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ORIGINAL COMMUNICATION

Thrombolytic therapy and visuoperceptual functions in right hemisphere infarct patients

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Abstract This study examines the association between thrombolysis and visuoperceptual functions in right hemisphere (RH) infarct patients. Fifty-six consecutive patients with first acute RH infarct were matched for age, years of education and stroke severity at the time of admission to the emergency department (baseline NIHSS; National Institute of Health Stroke Scale), compared according to whether (T+) or not (T−) they received thrombolysis. Neurological (NIHSS at hospital ward; Barthel index; BI) and neuropsychological examinations were conducted 4 days after onset. Visuoconstructive abilities were assessed with the block design and visual search and reasoning with the picture completion subtests of the Wechsler Adult Intelligence Scale revised. Visual neglect was assessed with the conventional subtests of the Behavioural Inattention test and visual memory with the visual reproduction subtest of the Wechsler Memory Scale Revised. T+ and T− patients did not differ in baseline NIHSS, age, years of education, hemianopia, hemiparesis, or in basic ADL (BI). T− patients had more severe strokes (NIHSS at hospital ward) and poorer visuoconstructive abilities than T+ patients. Our results indicate that thrombolysis has a favourable effect on visuoperceptual functions in acute stroke.

Keywords Cognition · Stroke · Thrombolysis · Visuoperceptual functions

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Introduction

Stroke is known to lead to serious cognitive decline [1–3], and cognitive impairments after stroke have independent prognostic implications [4–6]. Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) is of proven and substantial benefit in terms of functional outcome for patients with acute cerebral ischemia [7, 8]. However, little is known about the effect of thrombolysis on stroke patients' cognitive functioning. In the first and only report on cognitive outcome after thrombolysis, Nys et al. [8] found that thrombolytic therapy is associated with favourable basic (ADL) and instrumental activities of daily living (IADL) outcome, but not with a beneficial cognitive outcome at approximately 6 months after stroke. Their study group consisted of 92 right hemisphere (RH) and left hemisphere (LH) first-ever stroke patients, of whom 25 were treated with thrombolytic therapy. To date there has been no work on the cognitive functioning of thrombolytic patients in the acute phase of stroke. None of the studies in the literature examine the association between thrombolytic treatment and the cognitive functioning after RH stroke.

RH lesions can result in various cognitive defects, such as visuoperceptual impairments which are defects in visual search and reasoning, deficits in visuoconstructive

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functions, left neglect, and disorders in visual memory [9, 10]. Impairment in visuoperceptual functioning is common in stroke patients, although there are some variations in the reported incidence. Hier et al. [11] reported that 93% of their RH stroke patients had constructional difficulties. In the study by Nys et al. [5] the incidence of deficits in visual perception and construction was 31% in patients with LH or RH stroke. Both these studies included patients with haemorrhage or infarct, and the evaluation was conducted at the acute phase of stroke (on average 8 days after onset) [5, 11]. In RH stroke patients the reported incidence of neglect ranges from 13 to 82%, median 43% [12]. In a study of 57 consecutive first-ever RH infarct patients, the incidence of neglect in the acute phase was reported at 35% (on average 6 days after onset) [13]. Neglect and visuoperceptual deficits have been found to be strongly related to poor functional outcome after stroke [13, 14] and, therefore, it is important that they are evaluated at the acute stage of stroke.

In this study, we wanted to find out whether cognitive functioning in the acute phase of stroke differed between RH stroke patients with (T+) and without (T−) thrombolytic therapy. Our focus here is on visuoconstructive abilities, visual search and reasoning, visual memory, and visual neglect, since these visuoperceptual functions are known to be defective after RH damage. This research is the very first to explore the association between thrombolytic therapy and visuoperceptual functioning after acute RH infarct.

Patients and methods

Patients

A total of 1,458 consecutive patients with acute stroke admitted to a university hospital as emergency cases were screened for this study between June 2005 and July 2008. The excluded patients were as follows: LH stroke ($n = 276$), brain stem or cerebellar stroke ($n = 57$), transient ischemic attack ($n = 200$), cerebral haemorrhage ($n = 139$), other neurological diagnosis ($n = 137$), previous stroke ($n = 185$), significant findings in CT not related to acute stroke ($n = 92$), traumatic brain injury ($n = 6$), substance abuse ($n = 21$), psychiatric disorder ($n = 20$), age over 80 years ($n = 144$), left-handedness ($n = 5$), native language other than Finnish ($n = 4$), and not able to participate in neuropsychological examination ($n = 95$). Thus, the study population consisted of 77 consecutive patients with first-ever RH infarct. In order to investigate the effect of thrombolytic therapy, the patients were divided into two groups, T+ and T−, and matched for stroke severity at the time of admission to the emergency department (±2 points in the National Institute of Health Stroke Scale sum score (NIHSS) [15]. Since it has been shown that age has a negative effect on patient outcome after thrombolysis [16], and since limited formal education is often associated with lower cognitive functioning [17], our patients were also matched for age (±5 years) and education (±5 years) to rule out the influence of these factors. This gave us 28 matched pairs which were compared according to whether or not they were given thrombolytic therapy. The research protocol was approved by the Ethical Committee of the university hospital. During their hospital stay all patients were treated according to standard procedures for stroke patients. Informed consent was obtained from all participating patients.

Methods

All patients underwent a neuropsychological, neurological and neuroradiological examination (CT) within, on average, 4 days of stroke (range = 2–11 days). In the neuropsychological examination visuoperceptual abilities were evaluated using the block design (visuoconstructive abilities; range = 0–51) and picture completion (visual search and reasoning; range = 0–22) subtests of the Wechsler Adult Intelligence Scale Revised (WAIS-R) [18], the visual reproduction (immediate and delayed visual memory; range = 0–41) subtest of the Wechsler Memory Scale Revised (WMS-R) [19]. In addition, visual neglect was evaluated using the sum score of the conventional subtests of Behavioral Inattention Test (BITC; range = 0–146, cut-off for neglect ≤129) [20, 21]. Neuropsychological test results were transformed into z scores based on the performance of a stroke-free normative group. z scores were dichotomized: cut-off for cognitive impairment within each domain was determined by a performance that was one or more standard deviations below the mean performance of the normative group.

In the neurological examination, stroke severity, hemiparesis and hemianopia were evaluated using NIHSS at the time of admission to the emergency department (baseline NIHSS) and at the hospital ward (NIHSS at ward) on the same day as the neuropsychological examination, or not more than 1 day before or after that examination. Stroke severity was defined according to the NIHSS sum score (range = 0–34; 0 = no defect; 34 = severe stroke). Hemiparesis was scored using a scale from 0 (no motor defect) to 4 (severe hemiparesis) for leg and arm separately, and these scores were summed to give a range from 0 to 8. Hemiparesis scores were dichotomized (cut-off score = 1; presence of hemiparesis was scored as 1, absence of hemiparesis as 0). The presence of visual field defect was scored as 1 and absence of hemianopia as 0. Basic ADL were evaluated with the Barthel index (BI; range = 0–100; 0 = dependent; 100 = independent) [22].

A CT of the brain was performed to verify the side of the infarction and to make a decision on thrombolytic treatment. Native axial 5 mm/7.5 mm slices were taken from the level of foramen magnum to the vertex of the skull on a modern 16 multi-detector CT machine (GE LIGHTSPEED RT16, Wisconsin, USA).

Intravenous administration of thrombolysis was supplied within 3 h of stroke in accordance with the recommendations of the National Institute of Neurological Disorders and Stroke (NINDS) study [7]. Apart from the thrombolytic therapy, all patients were treated in the same way following the same standardized protocol.

Statistical analyses

Since some of the parameters were not normally distributed and the sample sizes were small, we chose to use median (Md) and quartiles (Q_1, Q_3) and non-parametric tests (the Wilcoxon test) to compare continuous variables between the matched pairs of T+ and T− patients. Cross-tabulations and McNemar tests were used to compare categorical variables between the T+ and T− groups. All reported p values are based on 2-tailed tests. p Values lower than 0.05 were considered statistically significant.

Results

The demographic and clinical characteristics of the stroke subgroups (T+ and T−) are shown in Table 1. The two groups did not differ statistically significantly in baseline NIHSS, age, education, basic ADL (BI), hemiparesis or hemianopia. T− patients had more severe strokes than T+ patients at the hospital ward on average 4 days after the onset of stroke ($p = 0.017$).

The results of the neuropsychological examination are shown in Table 2. One (4%) patient in the T+ group and 10 (36%) patients in the T− group had impairment in visuoconstructive functioning. Patients in the T+ group had significantly better test results in visuoconstructive functioning ($p = 0.002$), and significantly fewer T+ patients had impairment in visuoconstructive functioning ($p = 0.004$). Neglect was present in 9 (16%) patients, 6 (21%) in the T− group and 3 (11%) in the T+ group. The difference in the presence of neglect between the two groups did not reach statistical significance. The two groups did not differ in visual reasoning skills, or in immediate or delayed visual memory. Visual reasoning skills were impaired in 7 (25%) patients in the T+ group and in 11 (39%) patients in the T− group. In immediate visual memory, 11 (39%) patients in the T+ group and 17 (61%) patients in the T− group had impairment. Impaired delayed visual memory was found in 20 (71%) patients in the T+ group and 23 (82%) patients in the T− group.

Discussion

This study is the very first to explore cognitive functioning in a homogenous group of patients with first-ever RH infarct. We were particularly interested to find out whether thrombolytic therapy was associated with visuoperceptual abilities at the acute phase of stroke.

Our results indicate that thrombolytic therapy might have a positive effect on stroke severity and on visuoperceptual functioning at the acute stage of stroke. Stroke

Table 1 Clinical characteristics and comparison of patients with (T+) and without thrombolysis (T−) after matching by baseline NIHSS, age and education

	T+ ($n = 28$)	T− ($n = 28$)	p
Age: Md (Q_1; Q_3)	63.5 (55.3; 71.8)	64.0 (56.3; 72.5)	0.860
Male/female	18/10	21/7	0.180
Education in years: Md (Q_1; Q_3)	10.0 (8.1; 11.9)	9.0 (8.0; 10.9)	0.491
Days from onset to examination: Md (Q_1; Q_3)	4.0 (2.0; 5.0)	3.0 (2.0; 5.0)	0.275
Hemianopia: present	4	4[a]	1.000
Hemiparesis: present	9	12[a]	0.388
Baseline NIHSS: Md (Q_1; Q_3)	5.0 (3.0; 7.0)	5.0 (3.0; 7.0)	0.868
BI at ward: Md (Q_1; Q_3)	100.0[b] (70.0; 100.0)	92.5[a] (72.5; 100.0)	0.850
NIHSS at ward: Md (Q_1; Q_3)	0.0 (0.0; 3.0)	3.0[a] (1.8; 6.3)	0.017

Baseline NIHSS sum score of National Institutes of Health Stroke Scale at the time of admission to the emergency department, (range = 0–34; 0 = no defect, 34 = severe stroke), *BI at ward* sum score of Barthel index at the hospital ward (range = 0–100; 0 = dependent, 100 = independent), *NIHSS at ward* sum score of NIHSS at the hospital ward, *Md* median, Q_1 lower quartile, Q_3 upper quartile

[a] Two patients have missing values

[b] Four patients have missing values

Table 2 Results of the neuropsychological examination and comparison of patients with (T+) and without thrombolysis (T−) after matching by baseline NIHSS, age and education

	T+ ($n = 28$)	T− ($n = 28$)	p
Block design: Md (Q_1; Q_3)	21.5 (13.5; 28.8)	13.5 (6.0; 22.0)	0.002
Defect in block design: present[a]	1	10	0.004
Picture completion: Md (Q_1; Q_3)	15.0 (10.0; 17.0)	12.5 (8.3; 16.0)	0.153
Defect in picture completion: present[a]	7	11	0.454
BITC: Md (Q_1; Q_3)	143.5 (139.3; 145.0)	142.0 (130.5; 144.8)	0.100
Visual neglect: present[b]	3	6	0.453
Visual memory immediate: Md (Q_1; Q_3)	33.5 (26.0; 36.8)	29.0 (23.5; 37.0)	0.301
Defect in visual memory immediate: present[a]	11	17	0.180
Visual memory delayed: Md (Q_1; Q_3)	19.0 (8.3; 28.5)	19.0 (8.0; 25.8)	0.855
Defect in visual memory delayed: present[a]	20	23	0.508

Baseline NIHSS sum score of National Institutes of Health Stroke Scale at the time of admission to the emergency department, (range = 0–34; 0 = no defect, 34 = severe stroke), *BITC* sum score of conventional subtests of Behavioural Inattention Test, (range = 0–146; 0–129 = neglect, 130–146 = no neglect), *Md* median; Q_1 lower quartile; Q_3 upper quartile

[a] Performance was determined to be impaired if the z scores of the neuropsychological tests were one or more standard deviations below the mean of the normative group

[b] The presence of neglect was determined on the basis of the BITC sum score

severity was lower in the T+ group than in the T− group at the hospital ward 4 days after onset, which might be due to the positive effects of thrombolytic therapy. This suggestion is in line with the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study [7], in which rt-PA-treated patients had milder stroke severity at 24 h. In our patient sample the T+ patients had significantly better visuoconstructive abilities than the T− patients. It is possible that thrombolytic therapy reduces the incidence of visuoconstructive deficits in acute RH stroke. This suggestion is supported by the fact that the incidence of visuoconstructive deficits was lower in the T+ group (4%) than in the T− group (36%). In this sample of patients visuoconstructive deficits were less common than reported in previous studies, and especially among the T+ patients the incidence was low. Hier et al. [11] reported that 93% of RH stroke patients had deficits in visual construction, and Nys et al. [5] found that 31% of LH and RH stroke patients had deficits in visual perception and construction at the acute phase of stroke. Both of these studies included patients with hemorrhage or infarct, but it is unlikely that this explains the difference in the incidence of visuoconstructive deficits. It is possible that thrombolysis has the effect of reducing this incidence.

There were also fewer neglect patients in the T+ group (11%) than in the T− group (21%), although this difference was not statistically significant, which might be due to the small size of the patient groups. The incidence of neglect was relatively low in T+ patients when compared to previous studies with RH patients [12, 13]. In T+ patients 11% had neglect, whereas Jehkonen [13] reported an incidence of 35%. The exclusion criteria and the setting used in the study by Jehkonen [13] were the same as in ours, with one exception: none of the patients received thrombolytic therapy. Interestingly, T+ patients did not differ from T− patients in visual search and reasoning skills or in visual memory.

One could argue that thrombolysis reduces the amount of infarcted tissue at the acute phase of stroke, which is seen in the difference in stroke severity as well as in the incidence of visuoconstructive deficits between T+ and T− groups. It also might be that the presence of neglect was lower in the T+ group due to the same phenomena. However, location of the lesion, not size of the infarct alone, is critical to eventual clinical outcome. Perhaps, therefore, the estimated effect of thrombolytic treatment is not seen in visual search and reasoning skills or in visual memory.

According to Nys et al. [8], a neuropsychological evaluation conducted 6 months after onset showed that thrombolytic therapy had no effect. They did not, however, examine patients' cognitive abilities at the acute phase. On the other hand, Nys et al. [8] did find that thrombolytic therapy had a favourable effect on basic and instrumental ADL skills 6 months after onset. This was not confirmed by our findings at the acute phase. In fact, our results indicated the opposite, as we found that thrombolysis might have a favourable effect on cognitive functioning and not on basic ADL at the acute stage of stroke. Nys et al. [8] suggested that thrombolytic therapy has a short-term effect on cognitive outcome, but this effect is not sustained at 6 months since the difference disappears in the long term due to a gradual recovery in untreated patients. Our results support their suggestion. When our results are compared with those of Nys et al. [8], it is also necessary to bear in mind that their patient group was more heterogeneous than ours since it included both RH and LH patients and both infarct and haemorrhage patients.

Our results indicate that thrombolytic therapy might have a positive effect on stroke severity and on visuoperceptual functioning at the acute stage of stroke. To the best of our knowledge this is the very first study to report on the association between thrombolytic therapy and visual functioning after acute stroke. However, it must be noted that our sample was restricted to patients with first-ever RH infarct and the sample size was relatively small. Therefore, these findings cannot be directly generalised to the stroke population as a whole, and our results need to be verified with a larger patient group including both LH and RH stroke patients. Furthermore, we were unable to randomize thrombolysis because our patients were excluded from that treatment on the basis of standard clinical procedures: (1) NINDS criteria [7], or (2) time window for the treatment (>3 h post-stroke). We wanted to minimize the influence of possible factors diminishing the estimated effect of treatment. Therefore, our patients were matched for age, education and stroke severity at the time of admission to the emergency department.

The strength of this study lies in its focus on a homogeneous group of consecutive patients with first RH infarct. Since our study is the first to examine the effect of thrombolysis on cognitive functioning at the acute stage of stroke, and since not all of the differences reached statistical significance, the results need to be verified with a larger patient group. Our ongoing research is aimed at clarifying the effect of thrombolysis on the recovery of cognitive functioning. To conclude, our results indicate that thrombolysis has a favourable effect on visuoperceptual functions in acute stroke.

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Conflicts of interest The authors have no conflicts of interest.

References

1. Hochstenbach J, Mulder T, van Limbeek J, Donders R, Schoonderwaldt H (1998) Cognitive decline following stroke: a comprehensive study of cognitive decline following stroke. J Clin Exp Neuropsychol 20:503–518
2. Kase CS, Wolf PA, Kelly-Hayes M, Kannel WB, Beiser A, D'Agostino RB (1998) Intellectual decline after stroke: the Framingham study. Stroke 29:805–812
3. Nys GMS, van Zandvoort MJE, de Kort PLM, Jansen BPW, de Haan EHF, Kappelle LJ (2007) Cognitive disorders in acute stroke: prevalence and clinical determinants. Cerebrovasc Dis 23:408–416
4. Patel M, Coshall C, Rudd AG, Wolfe CDA (2002) Natural history of cognitive impairment after stroke and factors associated with its recovery. Clin Rehabil 17:158–166
5. Nys GMS, van Zandvoort MJE, de Kort PLM, van der Worp HB, Jansen BPW, Algra A, de Haan EHF, Kappelle LJ (2005) The prognostic value of domain-specific cognitive abilities in acute first-ever stroke. Neurology 64:821–827
6. Jehkonen M, Laihosalo M, Kettunen JE (2006) Impact of neglect on functional outcome after stroke—a review of methodological issues and recent research findings. Restor Neurol Neurosci 24:209–215
7. The National Institute of Neurological Disorders, Stroke rt-PA Stroke Study Group (1995) Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 333:1581–1587
8. Nys GMS, van Zandvoort MJE, Algra A, Kappelle LJ, de Haan EHF (2005) Cognitive and functional outcome after intravenous recombinant tissue plasminogen activator treatment in patients with a first symptomatic brain infarct. J Neurol 253:237–241
9. Caplan LR, Bogousslavsky J (1995) Abnormalities of the right cerebral hemisphere. In: Bogousslavsky J, Caplan LR (eds) Stroke syndromes. Cambridge University Press, New York, pp 162–168
10. Lezak MD (1995) Neuropsychological assessment, 3rd edn. Oxford University Press, New York
11. Hier DB, Mondlock BA, Caplan LR (1983) Behavioral abnormalities after right hemisphere stroke. Neurology 33:337–344
12. Bowen A, McKenna K, Tallis RC (1999) Reasons for variability in the reported rate of occurrence of unilateral spatial neglect after stroke. Stroke 30:1196–1202
13. Jehkonen M (2002) The role of visual neglect and anosognosias in functional recovery after right hemisphere stroke. Dissertation. http://acta.uta.fi/pdf/951-44-5167-8.pdf
14. Cherney LR, Halper AS, Kwasnica CM, Harvey RL, Zhang M (2001) Recovery of functional status after right hemisphere stroke: relationship with unilateral neglect. Arch Phys Med Rehabil 82:322–328
15. Goldstein LB, Bertels C, Davis JN (1989) Interrater reliability of the NIH stroke Scale. Arch Neurol 46:660–662
16. Brown DL, Johnston KC, Wagner DP, Haley EC (2004) Predicting major neurological improvement with intravenous recombinant tissue plasminogen activator treatment of stroke. Stroke 35:147–150
17. Schmand B, Smit JH, Geerlings MI, Lindeboom J (1997) The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. Psychol Med 27:1337–1344
18. Wechler D (1992) Wechsler Adult Intelligence Scale-Revised. WAIS-R Manual. Psykologien Kustannus Oy, Helsinki (in Finnish)
19. Wechler D (1996) Wechsler Memory Scale-Revised. WMS-R Manual. Psykologien Kustannus Oy, Helsinki (in Finnish)
20. Wilson B, Cockburn J, Halligan P (1987) Behavioural Inattention Test. Thames Valley Test Company, Titchfield
21. Halligan PW, Cockburn J, Wilson B (1991) The behavioural assessment of visual neglect. Neuropsychol Rehabil 1:5–32
22. Mahoney FI, Barthel DW (1965) Functional evaluation: the Barthel index. Md Med J 14:61–65