Medical and Neurological Complications of Ischemic Stroke

Experience From the RANTTAS Trial

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Background and Purpose—Medical and neurological complications after acute ischemic stroke may adversely impact outcome and in some cases may be preventable. Limited data exist regarding the frequency of such complications occurring in the first days after the ictus and the relationship of these complications to outcome. Our objective was to identify the types, severity, and frequency of medical and neurological complications following acute ischemic stroke and to determine their role in mortality and functional outcome.

Methods—Rates of serious (life-threatening) and nonserious medical and neurological complications and mortality were derived from the placebo limb of the Randomized Trial of Tirilazad Mesylate in Acute Stroke (RANTTAS) database (n=279). Complications were correlated with clinical outcome using logistic regression techniques.

Results—Of all patients, 95% had at least one complication. The most common serious medical complication was pneumonia (5%), and the most common serious neurological complication was new cerebral infarction or extension of the admission infarction (5%). The 3-month mortality was 14%; 51% of these deaths were attributed primarily to medical complications. Outcome was significantly worse in patients with serious medical complications, after adjustment for baseline imbalances, as measured by the Barthel Index (odds ratio [OR], 6.1; 95% confidence interval [CI], 2.5 to 15.1) and by the Glasgow Outcome Scale (OR, 11.6; 95% CI, 4.3 to 30.9). After death was discounted, serious medical complications were associated with severe disability at 3 months as determined by the Glasgow Outcome Scale (OR, 4.4; 95% CI, 1.3 to 14.8).

Conclusions—Medical complications that follow ischemic stroke not only influence mortality but may influence functional outcome. **(*Stroke*. 1998;29:447-453.)**

Key Words: complications ■ stroke ■ stroke, acute ■ stroke outcome

Ischemic stroke remains the third leading cause of death after heart disease and cancer in the United States.[1] Mortality rates have declined over the last several decades[1] and are now consistently reported to be approximately 20%,[2–5] although this rate varies from 15% to 58% depending on stroke subtype.[3] Medical complications are also known to be common in stroke patients, although the implications of these complications have less frequently been studied. Davenport et al[6] retrospectively reported complication rates in 597 stroke patients (ischemic and hemorrhagic). They found 59% had complications and 23% died in the hospital. Silver et al[3] reported that approximately 40% of deaths were from medical complications in a series of nearly 1000 ischemic stroke patients. They also noted that while most deaths occurring in the first week were due to brain edema associated with stroke, most deaths in the second and third weeks after stroke could be attributed to medical complications.[3] In a retrospective autopsy review from 1966 to 1975, Bounds et al[7] found that >50% of deaths occurred secondary to medical complications. Kalra et al[8] reported medical complications occurring in 60% of the 245 patients involved in a stroke rehabilitation program.

The relationship between serious medical complications and functional outcome has not been systematically examined. The purpose of this study was to describe the rates of medical and neurological complications in an acute ischemic stroke cohort and then to investigate the impact of these complications on functional outcome and mortality.

Subjects and Methods

Our study population included the 279 fully eligible, vehicle-treated stroke patients from the Randomized Trial of Tirilazad Mesylate in

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*The investigators and participating centers are listed in the Appendix.

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Selected Abbreviations and Acronyms

BI = Barthel Index
CI = confidence interval
GOS = Glasgow Outcome Scale
NIHSS = National Institutes of Health Stroke Scale
OR = odds ratio
RANTTAS = Randomized Trial of Tirilazad Mesylate in Acute Stroke

Patients with Acute Stroke (RANTTAS).[9] This was a multicenter, randomized, double-blinded, vehicle-controlled trial that evaluated the efficacy and safety of intravenous tirilazad mesylate in patients with acute ischemic stroke. Patients were selected based on eligibility criteria (see below) from all patients with acute ischemic stroke admitted to each of 27 participating North American centers from May 1993 through December 1994. The protocol was approved by each center's institutional review board.

Eligible patients included those who had a serious neurological deficit due to focal ischemia, could be treated within 6 hours of stroke onset, were 18 years of age or older, were not pregnant if female, and from whom informed consent could be obtained (patient and/or representative). Subjects were excluded if they had sensory loss, ataxia, or dysarthria alone; coma due to mass effect by CT scan; severe hypertension (mean arterial pressure of >160 mm Hg); seizure at onset; stroke as a complication of a medical or surgical procedure (not including cardiac catheterization or cerebral angiography); hemorrhage on initial CT scan; or severe concomitant medical, neurological, or psychiatric illness. The most frequent reasons for exclusion included stroke onset >6 hours (36%) and transient deficit (12%). Further details of the study population have been described previously.[9] Each patient who met eligibility criteria was randomly assigned to receive either tirilazad mesylate or vehicle (sodium citrate) diluted with sodium chloride (recommended concentration, 0.9% or 0.45%) for a total volume of 250 mL administered as a rapid intravenous infusion over 10 to 30 minutes. A head CT scan without contrast was required before administration of subsequent doses. If each component of the complete evaluation (including laboratory work, CT scan, and clinical examination) obtained before the second dose met the eligibility criteria, then the patient was allowed to continue participation in the study as a fully eligible patient. Only the fully eligible patients received subsequent doses (250 mL per dose or an alternatively lower volume [based on weight] for patients with central lines or who could not tolerate the total volume) of study drug or vehicle every 6 hours for 11 additional doses (12 doses total).

Patients in the RANTTAS study were managed in an acute-care area with current 1990s medical therapy according to standard practice in each center. Treatment with corticosteroids and the calcium channel blockers nicardipine and nimodipine, or any experimental stroke therapy (including thrombolytic therapy at that time), was prohibited. Allowed medical therapies included heparin, antiplatelet agents, volume expansion, vasopressors, mannitol, anticonvulsants, and all antihypertensive agents except for nicardipine and nimodipine. Emergency surgery was also allowed if judged to be clinically indicated.

The frequency of complications and death was monitored continuously and prospectively by the investigators and coordinators at each site during the trial. A standardized medical event coding guide based on the COSTART medical dictionary was used to code complication events.[10] This dictionary includes both symptoms and diagnoses. Specific diagnoses are used when known; however, the system allows a default to a symptom when the diagnosis is unknown. Adverse events were only reported if clinically significant. Data on serious complications (ie, those that were immediately life-threatening, prolonged or resulted in hospitalization, or resulted in death) were collected by investigators and coordinators at each site for 3 months. Data on nonserious complications were collected for the first 7 to 10 days only. Neurological complications included those that occurred in the nervous system, whereas medical complications were all other events reported. Clinical outcome was measured at 7 to 10 days, discharge, and at 3 months according to the BI,[11] the GOS,[12] and the NIHSS.[13] Primary and contributing causes of death and disability were designated by the treating investigator based on clinical judgment. New infarction and extension of infarction were combined for the analysis due to the somewhat arbitrary assignment of the event in some cases of limited information.

Statistical Analysis

Poor outcome was defined as severe disability (a BI score of <60[14] or a GOS rating of severe disability or vegetative survival) or death at 3 months. For patients who were dead at 3 months, the worst possible score (BI=0, GOS=5) was assigned. Logistic regression analysis[15] was used to evaluate the association between (1) serious events and poor outcome (severe disability and death) and (2) serious events and severe disability. Each analysis was adjusted for admission NIHSS score, patient age, and the presence of diabetes mellitus, since each of these factors was independently associated with outcome in the RANTTAS trial.[9]

Results

From May 1993 through December 1994, trial subjects were selected by eligibility criteria from a total of 3853 patients admitted within 12 hours of stroke onset registered in the combined stroke logs of the centers. A total of 660 patients (329 vehicle-treated and 331 tirilazad-treated) were randomized. Of those who received treatment, 556 (280 vehicle and 276 tirilazad) were fully eligible and 104 (49 vehicle and 55 tirilazad) were subsequently excluded. Of the 280 fully eligible, vehicle-treated group, 1 patient was determined to not have a stroke but to have a conversion disorder, and this patient was excluded from this analysis. The fully eligible, vehicle-treated stroke group used for this analysis included 279 patients. Patients in the tirilazad-treated group were excluded because this is not considered standard stroke care, and the possibility that some of the events were drug related could not be excluded. Patient characteristics are summarized in Table 1. The median time from onset of symptoms to admission to the emergency department was slightly more than 1 hour. The mean age was 69 years, most patients were white with a slight male preponderance, and the median NIHSS score reflected a moderate deficit with a minimum NIHSS score of 1 and a maximum of 30. Over 60% of patients had a history of hypertension, over 50% had a history of cardiac disease, and less than one quarter had a history of prior transient ischemic attack or stroke. Over 90% of patients were able to lead a full and independent life before the presenting stroke. The rates of antiplatelet and anticoagulant treatment prescribed for these patients, both in the first 10 days and at the 3-month follow-up are reflected in Table 2. Nearly half of patients were treated with aspirin in the first 10 days, and a slightly lower proportion were taking aspirin at 3 months. Intravenous heparin was used in 40% of patients in the first 10 days. Warfarin therapy was prescribed in approximately one third of patients in the first 10 days and at 3 months.

Table 3 shows the ischemic stroke subtypes as determined by the investigator at 7 to 10 days using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[16] Cardioembolic stroke was the most common subtype, accounting for nearly a third of strokes. Small-vessel occlusive disease and large-vessel atherosclerosis each accounted for approximately one quarter of the strokes.

Fig 1 displays the rates of complications and death in the full cohort of 279 patients. Ninety-five percent of patients had at least one event, 32% had at least one serious event, and 14% of patients were dead at 3 months.

TABLE 1. Baseline Characteristics of Fully Eligible Vehicle-Treated Patients (n=279)

Time to evaluation, median h	1.3
Age, y (mean±SD)	69±13
Male, %	57
Race, %	
White	76
African American	19
Hispanic	3
Oriental/Asian	1
Other	1
Admission SBP/DBP, mean	159/87
Admission NIHSS median (interquartile range)	9.0 (5–16)
Past history, %	
Prior TIA/stroke	21
Hypertension	63
Diabetes mellitus	22
Cardiac disease (all)	53
Myocardial infarction	22
Cardiac arrhythmia	30
Angina	21
Congestive heart failure	17
Other cardiac	36
Peripheral vascular disease	17
Smoking (current)	26
No prior disability*	91

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and TIA, transient ischemic attack.

*Historically, subject able to lead a full and independent life with or without minimal neurological deficit before stroke.

Tables 4 and 5 list all of the serious medical complications reported, and Table 4 lists the rates of combined serious and nonserious events. Nonserious injection site reactions were excluded from this table because these were assumed to be a response to the vehicle injection (known to cause a high rate of local reaction[17]) not the stroke itself. Pneumonia (both aspiration and other) was the most common serious medical event, reported in 5% of patients. Aspiration pneumonia accounted for 60% of the serious pneumonias. Congestive heart failure and gastrointestinal bleeding were reported as a serious event in 3%. Cardiac ischemia, sepsis, urinary tract infection, deep venous thrombosis, and pulmonary embolism were less frequently reported as serious events, although urinary tract infection was frequently reported as a nonserious event (11%). Table 6 displays some common complications

TABLE 2. Recurrent Stroke Prevention Therapy (n=279)

	Days 1–10, %	3 Mo, %
Aspirin (stroke/MI prevention)	47	37
Heparin		
Intravenous	40	0
Subcutaneous	29	3
Warfarin	31	35
Ticlopidine	11	10

MI indicates myocardial infarction.

TABLE 3. Ischemic Stroke Subtype: Day 7 to 10 (n=279)

Stroke Subtype	n	%
Cardioembolic stroke	84	30.1
Small-vessel occlusive disease	72	25.8
Large-vessel atherosclerosis	61	21.9
Unknown	48	17.2
Other identified cause of stroke	14	5.0

that were reported as nonserious events. Nausea/vomiting, fever, and constipation were the most frequently reported.

All reported serious neurological complications are shown in Table 7, again with the combined (serious and nonserious) rates also reported. New stroke/extension of stroke (5%) and brain edema (4%) were the two most frequently reported serious neurological events. Table 8 lists common nonserious neurological complications. Headache was reported in 22% of patients and never as a serious event. Agitation and insomnia were not uncommon.

The primary and contributing causes of death of the 37 patients who were dead at 3 months are shown in Fig 2. Medical complications were reported to be the primary cause of death in over 50% of patients and at least contributed to death in an even larger proportion. Direct effect of stroke was the primary cause of death in one third of patients and contributed to nearly another 20% of deaths. New stroke was the primary cause in <10%. The timing of these deaths, shown in Fig 3, reflects the bimodal distribution previously reported.[3,5,7] The first peak, occurring in the first week, predominantly reflects deaths from direct effect of stroke. The second peak occurred several weeks after the stroke, and the majority of these deaths were attributed to medical complications.

At 3 months, 41% of patients were alive and newly disabled since their admission stroke. Fig 4 shows the primary and contributing causes of disability in these patients as determined by the investigators at 3 months. This includes mild, moderate, and severe disability. Direct effect of stroke was cited as the primary cause of disability in 86% of patients and at least contributed to disability in over 90%. Medical complications were rarely reported by the investigators as the primary or contributing cause of their patient's disability at 3 months. The "other" category primarily included chronic diagnoses that

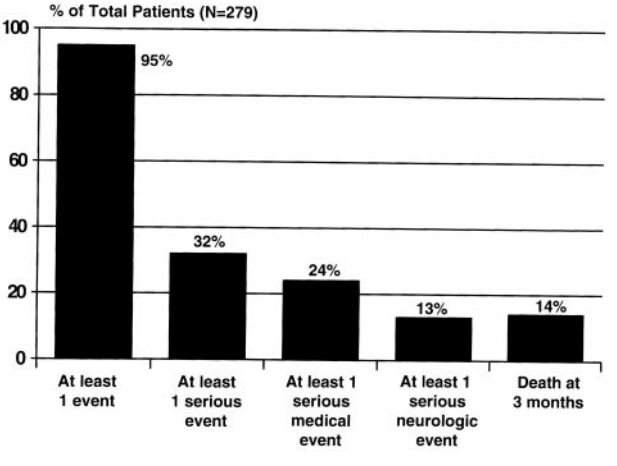

Figure 1. Rates of complications and death in the full cohort of 279 patients.

TABLE 4. Most Common Serious Medical Events

Event	Serious, n	%	Total, n	%
Sepsis	3	1	3	1
Cellulitis	2	1	5	2
Congestive heart failure	7	3	30	11
Cardiac arrest	5	2	5	2
Angina/MI/cardiac ischemia	4	1	16	6
Deep venous thrombosis	3	1	6	2
Pulmonary embolism	3	1	4	1
Peripheral vascular disorder	2	1	2	1
Pneumonia (all)	13	5	27	10
Aspiration pneumonia alone	8	3	16	6
Dyspnea	3	1	11	4
Pulmonary edema	3	1	9	3
Gastrointestinal bleed	7	3	15	5
Dehydration	3	1	6	2
Hypoxia	2	1	8	3
Urinary tract infection	3	1	30	11

MI indicates myocardial infarction.

were not previously disabling but became the primary cause of disability after stroke. This category included such diagnoses as arthritis, dementia, and alcohol use.

Logistic regression analysis, adjusted for admission NIHSS score, age, and history of diabetes mellitus, demonstrated that serious medical and serious neurological events were each associated with poor outcome at 3 months. For patients with a serious medical event, the OR for a poor outcome as measured by the BI was 6.1 (95% CI, 2.5 to 15.1); by the GOS it was 11.6 (95% CI, 4.3 to 30.9). The OR in patients with serious neurological complications was 11.3 (95% CI, 3.8 to 33.4) for the BI and 9.4 (95% CI, 3.2 to 27.4) for the GOS.

Because this analysis included mortality as poor outcome, and to clarify whether death was driving the association, the association between serious events and severe disability alone was examined, excluding the patients who were dead at 3 months. Serious medical events were associated with severe disability as determined by the GOS (OR, 4.4; 95% CI, 1.3 to 14.8) but not the BI (OR, 1.2; 95% CI, 0.3 to 4.4). For comparison, serious neurological complications were associated with severe disability as measured by the BI (OR, 6.1; 95% CI, 1.4 to 26.1) and the GOS (OR, 4.6; 95% CI, 1.2 to 17.8).

TABLE 5. Uncommon (<1%) Serious Medical Events

Back pain	Respiratory failure
Wound infection	Respiratory arrest
Hypertension	Abdominal pain
Ventricular extrasystole	Intestinal gangrene
Atrial fibrillation	Gastrointestinal carcinoma
Hypotension	Thrombotic thrombocytopenic purpura
Ventricular tachycardia	Ruptured spleen
Bowel infarct	Septic joint
Syncope	Bursitis
Cardiac thrombus	Urinary retention
Bronchitis	Hematuria
Hemoptysis	Prostate cancer
Laryngeal edema	Acute renal failure
Lung hemorrhage	Uterine hemorrhage

TABLE 6. Frequent Nonserious Medical Events

Event	Total, n	%
Nausea/vomiting	54	19
Fever	45	16
Constipation	44	16
Hypokalemia	31	11
Hyperglycemia	30	11
Bradycardia	18	6
Dysphagia	15	5
Skin rash	14	5
Urinary incontinence	14	5
Diarrhea	8	3
Anemia	8	3
Dyspepsia	7	3

Discussion

This study provides prospectively collected multicenter data on medical and neurological complications in an acute ischemic stroke cohort admitted within 6 hours of onset of symptoms. It furnishes the prospective data suggested by Davenport et al[6] for a fixed period of time after stroke. The frequency of complications in this series is higher than previously reported. We speculate that this is a result of the rigorous, acute, and prospective method used for collection of complication data. The detailed safety data collection used in this clinical trial was necessary for potential registration of a new compound, and it likely provides a more complete representation of complication events than previously reported rates. The mortality rate in this cohort is similar to those previously reported for ischemic stroke.[2–5] The frequency of severe disability (nonambulatory and totally dependent) has been reported to be from 7% to 19%,[18] which is consistent with the 16% severe disability rate in this study. Primary as well as primary and contributing cause of death or disability were reported because the cause of death or disability in this population is often multifactorial, and the primary cause may be chosen arbitrarily. We therefore report primary alone and primary and contributing

TABLE 7. All Serious Neurological Events

Event	Serious, n	%	All, n	%
New infarct/extension	14	5	49	18
Brain edema	10	4	21	8
Intraparenchymal hemorrhage	6	2	12	4
Carotid stenosis	6	2	9	3
Brain herniation	6	2	7	3
Diminished level of consciousness	2	1	13	5
Seizure	2	1	8	3
Dizziness	1	<1	6	2
Depression	1	<1	4	1
Transient ischemic attack	1	<1	2	1
Hydrocephalus	1	<1	2	1
Acute toxic encephalopathy	1	<1	1	<1
Hallucination	1	<1	1	<1
Intracranial hypertension	1	<1	1	<1

TABLE 8. Frequent Nonserious Neurological Events

Event	All, n	%
Headache	61	22
Agitation	22	8
Insomnia	18	6
Confusion	7	3
Anxiety	7	3

together in an attempt to more closely approximate the true cause of death. This approach has been used previously in the subarachnoid hemorrhage literature for similar reasons.[19] These rates of complications and disability may be helpful for reference for future clinical stroke trials. The recent literature continues to suggest that rates of stroke mortality vary widely across regions of the United States,[20] which may make reference rates from this multicenter trial more generalizable to other multicenter stroke trials.

An unintentional bias may have slightly affected our study population. Despite the fact that coma was not exclusionary unless due to mass effect seen on the initial CT, there were no patients in this cohort of 279 with an NIHSS level of consciousness score of 3 (unresponsive) on baseline examination. Twelve patients (4.3%) had level of consciousness scores of 2 (obtunded). Of the 3193 patients excluded from the 3853 screened in this trial, however, only 19 (0.6%) were excluded for coma due to mass effect. Therefore, while this may have biased the population in this cohort, we would argue that the effect of this bias is minimal.

The influence of medical complications on outcome in stroke patients has been studied. Davenport et al[6] found that complications in ischemic and hemorrhagic stroke patients were associated with an increased risk of death during admission. Chambers et al[5] looked at potential prognostic factors in predicting outcome in stroke patients and concluded that deaths after 2 weeks were primarily due to cardiac and pulmonary complications. They developed a short-term and long-term model that could predict poststroke outcome and reported that a history of heart disease and hypertension were in the long-term model.[5] They did not address the relevance of peristroke complications in their model. Sacco et al,[2] using the Framingham study data, concluded that if patients survived their initial stroke, being free of hypertension and cardiac comorbidity increased their chances of survival.

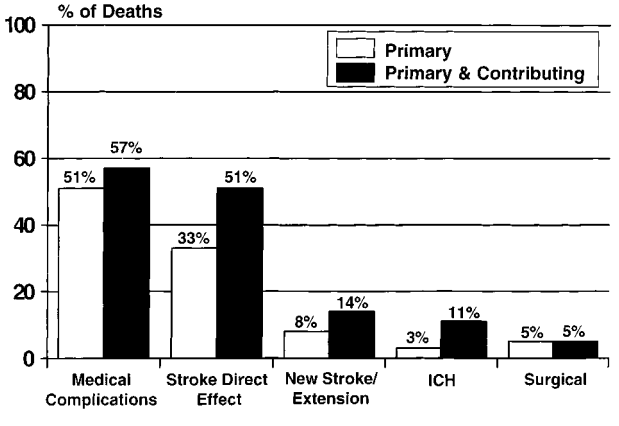

Figure 2. Rates of primary and contributing causes of death in the 37 patients (14%) who were dead at 3 months. ICH indicates intracerebral hemorrhage.

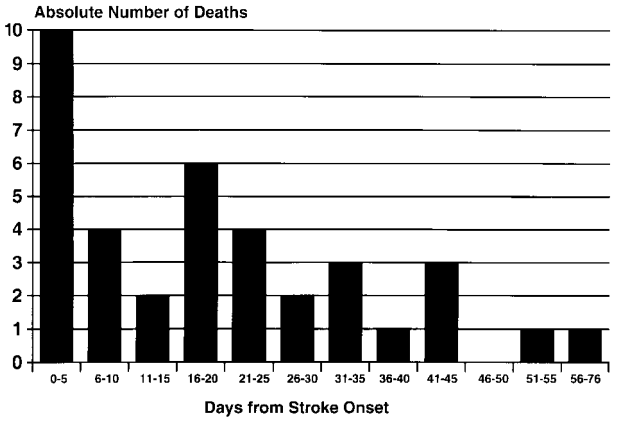

Figure 3. Distribution of the timing of death in the 37 patients who were dead at 3 months.

Medical complications are clearly a leading cause of death in acute ischemic stroke patients. The attribution of 50% of deaths in this study to medical complications is consistent with that previously reported.[3,7,8] Medical complications, however, were not frequently reported as a cause of 3-month disability in this cohort. Despite the investigators' impressions that their patients' disability was not secondary to medical complications, logistic regression analysis, corrected for severity of stroke, showed an association between serious medical events and severe disability. This suggests that there is a relationship between serious medical complications and severe disability that was not due to severity of stroke and was not attributed to medical complications by the investigators. The etiology of this association is unclear. Several of the following mechanisms may be at play: (1) Serious medical complications may delay or prevent aggressive rehabilitation, resulting in worse disability. (2) Serious medical complications and/or their treatments may result in neurological worsening that may not be appreciated by caretakers as other than the natural evolution of the stroke.

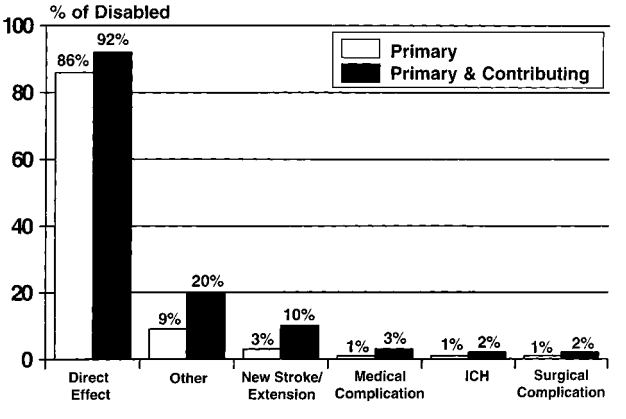

Figure 4. Rates of primary and contributing causes of disability in the 115 patients (41%) of patients disabled at 3 months. This includes patients who were alive, not previously disabled, and who had a GOS score of moderate disability, severe disability, or vegetative survival at 3 months. ICH indicates intracerebral hemorrhage.

(3) Tenuous prestroke medical conditions (ie, borderline disabling conditions) may result in disability after stroke and serious medical complication. (4) Depression accompanying life-threatening events may reduce motivation, producing worse scores on functional and neurological scales, and magnify existing disability. (5) Medical complications may be a marker for, not a cause of, severe disability. Because of the relatively small number of patients who had a serious medical event and severe disability in this cohort (n=13), definitive conclusions cannot be drawn. These hypotheses should be tested in larger studies.

The clinical significance of these findings rests in the fact that some of these complications may be preventable. Some pneumonias, for example, may be preventable with the development of protocols for airway protection before oral feeding.[21]

These data provide valuable information regarding rates of complications in an ischemic stroke cohort treated within 6 hours excluding the very mild strokes (ie, pure sensory). This information not only provides a benchmark of event rates that may help physicians measure the success of their individual care, but it also sheds some light on necessary preventative therapy. In addition, these rates may be helpful as reference for stroke clinical trials that are introducing new compounds that may have previously undetected side effects. Baseline rates such as those provided may alert investigators to potential safety concerns early in drug development, when only small numbers of patients are being exposed, with equally small or smaller numbers included in the placebo group. As we have seen a marked decrease in urinary and skin complications with improved medical therapies, these rates will also likely improve.

The association between medical complications and severe disability shown by our data is provocative, although it clearly requires further exploration.

Appendix

RANTTAS Participants

Participating Centers

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