[N=113]</td>
<td></td>
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</tbody>
</table>

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**COMMENTS**

Medical treatment of acute stroke remains controversial. Currently no single therapeutical measure gained wide consensus for routine use, but evidence suggests that early and intensive care positively influences outcome. The experience of acute medical treatment combined with intensive rehabilitation measures in a "Stroke Unit" as reported, seems to significantly affect functional state but remains inaccessible to most of our hospitals. Strategies to overlap our difficulties must include institution of standards of management with a well-trained team and rationale for cost-effective diagnostic and therapeutic measures in general hospital setting, outside of specialized units.
In order to shorten time-to-start therapy, a standardized protocol was instituted to be used in consecutive cases of “clinically probable non-categorized stroke”, just at admittance to the Emergency Room\[^{10}\]. This protocol was designed to be readily accessible to the non-specialist and costly adjusted to our reality. After first year, 157 patients entered study: reliability of entry diagnosis, made by a non-specialist based on appropriate clinical data, was 94.69%. The protocol proved to be practical and suitable for routine apply in Emergency Room. Mean time for beginning therapy was shortened from prior 14.79 hours, of control group, to 8.34 hours, still far from ideal but a significative advance.

Early mortality rate was reduced from 16.8% to 11.3%\[^{10}\].

Early onset of intensive medical care and rehabilitation undoubtedly reduced secondary complications: “silent” bronchoaspiration, a preventable and commonly unsuspected condition in stroke patients, even with no brainstem involvement\[^{12}\], and pulmonary thromboembolism from deep vein thrombosis\[^{22}\], are major factors for mortality and morbidity after second week of stroke requiring anticipation and prophylaxis. Despite preventive measures, as the liberal use of early nasoenteral feeding, there were still 6 cases of death secondary to aspirative pneumonia, a too high number that emphasizes needing for further studies for identification of patients at high risk, perhaps with associated factors contributing to aspiration.

First week mortality relates almost exclusively with mass effect leading to transtentorial herniation, due to a “cytotoxic edema”, mostly seen in large vessel strokes\[^{17}\]. Fluid accumulation, with intact blood-brain barrier, begins minutes after ischemic insult, reaching its maximum in 3-4 days. Metabolic studies provided evidence that ischemically threatened neurons become acidic, with intracellular energy failure. Post-ischemic reperfusion exposes acidic cells to glucose with further stimulation of anaerobic glycolysis and production of more acid, “acidotoxicity”\[^{15}\], with panneceosis, i.e., cellular necrosis involving neurons, glia and vascular elements; at the same time, energy deprivation in presynaptic neurons leads to release of excitatory neurotransmitter, particularly glutamate and aspartate, “excitotoxicity”. Postsynaptic specific receptors, specially NMDA, are overstimulated leading to an intracellular flow of calcium\[^{6,19}\]. Calcium binds to calmodulin and activates nitric oxide synthase, the enzyme that converts arginine in nitric oxide, a free-radical highly reactive and cytotoxic, that might be a final pathway of this calcium-overload induced neurotoxicity\[^{4}\], marked by a “selective ischemic neuronal necrosis”, damaging neurons where NMDA receptors are located, sparing glia and vascular endothelia\[^{6,19}\].

A sequence of cellular metabolic changes in first phase of stroke dictates the biological destiny of ischemic neurons and as a consequence, functional outcome. Therapeutical cytoprotective measures might be instituted as earlier as possible, to have efficiency. Much controversy exists about duration of this “therapeutic window”. As a rule for experimental trials, acute treatment must begin within first 6 to 8 hours from onset of symptoms, but current evidence from magnetic resonance spectroscopy demonstrates that “... metabolic disturbances, potentially correctable, persists for days after stroke onset”\[^{23}\].

Our preliminary results demonstrate that functional outcome can be positively affected by time-to-start therapy (Fig 1). In large vessel atherosclerotic disease group, with the greater number of patients and lower mean CNSS at entry, functional evolution showed a significant difference between patients attended on first 6 hours as well as from 6 to 12 hours, compared with control scores (Fig 2). In more than 12 hours group, results became contradictory by low number of cases, but disability scores at discharge, in the whole group and in each subpopulation, when compared with control, revealed a very favorable difference for early care cases (Table 1). Lack of clear-cut biological markers besides with poor prognosis at discharge, renders worsening stroke patients a distinct group, yet full of cloudy pathophysiological implications; further studies to distinguish such patients at higher risk and thus develop therapeutic strategies for specific early and intensive management are needed.
Despite few cases, other groups demonstrated the same trend for better outcomes in earlier care patients. However, results cannot be compared in heterogeneous subpopulations, where mechanisms of disease, as well as prognosis, are not the same. Additional data from larger samples, providing larger subsets of patients, larger enough for statistically significative analysis, maybe through a national multicentric cooperative study, are required. Whether the result of some specific therapeutic measure or adequate management of variables as hypertension, hyperthermia and hyperglycaemia, our preliminary results, as in other studies, have demonstrated that multiple drug therapy combined with intensive rehabilitation care early in the course of the disease, might alter favorably outcome in stroke. Stroke Study Group protocol proved suitable and adequate to our reality. These results are difficult to explain only by secondary prevention care.

The cascade of events in stroke, beginning with blood flow reduction at some degree, triggering a sequence of metabolic changes at cellular level and leading to neuronal death, remains far from being completely elucidated. Further pathophysiology studies are required after routines widely acceptables for management of these patients can be clearly defined.

**CONCLUSIONS**

After 1 year, a protocol for standardization on acute care for stroke patients designed to be costly effective and suitable for use in Emergency Room by a non-specialist, proved to reduce time-to-start therapy, with a diagnosis reliability of more than 94%.

Despite still low number of patients entering study, at least in large vessel disease early management improved outcome. Overall mortality was also reduced, but results from other groups require additional observation, with greater sample, maybe through a large national multicentric cooperative study.

Stroke sufferers are marked by morbidity: rather than mortality, functional outcome might be the primary end-point for further studies on therapeutic measures for cerebrovascular diseases.

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REFERENCES