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Recruitment of Ischemic Stroke Patients in Clinical trials in General Practice and Implications for Generalizability of Results

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Abstract

Background: While results of clinical trials are used to impact practice among patients with ischemic stroke, very little information is available regarding proportion and characteristics of patients recruited in clinical trials in general practice.

Methods: We performed this analysis to provide an audit of recruitment in clinical trials among patients with acute ischemic stroke using data from the University Healthsystems Consortium benchmarking project. A review of 40 consecutive ischemic stroke cases meeting inclusion criteria and discharge within a 6-month period was conducted in 32 hospitals.

Results: A total of 1256 patients (mean age 67 years, range 18--99 years) were included. A total of 77 (6%) patients were recruited in clinical trials; 33 and 14 patients recruited in drug or device trials, respectively. In the multivariate analysis, age under 80 years (odd ratio [OR] 2.2, 95% confidence interval [CI] 1.0--4.9), white or African-American race as compared with others (OR 2.5, 95% CI 0.98--6.6), evaluation by a neurologist or stroke team (OR 14.8, 95% CI 2.0--108), the use of intravenous thrombolysis (OR 8.4, 95% CI 4.9--14.4), and history of hypertension (OR 1.9, 95% CI 1.0--3.4) were associated with recruitment in clinical trials. There was no relationship between patient's gender and recruitment in clinical trials. The rate of intracranial hemorrhage (6% vs 2%, $p<0.05$) and progression of stroke (12% vs 3%, $p<0.05$) were higher among those recruited in clinical trials.

Conclusions: Patients recruited in clinical trials appear to have different characteristics from those who are not recruited limiting the generalizability of results from current trials.

Keywords

Acute stroke; clinical trials; enrollment

Introduction

Although clinical trials provide the most reliable information about the safety and efficacy of a treatment, the generalization and broad acceptance of the derived results is a common issue. Patient population recruited in clinical trials can be different from the general population because of inclusion and exclusion criteria, patients willing to participate in research[1–7], or physician bias in patient selection[1,8,9]. It is unknown how the patient population selected for acute stroke treatment trials differs from the patient population admitted for stroke but not recruited in clinical trials. We performed this study to determine the proportion and characteristics of ischemic stroke patients recruited in clinical trials using data collected as part of a multicenter bench marking project.

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Methods

Study population

We used the data from University HealthSystems Consortium (UHC) benchmarking project conducted in 2005. Clinical data for this project were collected from retrospective chart review of 40 consecutive admissions from each of 32 participating centers. Patients' inclusion criteria included age of 18 years or older and primary discharge diagnosis of ischemic stroke admitted between January 1, 2004 and June 30, 2004. Patients transferred from other emergency departments were included. Inpatients from other acute care facility were not included.

Data variables

Data collected for UHC benchmarking project included administrative information, patient demographics, clinical presentation, key patient management factors, past medical history, diagnostic testing, in-hospital complications, and discharge information. Information regarding whether the patient was included in a drug-related, device-related, or other research protocol was also collected. We used participation in any research protocol as the outcome variable. Independent variables examined for association included age, sex, race (white, African-American, other), history of vascular risk factors (diabetes mellitus, hypertension, hyperlipidemia, and cigarette smoking), admission to a specialty team (neurologist, neurointensivist, or neurosurgeon), Wake Forest Stroke Severity Scale10, and administration of intravenous thrombolytics. We also determined if patient participation in research protocol affects the outcome---including intracerebral hemorrhage, length of hospitalization, in-hospital complications (pneumonia, myocardial infarction, and urinary tract infection), and discharge destination.

Statistical analysis

We determined the association of independent variables with participation in research protocol using *t*-test for continuous and chi-square for categorical variables. Association of variables of selected variables was then determined in multivariate analysis using forward stepwise logistic regression. The variables selected in multivariable regression analysis included those variables that were significantly associated with recruitment in clinical trials in the univariate analysis and those that were noted to be associated with recruitment in clinical trials in previous studies. Another analysis was performed comparing the rates of in-hospital outcomes using *t*-test for continuous and chi-square for categorical variables between the two patient groups defined by recruitment and not in clinical trials. All analysis was performed in SAS software v9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Data were collected from a total of 1256 (mean age 67 years, range 18--99 years) consecutive acute stroke cases derived from 32 hospitals participating in UHC benchmarking project in 2005. Most patients presented through the emergency departments (n=1035). A total of 77 (6%) patients were recruited in clinical trials; 33 and 14 patients recruited in drug or device trials, respectively. One patient was recruited in both device and drug protocol.

Table 1 demonstrates a comparison of clinical characteristics of patients who were recruited and those not recruited in clinical trials. The mean age (±SD) of patients recruited in clinical trials (64.2±13.0) and those not recruited in clinical trials (66.7±14.7) was similar. The proportion of men (6.7%) recruited in clinical trials was similar to women (5.6%). The proportion of white (6.4%) and African-American (6.8%) patients recruited was higher than other races (3.1%). There was no difference in demographic or clinical characteristics of patients who were recruited in device protocol compared to patients who were recruited in drug protocol (data not shown).

Factors associated with recruitment in clinical trials using stepwise logistic regression analysis are shown in table 2. Age under 80 years, white or African-American race (compared with others), history of hypertension, evaluation by a specialty team (compared with general practitioner), and the use of intravenous thrombolysis were independently associated with recruitment in clinical trials. There was no relationship between patient's gender and recruitment in clinical trials.

Patients who were recruited in clinical trials were more likely to have intracranial hemorrhage (6% vs 2%, $p<0.05$) and progression of stroke (12% vs 3%, $p<0.05$) during hospitalization compared to patients who were not recruited in clinical trials. There was no difference in other in-hospital complications, mortality, length of stay in hospital, and recurrence of stroke between two groups (see table 3).

Discussion

In our analysis, we found that patients under 80 years of age, of African-American or white race, and those in whom thrombolytics was administered or admitted to the stroke team are more likely to be recruited in a clini-

Table 1.

Comparison of demographic and clinical factors between patients recruited and those not recruited in clinical trials (UHC bench marking study 2005)

	Patients not recruited in clinical trials (N=1179)	Patients recruited in clinical trials (N=77)
Age (mean ± standard deviation)	66.7 ± 14.7	64.2 ± 13.0
Sex (Men)	602 (51%)	43 (56%)
Race		
White or African-American	1025 (87%)	72 (94%)
Other	154 (13%)	5 (6%)
History of hypertension	895 (76%)	61 (79%)
History of diabetes mellitus	413 (35%)	27 (35%)
History of hyperlipidemia	423 (36%)	32 (42%)
Cigarette smoking status		
Active smoker	299 (25%)	23 (30%)
Past	240 (20%)	20 (26%)
Never	640 (54%)	34 (44%)
History of stroke	398 (34%)	20 (26%)
Arrival to the emergency after		
3 hrs of symptom onset	850 (72%)	32 (42%)*
Intravenous thrombolytics administered	78 (7%)	30 (39%)*
Wake Forest stroke severity scale		
Mild stroke	544 (46%)	21 (27%)
Moderate stroke	311 (26%)	19 (25%)
Severe stroke	189 (16%)	25 (32%)
Unknown/undocumented	135 (11%)	12 (16%)
Specialty team		
Yes	927 (79%)	76 (99%)*
No	252 (21%)	1 (1%)

*p<0.05

Table 2.

Independent factors associated with patient recruitment in clinical trials (UHC bench marking study 2005)

Clinical variables*	Total patients	Patients recruited in clinical trial n(%)	Odds ratio (95% confidence interval)
Age			
Under 80 years	978	69 (7.1%)	2.2 (1.0-4.9)
80 years or older	278	8 (2.9%)	Reference
Race			
White or black	1097	72 (6.6%)	2.5 (0.98-6.6)
Others	159	5 (3.1%)	Reference
Specialty team			
Yes	1003	76 (7.6%)	14.8 (2.0-108)
No	253	1 (0.4%)	Reference
Thrombolytics administered			
Yes	108	30 (27.8%)	8.4 (4.9-14.4)
No	1148	47 (4.1%)	Reference
Hypertension			
Yes	956	61 (6.4%)	1.9 (1.0-3.4)
No	300	16 (5.3%)	Reference

*Variables selected using stepwise logistic regression from age(80+/<80), gender, race (white or black/others), smoking (current/past/ never), history of stroke (yes/no), history of hypertension (yes/no), history of hyperlipidemia (yes/no), history of diabetes mellitus (yes/no), time of arrival to ED (<2h/≥2h hours), thrombolytics administered (yes/no), stroke severity (mild/moderate, severe or unknown), primary team (speciality/nonspecialty).

Table 3.

Comparison of in-hospital complications and outcome variables between patients recruited and those not recruited in clinical trials (UHC bench marking study 2005)

	Patients not recruited in clinical trials (N= 1179)	Patients not recruited in clinical trials (N=77)
Hemorrhagic transformation or intracranial Hemorrhage	23 (2%)	5 (6%)*
Progression of stroke	36 (3%)	9 (12%)*
Recurrent of stroke	8 (1%)	0 (0%)
Acute myocardial infarction	13 (1.1%)	0
Pneumonia	63 (5%)	8 (10%)
Urinary tract infection	10 (9%)	10 (13%)
Pulmonary embolism or deep venous thrombosis	9 (0.8%)	0
In-hospital mortality	61 (5%)	5(6%)
Length of stay in days (mean ± standard deviation)	5.9 ± 6.9	6.8 ± 5.2

*p<0.05

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cal trial. Our finding that patients aged more than 80 years are less likely to be recruited in clinical trials is not an unexpected finding because acute stroke clinical trials such as Interventional Management of Stroke (IMS)[11–13] and ALbumin In Acute Stroke (ALIAS)14 commonly limit recruitment of patients to 80 years or younger. Since patients aged 80 years or older comprise about 25% of patients admitted with stroke[15], our study highlights need of inclusion of this age group in these clinical trials. There also appears to a be higher rate of death and disability among patients aged 80 or greater compared with those under 80 years following acute intra-arterial or intravenous thrombolysis[16–19]. The higher rate is attributable to higher rates of underlying comorbidities and limited collateral formation and plasticity[20]. Therefore, results related to acute treatment trials predominantly recruiting patients under 80 years cannot be extrapolated to general practice consisting of a prominent proportion of patients 80 years or greater with a different risk benefit ratio. Patients who received intravenous thrombolytics were more likely to be recruited in clinical trials is also not unexpected as receiving IV thrombolytics is a marker for early arrival to the hospital and many stroke trials are limited to patients receiving thrombolytics[11,14,21–23].

Interestingly, we noted that odds of patient recruitment in clinical trials were 15 times lower if the patient was evaluated with nonspecialty team compared to those evaluated by specialty teams. This appears to be the most modifiable of all the factors identified in our analysis. Individual physicians differential inclination toward entering their patients in clinical trials is well recognized[1,8,9]. Hunter et al. noted that out of 9900 cancer patients who were eligible for recruitment in a clinical trial, only 3300 were recruited8. Physician's preference for an alternate treatment and patient refusal were important reasons for nonparticipation in a clinical trial. Rahman et al. surveyed 122 Japanese physicians for reasons for not entering their patients in clinical trials and noted that the physicians who were concerned about detrimental effects of recruitment on doctor--patient relationship or expected the clinical trial to fail were less likely to enter their patients in clinical trials[9]. Fukui et al. surveyed 679 Japanese physicians who agreed to recruit patients in a clinical trial[1]. They did not find any difference in specialty (cardiology, internal medicine, others) or working site (University, other public or private) between physician inclination toward recruiting and nonrecruiting patients in clinical trials. The difference may be due to classification of physicians by different specialties in the study by Fukui et al. in contrast to our classification of specialty vs nonspecialty in relation to stroke management.

Other reasons have been implicated in physician surveys that have noted that different groups of physicians have different attitudes toward research. Taylor et al. surveyed 484 physicians for their attitude toward recruitment of their patients in clinical trials[24]. They noted that 70% of physicians' orientation was toward "therapist" rather than "experimenter" philosophy. Physicians with the "therapist" philosophy, in situations of controversy regarding optimal treatment, would select what they believe is the "best" treatment rather than consider it as an opportunity for a randomized clinical trial. Fallowfield surveyed oncologists and noted that medical oncologists compared to surgeons were more inclined toward research than clinical activities[25]. The difference between specialty and nonspecialty groups toward recruitment of their stroke patients in clinical trials may be because of different philosophy between the two groups. Patient's attitude also determines their inclusion in the clinical trial[1–7]. However, it is unclear if important vascular risk factors would affect their recruitment in clinical trials. We did not find any association of patients' clinical characteristics with recruitment that cannot be explained by inclusion criteria.

Specialty care associated selection bias has important implications. Since outcome of stroke patients may be better with specialized care[26,27], the outcome noted in the clinical trials is expected to be better than that observed in general practice. This finding also questions the generalizability of the research treatment to patients admitted to nonspecialty teams. About 20% of patients in UHC benchmarking study were admitted to nonspecialty teams. This proportion can be significantly larger in hospital settings other than those included in UHC benchmarking study. Increased incidence of intracranial hemorrhage in patients who were recruited in clinical trials (6%) as opposed to those who were not recruited in clinical trials (2%) is probably attributed due to the difference in proportion of thrombolytics administration between the two groups. Progression of stroke is more commonly seen in patients who were recruited in clinical trials. This is possibly because of patients presenting to the hospital earlier are more likely to be recruited in clinical trials. Such patients are more likely to have witnessed neurological deterioration due to close observation. Patients presenting earlier are also more likely to have more severe neurological deficits and thus more prone to neurological consequences[28].

In conclusion, the characteristics of patients who were recruited in clinical trials can be significantly different from those who were not recruited in clinical trials, therefore questioning the generalizability of the clinical

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trials. Certain modifiable factors are identified including early evaluation by specialty teams to improve recruitment in clinical trials.

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