Risk Factors for Early Infection after an Acute Cerebral Infarction

Suchat Hanchaiphiboolkul, MD*

** Prasat Neurological Institute, Department of Medical services, Ministry of Public Health*

Background and Objective: *Infection is a common complication after an acute stroke. This is important because it may cause death or delayed successful rehabilitation. Investigation of the risk factors for infection after an acute stroke is limited. The objective of this study was to determine the risk factors for early infection after an acute cerebral infarction.*

Design: *Retrospective analytical study.*

Material and Method: *The medical records of patients admitted within 48 hours of onset of symptoms to Prasat Neurological Institute from 1 January 2002 to 31 December 2003, with a diagnosis of cerebral infarction, confirmed with CT or MRI of the brain were retrospectively studied. Collected data included clinical features, risk factors for stroke, comorbid conditions, infection, and results of diagnosis tests. Univariate and multiple logistic regression analyses were used to determine factors that were associated with the risk of early infection.*

Results: *During the 24-month study period, 332 cerebral infarct patients were identified. Early infection occurred in 7.6%. The most common infection was pneumonia (4.3%). In the final multiple logistic model, independent risk factors for early infections were atrial fibrillation (OR, 9.31; 95%CI, 2.18-39.75), thromboembolic infarction (large vessel disease) (OR, 6.04; 95%CI, 1.97-18.54), admission conscious level (subconscious or unconscious/coma) (OR, 4.82; 95%CI, 1.60-14.55) and previous stroke (OR, 3.20; 95%CI, 1.21-8.47) respectively.*

Conclusion: *Atrial fibrillation, thromboembolic infarction (large vessel disease), admission conscious level (subconscious or unconscious/coma), and previous stroke were independent risk factors for development of early infection.*

Keywords: *Cerebral infarction, Complications, Infection, Risk factors*

J Med Assoc Thai 2005; 88(2): 150-5
Full text. e-Journal: *http://www.medassocthai.org/journal*

Cerebrovascular disease or stroke is a major health problem in Thailand[1,2]. Cerebral infarction was found about 70% of all stroke[3]. Patients who have had an acute stroke are at risk of developing a wide range of complications secondary to their stroke, these complications are important because they may cause death or delay successful rehabilitation[4-7]. The overall prognosis of patients with acute cerebral infarction is crucially dependent on the occurrence of medical complications in the course of the disease that have been found to occur in 59% of stroke patients, leading to death in up to 23% during the hospital stay[8]. Silver et al[9] reported that approximately 40% of deaths were from medical complications in a series of nearly 1,000 ischemic stroke patients. While most deaths occurring in the first week were due to brain edema associated with stroke, most deaths in the second and third week after a stroke could be attributed to medical complications, which were mainly infection[8-11]. Bounds et al[12], in a study of 100 autopsied patients with cerebral infarction, also found that the most common extracerebral causes of death were infections which were recognized premortem in only 44%. The most common sites of infections were the lungs and the urinary tract[8,13]. Attention to potential treatable medical complications such as infection, together with early indentification of high risk patients

Correspondence to : Hanchaiphiboolkul S, Prasat Neurological Institute, Department of Medical Services, Ministry of Public Health, Rajthevee, Bangkok 10400, Thailand.

and early management, may reduce mortality and disability, at least in the acute care setting[8,14]. Investigation of the risk factors for medical complications especially infection has been limited[15]. The objective of this study was to determine the risk factors of early infection after an acute cerebral infarction.

Material and Method

Medical records of patients admitted within 48 hours of the onset of symptoms to Prasat Neurological Institute from 1 January 2002 to 31 December 2003, with a diagnosis of cerebral infarction, confirmed with CT or MRI of the brain were retrospectively studied. All medical records of these patients and collected data were reviewed by using a standard designed form. Collected data included clinical features, risk factors for stroke, comorbid conditions, infection and results of diagnosis tests.

The following factors were accounted for statistical analysis: gender, age, hypertension, diabetes mellitus, smoking, previous stroke, ischemic heart disease, atrial fibrillation, admission conscious level, subtype of cerebral infarction, and early infection. The classification of specific factors were as follow:

Hypertension: On antihypertensive treatment at the time of admission or hypertension diagnosed during hospital stay by repeated detection of blood pressure > 140/90 mmHg.

Diabetes mellitus: On antidiabetes treatment at the time of admission or fasting plasma glucose > 120 mg/dl.

***Smoking*:** Daily smoking of any kind of tobacco. Ex smokers were coded as non smokers.

Previous stroke: Stroke was defined according to the World Health Organization criteria[16]: rapidly developed clinical signs of focal disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin.

Ischemic heart disease: A history of ischemic heart disease, or ischemic heart disease diagnosed during hospital stay.

***Atrial fibrillation*:** If present on admission electrocardiogram.

Admission conscious level: It was classified in to conscious, subconscious or unconscious, which were defined as follows; 1.conscious: alert, appropriate response to verbal commands; 2.subconscious: drowsy or stuporous; and 3.unconscious: coma or no eye opening to verbal stimuli.

Early infection: The definition was modification based on the study by Reith et al[17]: If clinically present, or if discovered by radiologic examination of the chest or analysis of urine during the first 5 days after admission.

For the subtype of cerebral infarction, the classification was as follows:

Lacunar infarction (small vessel disease): Acute onset of one of the five recognized lacunar syndromes (pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, dysarthria-clumsy hand syndrome) in which CT/MRI had excluded hemorrhage. In many cases the site of infarction was identified on CT/MRI, but this was not the absolute requirement for classification as lacunar infarction. When the infarction was seen on CT/MRI, the largest diameter had to be less than 1.5 cm.

Cardioembolic infarction: Cerebral infarction in patients who had a potential cardiac source of embolism.

Thromboembolic infarction (large vessel disease): Acute onset of focal neurological deficit in patients who had known risk factors of atherosclerosis and no other identificable cause.

Other causes: In patients with cerebral infarction and investigation showed a specific cause or cerebral infarction in which no possible cause was found, but non vascular cause was excluded by CT/MRI.

Statistical analysis

Continuous and categorical variables are expressed as mean $\pm$ SD and percentages respectively. Categorical data were analyzed by Chi-square test or Fisher's exact test estimating odd ratio for early infection development with corresponding 95% confidence intervals. Regarding continuous data, unpaired student's t test was used. Subsequently, a multivariable logistic regression model, controlling for possible confounding covariates, was fitted by backward elimination method. Variables initially included in the model were those with a probability value < 0.1 from the univariate analysis. The variable with probability value of Wald's test > 0.1 were removed from the model, and the log likelihood ratio test was performed each time to assess the fit of the more parsimonious model. All probability values are 2 sided, and the level of significance was set at $p < 0.05$. Statistical analyses were performed with SPSS 11.5 for Windows.

Results

During the 24-month study period, 332 cerebral infarct patients were identified. The basic charac-

teristics of patients are shown in Table 1. The most common comorbidity among the patients in the sample was hypertension (63.9%). According to the ischemic subtype, lacunar infarction (71.7%) was the most common subtype. Early infections were observed in 25 (7.6%) patients: pneumonia 14 (4.3%), urinary tract infection 13 (3.9%), and other infections 5 (1.5%). Six patients developed more than one site of infections.

Table 1. Basic characteristics of patients

	n (%)
1. Number of patients	332
2. Male: female	1.7:1
3. Age (years; mean, SD)	62 (11.4)
4. Hypertension	212 (63.9)
5. Diabetes	126 (38.2)
6. Smoking	121 (36.8)
7. Previous stroke	90 (27.5)
8. Ischemic heart disease	59 (19.0)
9. Atrial fibrillation	16 (5.0)
10. Subconscious or unconscious	31 (9.3)
11. Ischemic stroke subtype	
11.1 Lacunar infarction (small vessel disease)	238 (71.7)
11.2 Thromboembolic infarction (large vessel disease)	73 (22.0)
11.3 Cardioembolic infarction	9 (2.7)
11.4 Others	12 (3.6)

The overall mortality rate was 5.7%. Previous stroke, atrial fibrillation, admission conscious level (subconscious or unconscious/coma), and thromboembolic infarction (large vessel disease) were significantly associated with early infections in the univariate analysis (Table 2). In the final multivariate logistic model, independent risk factors for early infections were atrial fibrillation (OR, 9.31; 95%CI, 2.18-39.75), thromboembolic infarction (large vessel disease) (OR, 6.04; 95%CI, 1.97-18.54), admission conscious level (subconscious or unconscious/coma) (OR, 4.82; 95%CI, 1.60-14.55) and previous stroke (OR, 3.20; 95%CI, 1.21-8.47) respectively (Table 3).

Discussion

Patients who sustain a stroke usually have a high frequency of preexisting comorbidity[15,18]. In the present study, the most common comorbidity was hypertension (63.9%), similar to previous studies (63-74.5%)[6,7,15]. According to ischemic subtype, Hamidon et al[19], in a study of 163 patients with ischemic stroke in Malaysia found that lacunar infarction is the most common subtype (62.6%). In previous studies[6,20] from Western countries, however, lacunar infarction was found in only 25.8-32.9%. Lacunar infarction in developing countries seems to be more common than in the developed world[3]. These findings from previous studies were consistent with the 238 (71.7%)

Table 2. Univariate analysis of sample in term of infection

Variable	Infected (n = 25)	Non infected (n = 306)	p value	OR	95%CI
1. Gender (male, %)	56	63.4	0.462	0.74	0.32-1.67
2. Age (years; mean)	64.5	61.9	0.261	-	-
3. Hypertension (%)	68	63.4	0.645	1.23	0.51-2.93
4. Diabetes (%)	44	37.8	0.542	1.29	0.57-2.94
5. Smoking (%)	24	38	0.165	0.52	0.20-1.33
6. Previous stroke (%)	52	25.2	0.004	3.21	1.40-7.33
7. Ischemic heart disease (%)	33.3	17.8	0.099	2.30	0.94-5.67
8. Atrial fibrillation (%)	25	3.4	<0.001	9.50	3.10-29.08
9. Subconscious or unconscious (%)	48	6.2	<0.001	13.94	5.60-34.70
10. Thromboembolic infarction (%)	56	19.3	<0.001	5.33	2.30-12.33

Table 3. Multiple logistic regression analysis of infection

Variable	Coeff (b)	SE (b)	p value	OR	95%CI
Atrial fibrillation	2.23	0.74	0.003	9.31	2.18-39.75
Thromboembolic infarction	1.80	0.57	0.002	6.04	1.97-18.54
Consciousness	1.57	0.56	0.005	4.82	1.60-14.55
Previous stroke	1.16	0.50	0.019	3.20	1.21-8.47

patients with lacunar infarction in the present study. Early infection occurred in 7.6% of patients, compared to 16% of the patients in a previous study[19]. This difference may be due to different diagnostic criteria of the infection or baseline characteristics of the patients. The commonest early infection in the present study was pneumonia. This is consistent with other studies[6,8,19].

Early mortality after stroke exhibits a bimodal distribution[9]. One peak occurs during the first week, and a second during the second and third week[9]. The majority of deaths in the first week are due to trantentorial herniation[9,11,12]. After the first week, deaths due to immobility (pneumonia, pulmonary embolism, and sepsis) predominate[9,12]. In patients with cerebral infarction, 51% of deaths were due to complications of immobility[11].

Medical complications after a stroke, particularly infection, are common[5,8,13,15,21]. These complications not only influence mortality but may influence functional outcome[6-8,10]. Risk factors for medical complications that have been reported in the past include severity of stroke[4,15]; admission disability level[4]; length of rehabilitation stay[4]; low serum albumin level[15]; history of hypertension[15]; pre stroke disability[8]; location of stroke in the anterior circulation region[8]; and urinary incontinence[8]. However, investigation of the risk factors for early infection has been limited. Hamidon et al[19] found that the independent predictors of early infection after ischemic stroke were Barthel index less than 5 (OR, 4.23; 95%CI, 1.70-5.11), middle cerebral artery territory infarcts (OR, 4.91; 95%CI, 1.57-8.82) and a Glasgow coma score less than 9 (OR, 5.12; 95%CI, 2.98-15.52). In the present study, independent risk factors for early infection were atrial fibrillation (OR, 9.31; 95%CI, 2.18-39.75), thromboembolic infarction (large vessel disease) (OR, 6.04; 95%CI, 1.97-18.54), admission conscious level (subconscious or unconscious/coma) (OR, 4.82; 95%CI, 1.60-14.55) and previous stroke (OR, 3.20; 95%CI, 1.21-8.47) respectively.

Steger et al[22], in the multi-center study of 992 consecutive stroke patients, also found that patients with atrial fibrillation were associated with an increased rate of infections like pneumonia (OR, 2.86; 95%CI, 1.98-4.15) and urinary tract infection (OR, 1.58; 95%CI, 1.09-2.28). Several studies[22-27] have shown that patients with atrial fibrillation have more severe neurological deficit and experience a higher stroke related mortality. It is unclear why atrial fibrillation causes more severe strokes[28]. It has been hypothesised that atrial fibrillation may decrease cardiac output and thus compromise viable tissue in the penumbra surrounding the initial infarction.[29,30] Emboli in atrial fibrillation are probably more voluminous and therefore more easily obstruct larger brain vessels, but this has not been definitively established[28]. Patients with large vessel disease relatively had higher risk of multiple neurological deficits compared with patients with lacunar infarction[31]. Because lacunar infarction was the most prevalent in this study (71.7%), so patients with large vessel disease could have relatively more severe neurological deficit. Cerebral infarct patients with previous stroke could also have more severe neurological deficit compared with patients without previous stroke. An association between greater neurological deficit and occurence of general medical complications in stroke patients has been previously reported[4,15]. Greater neurological deficit may account for infection due to impaired consciousness, immobilization and incontinence, contributing to the development of pneumonia by aspiration, and urinary tract infection by the necessity of indwelling urinary catheters[22]. Stroke patients with paralysis and those with impaired level of consciousness also had had higher rate of pneumonia. These finding have been noted previously[8,32]. Patients with altered level of consciousness not only have more severe neurological impairments but also are less able to protect their airway effectively[32].

In conclusion, this study suggests that the independent risk factors for early infection after acute cerebral infarction are atrial fibrillation (OR, 9.31; 95%CI, 2.18-39.75), thromboembolic infarction (large vessel disease) (OR, 6.04; 95%CI, 1.97-18.54), admission conscious level (subconscious or unconscious/coma) (OR, 4.82; 95%CI, 1.60-14.55) and previous stroke (OR, 3.20; 95%CI, 1.21-8.47) respectively. Identifying these clinical factors that are associated with increased risk of experiencing early infection is valuable to facilitate the implementation of appropriate prevention and management interventions. Therefore, patients who have the forementioned risk factors should be carefully monitored and promptly treated.

References

1. Division of health statistic. Ministry of Public Health. Public Health statistics 1996: 84.
2. Ministry of Public Health. Burden of disease and injuries in Thailand: Priority setting for policy. 2002: A14-6.
3. Poungvarin N. Stroke in the developing world. Lancet 1998; 352(suppl III): 19-22.

4. Dromerick A, Reding M. Medical and neurological complications during inpatient stroke rehabilitation. Stroke 1994; 25: 358-61.
5. Kalra L, Yu G, Wilson K, Roots P. Medical complications during stroke rehabilitation. Stroke 1995; 26: 990-4.
6. Johnston KC, Li JY, Lyden PD, et al. Medical and neurological complications of ischemic stroke: experience from the RANTTAS trial. Stroke 1998; 29: 447-53.
7. Heuschmann PU, Kolominsky-Rabas PL, Misselwitz B, et al. Predictors of in-hospital mortality and attributable risks of death after ischemic stroke: The German stroke registers study group. Arch Intern Med 2004; 164:1761-8.
8. Davenport RJ, Dennis MS, Wellwood I, Warlow CP. Complications after acute stroke. Stroke 1996; 27: 415-20.
9. Silver FL, Norris JW, Lewis AJ, Hachinski VC. Early mortality following stroke: A prospective review. Stroke 1984; 15: 492-6.
10. Oppenheimer S, Hachinski V. Complications of acute stroke. Lancet 1992; 339: 721-4.
11. Bamford J, Dennis M, Sandercock P, Burn J, Warlow C. The frequency, causes and timing of death within 30 days of first stroke: the Oxfordshire community stroke project. J Neurol Neurosurg Psychiatry 1990; 53: 824-9.
12. Bounds JV, Wiebers DO, Whisnant JP, Okazaki H. Mechanisms and timing of deaths from cerebral in farction. Stroke 1981; 12: 474-7.
13. Langhorne P, Stott DJ, Robertson L, et al. Medical complications after stroke: a multicenter study. Stroke 2000; 31: 1223-9.
14. Vernino S, Brown RD, Sejvar JJ, Sicks JD, Petty GW, O'Fallon WM. Cause-specific mortality after first cerebral infarction: a population- based study. Stroke 2003; 34: 1828-32.
15. Roth EJ, Lovell L, Harvey RL, Heinemann AW, Semik P, Diaz S. Incidence and risk factors for medical complications during stroke rehabilitation. Stroke 2001; 32: 523-9.
16. Report of the WHO task force on stroke and other cerebrovascular disorders: Stroke 1989. Recommendation on stroke prevention, diagnosis and therapy. Stroke 1989; 20: 1407-31.
17. Reith J, Jorgensen HS, Pederson PM, et al. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. Lancet 1996; 347: 422-5.
18. Roth EJ, Mueller K, Green D. Stroke rehabilitation outcome: impact of coronary artery disease. Stroke 1988; 19: 42-7.
19. Hamidon BB, Raymond AA, Norlinah MI, Jefferelli SB. The predictors of early infections after an acute ischaemic stroke. Singapore Med J 2003; 44: 344-6.
20. Hajat C, Dundas R, Stewart JA, et al. Cerebrovascular risk factors and stroke subtypes: differences between ethnic groups. Stroke 2001; 32: 37-42.
21. Doshi VS, Say JH, Young SH-Y, Doraisamy P. Complications in stroke patients: a study carried out at the rehabilitation medicine service, Changi General Hospital. Singapore Med J 2003; 44: 643-52.
22. Steger C, Pratter A, Martinek-Bregel M, et al. Stroke patients with atrial fibrillation have a worse prognosis than patients without: data from the Austrian stroke registry. European Heart Journal 2004; 25: 1734-40.
23. Britton M, Gustafsson C. Non-rheumatic atrial fibrillation as a risk factor for stroke. Stroke 1985; 16: 182-8.
24. Candelise L, Pinardi G, Morabito A, et al. Mortality in acute stroke with atrial fibrillation. Stroke 1991; 22: 169-74.
25. Sandercock P, Bamford J, Dennis M, et al. Atrial fibrillation and stroke: prevalence in different types of stroke and influence on early and long term prognosis (Oxfordshire community stroke project). BMJ 1992; 305: 1460-5.
26. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Sroke severity in atrial fibrillation: the Framingham study. Stroke 1996; 27: 1760-4.
27. Lamassa M, Carlo AD, Pracucci G, et al. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (the European community stroke project). Stroke 2001; 32: 392-8.
28. Thijs V. More bad news about atrial fibrillation. European Heart Journal 2004; 25: 1670-1.
29. Oppenheimer SM, Lima J. Neurology and the heart. In: Hughes RAC, Perkin GD, eds. Neurology and medicine. London: BMJ books; 1999: 24-46.
30. Lavy S, Stern S, Melamed E, Cooper G, Keren A, Levy P. Effect of chronic atrial fibrillation on regional cerebral blood flow. Stroke 1980; 11: 35-8.
31. Evans A, Harraf F, Donaldson N, Kalra L. Randomized controlled study of stroke unit care versus stroke team care in different stroke subtypes. Stroke 2002; 33: 449-55.
32. Katzan IL, Cebul RD, Husak SH, Dawson NV, Baker DW. The effect of pneumonia on mortality among patients hospitalized for acute stroke. Neurology 2003; 60: 620-5.

ปัจจัยเสี่ยงของการติดเชื้อภายหลังการเกิดโรคหลอดเลือดสมองตีบหรืออุดตันในระยะเฉียบพลัน

สุชาติ หาญไชยพิบูลย์กุล

ความเป็นมาและวัตถุประสงค์: การติดเชื้อเป็นปัญหาแทรกซ้อนที่พบบ่อยในผู้ป่วยโรคหลอดเลือดสมองในระยะเฉียบพลัน การติดเชื้อนี้มีความสำคัญเนื่องจากอาจเป็นสาเหตุการเสียชีวิตหรือทำให้การฟื้นตัวของผู้ป่วยล่าช้าไป การศึกษาปัจจัยเสี่ยงต่อการติดเชื้อภายหลังการเกิดโรคหลอดเลือดสมองในระยะเฉียบพลันยังมีน้อย การศึกษานี้มีวัตถุประสงค์เพื่อหาปัจจัยเสี่ยงต่อการติดเชื้อภายหลังการเกิดโรคหลอดเลือดสมองตีบหรืออุดตันในระยะเฉียบพลัน

รูปแบบการศึกษา: Analytical study

วัสดุและวิธีการ: ศึกษาย้อนหลังจากเวชระเบียนผู้ป่วยโรคหลอดเลือดสมองตีบหรืออุดตันที่มารับการรักษาเป็นผู้ป่วยในของสถาบันประสาทวิทยาภายใน 48 ชั่วโมงหลังเกิดอาการในช่วง 1 มกราคม 2545 - 31 ธันวาคม 2546 โดยทุกรายได้รับการตรวจยืนยันด้วยเอกซเรย์คอมพิวเตอร์หรือแม่เหล็กไฟฟ้าบริเวณสมอง ข้อมูลที่ศึกษาประกอบด้วย ข้อมูลทางคลินิก ปัจจัยเสี่ยงโรคหลอดเลือดสมอง โรคอื่น ๆ ที่พบร่วม การติดเชื้อ และการตรวจทางห้องปฏิบัติการต่าง ๆ การวิเคราะห์ใช้ univariate analysis และ multiple logistic regression เพื่อหาปัจจัยเสี่ยงของการติดเชื้อ

ผลการศึกษา: ช่วง 24 เดือนที่ศึกษารวมผู้ป่วยได้ 332 ราย พบการติดเชื้อในระยะเฉียบพลันร้อยละ7.6 โดยภาวะปอดอักเสบ (ร้อยละ4.3) พบบ่อยที่สุด จากการวิเคราะห์ด้วย multiple logistic regression พบว่าปัจจัยเสี่ยงต่อการติดเชื้อได้แก่ ภาวะหัวใจเต้นริก (atrial fibrillation) (OR, 9.31; 95%CI, 2.18-39.75), thromboembolic infarction (large vessel disease) (OR, 6.04; 95%CI, 1.97-18.54), ระดับความรู้สึกตัวขณะแรกรับ (OR, 4.82; 95%CI, 1.60-14.55) และการเคยเป็นโรคหลอดเลือดสมองมาก่อน (OR, 3.20; 95%CI, 1.21-8.47)

สรุป: ภาวะหัวใจเต้นริก, thromboembolic infarction, ระดับความรู้สึกตัวขณะแรกรับ, และการเคยเป็นโรคหลอดเลือดสมองมาก่อนเป็นปัจจัยเสี่ยงของการติดเชื้อภายหลังการเกิดโรคหลอดเลือดสมองตีบหรืออุดตันในระยะเฉียบพลัน