

COAGULATION DISORDERS AFTER TRAUMATIC BRAIN INJURY

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Isolated traumatic brain injury (TBI) is often associated with abnormalities in coagulation parameters. Prehospital fluids exceeding 2,000 ml may be associated with coagulation disorders in patients with TBI. The aim of this study was to investigate the incidence of coagulation disorders, to establish its relation to the outcome, and to establish a correlation between prehospital fluid infusion and development of coagulation disorders.

The study included 82 patients with isolated brain injury. Coagulation parameters were determined using the values of prothrombin time (PT), activated partial thromboplastin time (APPT) and platelet count. We also analyzed a correlation between prehospital administered fluid and the occurrence of coagulopathy.

Pearson's correlation analysis showed that in terms of survival, there was no significant difference between the groups (group A OR 37 CI 0.11-1,27; group B OR 0,48 CI 0,16-1,49; group C OR 0,69, CI 0,24-1,98), but it also indicated that prehospital fluid administered in a larger amount was in a negative correlation with the treatment outcome (-0,240).

The results of our studies have confirmed the correlation of coagulation abnormalities with the lethal outcome in patients with TBI. Administration of more than 1,500 ml of fluid is associated with more frequent occurrence of coagulation disorders and with poor outcome.

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Key words: traumatic brain injury, coagulation disorders

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Introduction

Isolated traumatic brain injury (TBI) is often associated with abnormalities in coagulation parameters, although the incidence of such disturbances remains poorly defined. The presence of coagulation disorder has been linked to the progression of both hemorrhagic and ischemic lesions (1, 2) and is associated with increases in morbidity and mortality (3-7). The mechanisms underlying coagulopathy after TBI are still poorly understood. The most commonly accepted hypothesis of the pathogenesis of coagulopathy after TBI implies alterations in local and systemic coagulation and fibrinolytic pathways secondary to the release of tissue factor (TF) (8-10), disseminated intravascular coagulation (11-13), platelet dys-

function, (14-16), and activation of protein C pathways secondary to hypoperfusion (17, 18).

Early recognition of coagulopathy is of value in predicting the occurrence of delayed brain injury and may contribute to prevention of bleeding disorders (19).

Most studies report about early coagulopathy after the arrival at the emergency department, which was associated with increased morbidity and mortality (20). Although the prevalence of coagulopathy increases after the patient admission at the emergency department, there is a lack of evidence about delayed coagulopathy (21-23).

Recent findings also suggest that prehospital fluids exceeding 2,000ml may independently be associated with coagulopathy in patients with isolated blunt TBI (24).

The aim of this study was to investigate the incidence of early and delayed coagulopathy, and to establish a relation to the outcome; in addition, the aim was to establish a correlation between prehospital fluid infusion and development of coagulopathy.

Material and methods

The study included 82 patients of both genders and various ages with isolated brain injury. In all the patients, on admission to the ICU, the level of consciousness using the Glasgow comma score was assessed. Coagulation parameters were deter-

mined using the value of prothrombin time (PT), activated partial thromboplastin time (APPT), and platelet count.

Using the Marshal and Marshal modified scale, radiological classification of brain injury was performed. The study did not include patients with injuries of other organs or organ systems.

Coagulopathy is defined as an extension of aPTT > 40 seconds and < or PT, or platelet count less than 120x10⁹.

Patients were divided into two groups: a group which manifested coagulopathy and a group in which coagulopathy was not detected. The group with coagulopathy was divided into three groups: group A, consisting of patients who had coagulopathy upon their arrival, group B which included patients who developed coagulopathy after 24 hours, and group C which comprised patients in whom coagulopathy occurred 48 hours after the injury.

A correlation with the outcome was made, both of the groups with and without coagulation, as well as the analysis of outcome in subgroups with coagulopathy. In addition, we also analyzed a correlation between prehospital administered fluid and the occurrence of coagulopathy.

Statistical analysis was performed using the standard programs for data processing - MS EXCEL and software packages R. Using descriptive statisti-

cal analysis, the following statistical parameters were shown: number, percentage, arithmetic mean, standard deviation and median interval of variation (min-max).

Using analytical statistical methodology, we measured the statistical significance of mutual differences in the frequency of occurrence of certain characteristics in patients who had been divided into groups. The tests were performed (by Chi-square test). Comparisons of mean values between the groups were performed by t-test for independent samples or by nonparametric Mann-Whitney test (in case CV > 30%). For the purpose of measuring the relation of certain characteristics we performed the correlation analysis.

Results

The study included 82 patients with isolated severe traumatic brain injury. The presence of coagulopathy on hospital admission was registered in 17 % (20.7) patients with average age of 50.35 years (± 16.71) and its average value was GCS 5 (GCS 3-7); 11 patients were males (64.7%) and 6 patients were females (35.3%). Sixty-five patients on admission had no signs of coagulopathy. Their demographic characteristics are shown in Table 1.

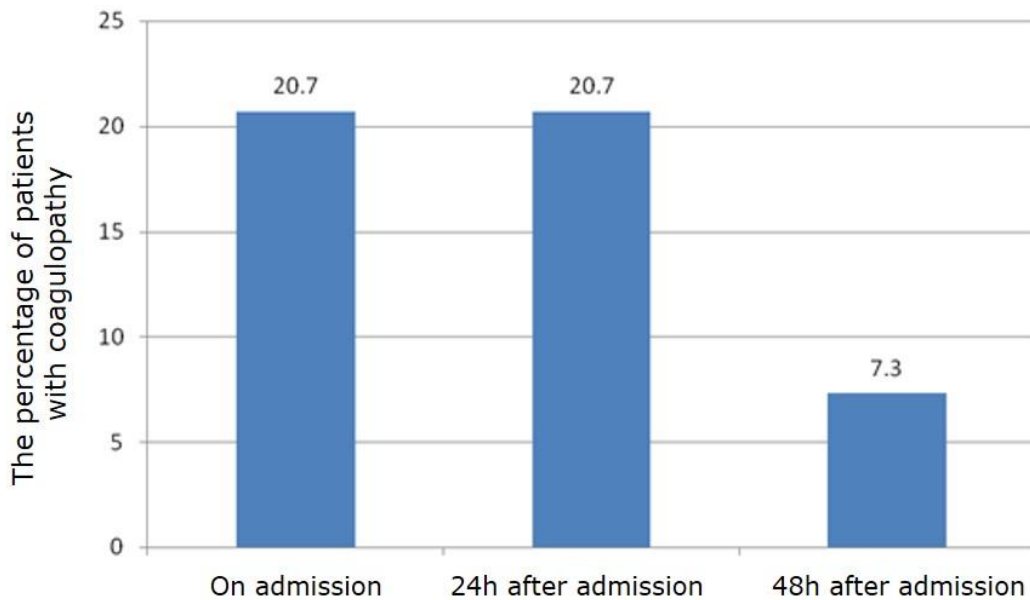
Table 1. Condition on admission

| | Coagulopathy | No coagulopathy | p |
|----------------------|-----------------------|---------------------|------|
| N (%) | 17 (20.7%) | 65 (79.3%) | n.s. |
| Age | 50.35 \pm 16.71 | 48.28 \pm 16.08 | n.s. |
| Male | 11/17 (64.7%) | 42/65 (64.6%) | n.s. |
| Female | 6/17 (35.3%) | 23/65 (35.4%) | |
| GCS (mediana) | 5 | 5 | n.s. |
| GCS (range) | 3-7 | 3-8 | |
| Pre - hospital fluid | 1,102.94 \pm 905.96 | 780.77 \pm 804.66 | n.s. |

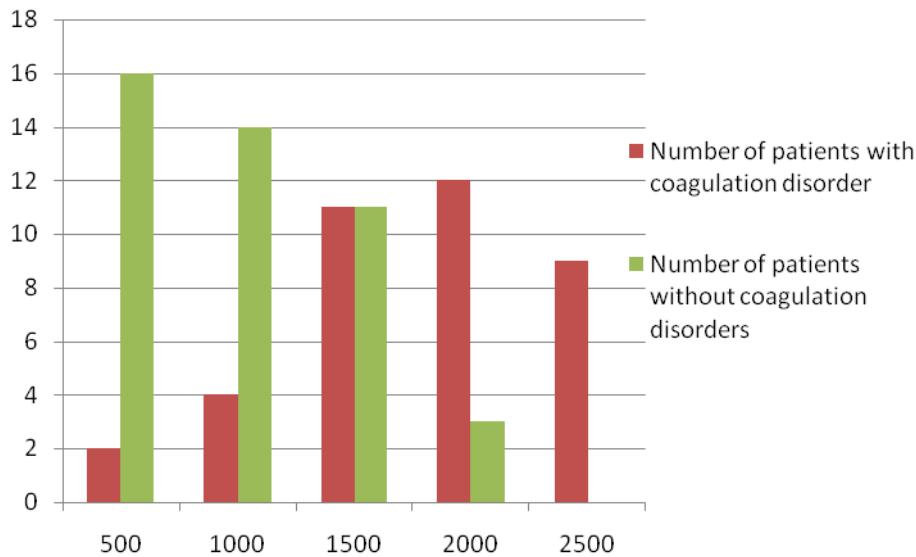
n.s. value of parameters among patients with coagulopathy and without coagulopathy do not differ significantly

There was no statistically significant difference found in the age structure and structure by gender. Also, the values of the Glasgow comma score were not statistically significant in the examined groups, which is also shown in Table 1.

Graph 1 shows the distribution of coagulation disorder development. The correlation between the development of bleeding disorders and the administered prehospital liquid is shown in Graph 2.



Graph 1. Distribution of patients with coagulopathy on admission, 24 hours after, and 48 hours after the admission



Graph 2. Number of patients with coagulation disorders compared to prehospital fluid administration

In the examined groups, there was no difference in gender and age distribution as well as in the values of GCS on admission.

Pearson’s correlation analysis showed that in terms of survival, there was no significant difference between the groups (group A OR 37 CI 0.11-1,27; group B OR 0,48 CI 0,16-1,49; group C OR 0,69, CI 0,24-1,98), but it also indicated that prehospital fluid administered in a larger amount was in the negative correlation with the treatment outcome (-0,240).

Discussion

The mechanism of development of coagulopathy after TBI is still controversial. It is believed that excessive release of tissue factor (TF) leads to the activation of the mechanisms of blood coagulation. TF, previously known as thromboplastin, is a protein that is localized in subendothelial tissue, leucocytes and platelets (25). A release of TF from the injured brain tissue thus leads to excessive acti-

vation of the mechanism of blood coagulation. A loss of balance between the mechanisms of coagulation, on the one hand, and those of anticoagulation, on the other hand, leads to the development of systemic coagulopathy. Also, it is considered that the level of coagulation is in direct proportion to the serum level of TF (26).

The occurrence of coagulation disorders after an isolated injury of CNS leads to a higher incidence of lethal outcome in patients who exhibit the disorder, which has been confirmed in a number of studies (27). The current theories indicate that liberated TF acts locally on the arterioles and venules forming microthrombi dimension 10-600 micrometers (28), which leads to ischemia of the brain parenchyma near the trauma. In the studies of Stain et al., a significant correlation between severity of ischemic changes and density of intravascular microthrombosis was found (27, 29, 30). The reduction of blood flow in the vicinity of contusion change is also attributed to microthrombosis. The local microthrombosis may occur as a delayed one and is considered to be the main cause of secondary ischemic brain injuries (31). Liberated TF can have its effect also on distant parts of the brain, as well as on distant organs considering that it passes through a damaged blood brain barrier (BBB). In that way, the ischemic changes may develop in almost all organs, thus creating conditions for the development of multiple organ failure syndrome (MOF) (31).

Besides the undeniable correlation with the lethal outcome, there is a clear link between coagulation and increase in intracranial hemorrhagic masses, which leads to a greater damage of the CNS tissue and more severe neurological sequelae (32, 33), but could also lead to the lethal outcome. Allard et al. observed a four-fold increase in mortality (32% compared to 8%) in patients with hemorrhagic progression of the injury, on the successive CT images. Their study found that the greatest risk is associated with those injured patients in whom the aPTT was increased on admission. Other coagulation parameters had lower correlation with progression of hemorrhage (34).

The presence of coagulopathy ranges from 10-86%. It is considered that the reason for the discrepancy lies in the definition of coagulopathy which was accepted by the authors, but also in a common consideration of early and delayed coagulation. One of our study objectives was the analysis of the time of the appearance of coagulation disorders and their correlation with the outcome. In our study, the early coagulopathy, which we defined as a disorder of one of the followed coagulation parameters on admission to the ICU, occurred in 20,7%. After 24 hours, the number of patients with coagulopathy was doubled (20,7% of the patients developed some form of coagulopathy), while on the third day, the occurrence of the disorder was found in additional 7.31% of the patients. Such dynamics of appearance of the disorder was also found in other studies i.e. data from a large German Registry of Patients (34) which are related to 3,000 patients indicating that during the first 24 hours the number of patients with coagulopathy doubled, and that coagulopathy was possible to detect also three days after the trauma (35).

In our study, there was no occurrence of coagulopathy after the third day, although in the available literature one may find data on a possibility of its occurrence even six days after the trauma (36, 37). Such data impose an obligation of subsequent laboratory analysis in relation to dynamics of disorder development.

Our study was designed to perform the analysis among the group with early coagulopathy, the group with coagulopathy detected after 24 hours, and the group where coagulopathy occurred after 48 hours, but also to make a correlation with the outcome. In terms of survival, there was no statistically significant difference between the groups of patients with early coagulopathy and both groups with delayed coagulopathy (the group with early coagulopathy on admission OR 37 CI 0.11-1,27; the group with delayed coagulopathy after 24 hours OR 0,48 CI 0,16 - 1,49; the group with delayed coagulopathy after 48 hours OR 0,69, CI 0,24-1,98). Our results show that the presence of coagulopathy is sufficient, while dynamics of its occurrence does not affect the appearance of undesirable outcome.

Our data showed that prehospital administration of 1,500 ml of fluid was associated with increased occurrence of coagulation disorders, while Pearson's correlation analysis showed that the amount of prehospital administered fluid was in a negative correlation with the survival (-0,240).

Treatment of patients with confirmed TBI involves treatment that includes prevention of secondary brain injuries. That means maneuvers which increase the arterial pressure, since even short episodes of hypotension are associated with significantly poorer prognosis (38). However, the excessive administration of fluids also has adverse effects probably due to dilution of coagulation factors, which leads to the development of a state similar to DIC and also correlates with poor outcome. Patients who were administered prehospital fluid had worse prognosis compared to the group of patients who did not receive prehospital fluid. Data presented by Meagele et al. (24) among other demonstrate that prehospital administration of more than 2,000 ml of fluid is associated with more frequent occurrence of coagulation disorder. Our study determined that administration of more than 1,500 ml of fluid is associated with more frequent occurrence of coagulation disorders and with poor outcome. The lack of our study is in the absence of data on the values of TA during transportation so that it is not possible to discuss the reasons for prehospital administration of fluids. Current recommendations suggest that in patients with TBI prehospital maintenance of systolic blood pressure above 110 mmHg is necessary. Yet, for definitive determination of desired value of TA, more extensive study is required.

Conclusion

The results of our studies have confirmed the correlation of coagulation abnormalities with the lethal outcome in patients with TBI, regardless of the chronology of its creation. Early or postponed coagulation disorder is directly connected with increased

mortality. This conclusion imposes an obligation of a regular, routine control coagulation status. Prehospital condition of the patient often requires

the use of physiological solution. However, if the situation allows, it is desirable to control the intake of fluids and limit their amount to 1500-2000ml.

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Originalni rad

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doi:10.5633/amm.2018.0201**POREMEĆAJ KOAGULACIONE FUNKCIJE NAKON
NEPENETRANTNIH POVREDA MOZGA***Miša Radisavljević^{1,3}, Nebojša Stojanović^{1,3}, Mirjana Radisavljević²,
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Izolovana nepenetrantna povreda mozga (TBI) često se povezuje sa abnormalnostima koagulacionih parametara. Prehospitalno data tečnost, koja prelazi 2.000 ml, može biti povezana sa poremećajima koagulacije kod bolesnika sa TBI. Cilj ove studije bio je da se ispita učestalost pojave poremećaja koagulacije i da se uspostavi odnos sa ishodom, kao i da se uspostavi korelacija između prehospitalno administrirane tečnosti i pojave poremećaja koagulacionih parametara.

Studija je obuhvatila 82 bolesnika sa izolovanom povredom mozga. Parametri koagulacije su definisani korišćenjem vrednost PT, apt i trombocita. Takođe, analizirali smo povezanost prehospitalno ordinirane tečnosti i pojave koagulacionih poremećaja.

Pirsonova analiza korelacije je pokazala da u pogledu preživljavanja nije bilo značajne razlike između grupa (grupa A ili 37 CI 0,11-1,27; grupe B ili 0,48 CI 0,16-1,49; grupi C ili 0,69, CI 0,24-1,98), ali je, takođe, ukazala da je prehospitalno ordinirana tečnost u količini većoj od 1500 ml u negativnoj korelaciji sa rezultatima lečenja (-0,240).

Rezultati naših istraživanja potvrdili su povezanost poremećaja koagulacije sa smrtnim ishodom kod bolesnika sa TBI. Administracija više od 1500 ml tečnosti je povezana sa češćim pojavama poremećaja koagulacije i sa lošim ishodom.

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Ključne reči: nepenetrantna povreda mozga, poremećaj koagulacije