ARAŞTIRMA YAZILARI **ORIGINAL ARTICLE**

VOLUME OF PERIHEMATOMAL EDEMA IN DIABETIC PATIENTS

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SUMMARY:

Development of edema is known to contribute poor outcome after spontaneous intracerebral hemorrhage (SICH). In this study, we measured the development of brain edema in 26 patients (12 diabetic, 14 non-diabetic) with SICH. The association between the formation of edema and diabetes mellitus was evaluated. "AxBxC/2" fomulation described by Suga was used to identify volume of hematoma and edema. The direct relation between the hematoma and edema volume is known, for this reason, a relative edema index was used by dividing the volume of hematoma and edematous tissue on control CT scans to the volume of initial hematoma. The other factors affecting formation of edema such as fever, hypoxia, anemia, metabolic abnormalities and platelet count were also compared. Clinical status of the patients were evaluated with modified Rankin Scale (mRS) at the end of the third week from the ictus. The mean initial hematoma volumes of two groups were approximately same (24,2±18,9 ml. vs 24,7±16,3 ml)(p=0,82). The mean hematoma and edematous tissue volume on control CT scans was 87,2 ± 58,8 ml for diabetic patients and 71,8 ± 55,2 ml for non-diabetic patients(p=0.59). The mean time from symptom onset to control CT for diabetic patients was 10,9±1,9 days and 10,1±1,7 days for non-diabetic patients(p=0,106). Mean relative edema index (Vhematoma+edema/ Vhematoma) was 3,9±1,9 for diabetic patients and 2,7 ± 0,9 for non-diabetic patients(p=0,006). The mean mRS score was 4,8 for diabetic and 3,9 for non-diabetic patients at the end of three weeks follow-up period.
Conclusion: The risk of edema development is found higher in diabetic patients than in non-diabetics.
Key Words: intracerebral hemorrhage, brain edema, diabetes mellitus

DIABETIK HASTALARDA PERIHEMATOMAL ÖDEM HACMI

Spontan intraserebral hemoraji sonrası ödem gelişiminin kötü prognozla ilişkili olduğu bilinmektedir. Bu çalışmada, spontan intraserebral hemorajisi olan 26 hastada (12 diabetik, 14 nondiabetik) beyin ödemi gelişimi incelendi ve diabetes mellitus ile perihematomal ödem gelişiminin ilişkisi araştırıldı. Hematom ve ödem hacimlerinin ölçümü için Suga tarafından tarif edilen "AxBxC/2" formülü kullanıldı. Hematom hacmi ile perihematomal ödem hacmi arasındaki ilişki bilinmektedir. Bu nedenle, kontrol beyin tomografisindeki hematom ve etrafındaki ödemli dokunun hacmi ilk tomografideki hematom hacmine bölünerek relatif bir ödem indeksi oluşturuldu. Ateş, hipoksi, anemi, metabolik bozukluklar ve trombosit sayısı gibi ödem gelişimini etkileyebilecek diğer faktörler de karşılaştırıldı. Hastaların klinik durumu inme gelişiminden sonraki üçüncü haftanın sonunda modifiye Rankin Skalası (mRS) ile değerlendirildi. İki grubunu başlangıç ortalama hematom hacmi hemen hemen aynıydı (24,2±18,9 ml. ye karşılık 24,7±16,3 ml)(p=0,82). Kontrol beyin tomografisindeki ortalama hematom ve ödemli doku hacmi diabetik hastalar için 87,2 ± 58,8 ml, nondiabetik hastalar için 71,8 ± 55,2 ml bulundu (p=0.59). Semptomların başlangıcı ile kontrol beyin tomografisi çekilene kadar geçen süre diabetik hastalar için 10,9±1,9 gün, nondiabetik hastalar için 10,1±1,7 gündü (p=0,106). Relatif ödem indeksi (Vhematom+ödem/ Vhematom) diabetik hastalar için 3,9±1,9 olarak bulunurken nondiabetik hastalar için 2,7 ± 0,9 bulundu (p=0,006). Ortalama mRS'u diabetik hastalarda 4,8 ve nondiabetik hastalarda 3,9 olarak saptandı.
Sonuç: Spontan intraserebral hemorajisi olan hastalarda perihematomal ödem gelişimi diabetik olanlarda diabetik olmayanlara kıyasla daha yüksek bulundu.
Anahtar Sözcükler: intraserebral hemoraji, beyin ödemi, diabetes mellitus

INTRODUCTION:

Spontaneous intracerebral hemorrhage (SICH) accounts for 10-15% of all strokes and SICH is responsible for 50% of all stroke related deaths. SICH induced death occurs during the first few days following stroke, in association with progressive edema (1). Edema and local tissue damage both cause independently to neurological deterioration after SICH (2). The mass effect generated by perifocal edema following SICH can produce clinical deterioration and increase the ratio of mortality and morbidity. For this reason, identification of factors associated with edema formation is important. Improving our knowledge about these factors will help to design better therapeutic interventions. Hypoxia, anemia, hypertension, fever are the major factors affecting edema growth (3). Gebel et al (2,4) defined the direct relation between the volume of the hematoma and

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edema. In this study, we evaluated the relation between diabetes mellitus and perihematomal edema.

MATERIAL AND METHOD:

We retrospectively identified 586 patients with the diagnosis of intracerebral hemorrhage admitted and treated at our clinic from January 1, 1997 to December 31, 2003. Inclusion criteria for the study were the followings: first supratentorial SICH without intraventricular hemorrhage, admission within 12 hours after onset of stroke, having control brain computerised tomography (CT) scan between 8-14th days. Twenty-six patients with these criterias were included in the study. Patients with ventricular hemorrhage (272 patients), infratentorial hemorrhage (76 patients) were excluded. Hemorrhages secondary to anticoagulation (16 patients), arteriovenous malformation (6 patients), neoplasm (4 patients), subarachnoid hemorrhage (8 patients) and hemorrhagic transformation of ischemic vascular lesions (9 patients) were also excluded. Patients were divided into two groups as diabetic (12 patients) and non-diabetic (14 patients).

Criterias for diabetes mellitus were accepted as:

1- History of diabetes mellitus and antidiabetic medication

2- Fasting blood glucose level >140 mg/dl and/or blood glucose level >200 mg/dl after feeding, the diagnosis of diabetes mellitus was approved by endocrinology department.

Patients' charts were reviewed for demographic information, medical history, medications taken at SICH onset, treatment, hospital course (prognosis). Age, gender, history for hypertension, diabetes mellitus and cardiac diseases were evaluated. Hemoglobin values, platelet and white blood cell counts, partial thromboplastin time, liver enzymes (ALT, AST), blood urea, creatin, cholesterol and triglyseride values were also evaluated. Localisation of hematomas were determined.

The patients are also evaluated for hematoma growth with control CT scans in the first few days. Horizontal CT slices were taken with one cm thickness. The volumes of edema and hematoma were measured with a semicantitative method described by Suga et al(5). "AxBxC/2" formulation was used for measurement. (A:longest diameter of hematoma on CT slice, B: the longest diameter perpendicular to A, C: the number of the slices taken with one cm thickness). Borders of the edematous tissue were evaluated with low density areas on CT scans. The radiologist measured the volume of edematous tissue and hematomas had no knowledge about the patients' group (diabetic or not). Direct relation between the volume of hematoma and edema is known (2,4). For this reason, a relative edema index was used by dividing the volume of hematoma and edematous tissue to the volume of initial hematoma. Diabetic and non-diabetic patients were also compared for edema index. Osmotic treatment and dexamathasone was used for preventing increase of intracranial pressure in all patients. Clinical status of the patients were evaluated with modified Rankin Scale (mRS) at the end of the third week from the ictus.

The parameters of diabetic and non-diabetic patients were statistically compared with Man-Whitney u test.

RESULTS:

Twenty-six patients (12 diabetic and 14 non-diabetic) were included in the study. There was no statistically significant difference for age between the diabetic (eight female, four male) and non-diabetic (nine female, five male) patients (65,1 ± 10,0 years vs 65,2 ± 11,6 years)(p=0,78). Ten of diabetic patients were hypertensive and six of them were taking antihypertensive treatmant. Thirteen of non-diabetic patients were hypertensive and eight of them were taking antihypertensive treatment. There was also no statistically significant difference for hypertension and antihypertensive treatment between the two groups(p>0,05). Nine of diabetic patients were of basal ganglionic and three were of lobar hemorrhages. Eleven of non-diabetic patients were of basal ganglionic,one was of thalamic and two were of lobar hemorrhages. The two groups were also compared for hemoglobin values, platelet counts and liver, kidney functions. Mean hemoglobin value was 13,4 ± 2,1 gr/dl, mean blood urea value was 46,4 ± 17,6, mean ALT value was 21,5 ± 8,1 IU and mean platelet count was 216000 ± 66000/ml for diabetic patients. Mean hemoglobin value was 14,4 ± 1,1 gr/dl, mean urea value was 36,5 ± 16,4, mean ALT value was 36,7 ± 49,8 IU and mean platelet count was 249000± 94000/ml for non-diabetic patients. No significant difference was found for hemoglobin values, platelet counts, liver and kidney functions(p>0,05).

There was also no significant difference for the other metabolic tests (cholesterol, triglyseride)

and haematological parameters (white blood cell counts, partial thromboplastin time).

Non of the patients had enlargement of hematoma on control CT scans. The cause of hemorrhage was presumed to be hypertension for all of the patients. Critical care of patients was standard, consisted of blood pressure control and airway protection. The patients were treated medically by osmotic diuretics and dexamethasone. None of the patients needed mechanical ventilation during the first three weeks (study period), and none of them underwent surgical evacuation of the hematoma. All patients with infections treated with appropriate antibyotics and body temperature of all the patients prevented under 38 cantigrad celcius.

The mean time from symptom onset to control CT for diabetic patients was 10,9 ± 1,9 days and 10,1 ± 1,7 days for nondiabetic patients. The difference was not statistically significant(p= 0,106). Mean initial hematom volumes of diabetic and non-diabetic patients was nearly same (24,2 ± 18,9 ml. vs 24,7 ± 16,3 ml.) (p=0,82). There was evident difference for the mean volume of hematom and edematous tissue on control CT scans but it was not statistically significant because of the small sample number (87,2 ± 58,8 ml. vs 71,8 ± 55,2 ml.)(p=0,59). Mean relative edema index (Vhematoma+edema/ Vhematoma) was 3,9±1,9 for diabetic patients and 2,7 ± 0,9 for non-diabetic patients. Mean edema index of diabetic patients was significantly higher than non-diabetic patients(p= 0,006). At the end of three weeks follow-up period, mean mRS score was 4,8 for diabetic and 3,9 for non-diabetic patients. There was difference for mRS scores between the two groups but it was not statistically significant(p=0,17). We thought that it may be due to the number of the patients.

Table 1: Demographic features of diabetic and non-diabetic patients

	Diabetic patients (n=12)	Non-diabetic patients (n=14)	p value
Mean age	65,1 ± 10,0	65,2 ± 11,6	0,78
Gender	8 women, 4 men	9 women, 5 men	
Hypertension	10 patient	13 patient	>0,05
Localisation of ICH	9 basal ganglia, 3 lobar	11 basal ganglia, 1 thalamus 2 lobar	
Duration of control CT	10,9 ± 1,9 days	10,1 ± 1,7 days	0,10
V hematoma (on first CT)	24,2 ± 18,9 ml	24,7 ± 16,3 ml	0,82
V hematoma+edema (on control CT)	87,2 ± 58,8 ml	71,8 ± 55,2 ml	0,59
Edema index	3,9 ± 1,9	2,7 ± 0,9	0,006
mean mRS	4,8	3,9	0,17

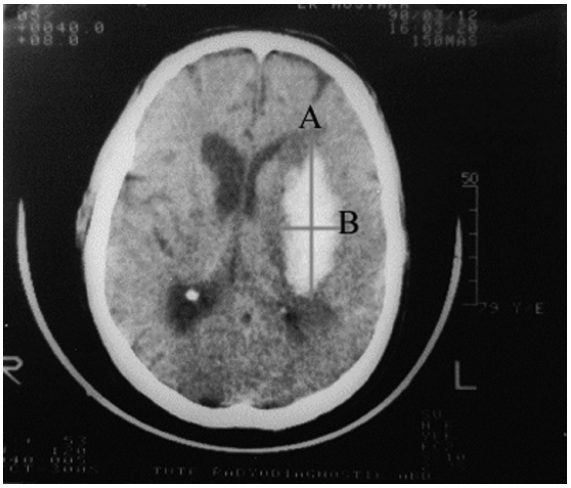
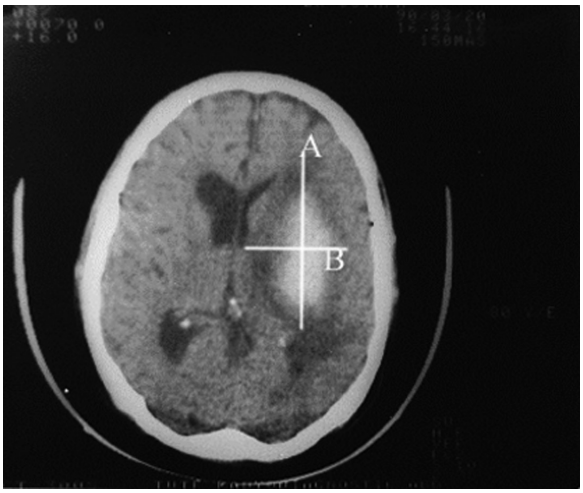


Figure I: Initial hematoma (a) on the first CT and hematoma+ edema



(b) images on control CT

DISCUSSION:

Development of brain edema after SICH is known to lead deterioration of the clinical course and a lot of factors may increase brain edema after SICH (7,8). In this study, we aimed to evaluate the effect of diabetes mellitus to perihematomal edema in patients with SICH (12 diabetic, 14 non-diabetic). For this reason, we tried to control all other factors affecting the formation of edema. Hypoxia, metabolic abnormalities, hypertension, hemoglobin value, platelet count and the volume of hematoma are known as the factors affecting edema volume(2-4). No statistically significant difference was found for metabolic tests between the two groups. There was also no significant difference for the history of hypertension and

antihypertensive treatment between the two groups, and none of the patients needed mechanical ventilation during the study period.

Sansing et al(1) evaluated the factors associated with edema development and outcome in 80 patients with SICH. They found larger SICH volume, edema volume, elevated blood glucose, fever, and the presence of intraventricular hemorrhage as predictors of poor outcome. They also reported significant correlation between platelet count and edema volume. Poungvarin et al (9) also reported the relation between hyperglycemia and edema. In our study, no significant difference was found for platelet count between the two groups. Suga et al(5) detected the peak brain edema volume following intracerebral hemorrhage at two weeks after onset. For this reason, patients with control CT scans between 8-14th days were included in our study. The mean time from symptom onset to control CT scan was 10,9 ± 1,9 days for diabetic patients and 10,1 ± 1,7 days for non-diabetic patients. There was also no significant difference for duration of control CT scans between the two groups(p= 0,106).

Association between hematoma volume and edema formation is known(2,5,11). Mayer et al (6) reported the direct relation between the hematoma volume(>45 ml) and poor prognosis. In our study, the mean hematoma volumes of two groups were similar (24,2 ± 18,9 ml. vs 24,7 ± 16,3 ml.)(p=0,82). We used a relative edema index (V hematoma + V edema / Vhematoma) to determine the edematous effects of hemorrhages with different sizes. A similar index (V edema/ V hematoma) has been used in Gebel's study (2). There was difference for hematoma and edematous tissue volume (Vhematoma+edema) on control CT scans between the two groups (87,2 ± 58,8 ml. vs 71,8 ± 55,2 ml.), but it was not statistically significant(p=0,59). We thought that it will be statistically significant with higher sample numbers. However there was statistically significant difference for edema index between the diabetic and non-diabetic patients(3,9 ± 1,9 vs 2,7 ± 0,9) (p=0,006).

Song et al (10) showed hyperglycemia may increase edema formation in a rat model of intracerebral hemorrhage. Previous studies demonstrated that hyperglycemia worsens the blood brain barrier injury. It is reported that free radicals, nitric oxide formation, and the level of bradykinin, a potent vasodilator may increase due to hyperglycemia in diabetic patients. These products and inflammatory cytokines such as IL-1 and TNF-alpha, may increase the permeability of blood brain barrier, and cause edema formation (12-14).

In conclusion, perihematomal edema is the major factor leading to neurological deterioration and death in patients with SICH, and the risk of edema development in these patients is higher in diabetic patients than non-diabetics.

REFERENCES

1- Sansing LH, Kaznatcheeva EA, Perkins CJ, Komaroff E, Gutman FB, Newman GC. Edema after intracerebral hemorrhage: correlations with coagulation parameters and treatment. J.Neurosurg 2003; 98:985-992

2- Gebel JM, Jauch EC, Brott TG, Khoury J, Sauerbeck L, Salisbury S, Spilker J, Tomsick TA, Duldner J, Broderick JP. Natural history of perihematomal edema in patients with hyperacute spontaneous intracerebral hemorrhage. Stroke 2002;33(11):2631-5

3- Carhuapoma JR, Hanley DF, Banerjee M, Beauchamp NJ. Brain edema after human cerebral hemorrhage. Journal of Neurosurgical Anesthesiology 2003;15(3):230-3

4- Gebel JM, Jauch EC, Brott TG, Khoury J, Sauerbeck L, Salisbury S, Spilker J, Tomsick TA, Duldner J, Broderick JP. Relative edema volume is a predictor of outcome in patients with hyperacute spontaneous intracerebral hemorrhage. Stroke 2002;33:2636-42

5- Suga S, Sato S, Yunoki K, Mihara B. Sequential change of brain edema by semiquantitative measurement on MRI in patients with hypertensive intracerebral hemorrhage. Acta Neurochir 1994;60:564-7

6- Mayer SA, Sacco RL, Shi T, Mohr JP. Neurological deterioration in noncomatosa patients with supratentorial intracerebral hemorrhage. Neurology 1994;44(8):1379-84

7- Shmyrev VI, Arkhipov SL, Kuznetsova SE, Ternovoi SK. Neuroimaging diagnosis and aspect of theraphy of hemorrhagic stroke. Zh Nevrol Psikhiatr Im SS Korsakova 2001;101(1):27-31

8- Flemming KD, Wijdicks EF, St Louis EK, Li H. Predicting deterioration in patients with lobar hemorrhages. J Neurol Neurosurg Psychiatry 1999;66(5):600-5

9- Poungvarin N, Viriyavejakul A. Spontaneous supratentorial intracerebral haemorrhage: a prognostic study. J Med Assoc Thai. 1990 ;73(4):206-11.

10- Song EC, Chu K, Jeong SW, Jung KH, Kim SH, Kim M, Yoon BW. Hyperglycemia exacerbates brain edema and perihematomal cell death after intracerebral hemorrhage. Stroke 2003;34: 2215-2220

11- Inaji M, Tomita H, Tone O, Tamaki M, Suzuki R, Ohno K. Chronological changes of perihematomal edema of human intracerebral hematoma. Acta Neurochir Suppl 2003;86:445-8

12- Thiel VE, Audus KL. Nitric oxide and blood-brain barrier integrity. Antioxid Redox Signal. 2001;3(2):273-8

13- Schilling L, Wahl M. Mediators of cerebral edema. Adv Exp Med Biol. 1999;474:123-41

14- Plesnila N, Schulz J, Stoffel M, Eriskat J, Pruneau D, Baethmann A. Role of bradykinin B2 receptors in the formation of vasogenic brain edema in rats.J Neurotrauma 2001;18(10): 1049-58