Boosting The Chances To Improve Stroke Treatment

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Background and Purpose—There is a lack of agreement regarding measuring the effects of stroke treatment in clinical trials, which often relies on the dichotomized value of 1 outcome scale. Alternative analyses consist mainly of 2 strategies: use all the information from an ordinal scale and combine information from several outcome scales in a single estimate.

Methods—We reanalyzed 3 outcome scales that assessed patient recovery (modified Rankin Scale, National Institutes of Health Stroke Scale, and Barthel Index). With data collected from the 1652 patients in the Citicoline pooling data analysis, we used 2 standard techniques of exploratory multivariate analysis to analyze the distances among ranks and to isolate the common and the unique information provided by each of the 3 scales.

Results—The different scale values correspond to gradually different patient status, confirming that information is lost when a scale is collapsed to just 2 values, whether recovered or not. The scales shared 90.7% (95% CI, 84.5–96.9) of their information, with no individual scale contributing unique information.

Conclusions—Salient stroke outcome information is lost when an ordinal scale is collapsed into fewer categories. In contrast, the full scales provide a comprehensive patient outcome estimate. Furthermore, in the context of stroke clinical trials, those scales are highly correlated, providing the rationale to pool them into a single estimate. These insights may be used to optimize the analysis of stroke trials to increase study power to detect efficacious interventions. (Stroke. 2010;41:e143-e150.)

Key Words: analysis ■ biostatistics ■ clinical trials ■ scales ■ stroke management ■ stroke recovery

Stroke is the second most common cause of death and a major cause of disability worldwide. Although at least 178 randomized clinical trials enrolling >73,000 patients were conducted for 75 promising agents over the 20th century, only 3 trials reported positive findings and only 1 agent has been approved by the Food and Drug Administration for use in acute cerebral ischemia. The pivotal phase III clinical trial is used to guarantee the efficacy that are approved for application to patients. Statisticians have developed methods to maximize study power; that is, the proportion of interventions with true biological efficacy that are approved. In addition to the magnitude of the intervention effect and the sample size, power is mainly related to measurement reliability and statistical analysis. Although patient recovery after stroke is routinely measured by ordinal outcome scales, the most popular statistical analysis has been comparing the proportion of recovered patients, defined as those with scores above a single prespecified cut-point on a single outcome scale. As Wardlaw et al have shown, “a change of a single point on the Ranking scale can make the difference between ‘success’ and ‘failure’ of the trial.

In this article, we address 2 increasingly used though controversial alternatives to the traditional, dichotomized, single-scale analysis: (1) the use of the entire range of information captured in an ordinal scale; and (2) the use of more than just 1 single scale. For the former, opinions are clearly divided between those in favor of using all the ordinal information to maximize power and those in favor of dichotomization because of its readability. If the scale is truly ordinal—that is, if differences in scale categories are related to some progressive degree of biological or clinical difference in patient outcome—then some information is lost when different categories are merged. The second controversy confronts the classical univariate effect estimate based on just 1 scale with an effect estimate based on information pooled from several—often 3 to 4—scales (“global test”). The rationale is that if more information is used from every patient, fewer patients would be needed. One regulatory agency has argued that this global estimate causes difficulties in its clinical interpretation and its explanation to patients. An additional concern is how to interpret a single “global” effect if discordant treatment effects are observed on each component scale. The key point is whether those scales are

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measuring different patient characteristics or just 1 single dimension of patient recovery.

We use 2 well-established methods of explanatory multivariate analysis to study 2 assumptions underlying alternative methods. First is the existence of some progressive order among the different outcome values of ordinal scales. Do patients belong to just 2 alternative categories (success and failure), or may they be ranked within the full scope? To put it more simply, does an order make sense? Second is the amount of common vs unique information provided by the 3 most usual scales. Does a combination of outcome scores make sense, or does this pooling imply that some specific information is lost? In addition, the correspondence among values of different scales is provided.

Materials and Methods

Patient Population

We analyze the individual data pooled in a meta-analysis of Citicoline, which merged 4 clinical trials conducted in the United States between 1997 and 2001. They included 1652 patients with a 24-hour previous stroke. Main clinical and demographic characteristics can be found elsewhere.

Recovery Measures

Patients were assessed 12 weeks after stroke using the Modified Rankin Score (mRS), the National Institute of Health Stroke Score (NIHSS), and the Barthel Index (BI). The worst values on the NIHSS (42), BI (0), and mRS (6) were imputed to the 275 patients who died before 12 weeks had passed.

Bivariate Analysis of Ordering

To explore the existence of a genuine rank ordering of the levels of each scale, we analyze if there is a trend in the central values (means and medians) of 1 scale given the values of the other scales (eg, we compare the mean NIHSS scores for patients rated 0–6 on mRS).

Simultaneous 3-Dimensional Analysis of Ordering

Multiple correspondences analysis (MCA) explores the relationship between the categories of the different scales. It makes no assumption about their order. For all cases in each scale category (eg, mRS=1), it computes its profile, that is, the percentage of patients in each category of the remaining scales. Closer categories are expected to have more similar profiles. The degree of dissimilarity between the profiles of 2 categories is quantified by the $\chi^2$ distance. Based on algebra analysis, MCA defines a new multidimensional space and locates each category in this new space to reproduce their original distances with the minimum possible number of independent dimensions. As 2 analogies, the distances among 50 European cities should be able to be plotted in just 2 dimensions: north-to-south and east-to-west, but the distances between 50 railway stations of the same line should be plotted in just 2 dimensions: north-to-south and east-to-west, but the distances among 50 European cities should be able to be plotted in just 2 dimensions: north-to-south and east-to-west, but the distances between 50 railway stations of the same line should be able to be plotted in just 2 dimensions: north-to-south and east-to-west, but the distances among 50 European cities should be able to be plotted in just 2 dimensions: north-to-south and east-to-west, but the distances between 50 railway stations of the same line should be able to be plotted in just 2 dimensions: north-to-south and east-to-west, but the distances among 50 European cities should be able to be plotted in just 2 dimensions: north-to-south and east-to-west, but the distances between 50 railway stations of 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each correspond to different patient status and those values are gradually ordered. This finding supports the recommendation of the European Agency for the Evaluation of Medicinal Products that “dichotomization of outcome (positive–negative) is not recommended for neurological scales as patients in the same category may be clinically distinct and important information might be missed.”

However, from a medical point of view, the objective could be “whether subjects finish the study with minimal or no disability” and, then, the main analysis may rely on the proportion of patients reaching this goal. This medical objective should be weighted with the statistical objective of maximizing the trial power, as well as the need to provide regulators, clinicians, and patients with a readable treatment effect measure.

The binary correlations in Table 2 are lower than those reported by Tilley et al for the NINDS tissue plasminogen activator stroke trial (0.67 vs 0.75 for mRS–NIHSS and 0.58 vs 0.67 for BI–NIHSS). In addition to random sample variability, evaluator reliability, a different data imputation strategy, or a more heterogeneous patient population (ie, wider eligibility criteria, longer treatment delay, and so on) can also explain this result. In any case, the benefit of combining the univariate estimators in a single multivariate one (as the Generalized Estimating Equations [GEE] does) is higher for lower correlations."}

Uniform Unit

Our results show that the scales are not linear (Figure 2), with some clustering for the healthier scale values that may suggest smaller information loss when pooling mRS of 0 with mRS of 1 than when pooling from mRS of 2 to 6. However, the assumption of a uniform unit has a limited impact in correlation measures. In addition to the standard assumptions of independent and identical randomly distributed variables, the Pearson correlation coefficient also assumes a normal bivariate distribution and a linear relationship among the variables, but the Spearman correlation coefficient only assumes a linear relationship among the ranks calculated considering ties.

Any mathematical model is a simplification of nature, but our data agree much more with the oversimplification of unit measure (ie, that the difference between mRS=1 and mRS=2 equals the difference between mRS=4 and mRS=5) than the oversimplification of dichotomization (ie, that patients with mRS=2 are equal to patients with mRS=5). So, if in the quest for simplification researchers agree to pay the smaller penalty of unit measure, then parametric statistics may be used to quantify treatment effect size, probably leading to more powerful and readable analysis.

Figure 1. Univariate distributions for the outcome neurological scales on day 90. The mRS is a global measure of disability and handicap ranging from 0 (no symptoms) to 6 (death). NIHSS is a neurological impairment scale ranging from 0 (no deficits) to 42, rated by an expert neurologist. BI is a functional activities of daily living scale ranging from 0 (completely disabled) to 100 (fully independent), with only 21 possible values ending in 0 or 5 (eg, 0, 5, 10, . . ., 95, 100). The mRS is more uniform than the other scales, with a mode on the value of 4. NIHSS is skewed to the lowest values, although the worst value, 42, is strongly influenced by its imputation to dead patients. BI is U-shaped, with values concentrated at both extremes. Imputed values to the 275 patients who died are highlighted.

Table 1. Descriptive Statistics for the Neurological Scales on Day 90

<table>
<thead>
<tr>
<th>Scale</th>
<th>Median (IQR)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS</td>
<td>3 (2)</td>
<td>3.1 (1.9)</td>
</tr>
<tr>
<td>NIHSS</td>
<td>6 (12)</td>
<td>11.9 (14.5)</td>
</tr>
<tr>
<td>BI</td>
<td>75 (90)</td>
<td>59.7 (40.8)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.
The assumption of uniform unit has been widely used with those neurological scales. For example, scale means have been provided in the description of one-fifth of stroke clinical trials. In a review of their clinical interpretation, the NIHSS and BI reliability are quantified by the unit-measure intraclass correlation coefficient. In a more sophisticated way, the VISTA and the SAINT investigators used baseline NIHSS as a quantitative predictor variable of outcome in 2 similar logistic regression. Joint analysis of the 2 SAINT trials estimated that the odds of a favorable outcome is expected to be systematically multiplied $0.814\times$ for each 1-point increment on the NIHSS baseline, either in an increment from 1 to 2 or in an increment from 21 to 22.

Common vs Unique Information

The scales have traditionally been used to assess the different dimensions of health recognized by the World Health Organization: physical deficits (NIHSS), functional disability (BI and mRS), and social handicap (mRS). However, they are highly correlated, and all of them can also be conceived as measuring stroke recovery. Our results show that 90% of the value differences on each of the 3 scales reflect variation along a single common stroke recovery dimension. Because the remaining variability cannot be attributed to specific information indexed uniquely by an individual scale, controversial clinical trials results among scales are not expected. Furthermore, our results support interpreting the 3 scales as repetitive measures of the same parameter: patient recovery. As an analogy, cardiologists average 3 repetitions of independent determinations of blood pressure values to improve reliability. For example, the CONSORT statement, in item 6b, requires specifying “any methods used to enhance the quality of measurements (eg, multiple observations).” Our estimated value of 90.7% of common variance can be directly compared with the intraclass correlation coefficient obtained on blood pressure data. Montes et al estimated the concordance between a family doctor and a semiautomatic device to be 0.84 (95% CI, 0.78–0.90). In other settings, such as health-related quality-of-life measures, usual intraclass correlation coefficient values can range between 0.55 and 0.79. The assumption of a common correlation without specific contributions from any scale has been used in simulations to explain the extra power provided by the global statistic.

Readability and Transparency

In choosing a statistical method, in addition to the medical question and its statistical properties, its readability should...
also be considered to achieve the desired transparency to enhance physician advice and patient choice. Our results suggest that in the setting of clinical trials, the 3 outcome scales can be seen as a repeated measure of the same clinical feature: patient recovery. Provided that this assumption is not violated in the actual clinical trial data (ie, that different scales do not show true different estimations of effect size), it facilitates the interpretation. For example, the GEE odds ratio estimates a single treatment effect on “patient recovery” with “minimal or no disability.”

To check the transparency and readability of the different alternative statistical analyses, random surveys of the general population of potential stroke patients, of patients who have had a stroke, and of physicians who treat stroke patients should be conducted to ask the various groups what type of treatment effect size measure they find most interpretable.

### Limitations

External validity is maybe the most important limitation. To reach its main objective (to get an unbiased estimate of the treatment effect size), clinical trials rely on the random allocation of treatments to patients fulfilling the eligibility criteria. Because they are not based on random samples of patients, the extrapolation of their results needs the additional assumption that the treatment effect is still the same on the external, more general, new target population. Because our results rely on clinical trial data, we do not pretend that our conclusions apply to other conditions. Specifically, in contrast to our results, it is highly plausible that the 3 outcome scales should have a completely different meaning in settings other than stroke trials. So, we do not propose that the 3 scales should be interpreted as just measuring only 1 patient characteristic in the general population. Furthermore, the 3 outcome scales we used were recorded 12 weeks after stroke by evaluators blinded to treatment assignment but aware of the other scale values, violating a key design feature for

### Table 2. Correlations Between Pairs of Scales

<table>
<thead>
<tr>
<th>Correlations</th>
<th>Unit Measure (Pearson)</th>
<th>Ranks (Spearman)</th>
<th>Dichotomized† (Phi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS–NIHSS</td>
<td>0.84</td>
<td>0.91</td>
<td>0.68</td>
</tr>
<tr>
<td>mRS–BI</td>
<td>0.90</td>
<td>0.94</td>
<td>0.67</td>
</tr>
<tr>
<td>NIHSS–BI</td>
<td>0.84</td>
<td>0.89</td>
<td>0.58</td>
</tr>
</tbody>
</table>

†mRS=1, NIHSS=1, BI=95.

Rank correlations are slightly higher than unit measure correlations but much higher than their dichotomized version.
measuring concordance and diagnostic performance. To apply our results to other clinical settings, adequately collected data should be analyzed.

In all of our analyses we have assumed that the equivalence premise holds for all the scale values, that is, that patients sharing the same scale value are identical among each other but different from any other patient, at least in the measured characteristic. This premise is intrinsic to any measurement, irrespective of other measure properties such as rank or unit measure. However, this assumption is highly questionable in the case of the NIHSS scale. For example, a NIHSS of 3 could represent a major deficit in 1 area or a collection of 3 very minor deficits. Our analysis does not provide any evidence about the correspondence between these 2 different kinds of NIHSS of 3, but maybe a future MCA performed on the different components of this scale could add some new information. Taking into account the idiosyncrasies of stroke patients, it should also be studied to see if they can help in assessing the equivalence between those different NIHSS = 3 values.

In the interest of parsimony, our reported analyses have not considered 3 variables that may potentially affect the distribution of the outcome scales: study, allocated treatment, and Treatment delay. When those 3 variables have been included in our analyses, the results have been almost identical.

Implications for Phase III Clinical Trials

Our results point out that the frequent dichotomization of ordinal scales merges scale values that correspond to different patient status, suggesting the loss of power previously raised by several authors, either by using theoretical formulas of sample size or by reanalyzing previous stroke clinical trials. However, Savitz et al found that the Cochran-Mantel-Haenszel ordinal shift test failed to outperform the dichotomized Rankin outcome of 0 to 2 in the post hoc analysis of the NINDS and ECASS trials.

We have shown that the assumption of unit measurement has a modest impact on results, allowing parametric statistics, such as means and standard deviations, to display patient evolution on any of those scales and using design features to improve statistical efficiency (such as averaging repeated determination of the same scale to control either inter-rater or intrapatient variability). Researchers can avoid the assump-
tion of a constant scale unit by using an ordinal analysis, which retains much of the power and is less sensible to extreme values. In ordinal analyses, treatment effect estimates can take the form of odds ratios or the Mann-Whitney-Wilcoxon $c$-statistic; that is, the proportion of patients having better outcomes with the study intervention than with the control, which is a single and interpretable measure of stroke treatment effect.

Our results also provide a foundation for merging estimates from different scales. Because the scales do not statistically measure unique dimensions, results in different directions should not be encountered, and a single combined estimate will increase study power. The O'Brien test may combine quantitative variables from several outcomes. If the unit-measure assumption does not hold, the adjusted O'Brien rank–sum-type test can be applied to the ordinal outcome scales.

By interpreting the scales as repetitions of the measurement of patient recovery, we pose the question of "adding patients or adding measures," because extra information can also be provided by other scales, such as the Glasgow Outcome Scale.

Conclusion

Our results suggest that the common practice of using a single dichotomized scale in primary end point analysis is not optimal, and it may result in reduced study power, making trials needlessly larger or increasing the chance that studies will fail to detect the benefit of a genuinely efficacious agent. Our results indicate that more information can be used in the statistical analysis of stroke trials if dichotomization is avoided and several scales are joined to estimate a efficacy measure.

However, we have not studied the power of the suggested methods under different alternative treatment effects. To definitively boost the chances of improving stroke treatment, statistical simulation studies should be performed to consider the type of treatment effect of the new compound over the comparator.

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Disclosures

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