Research Article

New Predictor of In-Hospital Mortality of The Surgically Treated Haemorrhagic Stroke: Subanalysis

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Abstract

At present there are no specific limits on the level of inflammatory markers which can be used as a boundary between excessive or non-inflammatory responses. We investigate the leukocytes count at hospital admission of spontaneous intracerebral haemorrhage patients to be proposed as a boundary between excessive inflammation and not excessive. This is a subanalysis from the study of the neuroprotective effect of tigecycline on brain injury due to spontaneous intracerebral haemorrhage supratentorial who underwent evacuation of the hematoma. Leukocytosis defined as a leukocyte count ≥ 11.000 cells/mL. The primary outcome was inhospital mortality and the secondary outcome was length of hospital stay (LOS). Statistical analysis conducted by chi-square or Fisher's exact test and logistic regression. Seventy patients were included. Approximately 79% of the patients had leucocytosis. Leucocytosis was not associated with in-hospital mortality or LOS of 15 days or longer. However, a leucocyte count of 20,000 mm^3 or higher was associated with in-hospital mortality (odds ratio, 9.09; 95% confidence interval, 1.97 to 42.06; P = 0.005). A leucocyte count of 20,000/mm^3 or higher can be proposed as a boundary of the excessive inflammation on spontaneous intracerebral haemorrhage.

Keywords: *Haemorrhagic stroke, inflammation, leucocytosis.*

Prediktor Baru Kematian di Rumah Sakit untuk Pasien Stroke Hemoragik yang Dilakukan Operasi: Hasil Subanalisis

Abstrak

Saat ini belum ada penanda khusus untuk menilai suatu respons inflamasi yang berlebihan atau tidak. Penelitian ini bermaksud mengungkap jumlah leukosit tertentu sebagai penanda inflamasi yang berlebihan pada pasien perdarahan otak spontan yang dilakukan operasi evakuasi hematoma intracranial. Penelitian Ini adalah subanalisis dari studi efek neuroprotektif tigecycline pada cedera otak akibat perdarahan intraserebral spontan yang menjalani evakuasi hematoma. Leukositosis didefinisikan sebagai jumlah leukosit ≥ 11.000 sel / mL. Luaran utamanya adalah kematian di rumah sakit dan luaran sekundernya adalah lama perawatan di rumah sakit (LOS= length of stay). Analisis statistik dilakukan dengan chi-square atau uji eksak Fisher dan regresi logistik. Hasil: 70 pasien dilibatkan. Sekitar 79% dari pasien memiliki leukositosis. Leucocytosis tidak berhubungan dengan kematian di rumah sakit atau LOS 15 hari atau lebih. Namun, jumlah leukosit 20.000 mm3 atau lebih tinggi berhubungan dengan kematian di rumah sakit (rasio odds, 9,09; interval kepercayaan 95%, 1,97 hingga 42,06; P = 0,005). Jumlah leukosit 20.000 / mm3 atau lebih tinggi dapat diusulkan sebagai batas peradangan berlebihan pada perdarahan intraserebral spontan.

Kata kunci*: Stroke hemoragik, peradangan, leukositosis.*

Introduction

Spontaneous intracerebral haemorrhage (SICH) is an emergency condition. Prompt treatments; both medical and surgical are recommended to decrease progression of disease and fatality. Rapid identification of certain factors that influence the outcome is crucial in determining the wisest treatment options in the early stages of the disease and to obtain an informed consent from the family.

Over the past two decades; the outcomes or prognosis of patients with SICH are strongly associated with the hematoma volume and glasgow coma score (GCS).[1,2] However, hematoma evacuation through surgery has been proven to reduce in-hospital mortality or improve the survival.[3,4] The latest guidelines for SICH, patients with decreased consciousness are recommended for surgery.[4] Surgery showed a benefit in patients with large hematomas accompanied by decreased level of consciousness.[6] Therefore, the prognostic indicators in patients indicated for surgery need to be known.

The inflammatory response has an important role in the mechanism of brain injury after SICH, specifically on the secondary brain injury mechanisms.[7] Among the markers of an inflammation is an increase of the leukocytes count. It is reasonable that leukocytes count could be used as predictors of outcomes in patients with SICH. However, the role of leukocytosis on outcomes of patients with SICH is not aligned.[8,9] In addition, the role of leukocytosis on in-hospital mortality of patients with SICH who underwent surgery has not been studied. Tigecycline study in SICH patients undergoing surgery; including the leukocytes count, which are a part of routine laboratory examinations in emergency cases, as a baseline data.[10] This study aims to analysis the role of leucocytosis on the in-hospital mortality of patient with SICH who underwent surgery for hematoma evacuation.

Methods

This study is a subanalysis from a tigecycline study which was resulted in a reduction of inflammatory marker of TNF-alpha (TNF-α) and in-hospital mortality. Considering that the leukocytes count were obtained before the administration of tigecycline or fosfomycin, therefore the results most likely reflects an inflammatory response after SICH. The leukocytosis is defined as leukocyte count more than 11.000 cells/mm^3 and an excessive leucocytosis was set based on our clinical experience by the leukocyte count ≥20,000 cells/mm^3.

Tigecycline study enrolled 72 subjects. The leukocytes count at admission were missed in two subjects, therefore we only enrolled 70 subjects in this subanalysis. The primary outcome in this study was in-hospital mortality and the secondary outcome was length of hospital stay (LOS). We collected several factors to affect the severity of brain injury after SICH as well as factors that believed to be affect the outcomes. Statistical analysis was conducted by chi-square or Fisher's exact test, and multivariate analysis by logistic regression. Logistic regression was conducted for variables for which $p < 0.25$ in univariate analysis. Significance was defined as $p < 0.05$.

Results

Seventy subjects met the criteria for sub-analysis; 44 subjects were male, 26 subjects were female univariate analysis is shown in Table 1. ICH volume > 50 mL was found in 56% of subjects, a sign of increased intracranial pressure as indicated by midline shift > 10 mm was found in 27%, and GCS < 8 was found in 31% of subjects. Leukocytosis and excessive leukocytosis were found in 70% and 13% of subjects, respectively.

Table 1. Characteristic of the Subjects

Characteristics	n = 70
Gender (n,%)	
Male	44 (63)
Female	26 (37)
Age (mean, SD), years	52 (9)
Tigecycline admisnistrations (n,%)	34 (49)
ICH Volume (mL)	
ICH Volume > 50 mL (n,%)	39 (56)
Hematoma volume pre surgery (mean, SD)	51 (15)
Hematoma volume at the day 7 after surgery (mean, SD), n= 50	13 (14)
Midline shift > 10 mm (n,%)	19 (27)
GCS < 8 (n, %)	22 (31)
Leukocyete count (n=68)	
Presurgery (mean, SD)	14,843 (4,7)
Leukocytosis (n,%)	55 (79)
Excessive leukocytosis (n,%)	9 (13)
Day 1 after surgery (mean, SD)	16,305 (5,4)
Increased leukocytes count postsurgery (n,%)	44 (65)

The bivariate analysis for inhospital mortality showed that several variables reached p values ≤ 0.25 and and were proposed for multivariate analysis (Table 2). Leukocytes count at admission ≥ 20,000 cells/mL resulted in $p = 0.005$; odds ratio = 9.09;

95%, confidence interval, 1.97 to 42.06. Meanwhile, an abnormal MABP and excessive leukocytosis are proposed for multivariate analysis for the predictor of prolonged hospitalization (Table 2).

Table 2. Bivariate Analysis

Characteristics	Inhospital mortality			Prolonged hospitalization		
	Yes (n,%)	No (n,%)	p value	Yes	No	p value
Age						
Age > 60 y.o	4 (31)	9 (69)	0.721	5 (38,5)	8 (61,5)	0.753
Age ≤ 60 y.o	13 (23)	44 (77)		19 (33)	38 (67)	
Sex						
Male	8 (18)	36 (82)	0.207	15 (34)	29 (66)	1
Female	9 (35)	17 (65)		9 (35)	17 (65)	
GCS						
< 8	9 (41)	13 (59)	0.058	8 (36)	14 (64)	1
≥ 8	8 (17)	40 (83)		16 (33)	32 (67)	
Anisocoric pupil						
Yes	5 (24)	15 (76)	1	6 (29)	15 (71)	0.701
No	12 (24)	37 (76)		18 (37)	31 (63)	
Volume of hematoma ≥ 50 mL						
Yes	9 (23)	30 (77)	1	15 (38)	24 (62)	0.567
No	8 (26)	23 (74)		9 (29)	22 (71)	
Brain midline shift ≥ 10 mm						
Yes	6 (32)	13 (68)	0.531	9 (47)	10 (53)	0.261
No	11 (22)	40 (78)		15 (29)	36 (71)	
Obliterasion of the ambien cistern						
Yes	15 (27)	40 (73)	0.330	17 (31)	38 (69)	0.405
No	2 (13)	13 (87)		7 (47)	8 (53)	
Hiperglycemia						
≥ 140	14 (33)	29 (67)	0.152	14 (33)	29 (67)	1
< 140	3 (13)	20 (87)		8 (35)	15 (65)	
MABP ≥ 127						
Yes	9 (28)	23 (72)	0.684	14 (44)	18 (56)	0.201
No	8 (21)	30 (79)		10 (26)	28 (74)	
Prophylactic antibiotics						
Tigecycline	5 (15)	29 (83)	0.124	14 (41)	20 (59)	0.353
Fosfomycin	12 (33)	24 (67)		10 (28)	26 (72)	
Leukocyte at admission						
≥ 11,000 cells / mL	14 (25)	41 (75)	1	19 (34)	36 (66)	1
< 11,000 cells / mL	3 (20)	12 (80)		5 (33)	10 (67)	
≥ 20,000 cells / mL	6 (67)	3 (33)	0.005	1 (11)	8 (89)	0.151
< 20,000 cells / mL	11 (18)	50 (82)		23 (38)	38 (62)	
Reduction of the leukocytes count after surgery						
Yes	9 (37)	15 (63)	0.088	6 (25)	18 (75)	0.386
No	7 (16)	37 (84)		17 (39)	27 (61)	

Multivariate analysis by logistic regression found the leukocyte count > 20,000 cells/mL and GCS < 8 found as a predictor inhospital mortality of ICH patients (Table 3).

Table 3. Odds Ratio for Leukocytosis and GCS as Predictors of Hospital Mortality

Characteristics	OR (CI 95%)	p value
Leukocyte count 20,000	0.145 (0.024-0.880)	0.036
GCS < 8	0.230 (0.60-0.877)	0.031

GCS = Glasgow coma scale; OR = odds ratio; CI = confidence interval

Discussion

We found that the prevalence of leukocytosis was higher compared to previous studies.[8,9,11] The most likely cause was the volume of the hematoma in our patients is greater than the volume of the hematoma in patients from other studies. Bleeding, triggers activation of the coagulation cascade, including thrombin productions until blood clot formation (hematoma) was complete. Therefore a greater hematoma volume is likely to cause more abundant thrombin production. Thrombin, through NF-kB pathway regulate proinflammatory cytokines production which is an important contributor for the inflammatory response.[12,13] Among the signals of an increased systemic inflammation is an increase in the leukocytes count.[14] Unfortunately, we failed to show an association between hematoma volume of more or less than 50 cc and leukocytosis.

Inflammatory response plays significant role on the brain injury after SICH.[15,16] Inflammatory markers, including peripheral leukocytes, have a role as prognostic markers.[17] Unfortunately, the role of leukocytosis on outcomes was indecisive. Agnihotri et al[18] found worse outcome in patients with greater changes in the leucocyte count in the first 72 hours after admission. However, although leukocytosis is proven to be inversely proportional to the level of consciousness, Behrouz et al[9] found no association between leukocytosis and poor outcomes. Furthermore, Morotti et al[11] showed a beneficial effect of an increased of leucocytes count after ICH, a greater leukocytes count was associates with a lower risk of hematoma expansions. However, a systematic review by Yu et al[19] found that baseline leukocytes count increase is associated with the in-hospital mortality of SICH patients. Such inconsistent findings may occur due to differences in the volume of the hematoma and or the magnitude of leukocytosis. Shrestha et al[19] showed that the magnitude of immunological parameter, including leukocytes are associated with the severity of ICH. The inflammatory response after ICH have a dual role.[21] At a moderate level it is beneficial for recovery, but at an excessive rate is detrimental. We found that baseline leukocytosis of surgically treated ICH was not associated with in-hospital mortality until the leukocytosis was excessive.

Previous study showed that the volume of hematoma intracerebral is a strong predictor of mortality.[1,2] Daverat et al[22] even stated that the hematoma volume of 50 mL or greater as a lethal volume. Latest study showed that hematoma volume > 30 mm^3 is associated with early mortality.[23] Hematoma volume of 50 mL or bigger (56% of our subjects) is associated with a midline shift of 10 mm or more (27% of our subjects) (p = 0.034; OR = 4.219 [95% CI 1.230 to 14.468]). Midline shift is an indication of increased intracranial pressure.[24] Severe intracranial hypertension has been shown to be associated with a higher mortality rate.[25,26] Reducing intracranial pressure with a decompression craniectomy decreased mortality in patients with traumatic brain injury accompanied by severe intracranial hypertension[27] and evacuation of the hematoma on SICH patients reduced intracranial hypertension and prevent brain herniation.[28] In harmony with Hutchinson et al[27] and De Oliveira Manoel,[28] our study showed that hematoma volume of 50 ml or greater is no longer to be a lethal volume or a strong predictor of short-term mortality for SICH who underwent hematoma evacuation.

Our findings indicate that the role of hematoma volume in predicting death after SICH decreases in strength if the hematoma is evacuated. On the other hand; in line with Xiong et al,[21] our study showed that an excessive inflammatory response was detrimental for SICH patients. As a form of detrimental effect is a higher risk of death in patients who have an increased inflammatory response. Indeed our study failed to show the effect

of increasing excessive leukocytes with length of hospital stay, but this data needs to be studied further because most deaths in our study occur before the 7th postoperative day. Furthermore, our study introduces that among the signs of an excessive inflammatory response is a leukocyte count of 20,000 cells/mL or greater. Considering that the leukocytes count is a routine laboratory examination of each patient in the emergency department, our findings can be used in estimating SICH patient outcomes after treatment and considered in determining the wisest therapeutic choice. Our study findings need to be followed by further research.

Conclusion

Hematoma volume, which is believed to be a strong predictor of poor outcomes or death, in patients undergoing hematoma evacuation, is reduced in strength. Excessive leukocytosis is an important predictor of death after SICH, even when hematoma evacuation is performed. We found that the leukocytes count of 20,000 or greater as a marker of an excessive inflammatory response after SICH.

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