PAPER

Intravenous thrombolysis in acute ischaemic stroke: from trial exclusion criteria to clinical contraindications. An international Delphi study

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Objective: Several studies indicate that only a small proportion of patients with acute ischaemic stroke are treated with intravenous thrombolysis. Indications and contraindications for this treatment are usually based on the inclusion and exclusion criteria of randomised clinical trials. The trial context of these criteria hampers implementation in real life settings. We therefore aimed to obtain specialist opinion in a Delphi consensus on these contraindications.

Methods: We used the Delphi approach on an international group of specialists in the field of thrombolysis. Inclusion and exclusion criteria were reworded into 18 quantitatively phrased propositions. Feedback consisted of the median score, interquartile range and the panellist's own score in the previous round. For each item, we defined consensus as the achievement of an interdecile range within two prespecified clinically relevant units.

Results: Thirty-one specialists participated in the first round and 30 completed all three rounds. Consensus was reached on 12 of the 18 propositions: previous ischaemic stroke, head trauma and gastrointestinal tract bleeding should not have taken place earlier than 1.5 months, 2 months and 14 days, respectively; the severity of the neurological deficit is defined as a National Institutes of Health Stroke Scale (NIHSS) score of 2–3 or more, and blood pressure level should not be >185/110 mmHg; platelet count should be >90×10¹²/l, glucose levels 2.7–22 mmol/l, international normalised ratio <1.5 and activated partial thromboplastin time <50 s. No consensus was reached on propositions concerning the stroke onset to treatment time, patient's age, recent medical procedures, spontaneous improvement rate and blood pressure treatment.

Conclusions: We present specialists' opinion on contraindications for intravenous thrombolysis in ischaemic stroke. The results of this study may be relevant for routine clinical practice as they may help to increase the number of treated patients.

Thrombolysis with intravenous recombinant tissue plasminogen activator (rtPA) is an effective treatment for patients with acute ischaemic stroke.¹ Four large randomised placebo controlled clinical trials of thrombolysis with intravenous rtPA have been carried out.^{2–6} The National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Study reported a clinically and statistically significant benefit.⁶ However, the proportion of patients who are treated with thrombolysis in survey studies ranges from only 3% to 7%.^{7–10}

In most guidelines on stroke, indications and contraindications for intravenous thrombolysis are based on the inclusion and exclusion criteria of the NINDS Study.^{11–14} Although reasonable, this approach may not be ideal. Criteria may be set to exclude patients who are expected not to benefit or who may suffer harm from the intervention. Clearly, such criteria should also be used when the results are implemented in clinical practice. Other enrolment criteria for a study, however, are not designed to protect patients, but to exclude outliers and to ensure a homogenous patient population in statistical analysis. This applies, for example, to the use of the exclusion criteria "mild neurological impairment" and "rapidly improving symptoms". In clinical practice, it may be unnecessary to exclude patients based on these latter criteria if they are not actually at an increased risk from the treatment and if they may benefit. Also, not all exclusion criteria in the NINDS rtPA Stroke Study have been defined in terms that can be easily

translated into clinical practice. This may have led physicians to withhold treatment in a considerable number of patients who could benefit from thrombolysis. For example, in a survey conducted in Cleveland, Ohio, USA, only 20% of patients with acute stroke, admitted within 3 h of the onset of symptoms, were actually treated with thrombolysis. Reasons for not treating were "mild neurological impairment" (77%) and "rapidly improving symptoms" (44%).¹⁵ These contraindications were not defined further. Both criteria were not operationalised in the NINDS trial protocol. Other non-operationalised exclusion criteria were "patients who were taking anticoagulants or who had received heparin within the 48 h preceding the onset of stroke and had an elevated partial thromboplastin time" because no threshold international normalised ratio (INR) or partial thromboplastin time are given. Overly conservative interpretation of these exclusion criteria of the NINDS rtPA Stroke Study undoubtedly reduces the number of treated patients. Lastly, analogous with treatment in acute myocardial infarction, clinicians may be withholding thrombolysis on account of perceived contraindications of increased haemorrhagic risk for which there is no evidence.¹⁶

Abbreviations: INR, international normalised ratio; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; rtPA, recombinant tissue plasminogen activator

Table 1 Eighteen exclusion criteria from the NINDS rtPA Stroke Study,⁶ clinically relevant unit and range

No	Proposed contraindication	Clinically relevant unit	Range
1	Maximum time between stroke onset and treatment (h)	0.5	3–6
2	Maximum patient's age (y)	5	80–110
3	Minimum time interval if previous stroke in history (months)	1	3–0
4	Minimum time interval if previous serious head trauma in history (months)	1	3–0
5	Minimum time interval if previous major surgery in history (days)	1	14–0
6	Minimum time interval if previous gastrointestinal haemorrhage in history (days)	0.5 wk	21–0
7	Minimum time interval if previous urinary tract haemorrhage in history (days)	0.5 wk	21–0
8	Minimum time interval if previous arterial puncture at a non-compressible site in history (days)	1	7–0
9	Minimum stroke severity, indicated by NIHSS score	1	5–0
10	Maximum rate of improvement of symptoms (%)	10	0–100%/h
11	Maximum systolic blood pressure (mm Hg)	10	180–250
12	Maximum diastolic blood pressure (mm Hg)	5	110–160
13	Maximum blood pressure reduction (mm Hg)	10	0–100
14	Minimum platelet count (/l)	10×10 ¹²	<100–40×10 ¹²
15	Maximum serum glucose level (mmol/l)	2	>22.2–40
16	Minimum serum glucose level (mmol/l)	1	<2.7–0
17	Maximum INR as a result of current anticoagulant treatment	0.2	1–2.2
18	Maximum APTT as a result of treatment with heparin within the previous 48 h (s)	10	40–100

APTT, activated partial thromboplastin time; INR, international normalised ratio; NIHSS, National Institutes of Health Stroke Scale.

The number correlates with the number of the listed propositions in the supplementary appendix (the appendix can be viewed on the JNNP website at <http://www.jnnp.com/supplemental>).

The aim of our study was to modulate clinical inclusion and exclusion criteria for thrombolysis in ischaemic stroke based on agreement among clinicians with scientific experience in the treatment of acute stroke with thrombolysis.

METHODS

We applied the Delphi technique on a group of international specialists in the field of thrombolysis in acute ischaemic stroke. Consensus methods to elicit expert opinion, in particular the Delphi technique, are recommended when information from clinical trials is limited.¹⁷ A Delphi study uses expert judgements, and compares these judgements in several rounds with aggregate judgements of other experts, until consensus is reached for an item or group of items, according to prespecified criteria. The method is robust and several Delphi studies already exist that provide useful and practical clinical recommendations in cerebrovascular disease.^{18–22}

Proposed contraindications

Inclusion criteria for the NINDS rtPA Stroke Study were ischaemic stroke with clearly defined onset, with a measurable deficit on the National Institutes of Health Stroke Scale (NIHSS) and a baseline CT scan of the brain without evidence of intracranial haemorrhage. We rephrased the NINDS inclusion and exclusion criteria into single propositions. We also determined clinically relevant ranges and units for each proposed contraindication in advance. A range started with the most conservative value, as defined by the NINDS rtPA Stroke Study threshold value (table 1). Three exclusion criteria were not included in the Delphi rounds: a history of intracranial haemorrhage, symptoms suggestive of subarachnoid haemorrhage and seizure at onset of the stroke. These criteria are beyond the scope of this study, not because they are not relevant or disputable, but because they are difficult to rephrase as propositions with other than a dichotomous calibration. The supplementary appendix comprises all propositions as presented to the panellists (the appendix can be viewed on the JNNP website at <http://www.jnnp.com/supplemental>).

Panellists

First or last author of at least one publication on intravenous thrombolysis in acute ischaemic stroke in a peer reviewed

medical journal was eligible for membership of the Delphi panel. Panellists were required to have personal clinical experience with thrombolysis and fluency in the English language. For identification, we systematically searched the MEDLINE database from January 1966 to December 2004 (fig 1). Panellists or “experts” in the Delphi methodology were invited by email and asked if they met the above mentioned criteria. They received information on the aim of the study and the Delphi procedure. Panel membership was not disclosed to other participants.

Delphi procedure

In the first Delphi round, each panellist rated the propositions. They were asked for their opinion on contraindications of thrombolysis for acute ischaemic stroke with alteplase 0.9 mg/kg (with a maximum of 90 mg), administered intravenously. The instruction was: “Mark the most extreme value that in your opinion does not compromise the effectiveness and safety of thrombolysis for ischaemic stroke. Assume that all other symptoms and risk factors are well within a safe range”. Each proposition had its appropriate scale and measurement unit within a clinically relevant range. The propositions were scored using a web based form.

In the second and third Delphi rounds, the panellists were informed of the group's median score, the interquartile range (the range between the 75th and 25th deciles) for each proposition, and their own rating in the previous round. They were asked to reconsider their answers in view of this information.

Analysis

Consensus was considered to have been reached if the interdecile range (the difference between the ninth and first deciles) was within two clinically relevant units. As mentioned previously, these clinically relevant units were determined in advance. Cronbach's alpha can be used as an index of reliability of a summation of entities.²³ In our analysis, we used it to quantify the reliability of the panellist's ratings. The acceptable level of Cronbach's alpha, indicating good reliability, is 0.90.²³ To compute Cronbach's alpha, all responses were standardised to a 0–1 range, with 0 being the most conservative value.

- 1 Cerebrovascular accident (MeSH)
- 2 Infarction, posterior cerebral artery (MeSH)
- 3 Brainstem infarctions (MeSH)
- 4 Infarction, middle cerebral artery (MeSH)
- 5 Infarction, anterior cerebral artery (MeSH)
- 6 1 or 2 or 3 or 4 or 5
- 7 Thrombolytic therapy (MeSH)
- 8 6 and 7
- 9 8 not myocardial infarction (MeSH)
- 10 9 not infusions, intra-arterial (MeSH)
- 11 10 not injections, intra-arterial (MeSH)
- 12 11 not catheters, indwelling (MeSH)
- 13 12 not nursing journals
- 14 13 not letters
- 15 14 not case reports (publication type)
- 16 15 limits: English, human, adult

Figure 1 MEDLINE search strategy.

RESULTS

Panellists

On the basis of the MEDLINE search and review of the articles, we identified email addresses of 93 first and last authors. Of the 46 authors who agreed to participate, 31 completed the first form in time; 30 panellists completed all three Delphi rounds (fig 2). The participating panellists were from 10 countries (Argentina, Australia, Canada, Germany, India, Israel, Korea, Spain, the UK and the USA).

Analysis

The panellists reached consensus on 12 of the 18 propositions (table 2). In four of the 12, the median value was the same as the NINDS rtPA Stroke Study limits (ie, for systolic and diastolic blood pressure, and maximum and minimum serum glucose levels). In three of the 12, the NINDS rtPA Stroke Study provided no limit, as in the case of minimum stroke severity, INR and activated partial thromboplastin time. In the remaining five of the 12, the median value was different from the NINDS rtPA Stroke Study limit (ie, for previous stroke, previous head trauma, gastrointestinal haemorrhage, urinary tract haemorrhage and platelet count).

No consensus was reached on six propositions. In three (minimum time interval if previous stroke, previous major surgery or previous arterial puncture at a non-compressible site in history), the NINDS rtPA Stroke Study limit was within the interdecile range of the last Delphi round. In two (maximum patient's age and maximum rate of improvement of symptoms), the NINDS rtPA Stroke Study had set no limit, and in the sixth (maximum blood pressure reduction), this limit was not within the interdecile range of the last Delphi round.

Cronbach's alpha was 0.95 in the first round, 0.97 in the second and 0.98 in the final round, indicating high reliability.

DISCUSSION

In this study, we used a Delphi approach to achieve consensus among an international group of specialists on indications and contraindications for intravenous thrombolysis in acute ischaemic stroke. We obtained consensus for 12 of the 18 propositions, which may facilitate the difficult implementation of these treatment criteria.

Interestingly, our Delphi panellists reached consensus on the INR value of 1.5, which is less than the value of 1.7 proposed in the guidelines of the American Heart Association.¹⁴ They also agreed on a minimal NIHSS score of 2 to 3 to warrant treatment. This definition of stroke severity is clinically relevant

Figure 2 Flow diagram of the formation of the Delphi panel.

as “minor symptoms” is a frequently mentioned contraindication in clinical practice although it was never defined and left to the clinicians’ interpretation.⁹ As the effect of treatment in these patients is consistent with the overall effect,²⁴ and 27% of the too-good-to-treat patients died or were not discharged home because of neurological worsening or persistent “mild” neurological deficit, we believe the proposed limit of stroke severity is a useful definition which might result in higher treatment rates.²⁵

Consensus was not reached in our study on some important contraindications. The interdecile range for maximum stroke onset to treatment time was narrowed (from 3–6 to 3–4.5), but consensus was not reached. Results of ongoing clinical trials such as the IST-3 or ECASS-3 will be helpful as they are designed to study the time effectiveness relation beyond the 3 h window.²⁶ Neither was consensus reached concerning age. Age is a prognostic factor; risks of mortality and poor outcome rise steeply with advancing age.^{27–29} Chen *et al* showed that patients older than 80 years have similar rates of recanalisation, short term improvement and symptomatic intracranial haemorrhage as younger patients.³⁰ Whether there should be an upper age limit remains controversial; a meta-analysis across cohort studies could not answer this question.³¹ Although cohort studies have demonstrated that age is an important outcome predictor, these studies were unable to evaluate the effectiveness of rtPA in patients with increasing age because they could not compare “standard treatment and rtPA” with “standard treatment” alone.³² Also, no consensus was reached concerning blood pressure management. In a large cohort study, elevated pretreatment blood pressure was related to intracranial haemorrhage and poor outcome.²⁸ Larrue *et al* reported that for every 1 mm Hg increase in baseline systolic blood pressure, the relative risk (odds ratio) of haemorrhagic transformation increased by 2%.²⁷ This information, however, is not sufficient

Table 2 All 18 propositions with the results in the three Delphi rounds (indicated by DI, DII and DIII)

No	Keywords proposed contraindication	Unit	Criterion	DI		DII		DIII		Consensus
				Median	Interdecile range	Median	Interdecile range	Median	Interdecile range	
1	Stroke onset to treatment time	h	3	4.5	(3–6)	4.25	(3–5.9)	4	(3–4.5)	No
2	Patient's age	y	–	92.5	(80.5–110)	90	(80–110)	90	(80–110)	No
3	Previous stroke	Month	3	1.5	(1–3)	1.5	(1–2.9)	1.5	(1–2)	Yes
4	Previous head trauma	Month	3	2	(1–3)	2	(1.5–3)	2	(1.6–3)	Yes
5	Recent major surgery	Day	14	14	(7–14)	14	(10–14)	14	(10–14)	No
6	Recent gastrointestinal haemorrhage	Day	21	14	(9–28)	14	(14–21)	14	(14–21)	Yes
7	Recent urinary tract haemorrhage	Day	21	14	(4–20.8)	14	(4.3–19.8)	14	(7–19.4)	Yes
8	Recent arterial puncture	Day	7	6	(2–7)	6	(2.1–7)	5.5	(3–7)	No
9	Stroke severity	NIHSS	–	3	(1–4.8)	3	(2–4)	2.5	(2–4)	Yes
10	Improvement rate	%	–	37.5	(20–80)	37.5	(20.5–79.5)	40	(30–74.5)	No
11	Systolic blood pressure	mm Hg	185	185	(180–208)	185	(180–200)	185	(180–199)	Yes
12	Diastolic blood pressure	mm Hg	110	110	(106–120)	110	(110–119.5)	110	(110–110)	Yes
13	Blood pressure reduction	mm Hg	0	30	(12–68)	30	(20–49)	30	(20–49)	No
14	Platelet count	$\times 10^9/l$	100	90	(62–100)	90	(71–100)	90	(80–100)	Yes
15	Maximum serum glucose level	mmol/l	22.2	22	(22–28)	22	(22–25)	22	(22–25)	Yes
16	Minimum serum glucose level	mmol/l	2.7	2.7	(1.8–2.7)	2.6	(2.0–2.7)	2.7	(2.1–2.7)	Yes
17	INR	–	–	1.5	(1.2–1.8)	1.5	(1.2–1.7)	1.5	(1.3–1.6)	Yes
18	APTT	s	–	50	(40–60)	50	(40–50)	50	(40–50)	Yes

APTT, activated partial thromboplastin time; INR, international normalised ratio; NIHSS, National Institutes of Health Stroke Scale.

The results are presented as median score (interdecile range). The last column indicates whether consensus was reached.

The number correlates with the number of the listed propositions in the appendix (the appendix can be viewed on the JNNP website at <http://www.jnnp.com/supplemental>).

for justifying a treatment decision, as the modification of the treatment effect on overall outcome by blood pressure was not reported. In our opinion, the lack of consensus on the points mentioned above should not be surprising, given the availability of randomised evidence. It illustrates the differential nature and quality of a Delphi method. More randomised evidence should be pursued in these areas. The lack of consensus on the proposition dealing with the improvement rate is probably because of the difficult interpretation of this concept. We defined the improvement rate as the relative difference between the NIHSS score at 3 h and the highest NIHSS score ever, but symptoms fluctuate over time. Because of the difficulty in interpreting the exclusion criterion “rapidly improving”, we would propose using only a threshold NIHSS score to treat, if it involves interpretation of symptoms.

Our study has some limitations. Firstly, expert opinion can only complement evidence from randomised clinical trials. However, whether thrombolysis is effective in subgroups of specific indications or contraindications remains unclear because subgroup analyses from randomised trials of thrombolysis were not powered for this purpose.^{1–33} The results of our Delphi study may also help in interpreting existing guidelines for thrombolysis in ischaemic stroke in anticipation of the results of ongoing clinical trials (IST-3, ECASS-3 and EPITHET).^{20–22} In particular, IST-3, which seeks to recruit 6000 patients, may provide information on the balance of risks and benefits in a much wider variety of patients than are defined by the NINDS trial criteria.²⁶

Secondly, of the 44 panellists who were invited to participate and complete the Delphi forms, 29 (66%) responded. This can be explained by the short time allowed for reply in this methodology, and in our view does not suggest the introduction of bias. The relatively large number of participants contributes to the validity of this Delphi study. Moreover, 30 of the 31 panellists who began this consensus process by completing the first questionnaire continued through each of the subsequent rounds and completed the study. Unavoidably, some panellists have also played a role in international guideline development; this may have influenced their opinion. The origin of the panellists was North America (13), Europe (11), Australia (2), Asia (3) and South America (1). We consider them a

representative group of specialists. The high reliability index (Cronbach's $\alpha > 0.95$) suggests excellent reproducibility.

Thirdly, we selected the clinically relevant ranges and units for each proposed contraindication based on common clinical practice. One may challenge these initial choices on strict methodological grounds, but other selections would most likely lead to similar clinical judgements. The extent of early ischaemic changes on pretreatment CT was not included. We did not include this item because these changes do not seem to be independently associated with an increased risk of adverse outcome, or lack of effect after rTPA treatment, and inter-observer reliability of these signs is limited.^{34–35}

In conclusion, consensus was reached for one of the most frequently mentioned and clinically relevant criteria, namely the exclusion criterion of minor symptoms. Yet, no consensus was reached in the propositions concerning important issues such as maximum stroke onset to treatment time, patient's age and treatment of elevated blood pressure. The Delphi panel results might be helpful in translating trial results on thrombolysis in acute ischaemic stroke into day-to-day clinical practice. The exact definition of “minor symptoms” may facilitate treatment decisions in many patients. Using the demographic information from the cohort study of Katzan *et al*, one could conclude that this may result in 2–3 times as many patients being treated.⁹

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The appendix can be viewed on the JNNP website at <http://www.jnnp.com/supplemental>.

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