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Abstract

Introduction:

There is practice variability in the treatment of patients with minor ischemic stroke with thrombolysis. We sought to determine which clinical factors physicians prioritize in thrombolysis decision-making for minor stroke using adaptive conjoint analysis.

Methods:

We conducted our conjoint analysis using the Potentially All Pairwise RanKings of all possible Alternatives methodology via the 1000Minds platform to design an online preference survey and circulated it to US physicians involved in stroke care. We evaluated 6 clinical attributes: language/speech deficits, motor deficits, other neurological deficits, history suggestive of increased risk of complication from thrombolysis, age, and premorbid disability. Survey participants were asked to choose between pairs of treatment scenarios with various clinical attributes; scenarios automatically adapted based on participants' prior responses. Preference weights representing the relative importance of each attribute were compared using unadjusted paired t tests. Statistical significance was set at $\alpha = .05$.

Results:

Fifty-four participants completed the survey; 61% were vascular neurologists and 93% worked in academic centers. All neurological deficits were ranked higher than age, premorbid status, or potential contraindications to thrombolysis. Differences between each successive mean preference weight were significant: motor (31.7%, standard deviation [SD]: 9.5), language/speech (24.1%, SD: 9.6), other neurological deficits (16.6%, SD: 6.4), premorbid status (12.9%, SD: 6.6), age (10.1%, SD: 6.3), and potential thrombolysis contraindication (4.7%, SD: 4.4).

Conclusion:

In a conjoint analysis, surveyed US physicians in academic practice assigned greater weight to motor and speech/language deficits than other neurological deficits, patient age, relative contraindications to thrombolysis, and premorbid disability when deciding to thrombolyse patients with minor stroke.

Keywords clinical decision-making, acute ischemic stroke, minor stroke, conjoint analysis

Introduction

Thrombolysis treatment rates for patients with acute ischemic stroke presenting with minor symptoms have increased over time[1] due to recognition of the disability associated with failure to treat and the relative safety of thrombolysis in minor stroke.[2] Labeling information for alteplase no longer lists minor symptoms as an exclusion criterion,[3] and the latest guidelines from the American Heart Association/American Stroke Association note that alteplase should not be withheld from otherwise eligible patients with mild but disabling strokes.[3] However, the most commonly documented reason for failure to treat with alteplase is having mild or rapidly improving stroke symptoms.[4]

A better understanding of clinical decision-making in minor stroke is needed to clarify current treatment patterns and facilitate targeted interventions to reduce variability.[5] Controversy exists among physicians regarding what constitutes a disabling minor deficit.[5,6] Additionally, empiric data regarding the risk-to-benefit ratio of thrombolysis in patients with nondisabling mild stroke symptoms are limited.[3,7] A recent randomized controlled trial of alteplase among patients with minor stroke without clearly disabling symptoms, The Potential of rtPA for Ischemic Strokes With Mild Symptoms (PRISMS) trial, was terminated early due to slow recruitment.[8] We, therefore, conducted a survey study using adaptive conjoint analysis (CA) to evaluate how

physicians weigh various clinical features when deciding whether or not to thrombolyse patients with minor stroke.

Methods

Conjoint analysis studies are implemented to quantitatively understand how decision makers consider and balance various aspects of a complex decision. Acute stroke thrombolysis decision-making is known to incorporate many factors,[9,10] making it a process well suited to CA. These analytical models are being increasingly used to understand decisions in the health-care environment via surveys directed toward patients, physicians, and other stakeholders to determine participants' stated preferences over a range of attributes.[11] Unlike more traditional vignette studies where a finite number of vignettes are constructed via variation of selected attributes that are then presented to subgroups of participants,[9,10,12] CA studies evaluate trade-offs in an individual's decision-making based on the interplay of all factors or attributes included in the survey.[13] A CA can thus be used to discover the relative importance of factors involved in a complex decision to a stakeholder.[11,13]

We used the Potentially All Pairwise RanKings of all possible Alternatives (PAPRIKA) method to construct our CA via the 1000Minds online software platform. This method determines participants' preference values (weights) by asking simple questions involving trade-offs between attributes included in the survey. In economics and other social sciences, an individual's preferences correspond to their underlying utility or desire for an option. There are, broadly speaking, 2 types of preferences: revealed and stated. Revealed preferences are derived from actual observed market activities, whereas stated preferences can be derived from surveys. The key principle behind the PAPRIKA method is that by repeatedly asking participants to choose 1 alternative from a set of 2 options, eventually enough information about their stated preferences will be generated to accurately rank all the attributes under consideration. Choosing between 2 alternatives is easier than choosing 1 alternative from among 3 or more options. The PAPRIKA method thus simplifies decision-making while still allowing the relative importance of each attribute included in the survey to each participant to be determined.[14]

Survey Design

Our preference survey contained 6 patient-level attributes with 2 to 5 levels each (Table 1): language/speech (communication) deficits, motor deficits, and other neurological deficits (sensory loss, quadrantanopia, single limb ataxia, and neglect), history suggestive of potential increased risk of thrombolysis complication, age, and premorbid disability. Attributes were chosen based on prior research available at the time of study design. We selected neurological symptoms across different domains with low National Institutes of Health Stroke Scale (NIHSS) in keeping with the definition of minor stroke as NIHSS ≤3[15] and an earlier physician survey which found that cases where NIHSS ≤2 had poor physician consensus.[12] Another prior survey study found that premorbid status and age greater than 80 were factors that influenced alteplase use[16]; patient age and cognitive status also played a role in thrombolysis decision-making in a recent UK study.[13] We selected relative treatment contraindications (non-ST-segment elevation myocardial infarction in previous 3 months and genitourinary bleeding in the previous 21 days) that physicians reported being willing to disregard when surveyed.[17] Given our focus on trade-offs between attributes, we sought to avoid extreme values (eg, advanced dementia or active bleeding) when constructing our survey study to avoid biasing our results.[11]

Table 1. Survey Attributes and Levels.

			Levels			
		Low	Medium		High	
	Communication deficit	Trace dysarthria	Mild dysarthria		Mild aphasia	

		Isolated facial droop	Isolated nondominant hand weakness	Isolated dominant hand weakness	Mild arm and mild leg weakness	Truncal ataxia leading to inability to walk
	Motor deficit					
Attributes	Other neurological deficit	Mild unilateral sensory loss	Quadrantanopia	Single limb ataxia	Visual or sensory neglect	
	Relative intravenous alteplase treatment contraindication		Non-ST-segment elevation myocardial infarction (NSTEMI) in previous 3 months		Genitourinary bleeding in previous 21 days	
	Age (years)	75	81		92	
	Premorbid functional status	Fully independent	Needs help paying bills	Needs a cane to ambulate	Needs a walker to ambulate	

Survey participants were informed prior to starting our survey that questions would involve trade-offs between clinical attributes, that their answers depend on personal opinion, and that each question is unique. Participants were then presented with thrombolysis treatment scenarios (eg, 92-year-old with isolated nondominant hand weakness versus 75-year-old with mild aphasia) based on a combination of 2, and only 2, attribute levels. They were asked "which of these 2 (hypothetical) alternatives do you prefer to treat with intravenous-type plasminogen activator (tPA)? (all else being equal)" for each scenario set. Participants could select either scenario or "they are equal" (Supplemental Figure 1). We imposed some constraints on the survey design to prohibit treatment scenarios with deficits that did not fit a typical single vascular syndrome (eg, ataxia and aphasia) or where total NIHSS >3. The attributes and levels presented in a treatment scenario automatically adapted based on a participant's prior choices. Each time a participant selected 1 option from a pair of hypothetical alternatives, the PAPRIKA method was applied to immediately identify all other pairs of alternatives that could be ranked based on that selection and eliminated those scenarios from being presented; primarily, the logical property of transitivity was used. The number of questions presented to each survey participant therefore was variable based on their individual choices.

Participant Recruitment

We recruited physicians treating patients with acute stroke in the US via StrokeNET (Regional Coordinating Center Principal Investigators and to their spoke investigators)[18] as well as via the official e-mail listings of vascular neurology fellowship directors, neurocritical care physicians, and emergency department physicians (total N = 853). The survey was opened for participation in January 2017 and closed in July 2017. Participants consented to our study by clicking on the hyperlink displayed in the survey invitation. Each participant was instructed to complete the survey only once. Participants completed a brief demographics questionnaire once they finished the preference survey. The Montefiore Medical Center institutional review board (no.: 2016-6921) approved this study.

Statistical Analysis

Stated participant preferences (weights) were generated using the PAPRIKA method to represent the relative importance of each attribute for each decision maker. Overall mean preference values with standard deviation (SD) and mean rank are reported for all included attributes. We used unadjusted paired t tests to compare mean preference values. Marginal rate of substitution, the rate at which a participant will substitute one attribute in exchange for another while maintaining the same level of utility, was determined. We used Kendall coefficient of concordance to assess agreement among all participants (1 = perfect agreement, 0 = perfect disagreement) across all possible alternatives. The threshold for statistical significance allowed for an α error of .05.

Results

Among 94 individuals who selected the survey link, 54 participants completed the survey in full. Among these 54 participants, 59% were male, 61% were vascular neurologists, 93% worked in academic centers, and 52% had been in practice for more than 10 years (Table 2). The median number of questions presented to each participant was 27 (interquartile range: 21-32); the number of questions did not exceed 49 for any participant. The survey took an average of 9 minutes to complete; the questionnaire following the survey took an average of 58 seconds to complete.

Table 2. Participant Questionnaire.[a]

	N (%)
Level of training	
Resident	1 (1.9)
Vascular neurology fellow	2 (3.7)
Other fellow	1 (1.9)
<5 years in practice	13 (24)
5-15 years in practice	19 (35.2)
>15 years in practice	18 (33.3)
Sex	
Female	22 (40.7)
Specialty	
Neurology resident	1 (1.9)
Neurocritical care	10 (18.5)
Vascular neurology	33 (61.1)
Emergency medicine	7 (13.0)
Other[b]	3 (5.6)
Hospital setting	
Academic	50 (92.6)
Community	4 (7.4)
US location	
Northeastern	13 (24.1)
Midwestern	17 (31.5)
Southern	18 (33.3)
Western	6 (11.1)
Career alteplase treatment volume	
None	2 (3.7)
<25 cases	5 (9.3)
25-100	12 (22.2)
100-300	12 (22.2)
>300	23 (42.6)

The preference weights of each participant and mean weight are depicted in Figure 1. Motor deficits were weighted most heavily (31.7%, SD: 9.5) followed by communication deficits (24.1%, SD: 9.6), other deficits (16.6%, SD: 6.4), premorbid status (12.9%, SD: 6.6), age (10.1%, SD: 6.3), and history of a potential contraindication to thrombolysis (4.7%, SD: 4.4). The difference between successive mean preference values was significant: communication versus motor deficits ($P < .001$), communication versus other neurological deficit ($P < .001$), other neurological deficits versus premorbid status ($P < .01$), premorbid status versus age ($P = .02$), and age versus history of potential contraindication ($P < .001$).
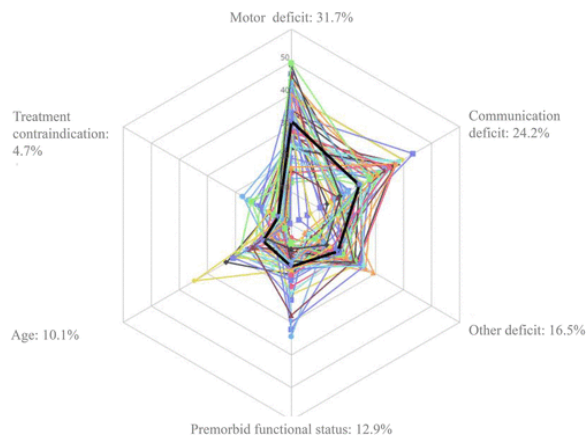

Figure 1. Radar chart depicting all attribute weights; thick black line and percentages represent mean values.

The mean rank of each of the 6 attributes was as follows: motor deficit = 1.6, communication deficit = 2.3, other deficit = 3.2, premorbid functional status = 3.9, age = 4.4, and relative alteplase contraindications = 5.5. The marginal rate of substitution of communication deficit for motor deficit was 1.3; the marginal rate of substitution of relative contraindication for thrombolysis treatment for motor deficit was 6.8 (Table 3). Kendall coefficient of concordance was .80 for all possible alternatives among all participants.

Table 3. Marginal Rate of Substitution (Ratio) of the Column Attribute for the Row Attribute.

	Motor Deficit	Communication Deficit	Other Neurological Deficit	Premorbid Functional Status	Age	Relative Contraindication
Motor deficit		1.3	1.9	2.5	3.1	6.8
Communication deficit	0.8		1.5	1.9	2.4	5.2
Other neurological deficit	0.5	0.7		1.3	1.6	3.6
Premorbid functional status	0.4	0.5	0.8		1.3	2.8
Age	0.3	0.4	0.6	0.8		2.2
Relative intravenous alteplase treatment contraindication	0.1	0.2	0.3	0.4	0.5	

Discussion

In an adaptive CA, we found that experienced, academic physicians practicing in the US consistently weigh motor and communication deficits more heavily than other neurological deficits, age, premorbid functional status, and potential contraindications for thrombolysis decision-making in patients with minor ischemic stroke.

We are not aware of any prior studies focused exclusively on minor stroke thrombolytic decision-making that use CA or other discrete-choice experimentation. A recent large, systematic US physician vignette survey regarding minor stroke treatment decision-making which included 7 clinical patient attributes failed to account for more than a small portion of the variance related to alteplase treatment.[10] None of the 4 attributes of highest relative importance (previous intracerebral hemorrhage, recent anticoagulation, NIHSS score, and previous ischemic stroke) in this recent study were included in our CA making cross-study comparisons challenging.[10] A smaller pilot survey on which the aforementioned recent large physician survey was based upon found that physicians were more likely to thrombolyse patients with minor stroke with language/neglect symptoms than with motor and visual/spatial/ataxia symptoms.[12] The different prioritization of deficit types by participants in our study may stem from the fact that we intentionally included patients with very minor syndromes (eg, isolated nondominant hand weakness) in our scenarios. A CA evaluating thrombolysis decision-making in the United Kingdom found significant heterogeneity among physician respondents on the influence of NIHSS 2 with aphasia versus NIHSS 5 without aphasia on thrombolysis decision-making, but other neurological deficits among patients with minor stroke were not evaluated.[13]

Our work adds to the extant literature by suggesting that physician decision-making in minor stroke at academic centers is more heavily influenced by the type of neurological deficit a patient presents with rather than physician concerns regarding potential treatment complications, age, or premorbid status. It is important to note that we did not evaluate how strong alteplase treatment exclusions (eg, active internal bleeding) affects decision-making in minor stroke and cannot comment on how including such an attribute would change our results. Future CA studies evaluating stroke decision-making may benefit from including different patient features or focusing on physician attributes, so that variance in minor stroke treatment can be further explained.[10] Characterizing physicians' motivation to withhold thrombolysis in minor stroke (eg expected recovery without treatment or meaningfulness of current deficit) is also an area for future research.

This study has some important limitations. First, we do not know the number of individuals who received our survey invite nor do we know the characteristics of physicians who started but did not complete it. This missing information prohibits us from reporting our survey response rate, thereby limiting our ability to generalize our findings without bias. Additionally, our final sample size is small and our results may not be applicable to nonacademic centers outside of the US given the makeup of our participants. Second, we did not include any patient neuroimaging or angiographic features in our survey nor did we include patient gender or race/ethnicity. Physician-level factors and patients' preferences are also probably important in minor stroke decision-making given the potential for patient–practitioner discordance regarding deficit significance.[6] We only include clinical patient factors in our survey. Third, we did not include the option of treating with tenecteplase tissue-type plasminogen activator (TNK-tPA) despite its favorable safety profile compared to alteplase among patients with minor stroke and intracranial occlusion.[19] Future minor stroke treatment decisions will likely be informed by results from the ongoing TNK-tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion 2 trial as well as the publication of PRISMS.[8]

Conclusion

In a CA of thrombolysis decision-making in patients with minor stroke, surveyed academic US physicians consistently assigned greater weight to motor and communication deficits than other neurological deficits,

patient age, premorbid functional status, and relative treatment contraindications. Additional sources of treatment variation among patients with minor stroke should be sought to identify opportunities for improvement in stroke decision-making.

Declaration of Conflicting Interests

Funding

Supplemental Material

Supplemental material for this article is available online.

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