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How common is isolated dysphasia among patients with stroke treated with intravenous thrombolysis, and what is their outcome? Results from the SITS-ISTR

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ABSTRACT

Objectives: To describe the frequency and outcome of isolated dysphasia among patients treated with intravenous thrombolysis (IVT).

Design: Patients registered in the SITS International Stroke Thrombolysis Register (SITS-ISTR).

Participants: Patients with stroke (N=58 293) treated with IVT between December 2002 and December 2012.

Setting: A multinational, prospective, observational monitoring register.

Main outcome measures: Isolated dysphasia and modified Rankin Scale (mRS).

Methods: We identified patients presenting with isolated dysphasia by reviewing items within the baseline National Institutes of Health Stroke Scale (NIHSS). We performed descriptive statistics for baseline and demographic data, and reported patients' characteristics, radiological data and changes in their NIHSS score within 7 days and mRS score at 3 months. We also reported corresponding data from the general SITS-ISTR cohort.

Results: We found isolated dysphasia at baseline in 1.14% (663/58 293) of all patients treated with IVT patients. Patients with isolated dysphasia had a longer onset to treatment time, lower proportion of visible infarctions on admission imaging scan and atrial fibrillation, and were less often classified as having large vessels causing strokes, in comparison with the rest of the SITS-ISTR. Symptomatic intracerebral haemorrhage occurred in 2.3% of patients per SITS-MOST definition and fatal outcome in 5.5%. At 7 days, 50% of patients with isolated dysphasia recovered completely and at 3 months, 86.3% patients were functionally independent (mRS score 0–2), 71.7% had an excellent outcome (mRS score 0–1) and 45.5% had an mRS score of 0.

Conclusions: A low proportion of patients with isolated dysphasia are treated with IVT. Half of these patients were fully recovered at 7 days.

Strengths and limitations of this study

- To the best of our knowledge, this is the largest study of patients with ischaemic stroke with isolated dysphasia treated with intravenous thrombolysis (IVT).
- We identified dysphasia using relevant scores on the National Institutes of Health Stroke Scale (NIHSS), although this method may be criticised as lacking in sensitivity; when including patients in the hyperacute phase, the use of a formal dysphasia battery is practically impossible.
- The study is observational and based on a retrospective analysis of an ongoing database, with all the limitations of this type of study design.
- Another major limitation is the lack of a control group of patients with untreated dysphasia.

INTRODUCTION

Stroke is an important cause of morbidity, with dysphasia as one of the most devastating symptoms.[1] Isolated dysphasia gives only up to three points on the National Institutes of Health Stroke Scale (NIHSS)[2] score, albeit additional points may be given for loss of orientation, and doctors might hesitate to prescribe thrombolysis to patients with low NIHSS scores, due to potential risk of intracranial haemorrhage.[3] Current guidelines lack the recommendation of whether to treat stroke with low NIHSS score or not,[4 5] and approximately 30% of these patients are not treated with intravenous thrombolysis (IVT).[6 7]

Our knowledge about the incidence and prognosis of isolated dysphasia is sparse. Most of our information is from case series.[8–14] These studies identify the rate of isolated dysphasia as between 2.4% and 7.5%.[12–14] There are, however, very limited safety and outcome data of isolated dysphasia following intravenous thrombolysis.

We aimed to describe the frequency and outcome of isolated dysphasia among patients treated with IVT, as documented in

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the Safe Implementation of Treatment in Stroke—International Stroke Thrombolysis Register (SITS-ISTR). We also presented the rest of the SITS-ISTR cohort for an overview.

METHODS

The SITS-ISTR is a multinational, prospective, observational monitoring register documenting unselected patients with ischaemic stroke treated with IVT. Details of the methods and management can be found elsewhere.[15 16] Between December 2002 and December 2012, 58 293 patients treated with IVT were recorded in SITS-ISTR. We searched the SITS register for patients presenting with isolated dysphasia, that is, patients who scored points only on item 9 (Best Language) of NIHSS at baseline. A patient can score a maximum of three points on item 9. However, it is likely that a patient with dysphasia will score additional points on item 1b (Level of Consciousness Questions; maximum 2 points) and item 1c (Level of Consciousness Command; maximum 2 points), achieving up to 7 points for dysphasia in total on the NIHSS. Thus, we defined isolated dysphasia as a score of 1–3 points on item 9 only, with or without points on 1b and 1c.

The stroke subtype was classified according to the TOAST criteria.[17]

We assessed early outcomes by the change in the NIHSS score within 7 days after thrombolysis. We reported dysphasia as completely improved if the NIHSS scored 0 on day 7, partially improved if NIHSS score ranged between 1 and 6 points, and not improved if no change was observed on NIHSS score.

The primary outcome of this study was full recovery, that is, no symptoms at all, excluding also dysphasia (modified Rankin Scale, mRS=0) at 3 months. Secondary outcomes were functional independence (mRS score of ≤2), excellent outcome (mRS ≤1) and death at 3 months. We defined symptomatic intracerebral haemorrhage (SICH) per the SITS-MOST protocol[18] as a local or remote parenchymal haemorrhage type 2 on the 22–36 h post-treatment imaging scan or earlier if clinically indicated, combined with a neurological worsening of ≥4 points between baseline and 24 h, or that leading to death. For comparison with other published work, we also report SICH per the National Institute of Neurological Disorders and Stroke (NINDS) definition:[19] Any intracerebral haemorrhage on any post-treatment imaging scans combined with any decline in neurological status as measured by NIHSS between baseline and 7 days; and SICH per the Second European-Australasian Acute Stroke Study (ECASS-II) protocol:[20] Any intracerebral haemorrhage on any post-treatment imaging scans combined with NIHSS worsening ≥4 points between baseline and day 7. All evaluations of imaging studies and neurological status were performed according to clinical routine by the local sites. All definitions of SICH were centrally adjudicated by the SITS International Coordination Office, based on the clinical and imaging data entered into the registry by the investigators. We also reported the corresponding data from the general SITS-ISTR cohort.

Statistical testing

We performed descriptive statistics for baseline and demographic data. For categorical variables, we calculated percentage proportions by dividing the number of events by the total number of patients, excluding missing or unknown cases. We did not perform any formal statistical testing between patients with and without isolated dysphasia, since this was not within the primary purpose of the study. We performed all analyses using STATISTICA software V.11.0.

RESULTS

At baseline, we identified 1.14% (663/58 293) patients with isolated dysphasia treated with IVT.

Patients with isolated dysphasia had a longer onset to treatment time, lower proportion of visible infarctions on admission imaging scan, lower proportion of atrial fibrillation (AF) and were less often classified as large vessel disease causing strokes, in comparison with the whole SITS-ISTR (table 1).

Within the range 2–7 points on the baseline NIHSS, approximately 45% of patients improved completely, whereas among patients with a score of 1 on the NIHSS, 75% completely improved. Only one patient with one point on the NIHSS worsened (table 2).

Of these patient with available data, 50% (251/505) were completely improved on the NIHSS at day 7 and 45.5% (240/527) had an mRS score of 0 at 3 months, indicating no residual dysphasia (table 3). Altogether, 86.3% patients were functionally independent (mRS score 0–2) and 71.7% had an excellent outcome (mRS score 0–1) at 3 months. Table 3 shows the outcome at 3 months follow-up for patients with dysphasia, for example, with an initial 1–3 points on item 9 on the NIHSS (N=527).

Patients with isolated dysphasia had slightly higher rates of SICH according to SITS-MOST definition (2.3% vs 1.8%, fatal 0.61% vs 0.29%) than the general SITS population but had lower rates of SICH per the ECASS2 (3.2% vs 5.3%, fatal 1.3% vs 2.5%) and NINDS (5.0% vs 7.0%, fatal 1.3% vs 2.5%) definitions (table 4). For all types of haemorrhages, the percentage was lower in isolated dysphasia than in the SITS-ISTR in general. Table 4 illustrates local haemorrhage at 22–36 h for patients with dysphasia in comparison with those in the SITS-ISTR.

The mortality was 5.5% at 3 months compared to 15.6% in the SITS-ISTR.

The cause of death was known in 26 of 29 cases, and of the 26 cases, the most common causes of death were cerebral infarction (n=5), cerebral haemorrhage (n=5) and pneumonia (n=3); however, one patient died of

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Table 1 Demographic and baseline characteristics of patients

Characteristic	Isolated dysphasia (n=663)	All patients in the SITS-ISTR (n=58 293)
Age, years, median (IQR)	71 (62–78)	70 (61–77)
Female, %	45.3	43.5
OTT, min, median (IQR)	160 (124–190)	149 (118–175)
Baseline NIHSS score, median (IQR)	4 (3–5)	12 (7–17)
No visible infarct signs on admission CT/MRI scan, %	15.6	21.0
Systolic BP before tPA, mm Hg, median (IQR)	154 (140–168)	150 (137–168)
Diastolic BP before tPA, mm Hg, median (IQR)	81 (74–90)	81 (73–90)
Baseline blood glucose, mmol/L, median (IQR)	6.3 (5.5–7.6)	6.6 (5.7–7.9)
Medical history and medication, %		
Hypertension	59.8	64.5
Diabetes mellitus	18.4	17.6
Previous stroke	13.0	12.8
Hyperlipidaemia	31.7	33.4
Atrial fibrillation	19.6	24.6
Congestive heart failure	6.4	8.6
Aspirin	37.0	32.5
Other antiplatelet agent	10.8	8.1
Oral antihypertensive	51.5	51.7
Any oral anticoagulation	2.0	2.8
Aetiology[17]		
Large vessel disease	29.3	38.3
Cardiac source	31.8	32.8
Small vessel disease	10.4	10.4
Other determined aetiology	6.8	4.0
Undetermined aetiology	21.7	14.5

BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale; OTT, onset to treatment time; SITS-ISTR, SITS International Stroke Thrombolysis Register; tPA, tissue plasminogen activator.

myocardial infarction and one died of pulmonary embolism.

Figure 1 illustrates the individual mRS scores at 3 months. Patients with isolated dysphasia had a more favourable prognosis than the SITS-ISTR in general.

DISCUSSION

To the best of our knowledge, this is the largest study of patients with ischaemic stroke with isolated dysphasia treated with IVT. The proportion of isolated dysphasia in our IVT-treated study cohort is lower (1.14%) than those of other studies (2.4–7.5%) investigating isolated dysphasia without IVT.[13 14] One reason for this finding may be that patients with isolated dysphasia often do not receive IVT, probably due to uncertainty of the benefit/risk balance.

Fifty per cent of patients with isolated dysphasia in our study improved completely at day 7 and about 72% patients had excellent recovery (mRS 0–1) at 3 months, which is comparable with that of Maas *et al*'s[12] study (58.8%) at 6 months. However, it is important to note that the follow-up in our cohort was earlier than in their study and both studies are observational and demographic, and baseline factors may differ. Moreover, comparisons between the studies are difficult because of the

Table 2 The changes in the National Institutes of Health Stroke Scale (NIHSS) score within 7 days after thrombolysis according to baseline NIHSS

Baseline NIHSS (n=505)	Complete improvement (n=251; 50%) n (%)	Partial improvement (n=174; 34%) n (%)	No improvement (n=28; 6%) n (%)	Worsening (n=52;10%) n (%)
7 (n=30)	14 (47)	14 (47)	0/(0)	2/(7)
6 (n=82)	36 (44)	38 (47)	1/(1)	7/(9)
5 (n=104)	49 (47)	43 (42)	1/(1)	11/(11)
4 (n=119)	54 (45)	40 (33)	9/(8)	16/(13)
3 (n=56)	32 (57)	15 (27)	1/(2)	8/(14)
2 (n=66)	30 (45)	24 (36)	5/(8)	7/(11)
1 (n=48)	36 (75)	0 (0)	11/(23)	1/(2)

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Table 3 Outcome at 3-month follow-up for patients with dysphasia, for example, with initial 1–3 points on item 9 on the National Institutes of Health Stroke Scale (NIHSS) (N=527)

Modified Rankin Scale at 3 months	1 Point on item 9 NIHSS at baseline (n/N%)	2 Points on item 9 NIHSS at baseline (n/N%)	3 Points on item 9 NIHSS at baseline (n/N%)	All groups
0	65 (12.3)	148 (28.1)	27 (5.1)	240 (45.5%)
1	29 (5.5)	96 (18.2)	13 (2.5)	138 (26.2%)
2	6 (1.1)	64 (12.1)	7 (1.3)	77 (14.6%)
3	4 (0.8)	15 (2.8)	6 (1.1)	25 (4.7%)
4	1 (0.2)	11 (2.1)	2 (0.4)	14 (2.7%)
5	0	4 (0.76)	0	4 (0.8%)
6	3 (0.6)	22 (4.2)	4 (0.8)	29 (5.5%)

low number of patients with isolated dysphasia (n=17) in Maas *et al*'s study.[12] In a study by Nesi *et al*, the presence of dysphasia was an independent predictor of unfavourable outcome. They observed that patients with dysphasia treated with thrombolysis had a favourable outcome (83%, 10/12) compared to those who did not receive thrombolysis (50%, 5/10). However, due to the low number of patients with isolated dysphasia (n=13), it becomes hard to make any certain conclusions from their study.

Dysphasia has a substantial spontaneous improvement within the first months,[21–24] and stroke severity is correlated to the prognosis.[22 25] We observed a similar proportion of complete improvement as Maas *et al* observed in their study for those with baseline NIHSS score from 2 to 7.

At 3-months follow-up, 45.5% of our patients had mRS score of 0, indicating no remaining dysphasia. Maas *et al*[12] found that nearly twice as many, 85.7% (12/14), recovered at their 6-month follow-up. Unfortunately, there is no further information on the prognosis of isolated dysphasia in the literature. There are several explanations for the discrepancy between our study and that of Maas *et al*. First, NIHSS is not included in our 3-month follow-up. Second, the mRS is not a measure of language impairment—it is an overall assessment of disability—and it is quite possible that patients with an mRS=1 or even mRS=2 do not have dysphasia. Another reason is that Maas *et al* evaluated outcome after 6 months, 3 months later than it was carried out in our study, and further improvement may have occurred within that time period.

As expected, patients with isolated dysphasia differed in several ways from the rest of the SITS cohort. They had less severe stroke and lower proportion of visible infarctions on admission CT scan. The lower proportion of patients with AF and large vessels disease (LVD) in the dysphasic group might be explained by the fact that AF and LVD are often associated with more severe strokes.[26]

In our study, 86.3% had a good outcome (mRS 0–2) at 3 months. This proportion is more than 30% higher than in the SITS-ISTR in general. Lower rates of local as well as remote types of haemorrhage following IVT indicate that this treatment is at least as safe in the isolated dysphasia group as it is in the general SITS-ISTR cohort.

Table 4 Local haemorrhage at 22–36 h for patients with dysphasia in comparison with the SITS-ISTR

Local haemorrhages	Isolated dysphasia (N=641) n (%)	All patients in the SITS-ISTR (N=54 993) n (%)
No local haemorrhages	576 (89.9)	47 515 (86.4)
PH1	12 (1.9)	1518 (2.8)
PH2	16 (2.5)	1566 (2.9)
HI1	18 (2.8)	2615 (4.8)
HI2	19 (3.0)	1779 (3.2)
Remote haemorrhages	N=642	N=54 987
No remote haemorrhages	625 (97.4)	53 327 (97.0)
PHr1	11 (1.7)	1061 (1.9)
PHr2	6 (0.9)	599 (1.1)
SICH per SITS-MOST	2.30 (15/652)	1.84 (1022/55 623)
SICH per ECASS-2	3.2 (20/632)	5.3 (2893/54 330)
SICH per NINDS	5.0 (32/635)	7.0 (3833/54 450)

Haemorrhage was classified, using clinical and radiological criteria, as: HI1=small petechiae along the margins of the infarct, HI2=confluent petechiae within the infarcted area but not space-occupying, PH1=blood clots in <30% of the infarcted area with some slight space-occupying effect, and PH2=blood clot in >30% of the infarcted area with a substantial space-occupying effect.
ECASS-2, Second European-Australasian Acute Stroke Study; NINDS, National Institute of Neurological Disorders and Stroke; SICH, symptomatic intracerebral haemorrhage.

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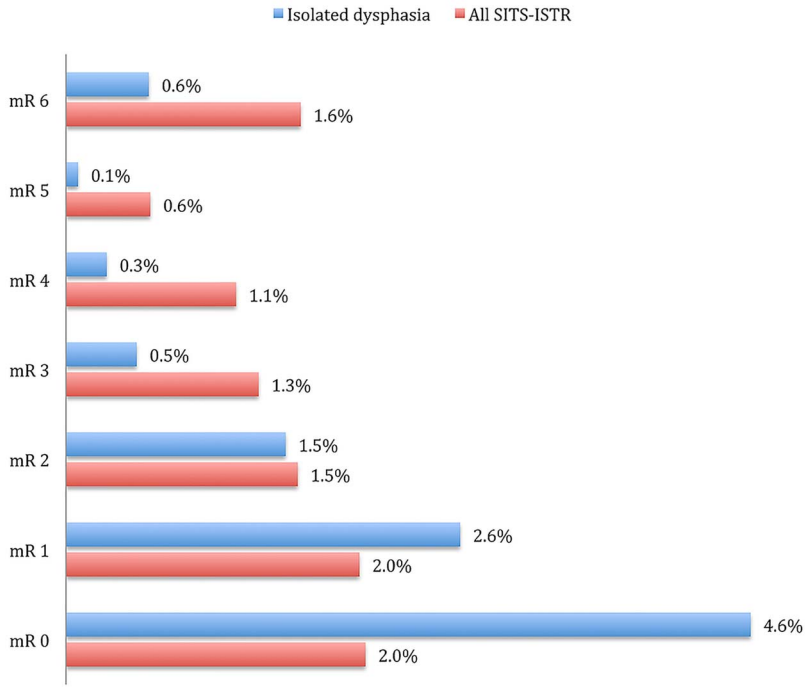

Figure 1 The modified Rankin Scale (mRS) at 3 months for patients with isolated dysphasia and all patients in the SITS International Stroke Thrombolysis Register (SITS-ISTR).

In contrast to the ECASS 2 and NINDS definitions of SICH, the SITS-MOST definition results in slightly higher values for isolated dysphasia. We cannot exclude, however, that the SITS-MOST definition, requiring four points deterioration in combination with a PH2 or PH2r type of haemorrhage, may slightly overestimate the risk in patients with a low baseline NIHSS compared to those seen in the general SITS-ISTR population.

We identified dysphasia using relevant scores on the NIHSS. This method may be criticised as lacking in sensitivity.[27] Many of the previous studies of isolated dysphasia used more sensitive and time-consuming dysphasia batteries. Those studies,[8–11] however, are case series, and do not include patients in the hyperacute phase, in which the use of a formal dysphasia battery is practically impossible. Consequently, most of the acute stroke trials use item 9 on the NIHSS[28] as a dysphasia symptom. Our definition of dysphasia was somewhat broader than the previous definitions because we allowed patients to have scores on items 1b and 1c on the NIHSS. This was necessary because patients with dysphasia often give incomplete responses on the consciousness questions and commands.

Our study has several limitations. It is observational and based on a retrospective analysis of an ongoing database, with all the limitations of this type of study design. Another major limitation is the lack of control group of patients with untreated dysphasia. No data from randomised controlled trials on thrombolysis in isolated dysphasia are currently available.

Our strength is that we retrieved the largest cohort of isolated dysphasia treated with IVT.

In conclusion, our study suggests that patients with isolated dysphasia often do not receive IVT. Half of the patients with isolated dysphasia treated with IVT recovered fully within 7 days and 72% had an excellent outcome at 3 months. The risk of serious haemorrhagic complications and death is low. Considering the solid evidence in favour of IVT, our study suggests that this subgroup of patients should not be treated differently than others.

Contributors NW and NA coordinated the study. NA performed the statistical analysis. EL, NA and NW wrote the initial draft of the manuscript. AZ was local coordinator of a leading recruiting centre. All the authors read and commented on the first draft, with regard to interpretation of the data and editing of the manuscript, and have seen and approved the final version. EL, NA and NW have direct access to the original data, and vouch for the accuracy and completeness of this report.

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Competing interests NA is a senior researcher in SITS International, which receives an unrestricted grant from Boehringer Ingelheim and Ferrer for the SITS-MOST/SITS-ISTR. NW has received expenses from Boehringer Ingelheim for his role as member of the Steering Committee in relation to the ECASS III trial with alteplase and served as a consultant to Thrombogenics as chairman of the DSMB. SITS International (chaired by NW) received a grant from Boehringer Ingelheim and Ferrer for the SITS-MOST/SITS-ISTR. NW has also received lecture fees from Boehringer Ingelheim and Ferrer. This study is a part of the Fighting Stroke Project supported by the Swedish Heart and Lung Foundation and Karolinska Institutet; the project is supported by funding from Friends of Karolinska Institutet, USA, and Johanniterorden. The views expressed are those of the authors.

Ethics approval Ethics approval was obtained in countries that required this; other countries approved the register for conduct as an anonymised audit. The SITS Monitoring Study data (SITS-MOST) are embedded within the SITS-ISTR. The SITS-MOST, and subsequently the SITS-ISTR, was approved by the Ethics Committee of Karolinska Institutet, Stockholm.

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