Is White Matter Involved in Patients Entered into Typical Trials of Neuroprotection?

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Background and Purpose—One of the reasons for the failure of trials of neuroprotection in stroke may be the lack of white matter (WM) protection. However, whether patients entered into typical neuroprotection trials have WM involved in the ischemic process is unknown. We studied patients who were enrolled in neuroprotection trials at our center and used a neuroimaging coregistration approach to determine whether final infarcts involved WM and, if so, in what proportion. We also aimed to provide the first in vivo volume distribution of gray matter (GM) and WM in normal stroke-aged brains. These were then superimposed on a probabilistic map of GM and WM, which was developed from age-matched normal controls in whom GM and WM volumes were assessed.

Methods—Patients enrolled in trials of neuroprotection had late computed tomography or magnetic resonance scans coregistered in standard stereotaxic coordinate space after segmentation of symptomatic cerebral infarcts. These were then superimposed on a probabilistic map of GM and WM, which was developed from age-matched normal controls in whom GM and WM volumes were assessed.

Results—Forty-two patients (mean age, 73.7 ± 10.5 years) were studied from 6 trials of neuroprotection. WM formed 41.7% of the brain volume in 37 control subjects (mean age, 73.5 ± 8.4 years). In the segmented infarcts, WM comprised a median of 49% (interquartile range, 36.5 to 77.9) of the infarct volume. Ninety-five percent of infarcts had some involvement of WM tracts.

Conclusions—WM occupies ≈ 42% by volume of the normal stroke-aged brain. Patients entered into typical trials of neuroprotection may have significant WM volumes involved in the ischemic process, thus providing a rationale for the development of neuroprotectants for this compartment. (Stroke. 2005;36:000-000.)

Key Words: imaging ■ neuroprotective agents ■ ischemia

There have been numerous trials of neuroprotectants in patients with ischemic stroke, but none have shown a definite benefit.1 Interestingly, in the recently concluded Intravenous Magnesium Efficacy in Stroke (IMAGES) trial using magnesium, an a priori subanalysis revealed a possible benefit for subcortical lacunar strokes.2 This raises the question as to whether neuroprotectants may have a differential effect on central white matter (WM) compared with gray matter (GM). There are inherent differences between these brain compartments; the ischemic cascade is dominated by glutamate toxicity in GM,3 whereas, in WM, ion exchange channels and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors are more important.4 The majority of neuroprotectants have been developed in small animal models, particularly the rat, in which ≈10% of brain volume is WM. In contrast, the proportion in human brain is ≈50%, although this is less certain in stroke-aged brains.5 Hence, the efficacy of most neuroprotectants is GM based with scant attention paid to WM effects.

This issue may not be important if neuroprotection trial patient populations have ischemic lesions involving mainly GM; this is possible, because most of the trial entry criteria favor patients with hemispheric stroke and cortical signs.2,6–8 We thought it important to establish this more certainly in a small sample of patients who were entered into trials of neuroprotection in our center by using neuroimaging coregistration techniques. Specifically, we wished to test the hypothesis that significant proportions of WM are involved in the ischemic process in patients entered into trials of neuroprotection, thus providing a rational for developing compounds, which may protect this compartment. We also wished to establish with more certainty the in vivo volume distribution of GM and WM in the human brain, particularly in stroke-aged patients.

Methods

All of the patients with ischemic stroke entered into neuroprotection trials at the Austin Hospital between April 1997 and June 2001 in whom cerebral infarcts were evident on computed tomography (CT) or MRI were considered. To provide a magnetic resonance (MR) template to allow GM and WM segmentation, age-matched, neurologically normal volunteers were recruited.
Imaging Protocol
All of the patients had a CT scan before therapy and repeated at 7 to
10 days. MRI scans were performed on a 1.5-T SIGNA GE or
Siemens Magnetom 63. A MR probabilistic map was generated from
controls using a 3D T1-weighted, radiofrequency-spoiled gradient
echo sequence (echo time, 2.2 ms; repetition time, 10.5 ms; inversion
time, 350 ms; flip angle, 20°; matrix size, 256×256; number of
excitations, 1; field of view, 25 cm).

Image Registration, Segmentation, and Analysis
All of the patient and control images were register into standard
stereotaxic coordinate space using automated image registration
(AIR 3.0). All of the control standard space images were then
classified into GM, WM, and cerebrospinal fluid using SPM 99
software. Each image was smoothed using a Gaussian kernel of
8 mm. These images were averaged to create a probabilistic map with
each voxel classified using a threshold probability of 50%.

Statistical Analyses
Nonparametric statistical analyses (Wilcoxon signed-rank and
Kruskal-Wallis tests) were used to compare the compartmental
distribution of infarct volumes among patients and between trials,
respectively.

Results
Seventy-seven patients were entered into 5 neuroprotection trials
during the study period. The trials were as follows: (1) Glycine
Antagonist In Neuroprotection (GAIN), time window 6 hours, 8
patients, 19.0%; (2) IMAGES, time window 12 hours, 7 pa-
tients, 16.7%; (3) European-Australian Fiblast Acute Stroke
Trial, time window 6 hours, 1 patient, 2.4%; (4) Potassium-
Channel Opening Stroke Trial, time window 6 hours, 18 patients
42.9%; and (5) Acute Stroke Therapy by Inhibition of Neutro-
phils, time window 6 hours, 8 patients, 19.0%. Nine patients
were excluded because no lesion was evident on imaging, and
16 were excluded because of corrupted images. The mean age of
the 42 patients was 73.7±10.5 (±SD) years and the range was
42 to 88 years, 26 of whom were men and 16 of whom were
women. Scan times were 2 to 95 days after stroke (mean, 25
days).

Thirty-seven control subjects (17 men and 20 women) of
mean age 73.5±8.4 years (range, 60 to 90 years) had MR
scans to generate the probabilistic map. The total brain
volume was 1473±8.5 mL, GM volume was 724.5±43.8 mL
(58.2±2.6%), and WM volume was 519.6±34.1 mL
(41.8±2.6%) excluding cerebrospinal fluid, cerebellum, and
brain stem (Figure 2).

The median total infarct volume was 19.6 mL (interquartile
range [IQR] 3.2 to 103.6 mL) with 8.8 mL (IQR, 0.4 to 48.1
mL) in GM (51%; IQR, 22.1% to 63.4%) and 10.5 mL (2.0 to
37.5 mL) in WM (49%; IQR, 36.5% to 77.9%). By increasing
the control map probability to 60%, WM infarct proportion
changed to 64% and did not alter our conclusions. There was
no significant difference in this distribution (P=0.392; Figure
2). If the 9 negative scans were considered to be WM, the
median WM proportion was 60.2% (IQR, 42.5% to 97.1%); if
all were considered GM, the proportion was 45.2% (IQR,
15.5% to 73.2%). Ninety-five percent of all patients had at
least some WM involvement (Figure 3) or 96% if all 9 of
the negative scans were WM infarcts and 78% if all were GM.

Between trials, there was no significant difference in the
median WM proportions, although the highest was seen in the
GAIN trial (89.6%; P=0.138).
we need to develop compounds that are likely to be effective introduction of neuroprotective drugs into clinical trials. First, and subhuman primates have tree; rats and mice have only proportion of WM in the brains of animals as one ascends the phylogenic Interestingly, there is a close relationship between the proportion WM components of the normal human brain, these were either autopsy studies or imaging studies, which did not implicitly generate GM and WM proportions in stroke-aged individuals. Our finding, that 42% of brain tissue is WM, is the first in both GM and WM. Second, we need to establish efficacy in small animal models to test these in animal models where both compartments are adequately represented. Third, we need to consider phase II testing in humans with imaging outcome measures involving WM and GM. This may help eliminate compounds that are less likely to improve clinical outcomes.

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**References**

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