Brain Lesion Volume and Capacity for Consent in Stroke Trials
Potential Regulatory Barriers to the Use of Surrogate Markers

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Background and Purpose—European directives and legislation in some countries forbid inclusion of subjects incapable of consent in research if recruitment of patients capable of consent will yield similar results. We compared brain lesion volumes in stroke patients deemed to have capacity to consent with those defined as incapacitated.

Methods—Data were obtained from 3 trials recruiting patients primarily with cortical stroke syndromes. Patients were recruited within 24 hours of onset and used MRI based selection or outcome criteria. Method of recruitment was recorded with stroke severity, age, and brain lesion volumes on Diffusion Weighted Imaging.

Results—Of the 56 subjects included, 38 (68%) were recruited by assent and 18 (32%) by consent. The assent group had a median lesion volume of 18.35 cubic centimetres (cc) (interquartile range [IQR] 8.27–110.31 cc), compared to 2.79 cc (IQR 1.31–12.33 cc) when patients consented ($P=0.0004$). Lesions were smaller than 5 cc in 7/38 (18%) in the assent group and 11/18 (61%) in the consent group ($P=0.0024$). There was good correlation between neurological deficit by NIH stroke scale score and lesion volume ($r=0.584$, $P<0.0001$). Logistic regression demonstrated NIHSS or lesion volume predicted capacity to consent.

Conclusions—Patients with acute stroke who retain capacity to consent have significantly smaller infarct volumes than those incapable of consent, and these are frequently below the limits where measurement error significantly compromises valid use of volumetric end points. Only a small proportion of patients with capacity to consent would be eligible for, and contribute usefully to, most acute stroke trial protocols. (Stroke. 2008;39:2336-2340.)

Key Words: clinical trials ■ informed consent ■ magnetic resonance imaging ■ ethics

The Declaration of Helsinki stipulates that patients who are incapable of consent “... should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.” This allows for research participation by incapacitated individuals provided that the interests of the patient group overall are best served by such participation. However, the more recent European Clinical Trials Directive (ECTD) stipulates that if the “same results” could be achieved by recruitment of persons who are capable of consent, then subjects should not be recruited by assent. The position is further complicated by locale-specific legal protections, such as the Adults With Incapacity Act in Scotland, which states that the research must provide “real and direct benefit to the adult or to other persons having the same incapacity.”

One fundamental issue regarding participation by acute stroke patients in clinical trials is whether there are important differences between those with and without capacity to consent. If there is no difference, then both the Declaration of Helsinki and the ECTD advise that only those with capacity to consent should be included. Demarquay and colleagues showed that capacity diminishes with increasing age and baseline neurological deficit. Similarly, data from the first 300 patients recruited to the third International Stroke Trial (IST3) show that those with more severe stroke were less likely to have been recruited by consent, with clinical syndrome being an important determinant.

Brain imaging is increasingly included as a biomarker of treatment effect in clinical trials, and trials designed with imaging end points generally include imaging selection criteria. We hypothesized that imaging based trials, and indeed most acute stroke trials, would be significantly compromised if recruitment were restricted to subjects who retain capacity. We therefore assessed the lesion volumes from patients included in 3 studies of acute stroke at our institution and compared the volumes in those who had been recruited by consent to those recruited by assent.

Methods

Studies

Three acute stroke studies that used magnetic resonance imaging (MRI) in our institution were identified. All studies had been approved by local
Clinical Data

The following data were recorded for each individual: age, sex, stroke lateralization, clinical syndrome using the Oxfordshire Community Stroke Project (OCSP), stroke severity by the National Institutes of Health Stroke Scale (NIHSS), time to imaging, and whether or not an individual was treated with recombinant tissue Plasminogen Activator (rt-PA).

Image Analysis

Lesion volumes on admission were retrospectively assessed by 2 investigators; M.T.M. (Studies 2 and 3) and K.A.D. (study 1). The software package Cheshire (Perceptive Informatics, PAREXEL) was used to calculate lesion volumes on diffusion weighted imaging (DWI) sequences. After identification of the lesion by the rater, a semiautomated method was used to define lesion borders on each slice. Further manual refinement on each slice produced final lesion boundaries. The lesion volume was then calculated automatically. Where available, formal reports of angiographic examinations (CT angiography and time of flight magnetic resonance angiography) by experienced neuroradiologists were reviewed and the site of any occlusion noted. Results of perfusion imaging, when undertaken, were also assessed.

Statistical Analysis

Statistical analyses were mainly performed with Minitab (Version 14.0). The distribution of data were assessed using a Kolmogorov–Smirnov Test, and a Mann–Whitney test was subsequently used to investigate whether lesion volumes in the group recruited by assent differed from those of the group recruited by consent. Spearman’s Rank test was used to assess the correlation between admission NIHSS score and lesion volume. A number of other clinical parameters were compared between groups (Table). Finally a binary logistic regression analysis was performed to determine the effects of NIHSS, lesion volume, age, and lateralization on the capacity to consent (SPSS v14.0).

Results

Baseline Data

Scans from 56 patients were analyzed. Thirty-eight patients (68%) were recruited by assent and 18 patients (32%) by consent. Studies 1, 2, and 3 contributed 15, 29, and 12 patients, respectively, with 33%, 21%, and 58% of patients being recruited by consent. Studies 1, 2, and 3 contributed 15, 29, and 12 patients, respectively, with 33%, 21%, and 58% of patients being recruited by consent. Studies 1, 2, and 3 contributed 15, 29, and 12 patients, respectively, with 33%, 21%, and 58% of patients being recruited by consent. Studies 1, 2, and 3 contributed 15, 29, and 12 patients, respectively, with 33%, 21%, and 58% of patients being recruited by consent. Studies 1, 2, and 3...
Lesion Volume in Assent and Consent Groups
Lesion volume data were not of normal distribution \((P<0.010,\) Kolmogorov-Smirnov) and were positively skewed. The assenting group had a median lesion volume of 18.35 cubic centimetres (cc) \((\text{IQR} 8.27 \text{ to } 110.31 \text{ cc})\) and a mean \((\pm SD) 63.7 \text{ cc} \pm 78.5)\). In the consenting group, the median lesion volume was 2.79 cc \((\text{IQR} 1.31 \text{ to } 9.9 \text{ cc})\) and a mean \((\pm SD) 110.0 \text{ cc} \pm 23.1)\).

There was no significant difference in lesion volume \((P=0.052,\) Mann–Whitney) or median NIHSS \((P=0.1528,\) Mann–Whitney) between those with right hemisphere strokes compared with those with left hemisphere strokes. Perfusion imaging \((\text{PWI})\) was available for 7 patients, of whom none had PWI–DWI mismatch, consistent with the late imaging time in most cases.

The distribution of clinical syndromes defined by OCSP criteria differed significantly between groups \((P=0.0231,\) Fisher-Freeman-Halton Exact test). There was a trend toward more proximal occlusion in the assenting group but this did not reach statistical significance \((P=0.594,\) Fisher-Freeman-Halton Exact).

Discussion
Our findings support the need to recruit patients to trials by assent. We found significant differences in lesion volume, stroke severity, and clinical syndrome between those recruited by consent compared to those recruited by assent. Unsurprisingly we demonstrated that NIHSS is the best predictor of capacity to consent.

Two central ethical questions prompted by considering the application of the European Clinical Trials Directive in acute stroke trials are \((1)\) whether there are reasons to expect differences in the biology of stroke in those able to consent from those recruited by assent that would compromise the end points for a trial; and \((2)\) whether there are other practical issues that prevent clinically useful data being obtained from consenting patients. Imaging has the potential to identify the most appropriate subset of patients for recruitment, meaning fewer subjects may be required to produce informative data. However, it will be additionally important to know whether capacity for consent might signify a different biological response. Current indirect data suggest it does. For example, admission lesion volume is an independent predictor of intracerebral hemorrhage after the administration of intrave-
nous thrombolytic therapy,\(^9\) suggesting an increased risk in patients in the assenting group. In those patients deemed capable of consent, we found a predominance of lacunar syndromes, and distal MCA occlusions associated with lesser neurological deficit. Therefore this cohort is unlikely to provide useful data regarding reperfusion or recanalization. Many of these patients are likely to improve spontaneously, unlike the larger strokes seen in the assent group. Therefore it is clear that significant differences exist in stroke etiology, presentation, natural history, and prognosis between consenting and assenting groups, and conclusions made from one cohort may not be applicable to the other.

With regard to the second issue, to find evidence of a biological effect, either by change in neurological impairment or by lesion volume, the test instruments used must be sensitive to the degree of change expected. Exclusion of patients with brain lesion volumes under 5 cc has been proposed because measurement error is too great to produce reliable results.\(^{10}\) If a change in radiological parameters is not measurable reliably, recruitment of a subject might be regarded as ethically dubious, irrespective of an individual’s capacity. Of note, only 13\% of patients recruited by assent had lesion volumes less than 5 cc, suggesting that even measurement error in imaging-based trials may be less in the assenting group.

What would have been the effect in our center of restricting recruitment to patients capable of consent? Typical inclusion criteria for imaging-based trials include both clinical measures of stroke severity selection and lesion size.\(^{10-14}\) If criteria such as minimum NIHSS score of 6 (as used in DEFUSE\(^{11}\)) and minimum lesion volume of 5 cc (to reduce measurement error\(^{10}\)) were applied to our population, recruitment by consent alone would have resulted in only 4 patients (7\%) being included, all of whom still had relatively small lesions (<20 cc). Of the remaining 28 patients where NIHSS data were available, 25 of these could also be included if assent was allowed. Therefore, if assent were not possible recruitment of the remaining eligible patients would allow only limited conclusions to be made, thus potentially leading to a situation of unethical recruitment of these “eligible” patients. Many stroke trials which are not primarily imaging-based also specify a minimum neurological deficit (NIHSS) for inclusion, and thus these issues are applicable to stroke trials in general.

The validity of consent is questionable in neurological disease and in acute illness. Even acute stroke patients eligible for thrombolysis who recover rapidly have limited recall of the nature of their event,\(^{15}\) and in subarachnoid hemorrhage trials only 28\% of patients felt that they had been capable of making an adequate decision.\(^{16}\) In this regard it is vital that the information sheets provided to patients in acute trials are clear and concise and aimed at patients with little medical knowledge.

Our findings relate to practice at a single site but behavior with respect to consent appeared reasonably consistent across a number of different investigators and studies, although clearly all were practicing in the same environment. Our site is experienced in recruitment to clinical trials in acute stroke and has not noted any substantial differences in interpretation of recruitment processes compared to other sites in any multicenter trial. The population described here is fairly typical of those in stroke trials.

We did not assess lesion localization or morphology. Our cohort is not entirely homogeneous with minor differences in time window of recruitment and clinical syndromes permitted between studies. We cannot exclude the possibility that knowledge of lesion volume might have influenced the decision regarding appropriate means of recruitment, but MRI was seldom used as the primary imaging modality during the period of these studies. We did not have repeated data on vessel occlusion or perfusion status, but findings remained significant after excluding rt-PA–treated patients whose initial NIHSS score may not have reflected accurately the DWI lesion volume attributable to reperfusion before imaging.

In conclusion, this study demonstrates that lesion volumes are greater in patients recruited to acute stroke studies by assent compared to consent. Given the biological and clinical differences between small and large lesions, and the methodological restrictions imposed by small lesions, this emphasizes the importance of recruitment by assent to many acute stroke studies. Neither safety nor efficacy outcomes may be measurably reliable from consenting patients alone, with effects on sample size, study duration, and validity of conclusions that may have a wider and potentially negative impact.

**Disclosures**

The authors are currently recruiting patients to a single-site imaging-based study by both assent and consent and have sought ethical approval for several imaging-based clinical trials, some of which have been refused for reasons pertaining to capacity to consent.

**References**


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