Cerebrolysin in traumatic brain injury – A pilot study of a neurotrophic and neurogenic agent in the treatment of acute traumatic brain injury

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Introduction

Numerous in-vitro studies have documented the neuroprotective, neurotrophic and neurogenetic properties of Cerebrolysin, a standardized porcine brain-derived, stabilized, aqueous protein solution, various protein molecules of which can pass the blood-brain barrier. We conducted a double-blind, placebo-controlled, add-on study of Cerebrolysin in the treatment of acute brain injury.

Methods

The study was conducted in 5 centers comprising 44 patients, 22 in each group. Vital parameters and laboratory values were controlled. Half of the patients received 50 ml Cerebrolysin together with 50 ml 0.9 % NaCl solution as i.v. drips. The placebo group was given 100 ml 0.9 % NaCl as i.v. drip, each for 15 minutes for a period of three weeks (21 days). We included patients of both sexes after cranio-cerebral trauma in an age range from 19–60 years with a degree of severity from>4 to<11 points on the Glasgow-Coma-Scale and only within the first 6 hours after injury. As comparative rating instruments we applied the Glasgow-Coma-Scale (GCS) and the Clinical-Global-Impression (CGI) rated by blinded experienced staff, cognitive capacities were assessed by qualified blinded neuropsychologists using the "Short Syndrome Scale" (Syndrom-Kurztest [SKT]). Adverse effects were documented with the DOTES/TWIS scale. These assessments were performed at inclusion and on days 7, 14, 21, 42 and 63. On days 7, 21 and 63, version B of the SKT and on days 14 and 42, version C were applied to prevent possible learning or habituation effects. Statistical computations were based on the "intent-to-treat" principle under application of the non-parametric Mantel-Haenszel-Test and multiple non-parametric u-tests for independent samples, controlled by t-tests. For intra-individual comparisons, the non-parametric Wilcoxon test was applied and categorical variables were calculated by chi-square-test, the statistics following the EU Guidelines for Statistics.

Fig. 1. Severity of illness in CGI during the course of the study

Statistically, the Mantel-Haenszel-Test showed a marginally significant group difference between placebo and Cerebrolysin (p = 0.059) for the severity of disease in the whole study period, indicating a marked and faster improvement with Cerebrolysin.

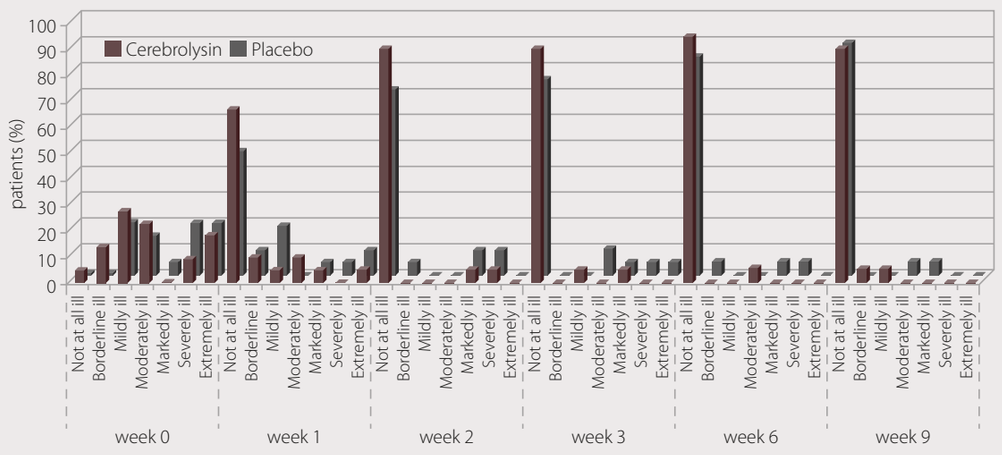
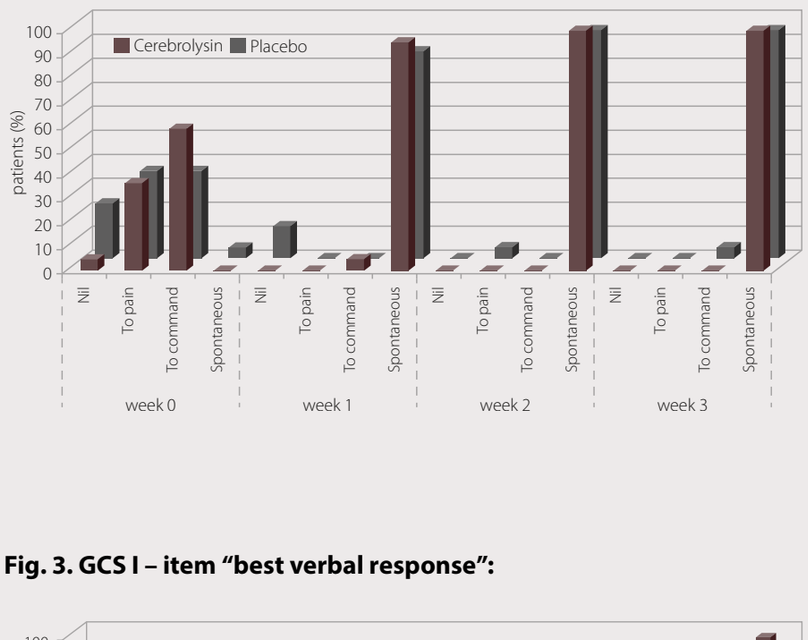
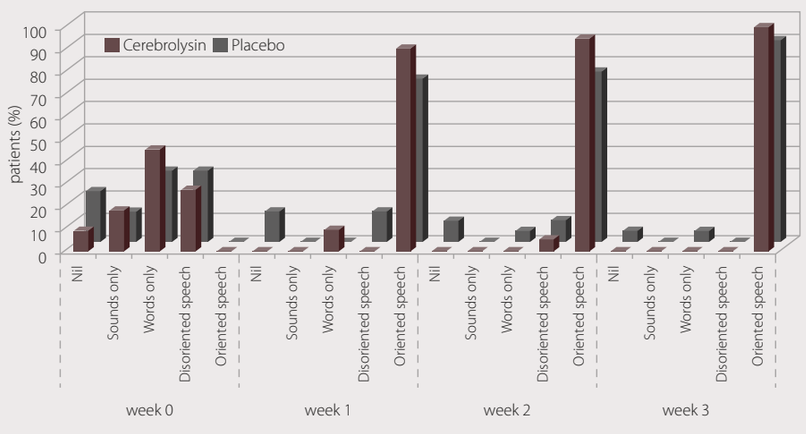


Fig. 2. GCS I – item "eye opening"



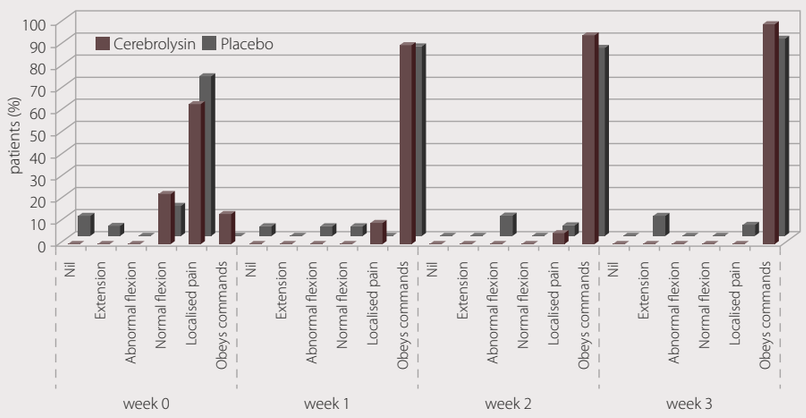
Analysing effects of treatment over time with the Mantel-Haenszel Test showed a statistically significant treatment difference of p = 0.018 on the two-tailed 5 % level. Eye opening to command in weeks 0 and 1 and also spontaneously only in week 1.

Fig. 3. GCS I – item "best verbal response":



The Mantel-Haenszel Test analysis of treatment effects over time again showed a statistically significant treatment difference of p = 0.012 on the two-tailed 5 % level. Similar distribution of results over time for Cerebrolysin and placebo in.

Fig. 4. GCS I – item "best motor response"

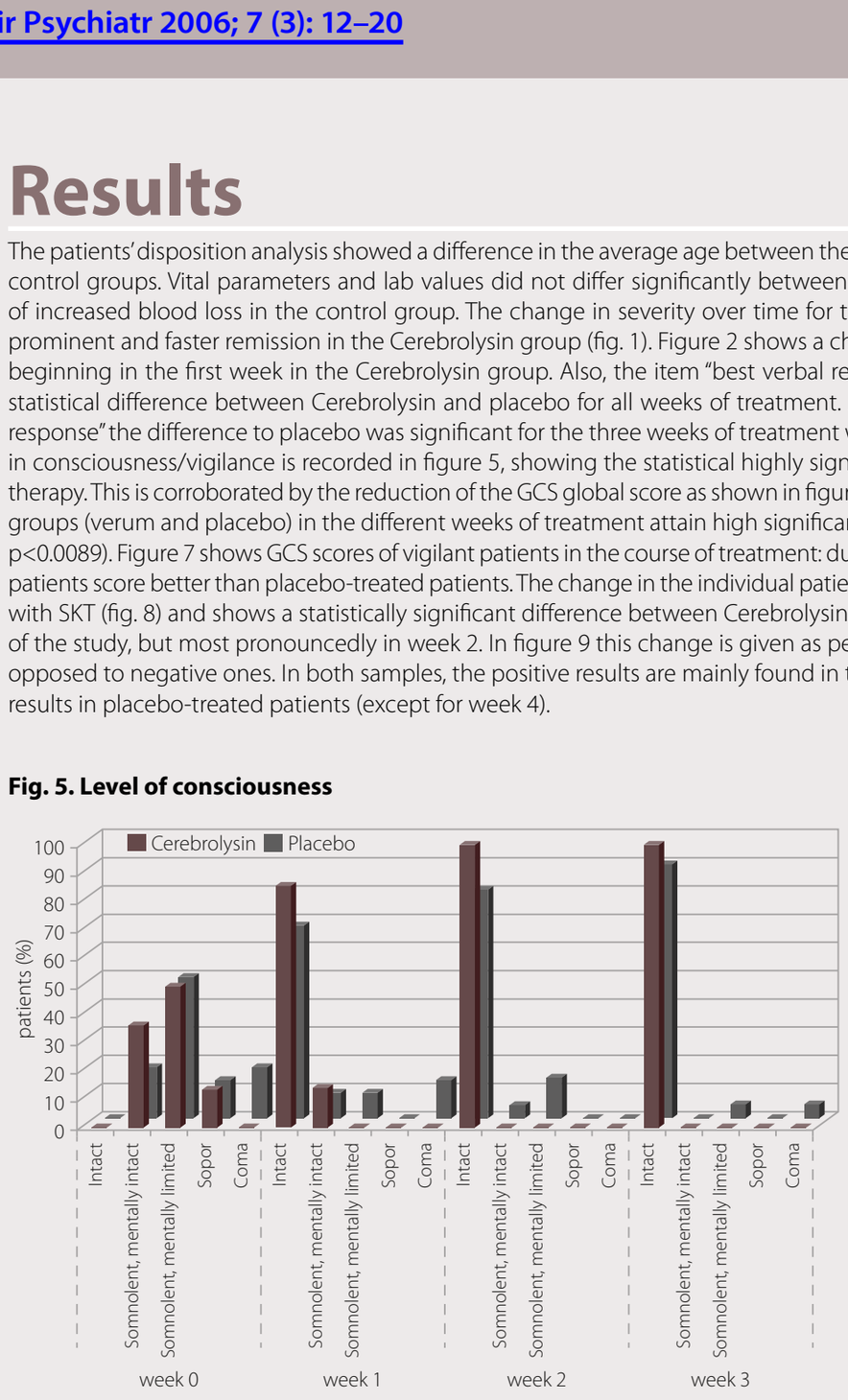


Also, for this item Mantel-Haenszel analysis of treatment effects over time showed a statistically significant treatment difference of p = 0.005 on the two-tailed 1 % level. The scores show a different pattern than the previous ones if flexion, localisation and answer to commands are taken into account.

Results

The patients' disposition analysis showed a difference in the average age between the Cerebrolysin (younger patients) and control groups. Vital parameters and lab values did not differ significantly between the two groups with the exception of increased blood loss in the control group. The change in severity over time for the study shows a significantly more prominent and faster remission in the Cerebrolysin group (fig. 1). Figure 2 shows a change of the GCS item "eye opening", beginning in the first week in the Cerebrolysin group. Also, the item "best verbal response" (fig. 3) showed a significant statistical difference between Cerebrolysin and placebo for all weeks of treatment. Again, for the GCS item "best motor response" the difference to placebo was significant for the three weeks of treatment with Cerebrolysin (fig. 4). The change in consciousness/vigilance is recorded in figure 5, showing the statistical highly significant remission under Cerebrolysin therapy. This is corroborated by the reduction of the GCS global score as shown in figure 6. The differences between the two groups (verum and placebo) in the different weeks of treatment attain high significance (p<0.0091 and also in chi-square p<0.0089). Figure 7 shows GCS scores of vigilant patients in the course of treatment: during the first two weeks, Cerebrolysin patients score better than placebo-treated patients. The change in the individual patient's cognitive performance was rated with SKT (fig. 8) and shows a statistically significant difference between Cerebrolysin and placebo for the whole duration of the study, but most pronouncedly in week 2. In figure 9 this change is given as percent-of-change, positive results are opposed to negative ones. In both samples, the positive results are mainly found in the Cerebrolysin group, the negative results in placebo-treated patients (except for week 4).

Fig. 5. Level of consciousness



Statistical analysis showed no significant group differences at any time but a trend towards significant heterogeneity at baseline (p<0.091, Kruskal-Wallis H-Test). However, Mantel-Haenszel analysis of effects of treatment over time showed a statistically significant treatment difference of p = 0.0003 on the two-tailed 0.1 % level, indicating a swifter recovery under Cerebrolysin.

Fig. 6. GCS scores for overall level of consciousness

Reduction of impaired consciousness over time of treatment. Differences between week 0 and weeks 1, 2 and 3 all p<0.001. Difference placebo, Cerebrolysin CHI-square p<0.0089.

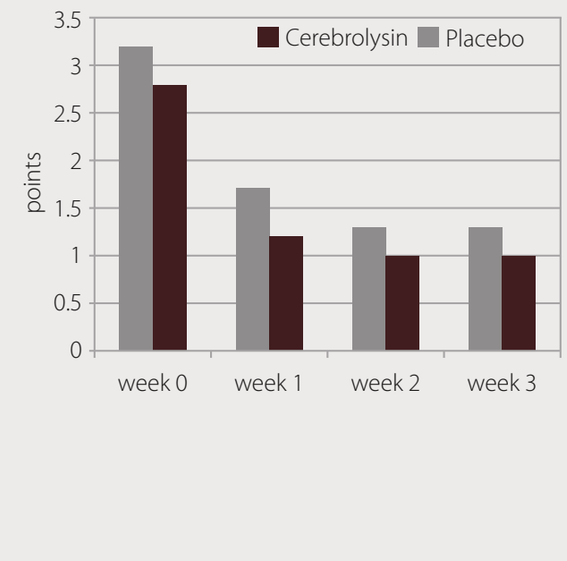


Fig. 7. Augmentation of number of cases (percent) with unimpaired consciousness in GCS over time of treatment

Swift, early recovery in weeks 0–2 under Cerebrolysin.

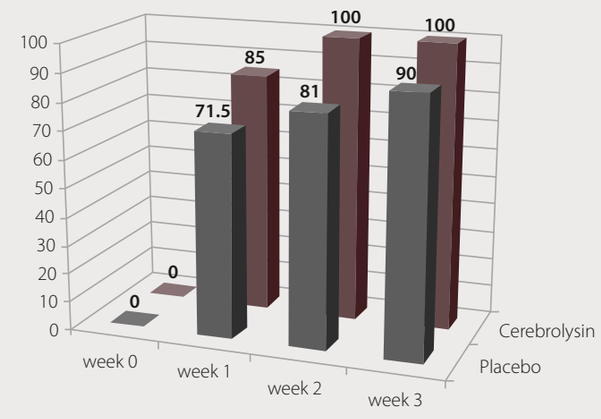


Fig. 8. Statically significant change in points of SKT in placebo- andCerebrolysin-treated patients

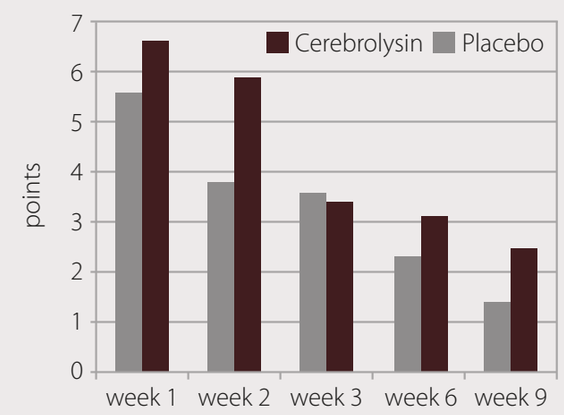
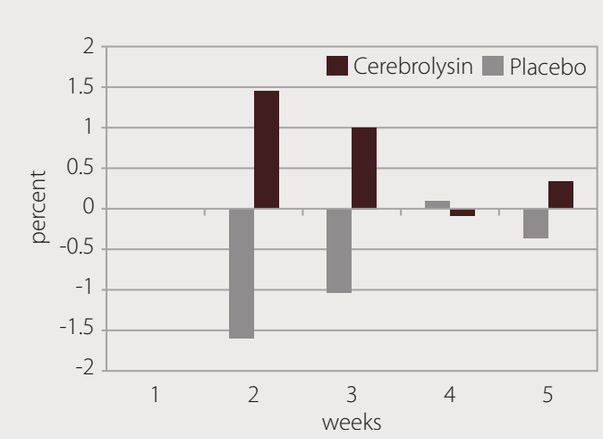


Fig. 9. Differences in percent of improvement (+ side of X-axis = increase of positive ratings) and percentage of negative results (– side of X-axis)



Conclusions

Optimal treatment of brain trauma should ideally attain several goals: in acute treatment, a reduction of the development of cytotoxic material should be supported, thus effecting a stabilization of exposed neurons. In a longer perspective, the optimization of rehabilitation is a paramount issue. As all measures in rehabilitation are learning processes, the pharmacological support of these mechanisms is most important and the differential activity of Cerebrolysin seems to support the physiological plasticity of neurons, which by itself is a central structural feature of neurons in learning processes. Reverting to the great scope of the problems connected with traumatic brain lesions, we strongly suggest a similar study on a larger scale to test our hypotheses and our results.

Related references

1. Original article: J Neurol Neurochirurgie Psychiatrie 2006;7:12-20