Coll. Antropol. **34** (2010) 4: 1391–1396
Original scientific paper

CT Perfusion and Noncontrast CT in Acute Ischemic Stroke Diagnosing – Is there Influence on early Thrombolytic Therapy Outcome?

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A B S T R A C T

The objective of this study was to compare noncontrast computed tomography (NCCT) and computed tomography perfusion (CTP) in early diagnosis of acute ischemic stroke and to define influence of these diagnostic procedures on early outcome of thrombolytic therapy (TLTH). The study included 45 patients, 35 patients submitted to NCCT and CTP and 10 patients who underwent only NCCT, before CTP was introduced. Based on the National Institute of Health Stroke Scale (NIHSS) score we compared early outcome of patients who received TLTH after NCCT only (group 1) with the early outcome of patients who received TLTH following NCCT and CTP (group 2). Statistically significant difference was found in acute stroke diagnosing between CTP and NCCT ($p=0.002$). There were no statistically significant differences in TLTH early outcome between group 1 and group 2. In conclusion, CTP should be done regulary in patients presenting with acute ischemic stroke symptoms. More research needs to be done in defining exact influence of CTP implementation on the TLTH outcome.

Key words: *stroke, computed tomography, perfusion, penumbra, thrombolytic therapy*

Introduction

Stroke is a heterogeneous syndrome caused by multiple disease mechanisms which all lead to cerebral blood flow impairment by blockage or rupture of an artery. It can be classified into two main categories: ischemic and hemorrhagic stroke. It is a third leading cause of death and a leading cause of long term disability in industrialized countries and a significant cause of dementia and depression in adults[1,2]. It is an urgent condition that requires a prompt patient transportation to an adequately equipped health institution for early diagnosis procedure and attendance. Early thrombolytic treatment, within 3 hours of symptoms onset, can restore blood flow before major brain damage has occurred and could improve recovery after stroke[3]. Early diagnosis is very important in identification of patients who can benefit most from thrombolytic therapy (TLTH)[4,5]. New generation computed tomography (CT) scanners and new software programs improve identification of normal and disrupted brain circulation and increase the possibility of acute stroke diagnosis in earliest phase of circulation impairment. Although, magnetic resonance (MR) is proven to be more sensitive in depiction of small brain infarcts, CT of the brain is still the first option in many diagnostic centers for making diagnosis of acute ischemia and hemorrhage exclusion[6]. In very early phase signs of acute ischemia are often not perceived on noncontrast CT (NCCT) because of its limited sensitivity and moderate interobserver variability in detecting acute infarcts. CTP can improve diagnostic accuracy over NCCT for patients presenting with stroke symptoms within 3 hour window[7]. The critical value of CTP is its ability to assess irreversibily infarcted brain tissue (infarct core) and se-

Received for publication September 20, 2010

verely ischemic but potentially salvageable tissue (penumbra). Visualisation of infarct core and penumbra is achieved by CTP mapping and generating information of cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT)[8].

We present first experiences with CTP and TLTH in Split University Hospital Center, Croatia. Our objective was to compare NCCT and CTP in early diagnosis of acute ischemic stroke and to define influence of these diagnostic procedures on early TLTH outcome.

Materials and Methods

The study included 45 patients with acute stroke symptoms who presented to the neurologic emergency department of Split University Hospital Center within 3 hours of symptoms onset. Patients who came after 3 hours, patients with acute infection or history of allergic reaction to any contrast media were excluded from the study. There were 35 patients who were submitted to NCCT and CTP (November 2008 – December 2009) and 10 additional patients who underwent only NCCT since they were submitted before CTP was introduced.
All scanning was done on Siemens multi-slice computed tomography (MSCT Sensation 16 Siemens, Siemens AG, Wittelsbacherplatz 2, 80333 Munchen, Germany). A nonionic intravenous contrast media iopamidol (Iopamiro 370, »Bracco«) was administrated with 50 ml for one bolus *per* layer (1.layer-basal ganglia, 2. layer-ventricles lateral roof), at rate of 10 ml/s. Total amount of contrast media was 100 ml. Contrast media injection took 5–6 seconds total, with a inevitable use of contrast media warmed approximately to body temperature. Scanning data processing took about 5 minutes: Cerebral blood volume (CBV), cerebral blood flow (CBF) and mean transit time (MTT) were estimated in early CTP diagnosis of acute ischemia with special attention to presence of infarct core and penumbra. Out of 45 patients, there were 23 who received TLTH. In the group 1 there were all 10 patients who received TLTH before the implementation of CTP, based on NCCT and clinical findings only. In the group 2 there were 37% (13/35) patients with ischemic stroke who received TLTH after NCCT and CTP.
Alteplase was used for TLTH (Actilyse, »Boehringer Ingelheim«, 0,9 mg/kg, 90 mg max).

NIHSS (National Institute of Health Stroke Scale) score was used as a measure of TLTH early outcome. NIHSS score was calculated for all patients receiving TLTH before the therapy, right after, after 24 hours, after 7 days and at the patient's discharge. It is a widely used systematic assessment tool that provides a quantitative measure of stroke related neurologic deficit. NIHSS provides estimation of stroke severity, determination of appropriate treatment and prediction of patient outcome. It includes 15- item neurologic examination which is simple, valid and reliable tool that can be administered at the bedside. NIHSS is used to evaluate the effect of acute ischemia on the levels of consciousness, language, neglect, visual field loss, extraocular movement, motor strength, ataxia, dysarthria and sensory loss. A trained physician rated patients ability to answer questions and perform activities. Ratings for each item were scored with 3 to 5 grades taking 0 as normal. NIHSS assessment of each patient took less than 10 minutes.

All data, including history, were noted into the Microsoft Excel table. Analysis was done using »Statistica 5.0« program (Statsoft, Tuisa, USA). McNemar test was applied in describing incidence in stroke diagnosing between NCCT and CTP. MannWhitney test was used in comparing outcomes of two groups undergoing TLTH. A P value of <0.05 was considered significant.

This study is a part of School of Medicine Split, Split University, project »Early diagnosis and thrombolytic therapy of acute ischemic stroke« and was approved by Ethic committee of Split University Hospital Center and Ethic committee of School of Medicine, Split, Croatia.

Results

A group of 45 patients (26 men and 19 women), age between 17 and 85 (mean age 64), with acute stroke symptoms were included in this study.

Ten patients were submitted to NCCT only (group 1). Five patients, out of 10, had early signs of ischemia on NCCT scans and five were without any signs of ischemia or hemorrhage on early NCCT scans but based on the history, clinical findings and NIHSS scale TLTH was introduced.

Stroke diagnosis, based on CTP, was made in 28 patients out of 35 who underwent both NCCT and CTP. Seven patients, out of 35, due to the neurologic analysis, were later diagnosed with conditions that mimic stroke (4 cases of TIA with symptoms withdrawal in period of few hours after onset, 2 cases of epilepsy seizures and one migraine).

We compared diagnostic accuracy of CTP and NCCT in the group 2, as these patients underwent both types of imaging. Based on NCCT, 16 patients out of 35 were identified as acute ishemic stroke, whereas CTP diagnosed 28 of 35 patients: in 12 of 28 patients (43%) acute ischemic stroke was not recognized by NCCT (Table 1). There was statistical significant difference in acute stroke diagnosing between CTP and NCCT ($p=0.002$).

TABLE 1
DESCRIPTION OF INCIDENCE IN STROKE DIAGNOSING BETWEEN NCCT AND CT

		CTP		
		Ischemia: yes	Ischemia: no	Total
NCCT	Ischemia: yes	16	0	16
	Ischemia: no	12	7	19
	Total	28	7	35

McNemar test: $\chi^2=10.1$; $p=0.002$

NCCT sensitivity (taking CTP as referent method) was 57.1% (16/28) and specificity was 100% (7/7). The accuracy of NCCT was 65.7% (23/35). Positive predictive value of NCCT was 100% (16/16), but negative predictive value was 37% (7/19).

In 15 patients, out of 28 diagnosed with acute ischemic stroke based on CTP, penumbra was found and 13 out of those 15 were submitted to TLTH. In one patient penumbra was not significant, as it was not at least 20% larger than the area of ischemic core, while second patient's overall clinical status was unsatisfactory so these 2 patients did not receive TLTH.

Table 2 includes data on 23 patients who received TLTH and also early TLTH outcome for each patient trough the presentation of NIHSS score calculated before TLTH, right after treatment, after 24 hours, after 7 days and at the discharge. Table also includes information of letal outcome placed in the table cell according to the time of death.

As an example of diagnostic procedure and a result of TLTH a case of 40-year old patient with left hemiplegia is presented (Figure 1-5).

Comparison was done between early TLTH outcome of group 1 and group 2. Although NIHSS scale median before TLTH, right after, 24 hours after, 7 days after TLTH and at the discharge was lower in group 2, there was no statistical significant difference between these two groups (Table 3). Letal outcome occurred in 2 patients in group 1 and in 3 patients in group 2.

Fig. 1. NCCT; There are no signs of ischemia on NCCT scan 2 hours after symptoms onset.

TABLE 2
PATIENTS WHO RECEIVED TLTH

Patient	Group	Age	Gender	Time of arrival (h)	NIHSS before TLTH	NIHSS after TLTH	NIHSS 24h after TLTH	NIHSS – 7 days	NIHSS--discharge
01	2	31	m	2	8	5	1	0	0
02	2	81	m	1.5	7	4	0	0	0
03	2	24	f	2.5	15	15	14	letal	
04	2	60	f	3	21	16	17		13
05	2	70	m	1.5	16	8	7		7
06	2	58	f	2	7	5	6	6	6
07	2	81	f	2	17	16	letal		
08	2	65	f	2.5	18	12	10	10	10
09	2	75	m	1	22	19	20	20	20
10	2	68	m	1	21	19	letal		
11	2	66	m	0.5	11	0	0		0
12	2	50	m	2	7	9	11	11	11
13	2	59	m	0.5	15	5	3		3
14	1	78	f	1.5	18	15	letal		
15	1	46	f	1	15	15	12	10	10
16	1	65	m	1.5	10	10	12	12	12
17	1	70	f	0.5	14	10	12	12	12
18	1	69	m	1	12	12	15	20	20
19	1	78	f	1	11	7	5	5	5
20	1	68	m	1.5	15	5	3	2	2
21	1	34	m	0.5	12	12	20	23	letal
22	1	67	m	2	12	10	8	5	5
23	1	68	m	2	11	9	7	5	5

f=female, m=male

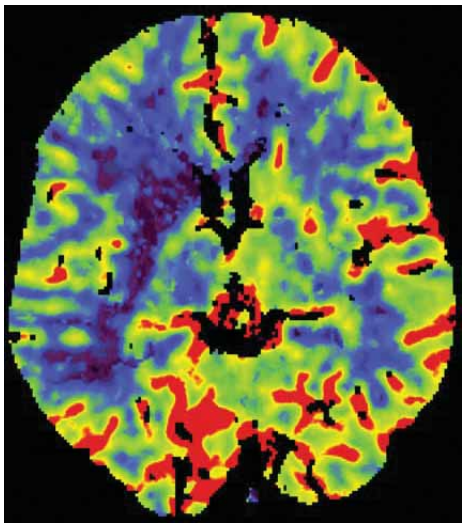

Fig. 2. CTP – CBF; Infarct core in right basal ganglia.

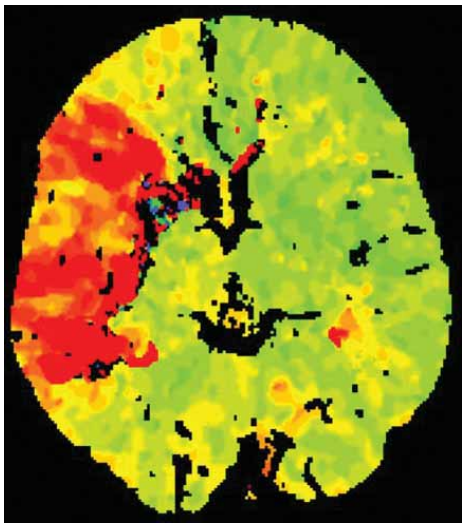

Fig. 4. CTP – MTT, Penumbra in the right middle cerebral artery irrigation area.

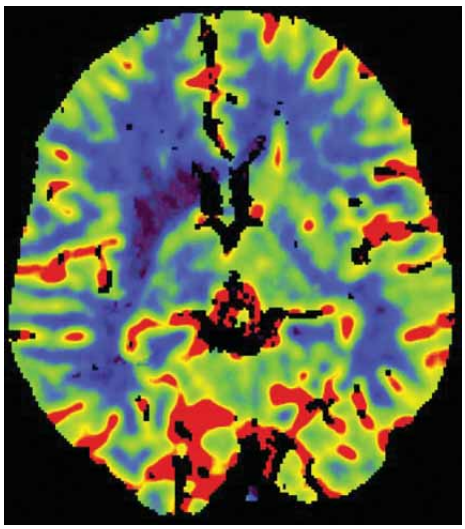

Fig. 3. CTP – CBV; Infarct core in right basal ganglia.

Fig. 5. control NCCT; Demarcated infarct in right basal ganglia 24 hours after TLTH.

Discussion

Although stroke is a clinical diagnosis, results of early diagnosis are essential in deciding about therapy that will be applied in the individual case of patient with ischemic stroke. NCCT is still the first step in many diagnostic centers worldwide for patients presenting with acute ishemic stroke symptoms and for excluding conditions that can mimic ischemic stroke (for example: TIA, intracranial hematoma, subdural hematoma, cerebritis, migraine and tumors). The fact that TLTH is being applied even beyond 4 hours of symptoms onset and also the fact that signs of early ischemia are often not present on NCCT scans, as seen in our study, resulted in need for new functional diagnostic methods that would detect earliest signs of ischemia and reversibly damaged brain tissue. This way introduction of TLTH consequently led to increased demand for early stroke diagnosis and made hyperacute ischemic stroke one of the most common urgent radiology issues. In fact, early diagnosis has crucial role in actual TLTH guidelines, but depiction of early signs of ischemia and hemorrhage on NCCT is necessary but not sufficient. We should always have in mind that stroke is preventable and treatable disease and that rapid treatment after early diagnosis improves stroke outcome[9].

Our research confirms CTP as valuable method in early depiction of ischemic stroke. Based on our results there are obvious advantages of CTP over NCCT that are in accordance with results of other studies[10–15]. Muir et al. reviewed NCCT and CTP scans from 52 patients sus-

TABLE 3
COMPARISON OF EARLY TLTH OUTCOME BETWEEN GROUP 1 AND GROUP 2

	Group 1	Group 2	p, z
Age (years)	68	65	z=0.684
Median (min-max)	(34–78)	(24–81)	p=0.494
Time of arrival (hours)	1.00	2.00	z=1.670
Median (min-max)	(0.50–2.00)	(1.00–2.50)	p=0.095
NIHSS before TLTH	12	7.50	z=0.655
Median (min-max)	(10.00–15.00)	(7.00–22.00)	p=0.512
NIHSS after TLTH	10.00	7.00	z=0.187
Median (min-max)	(5.00–15.00)	(4.00–19.00)	p=0.851
NIHSS – 24 h	12.00	8.00	z=0.991
Median (min-max)	(3.00–20.00)	(0.00–20.00)	p=0.322
NIHSS – 7 days	11.00	8.00	z=0.909
Median (min-max)	(2.00–23.00)	(0.00–20.00)	p=0.364
NIHSS discharge	11.00	8.00	z=0.985
Median (min-max)	(2.00–23.00)	(0.00–20.00)	p=0.325

Mann-Whitney test

pected for acute ischemic stroke. Although, some changes have been noted in brain tissue on NCCT scans they were not specific and ischemic penumbra and infarct core could not be identified based on NCCT only[16]. NCCT sensitivity in our study was 57.1% which is similar to 55.3% from the Kloska et al. study[17]. They had false negative findings on NCCT in 17 patients (out of 41) whereas false negative NCCT result was present in 12 patients, out of 35 in our study. Lin et al. have shown in their study that included 100 patients with stroke symptoms that CTP had better sensitivity and accuracy compared to NCCT. NCCT sensitivity was 26.2%, compared to 64.6% CTP sensitivity. NCCT accuracy was 52% compared to 76% of CTP[18]. According to Koenig et al. CTP sensitivity was 89%[10]. In all these earlier mentioned studies, as in our, NCCT positive predictive value was 100% which means that if NCCT is positive on ischemia, CTP will also be positive. This does not imply that after positive NCCT, CTP is unnecessary. On contrary, CTP is required because of its ability to identify infarct core and penumbra which can not be done based on NCCT scans only. Hence, the aim of CTP is to depict penumbra – viable tissue with reduced perfusion – that can be possibly salvaged with TLTH[19]. NCCT scans negative on ischemia do not indicate that there is no ischemia, it might not be detectable yet for NCCT. Negative predictive value in our study was 37% which suggests the need to proceed with CTP after NCCT. Besides helping in making decision about therapy in acute ischemic stroke, CTP can also help predict outcome based on extent of brain perfusion abnormality[20–22].

In this study we compared the early TLTH outcome of 10 patients who received TLTH in time period before the implementation of CTP in standard stroke procedure (group 1) with the outcome of 13 patients who underwent both NCCT and CTP (group 2). The statistically significant difference was not proven between early outcome of these two groups, although patients who underwent NCCT and CTP had lower NIHSS median before, right after, after 24 hours and at the discharge. We did not find any similar study to compare these results with, but it would be interesting to see the outcome comparison of these two groups when the sample gets larger. We expect better outcome of patients undergoing both NCCT and CTP in the future which should be proven in following research.

Active treatment of acute ischemic stroke can only be successful as long as tissue in the area of ischemic compromise is still viable. That makes the issue of penumbra surviving very important. Heiss et al. state that after 6 hours of stroke symptoms onset there is only 20% or less penumbra area, which implies the need of patients hospital admission as early as possible[23]. As the technology advances new teories arise regarding this matter. Using PET technology, Furlan et al. determined 30 % of penumbral tissue maintenance up to 7–17 hours[24]. In future clinicians might be able to use the information of penumbra duration as a more tailored approach in deciding about TLTH for every patient individualy[25]. Apart from the early diagnosing CTP is also mentioned in the literature because of its ability to help in predicting complications in stroke patients. Hemorrhagic transformation can be a very critical ischemic stroke complication, especially if following TLTH. Lin et al. concluded that measuring elevated microvascular permeability in acute ischemic stroke using first-pass dynamic perfusion CT imaging can help predicting hemorrhagic transformation in patients who have greater risk of hemorrhage developing[26]. This study is yet another example of CTP early diagnosis multiple benefit. Unless there is a significant penumbra, there is no use of TLTH application, regardless of infarct core or unsignificant penumbra presence. This way CTP can help in excluding patients with greater chance of potential complitations. It is necessary to decide about TLTH application taking all colected data about each patient in consideration and by all means patients general status.

In conclusion, it is extremely important to make prompt early diagnosis of acute ischemic stroke in order to initiate specific therapy, stabilise patients overall status and to start early prevention of potential complitations. Early diagnosis provides in time and quality care and if the diagnosis is made within 3 hours of symptoms onset TLTH is possible. This makes CTP multiply useful which is also demonstrated in this study. Beside revealing early signs of ischemia, that do not have to be present on NCCT, CTP is also helpful in deciding about TLTH application based on presence and size of ischemic penumbra. More research needs to be done on larger sample in defining the exact influence of CTP implementation on TLTH early outcome comparing patients who had CTP done in their diagnostic procedure with those who have been submitted to TLTH based on NCCT findings only.

Acknowledgements

The presented results arise from the scientific research project »Early diagnosing and thrombolytic therapy of ischemic stroke« conducted with the support of the Ministry of Science, Education and Sports of the Republic of Croatia.

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PERFUZIJSKI CT I NEKONTRASTNI CT U DIJAGNOSTICI AKUTNOG ISHEMIJSKOG MOŽDANOG UDARA – IMA LI UTJECAJA NA RANI ISHOD TROMBOLITIČKE TERAPIJE?

SAŽETAK

Cilj ovog istraživanja bio je usporediti nekontrastnu kompjutoriziranu tomografiju (NCCT) i perfuzijsku kompjutoriziranu tomografiju (CTP) u ranoj dijagnostici akutnog ishemijskog moždanog udara i definirati utjecaj ovih dijagnostičkih postupaka na rani ishod trombolitičke terapije (TLTH). Istraživanje je obuhvatilo 45 pacijenata, 35 pacijenata koji su bili podvrgnuti NCCT-u i CTP-u i 10 pacijenata kojima je provedena dijagnostika samo NCCT-om u razdoblju prije uvođenja CTP-a. Prema ljestvici moždanog udara National Institute of Health Stroke Scale (NIHSS) usporedili smo rani ishod pacijenata koji su primili TLTH nakon dijagnostike provedene samo NCCT-om (grupa 1) s ranim ishodom pacijenata kod kojih je TLTH uslijedila nakon NCCT-a i CTP-a (grupa 2). Statistički značajna razlika je dokazana u dijagnosticiranju akutnog ishemijskog moždanog udara između CTP-a i NCCT-a (p=0,002). Nije dokazana statistički značajna razlika u ranom ishodu TLTH između grupe 1 i grupe 2. Zaključujemo kako bi se CTP trebao koristiti redovito kod pacijenata koji se prezentiraju sa kliničkom slikom ishemijskog moždanog udara. Daljna istraživanja su potrebna kako bi se definirao točan utjecaj implementacije CTP-a na ishod TLTH.