IMPACT OF DIABETES MELLITUS AND ADMISSION HYPERGLYCEMIA ON OUTCOMES AFTER INTRAVENOUS THROMBOLYSIS IN ACUTE ISCHEMIC STROKE PATIENTS

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ABSTRACT

Diabetes mellitus (DM) is a major risk factor for stroke, which is associated with unfavorable outcome after acute ischemic stroke (AIS) and disability. The potential harmful effect of DM, and the role and importance of blood glucose (BG) at admission are currently unclear for a clinical outcome after AIS. The aim of this study is to look for correlations between the presence of DM and the initial level of BG, and the clinical outcome after an intravenous thrombolysis (IVT) in patients with acute AIS.

MATERIALS AND METHODS: IVT with Astylise© was conducted on 170 patients with AIS in the period September, 2011- September, 2015, of whom 20% (n=34) were with DM and 80% without DM (n=136). According to the values of the BG at admission they were divided into three groups: group I - (n=34) <6.0 mmol/l; group II (n=65) 6.1-8.0 mmol/l; group III (n=39) >8.1 mmol/l.

RESULTS: 60.2% of the patients without DM and 40% of those without, p= 0.05(OR-1.5, 95% CI 0.91-2.49), are with mRs (0-2) after 3 months, 35% and 24%, respectively, (p= 0.196), are with mRs (0-1). The probability of this outcome is 1.47 times higher in those without DM (OR 1,47, 95% CI: 0,7-3,09). Mortality at the third month is 20% in patients with DM and 8.8% in those without DM, p<0.05. The frequency of intracerebral hemorrhage (ICH) is similar - 5.9% and 6.6% (p=0.617). There is no statistically reliable dependence between the clinical outcome after 3 months and blood sugar levels at admission. 64.7% of the patients in group I, 58.5% of those in group II, and 46.2% of those in group III (p>0.05) are with mRs (0-2). 38.2%, 32.3% and 30.8% (p>0.05), respectively, are with mRs (0-1). Mortality is 15.4% in group III compared to 9.2% in group II, and 8.8% in group I (p>0.05). 38.4% of the patients from group III and 26.5% from group I (p>0.05) are with mRs (3-5).

CONCLUSION: Patients with DM have significantly higher mortality and lack of favorable functional outcome at the third month compared to those without DM, which cannot be explained by the presence of ICH. The initial HG is not significantly associated with an unfavorable clinical outcome, but it quickly identifies patients with an increased risk of such an outcome in whom the blood sugar levels should be closely monitored.

Keywords: *thrombolysis, ischemic stroke, hyperglycemia, diabetes mellitus*

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INTRODUCTION

Diabetes mellitus (DM) is a major risk factor for stroke.In the recent decades its frequency has increased progressively, especially among younger age groups (1). The frequency of AIS is 3-4 times higher in patients with DM compared to those without DM. The risk is highest in individuals under 65 years

of age (2). DM is associated with an unfavorable outcome after AIS and a disability (3). In 20-50% of the cases with AIS hyperglycemia (HG) is established at admission, even without a prior history of DM (4). HG is a significant clinical problem. Nowadays, the potential harmful effects of DM, and the role and importance of BG at admission are unclear for the clinical outcome after AIS and are a subject of research in several studies. Studies on animal models show that induced HG in rats causes a delayed recovery of cerebral blood flow in the ischemic hemisphere and increase of the attacked zone (5). Persistent HG is associated with an unfavorable clinical outcome and increased mortality (6,7). The increased production of thrombin HG leads to increased coagulation (8). HG also causes increased production of the plasminogen activator inhibitor (PAI -1) (9). Due to the harmful effect on the neurons it compromises the positive effect of reperfusion after IVT (10). Acute HG leads to a larger delay of the reperfusion of the penumbra than the chronic one (11). The aim of this study is to look for correlations between the presence of DM and the initial level of blood sugar, and the clinical outcome after IVT.

MATERIALS AND METHODS

In the period September, 2011- September, 2015, IVT was conducted on 170 patients with acute AIS, of which 20% (n=34) have a history of DM. Their clinical outcome was compared with that of patients without DM (n=136). According to the values of the initial blood sugar, the patients were divided into three groups: group I - (n=34) <6.0 mmol/l; group II (n=65) 6.1-8.0 mmol/l; group III (n=39) >8.1 mmol/l. IVT with Actylise© was conducted by an established protocol in accordance with the existing standards and criteria in the presence of inclusion criteria and the absence of contraindications. A total of 0.9 mg/kg body weight Actylise© of which 10% bolus was applied in a continuous intravenous infusion for 60 min, and a maximum of 90mg. The National Institute of Health Stroke Scale (NIHSS), a grading scale, was applied to assess the severity of the focal neurological deficit. The functional independence of the third month and the degree of disability were assessed by the modified Rankin (mRs) scale. CT examination of the head is done natively at admission and 24 hours after IVT. The laboratory panel includes blood count, serum glucose at admission, BSP, total cholesterol, LDL, HDL, INR, APTT.

RESULTS

The mean age of patients without DM (n=136) was 68.4 years (±12,1), and of those with DM (n=34) - 70.4 years (±10,2) with a slight prevalence of women (58.8%). The frequency of vascular risk factors is similar or the difference is statistically insignificant. Only the systolic blood pressure (SBP) at admission was significantly higher in diabetics (154.1mmHg and 145.5mmHg, respectively, p = 0.024). Onset-to-treatment time (OTT) and NIHSS were similar for both groups. The demographic and clinical signs are presented in (Table 1).

Table 1. Clinical characteristics of patients with and without DM

Indicator	Without DM (n=136)	With DM (n.(n=34)	p
Age. middle ±SD	68.4±12.1	70.4±10.2	0.393
Male	73 (53.7%)	14 (41.2%)	0.133
Female	63 (46.3%)	20 (58.8%)	
HD	121 (89.0%)	32 (94.1%)	0.296
Dyslipidaemia	31 (22.8%)	9 (26.5%)	0.402
AF	47 (34.6%)	12 (35.3%)	0.543
HF. IHD	38 (27.9%)	14 (41.2%)	0.100
SBPmm Hg*	145.5±19.4	154.1±20.4	0.024
DBP mm Hg	82.8±11.2	85.5±9.9	0.205
NIHSS	13.8 (6-21)	14.1 (6-21)	0.736
OTT	182.1 (65-270)	188.5 (45-260)	0.490

The favorable clinical outcome (mRs 0-2) at the third month is significantly more frequent in patients without DM compared to those with DM (60.2% and 40%, respectively, p = 0.05). A logistic regression analysis demonstrated 1.5 times greater probability for them of mRs (0-2) (OR-1.5, 95% CI 0.91-2.49). With a full recovery (mRs 0-1) are 35% of the patients without DM and 24% of those with DM (p=0.196).

The probability of this outcome is 1.47 times greater in those without DM (OR 1.47, 95% CI: 0.7-3.09). Mortality around the 3rd month is significantly higher in diabetics (20% vs. 8.8%, p<0.05). The frequency of ICH is similar - 5.9% and 6.6%, respectively (p=0.617). The results are presented in (Table 2).

Table 2. Comparative analysis of clinical outcome around 3rd month after AIS in patients with and without DM

Clinical result	Without DM(n.%) (n= 113)	DM(n.%) (n= 25)	p	OR(95 % CI)
mRS 0-2*	**68 (60.2%)**	**10(40.0%)**	**0.05**	**1.5 (0.91-2.49)**
mRS 0-1	40 (35.4%)	6 (24.0%)	0.196	1.47 (0.70-3.09)
mRS 6*	10 (8.80%)	5 (20.0%)	<0.05	0.44 (0.16-1.18)
ICH	9 (6.6 %)	2 (5.9%)	0.617	1.13 (0.25-4.96)

There is no statistically proven dependence between the clinical outcome at the 3rd month and the admission BG, despite the high frequency of mRs (0-2) in normal glycemic patients. They are 64.7% v/s 58.5% in group II and 46.2% in group III (p>0.05). With mRs (0-1) are 38.2%, 32.3% and 30.8% (p>0.05), respectively. Mortality is higher in group III (15.4%), compared to 9.2% and 8.8% in the other two groups (p>0.05). 38.4% from group III and 26.5% (p> 0.05) from group I are with disability (mRs3-5). The results are presented in (Table 3) and (Fig. 1).

Table 3. Three-month clinical outcome according to blood glucose values at admission

Result	< 6.0mmol/l (n = 34)	6.1 – 8.0mmol/l (n = 65)	> 8.1mmol/l (n=39)	p
mRs 0-2	22 (64.7%)	38 (58.5%)	18 (46.2%)	>0.05
mRs 0-1	13 (38.2%)	21(32.3%)	12(30.8%)	>0.05
mRs 6	3 (8.8%)	6 (9.2%)	6 (15.4%)	>0.05

DISCUSSION

In the present study, DM is associated with a significantly lower frequency of a favorable clinical outcome (mRs 0-2) and higher mortality at the 3rd month after AIS.The results are similar to those of a number of unadjusted studies (12,13). A significant correlation between DM and ICH is not proven. The predictive role of DM for the clinical outcome after IVT remains currently undefined. According to some authors DM is significantly associated with an increased risk of SICH (symptomatic intracerebral hemorrhage) (14). After IVT, the insulin resistance correlates with an unfavorable long-term clinical outcome (15). Analysis of the results from SITS-ISTR indicates an increased risk of mortality or an unfavorable outcome at the 3rd month after AIS in patients with DM, while the frequency of ICH is similar in those with and without DM (16). A recent study indicates an association between acute or chronic HG and higher risk of mortality and unfavorable outcome, despite previously diagnosed DM. The dependence is nonlinear, with a plateau of about 200 mg/dl and HbA1C - 8% (17). One possible explanation for the negative effect of HG is the comorbidity caused by DM. The unfavorable prognosis of AIS with concomitant DM depends on many factors - diabetic neuropathy, formation and accumulation of lactate, anaerobic metabolism in a HG (18). In the present study the initial HG does not correlate significantly with deteriorated clinical outcomes or death after 3 months. In other studies HG after IVT,

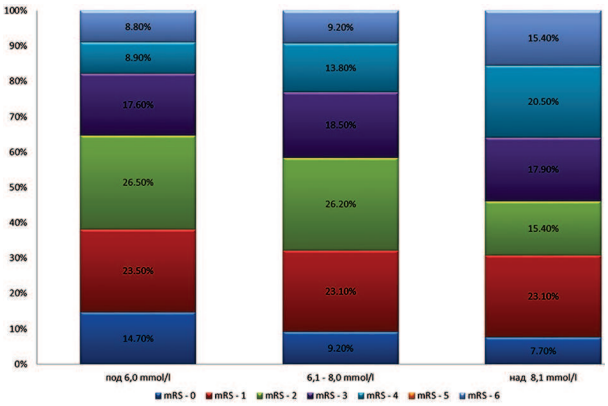

Fig. 1. Distribution of all clinical outcomes based on blood glucose values at admission

maximum HG and average HG are independent predictors of the clinical outcome and HG at admission is not an indicator of an unfavorable outcome (19). Post-hoc analysis of the results of the NINDS demonstrates that BG at admission correlates with an unfavorable functional outcome and occurrence of SICH. The dependence is linear, the risk increases 1.75 times for every 100 mg/dl increase, regardless of the severity of AIS and the history of DM (20). Another study establishes a significant correlation between HG at admission and SICH, mortality and unfavorable functional outcome at the 3rd month, as it is debatable whether HG directly damages the ischemic brain tissue, or it is an epiphenomenon of the gravity of AIS. A dose-dependent correlation between HG and the unfavorable clinical response remains still assumed only (21). The exact mechanisms by which HG influences the unfavorable clinical outcome after AIS are different and not well studied. They may be a distortion of the blood-brain barrier and an increased risk of hemorrhagic transformation (22). Increased production of free radicals, mitochondrial damage, cellular edema, and influx of extracellular Ca^2+ are also pathological damaging processes in the presence of HG (23). In the acute phase of AIS, HG at admission is a stress reaction in which, as a result of the involvement of the hypothalamic-pituitary-adrenal system, cortisol and catecholamines are excreted, and DM is a response to the gravity of the AIS (24).

CONCLUSION

Patients with DM have a significantly higher mortality rate and a lack of favorable functional outcome at the third month compared to those without DM, which cannot be explained by the presence of ICH. The BG at admission is not significantly associated with an unfavorable clinical outcome, but it quickly identifies patients with an increased risk of such an outcome in whom BG levels should be closely monitored.

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