CLINICAL STUDY

The use of controlled mild hypothermia and immune system status in patients with severe brain injury

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Abstract

Introduction: **Severe brain injuries pose one of the most important problems on our health care because of their high morbidity and mortality.**
Material and methods: **A group of 89 patients after severe brain injury (Glasgow Coma Scale≤8) was included into our research of detecting the changes of immune system parameters and their relation to the application of mild hypothermia during the early period after the insult.**
Results: **In both of the groups CD3+ and CD4+ lymphocytic levels decreased significantly after the insult and gradually got to normal (p<0.01). The NK cells levels have changed in correlation with the course of infection. Immunoglobulin (IgA, IgG) levels were normal or slightly increased. IgM levels changes had a close relation to the occurrence of inflammatory complications, especially that of pneumonia (p<0.01). The most surprising moment in our research was the level of IgE antibodies. They had been high and got even higher. They achieved the values typical for atopic reactions or parasitic diseases.**
77.52 % of the patients with decreased parameters of immune system developed extra cranial complications. Immune system disorders appeared more frequently in the patients with lower Glasgow Coma Scale after admission (p<0.01). The application of mild hypothermia caused an unimportant increase in extra cranial complications (p>0.05) having no relation to immunity disorders. ***Conclusion:*** **Intensive treatment of intracranial hypertension fundamentally affects results of our treatment (Glasgow Outcome Score). The application of controlled mild hypothermia doesn't escalate the occurrence of extra cranial inflammatory complications after severe brain injury** ***(Tab. 2, Fig. 11, Ref. 15)*****.**
Key words: immune system, severe brain injuries, controlled mild hypothermia.

Severe brain injuries currently pose one of the most important problems on our health care because of their high morbidity and mortality. 25 % of patients become severely disabled, 5 % end up vegetative and about 40 % of patients die. In addition to their medical importance (diagnosis, therapy), also the economic expenses related to temporary or permanent disability can play a notable role. Severe brain injuries (GCS ≤8) mostly occur at the age between 10 and 30 years.

The severity of brain injuries is determined by the extent of primary and secondary ischemic damage (1). There are a lot of other factors, which can definitely debase the outcome. We can hardly prevent the primary brain lesion, whereas there are some ways to influence the secondary lesions.

The breaking points of accomplishing the success in therapy reside in early surgical intervention as well as in the prevention of secondary ischemic damage by assuring adequate cerebral perfusion pressure of levels over 60 mmHg (2, 3). In many cases, despite the fact that no mistakes seem to have been done during the therapy, there are many patients ending up with bad outcome (4). Recently some promising therapeutic methods have been introduced increasing the possibility of improving our results. Controlled mild hypothermia seems to be a promising way to reduce the influence of secondary brain damage by reducing ICP levels and enhancing CPP (5, 6). It is strongly believed that con-

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Tab. 1. Monitored parameters of immune system.

Cellular parameters	CD3+, CD4+, CD8+, CD14+, CD16+,CD19+, CD20+, CD25+, CD45+, CD56+, CD69+, HLA DR, CD45dim+, CD3+25+, CD3+69+, CD3+HLA DR+, CD4+/CD8+
Humoral parameters	IgM, IgG, IgA, IgE
Other parameters	CRP, C3, C4, procalcitonin, ceruloplasmin, α_1 antitrypsin, (s)α_2 macroglobulin

trolled mild hypothermia can play an important role in cytoprotection. In spite of this fact, there are some studies reporting controversial results in coincidence with hypothermia.

The relation between the central nervous system and immune system has been well known for years. In our previous work we demonstrated the influence of severe brain injuries on immune system disorders represented by high occurrence of extra cranial inflammatory complications (7). Now we would like to determine the role of controlled mild hypothermia in coincidence with immune disorders and in the occurrence of extra cranial inflammatory complications in patients after severe brain injury.

Material and methods

A group of 89 patients with severe brain injury admitted at the Dpt of Neurosurgery underwent our study. They have been divided randomly into two groups, one group treated by hypothermia (p=28) and another without hypothermic treatment (p=61, most of these patients were analyzed retrospectively). The age of examined patients was 19–79 years, median 54 years. There were various types of brain damage (subdural haematoma – 43 (48 %), intracerebral haematoma – 37 (42 %), epidural haematoma – 9 (10 %). The patients have been treated conservatively or surgically. The groups have been analyzed in a prospective study. All patients underwent the investigation of cellular and humoral immune parameters as well as classical and differential blood counts repeated every three days till their discharge (Tab. 1). These investigations were performed at biochemical and flow-cytometric laboratories at the Department of Haematologic Oncology.

In the group treated with hypothermia, the process was started as soon as possible and it took 72 hours. We applied extra corporal hypothermia by means of Hypo 1 apparatus, which contains two mattresses with circulating cold water. The aim of this procedure was to reach the temperature of 34 °C. It was periodically controlled by taking rectal temperature. After 72 hours, the patients were passively warmed-up to reach normothermia. The intensive care of these patients was performed in compliance with the international standards for severe head injuries.

Furthermore, the levels of ICP, CPP and MAP were monitored continuously.

The results were statistically processed (Mann–Whitney U test, Wilcoxon Matched Pairs test). Moreover we evaluated the clinical changes during hospitalization using the Glasgow Coma Scale (GCS) and we recorded all complications arising

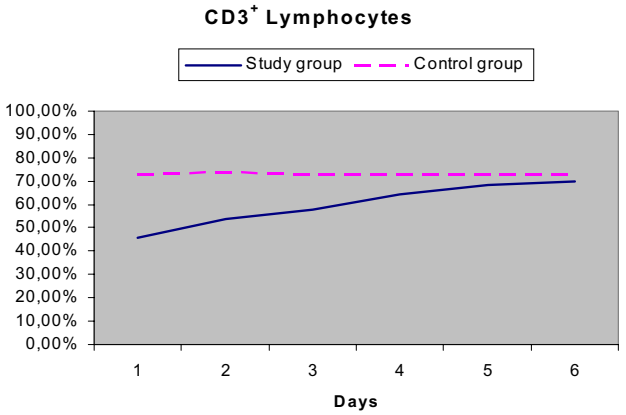

Fig. 1. CD3+ lymphocytes changes. CD3+ Lymphocytes right after the insult and their gradual normalization (p<0.01) during the hospitalization when compared to the levels of CD3+ lymphocytes in a group of healthy volunteers.

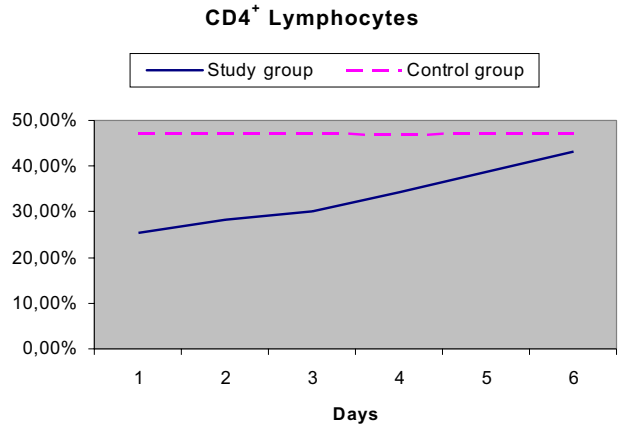

Fig. 2. CD4+ Lymphocytes changes. CD4+ Lymphocytes levels right after the insult and their gradual normalization (p<0.01) during the hospitalization when compared to the levels of CD4+ lymphocytes levels in the group of healthy volunteers.

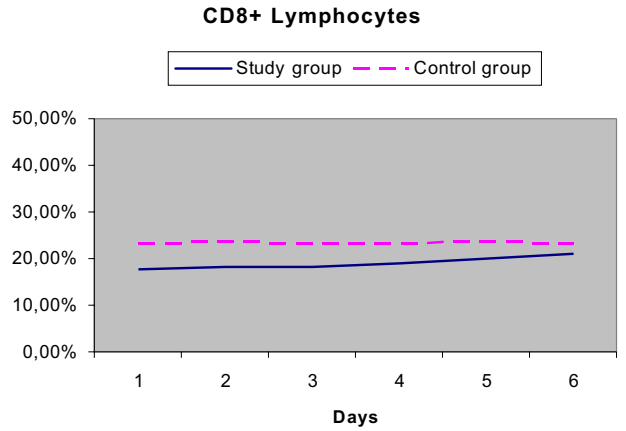

Fig. 3. CD8+ Lymphocytes changes. CD8+ Lymphocytes levels right after the insult and their gradual normalization (p<0,01) during the hospitalization when compared to the levels of CD8+ lymphocytes in the group of healthy volunteers.

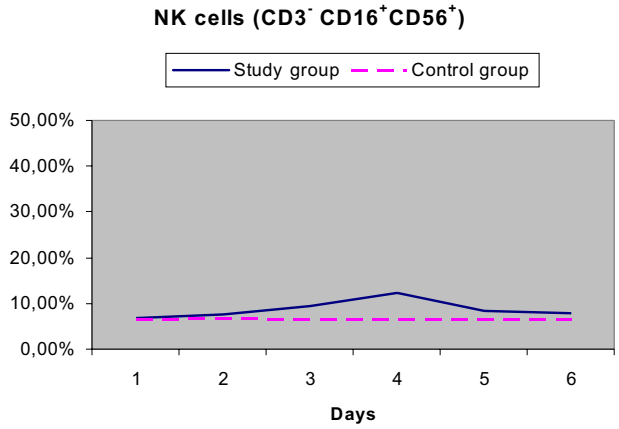

Fig. 4. NK cells levels changes. NK cells levels and their changes ($p<0.01$) during hospitalization when compared to NK cells levels in the group of healthy volunteers.

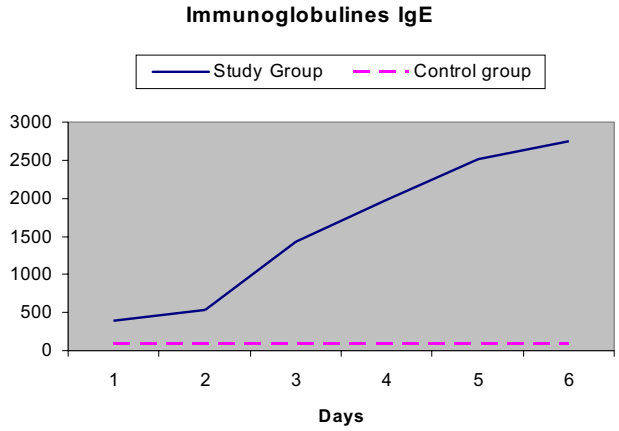

Fig. 5. IgE levels changes. Multiple elevation ($p<0.01$) of IgE levels in the group of patients after severe head injury compared to normal IgE levels.

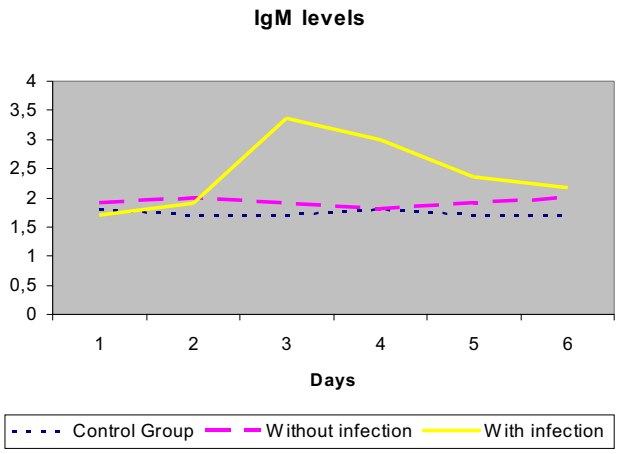

Fig. 6. IgM levels changes. IgM levels changes ($p<0.01$) in patients with head injuries complicated by infection when compared with infection-free patients and healthy volunteers.

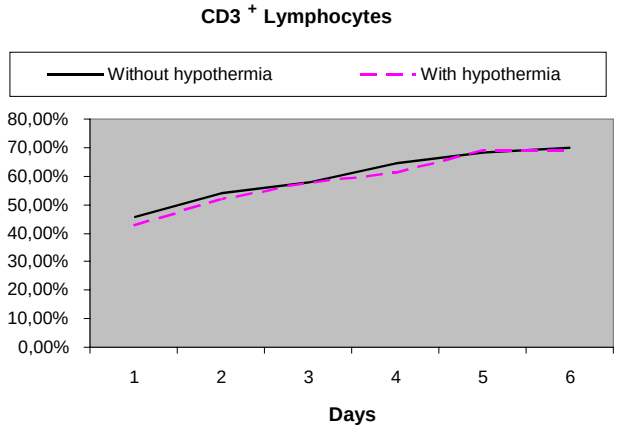

Fig. 7. CD3+ lymphocytes changes due to controlled mild hypothermia.

during our treatment. The whole group was retrospectively analyzed after six months by applying the Glasgow Outcome Score (favourable outcome = good recovery + moderate disability, unfavourable outcome = severe disability + vegetative status + death). In our group – favorable outcome in 40 pts (44.95 %), unfavorable outcome (including death) in 49 pts (55.05 %); in 36 pts 44.04 %.

Results

According to the Glasgow Outcome Score, 49 patients (55.05 %) ended their hospitalization with unfavourable outcome, the mortality of the whole group was 44.04 % (36 patients). Extra cranial inflammatory complications have occurred in 69 patients (77.52 %) and in some patients we have detected more types of inflammatory complications, namely 92 various types of infections – pneumonia – 44 times (48 %), sepsis – 12 times (12 %), urinary infection – 36 times (40 %) (8, 10).

As far as laboratory parameters are concerned, all patients were anaemic with haemoglobin levels under 110 g/l. Generally, the counts of white body cells were increased in all patients, and their high levels were caused by high levels of granulocytes. On the other hand, in most cases the counts of lymphocytes decreased. All patients had relatively low levels of T-lymphocytes (CD3+, $p<0.01$) (Fig. 1) and helper cells (CD4+, $p<0.01$) (Fig. 2) after admission. Gradually, it came to the increase of these parameters ($p<0.05$). The levels of cytotoxic/suppressor lymphocytes (CD8+) were also decreased after the insult ($p<0.01$) (Fig. 3) as well as the CD4+/CD8+ ratio. Both of these parameters were eventually normalized. The levels of monocytes (CD14+) didn't show any significant changes. The NK cells levels have changed correlating with a course of an infection and it didn't matter on a type of infection (Fig. 4).

Immunoglobulines (IgA, IgG) levels were normal or slightly increased. IgM levels changes have had a close relation to the occurrence of inflammatory complication, especially pneumonia (Fig. 5). IgE values were mostly multiple increased with

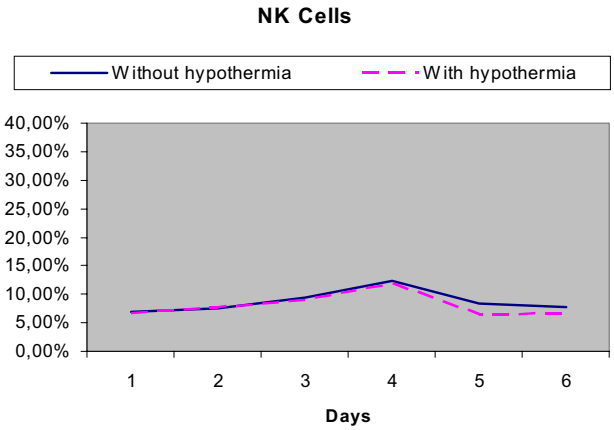

Fig. 8. NK cells levels changes due to hypothermia.

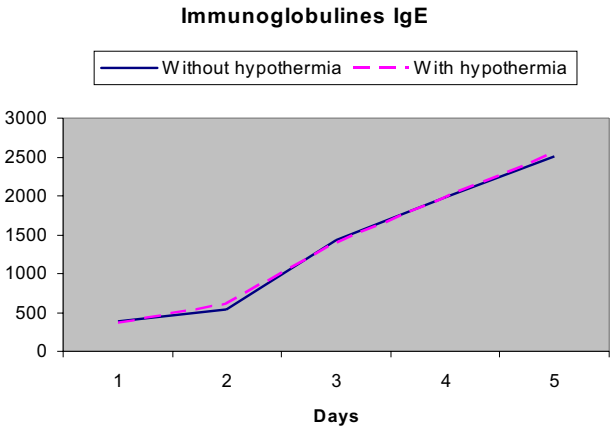

Fig. 9. IgE changes due to mild hypothermia.

a tendency to the further growth during the hospitalization ($p<0.01$) (Fig. 6). They have been raised even until the patients have been discharged. The achieved values looked almost like in patients with allergic reaction or parasitic disease.

From observed acute phase proteins, only CRP levels showed significant changes, they were high after the admission, but they slightly normalized. Other monitored parameters C3, C4 and circulating immunocomplexes didn't show prominent deviations (9).

However, mild controlled hypothermia didn't cause any important immune system disorders (Figs 7, 8, 9) and we didn't prove any impact on occurrence of the extra cranial inflammatory complications (Tab. 2).

Using mild controlled hypothermia has brought an important decrease in ICP levels together with CPP levels elevation ($p<0.01$) (Figs 10, 11). Finally it has led to better GOS – with

Tab. 2. Extracranial complications by using hypothermia.

	Pneumonia	Urinary infection	Sepsis
Without hypothermia	20	17	5
With hypothermia	24	19	7

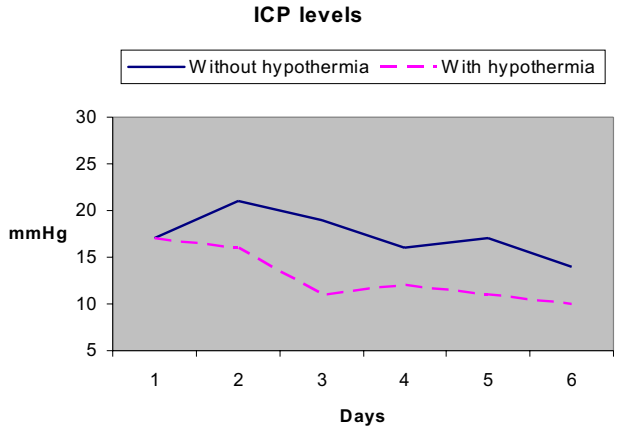

Fig. 10. ICP levels changes in the group of patients with head injuries and the benefit of applied hypothermia on ICP values ($p<0.01$).

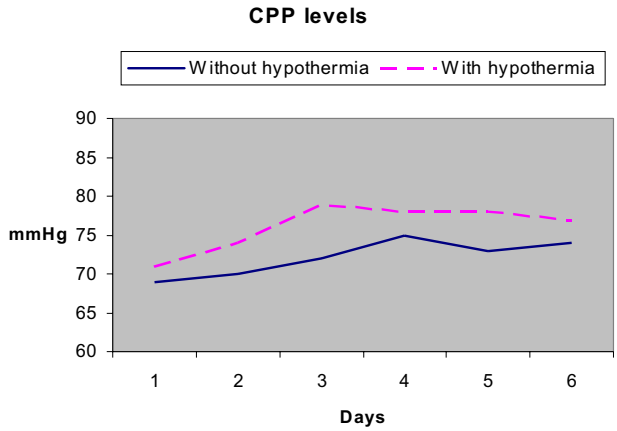

Fig. 11. CCP levels changes in the group of patients with head injuries and the benefit of applied hypothermia on CPP values ($p<0.01$).

hypothermia 4.16, without hypothermia 3.11. Evaluation of the influence of using mild controlled hypothermia on better value of Glasogw Outcome Score after 6 months ($p<0.01$).

Discussion

In our previous study we have demonstrated a close affinity between severe brain injuries and immune system disorders shortly after the insult. A foregoing immunosuppresion can increase the incidence of extra cranial inflammatory complications (7). The sequential normalization of some immune system parameters can possibly be the answer to simultaneous infection (10, 11). However, the dynamics of immune system disorders do not seem to be relevant direct markers determining the prognosis of our brain-injured patients (12,13). On the other hand - low ICP levels and high CPP levels caused by controlled mild hypothermia seem to have a notable influence on improving the prognosis (14). It is strongly believed, that the application of the controlled mild hypothermia is able to reduce the area of ischemic damage of brain tissue. Anyway, we did not find any evidence of significant influence of controlled mild hypothermia on immune

system disorders as well as on the occurrence of the inflammatory extra cranial complications. Threfore, controlled mild hypothermia stays a useful method of high ICP therapy and a promising cytoprotective method (15).

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