

Preliminary Results of Randomized Controlled Study on Decompressive Craniectomy in Treatment of Malignant Middle Cerebral Artery Stroke

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Summary. *Background and Objective.* Studies on decompressive craniectomy (DCE) after a malignant middle cerebral artery (MCA) stroke in selected population show an increased probability of survival without increasing the number of very severely disabled. Cerebral infarct volume (CIV) as a triage criterion for performing surgery has not been discussed in literature. The aim of this study was to investigate the value of CIV and initial National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS) scores as possible triage criteria in the surgical treatment of patients with “malignant” MCA stroke.

Material and Methods. According to the study protocol, 28 patients with a malignant MCA stroke were included and analyzed prospectively. The patients were randomly divided either into the DCE plus best medical treatment (BMT) group or BMT alone group. CIV and NIHSS and GCS scores were measured at time of enrollment in every case. Clinical outcome was evaluated 1 year after the treatment.

Results. Six patients survived: 5 in the DCE group (none of them was older than 60 years) and 1 in the BMT group ($P=0.03/0.06$). Among survivors, none had a cerebral infarct volume of more than 390 cm^3 ($P=0.05$). All survivors in the DCE group had favorable outcomes. There was no significant difference in the NIHSS and GCS scores between the groups and survivors/nonsurvivors ($P>0.05$).

Conclusions. Decompressive surgery in the selected patients is likely to increase the probability of survival with a favorable outcome without increasing the number of severely disabled survivors. Patients with CIV of more than 390 cm^3 may be bad candidates for DCE, and the prognosis is likely to be bad regardless the treatment strategy. The initial NIHSS and GCS scores did not prove any prognostic value in outcome.

Introduction

The management of ischemic stroke has improved significantly over the past decades. Large multicentre trials and studies have shown many evidence-based improvements in stroke care (such as intravenous thrombolysis, anticoagulants, antiplatelet agents, etc.) successfully introduced and used on a daily basis. However, despite all advances, stroke care is still one of the most challenging tasks in neurology and neurosurgery, and stroke remains the second most common cause of death worldwide (1).

There is a subdivision (up to 15%) of stroke patients (1–6) who deteriorate rapidly after hospital admission for cerebral infarction; when patients are treated conservatively, the treatment outcome is poor with a mortality rate reaching 80% (1, 2–4, 6, 7), and survivors remain severely disabled (7). The involvement of the entire middle cerebral artery

(MCA) territory produces the most devastating, massive hemispheric, space-occupying supratentorial infarct, which is known as a “malignant” MCA stroke. In such cases, most patients die within 1 week (1–8) due to brain herniation caused by infarct-related, space-occupying edema.

Several medical therapies, including endotracheal intubation, osmotherapy, barbiturates, steroids, hyperventilation, and blood pressure control, have been proposed to reduce the development of brain edema and elevated intracranial pressure, but so far, they have not proven to reduce mortality or disability (1–7). Several reports suggest that these therapies can even be detrimental (6).

Due to limitations of medical therapies, decompressive craniectomy (DCE) with duraplasty may ameliorate the effects of infarct-related edema and has been proposed as a surgical option for those experiencing a large-volume MCA stroke. The procedure has been known since the middle of the 20th century, but because of limitations in postopera-

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tive critical care, it was rarely performed before the 1990s. With many advances in postoperative critical care, there has been a resurgence of interest in DCE over the last 20 years. The rationale of this therapy is to create a compensatory space to accommodate the swollen brain, thus preventing the death spiral (vicious circle of extensive edema and further infarction) and thereby normalizing intracranial pressure and restoring the midline position of the brain stem and the diencephalon.

By now, there is still limited evidence regarding the efficiency of DCE. The results of recently done randomized controlled trials (RCTs) – DECIMAL, DESTINY, and HAMLET – exploring the impact of early decompressive surgery on mortality and functional outcome after malignant MCA stroke in a selected population have clearly shown an increased probability of survival without an increase in the number of very severely disabled (modified Rankin Scale [mRS] of 5) survivors (2, 3). Whereas most clinicians agree that the procedure is probably life-saving, the best indications for application of DCE are still far from clear, and the decision to perform DCE is still done on an individual basis in every patient. At the same time, cerebral infarct volume (CIV) as a triage criterion for performing surgery is not discussed in international literature. The team of neurosurgeons at Pauls Stradins Clinical University Hospital has initiated a prospective randomized controlled trial on decompressive craniotomies in the selected patients with a “malignant” MCA stroke. The aim of study was to investigate the value of CIV and the initial scores of the National Institutes of Health Stroke Scale (NIHSS) and the Glasgow Coma Scale (GCS) as the possible triage criteria in the surgical treatment of patients with a “malignant” MCA stroke.

Material and Methods

A sequential design-based, prospective, randomized, controlled trial was carried out.

Twenty-eight patients were prospectively analyzed during the period 2009–2012. The inclusion criteria into the study were as follows: age of at least 18 years of both sexes, major space-occupying cerebral infarction of at least 50% of the MCA territory as defined by computed tomography (CT) and/or magnetic resonance imaging (MRI) with or without additional infarction in the territory of the anterior or posterior cerebral artery on the same side, or cerebral infarct volume (CIV) of $>145 \text{ cm}^3$, with an acute onset of corresponding clinical signs and symptoms (NIHSS score, >15), and no absolute contraindications to perform DCE, and possibility to start surgery within 48 hours from onset. The exclusion criteria were as follows: the mRS score of 2 or more before stroke and other serious prestroke conditions that could affect a clinical course, GCS score of 5 or less, 2 fixed dilated pupils, known co-

agulopathy or systemic bleeding disorder, and contraindication for anesthesia. Patients were randomly divided (one-by-one randomization of patients who fulfilled the inclusion criteria) either into the DCE plus best medical treatment group or the best medical treatment (BMT) alone group. A parenchymal ICP monitoring gauge was implanted only for those in the DCE group, who had no signs of a cerebral midline shift on scans to avoid performing DCE in case if fatal brain edema is not going to develop. Decompression was performed if there were signs of elevated intracranial pressure on scans and clinically or ICP was more than 25 mm Hg for more than 1 hour despite the maximal conservative treatment. The NIHSS and GCS scores at time of surgery (DCE group) or at time of including into the trial (BMT group) were measured in every case. CIV was measured in every case on CT or MRI scans (no later than 3 hours before surgery [DCE]) or including into the trial [BMT]) according to the formula $0.5 \times A \times B \times C$, where A is the largest diameter of the infarct and B is the largest perpendicular diameter. The third vertical diameter (C) was determined by summing the thicknesses of the slices in which the lesion was visible (9).

DCE of at least 12 cm in diameter was done by removing the parts of the frontal, parietal, temporal, and occipital squama with removal of additional temporal bone so that the floor of the middle cerebral fossa could be reached. The wide durotomy was performed, and a dural patch was placed into the incision to enlarge the intradural space. The skin flap was then sutured. The infarcted brain tissue was not resected. Medical management was conducted in either a stroke unit or an intensive care unit (ICU) setting.

Clinical outcome was evaluated 1 year after the treatment and rated on the mRS and was classified as favorable (mRS score, 0–4) and unfavorable (mRS score, 5–6).

Data processing and statistical analysis were done by using the Statistical Package for the Social Sciences (SPSS) program version 18.0 and the MS Excel 2007 software. A statistical comparison of groups was done, and the mean values were calculated. Statistical significance was defined as a *P* value of less than 0.05. The chi-square, Fisher exact, and Student *t* tests were employed to check the statistical significance.

Results

A total of 28 patients with a malignant MCA stroke were included in the trial. The mean age of the patients was 61.5 years (range, 49 to 81 years); 12 (43%) were women. Eleven patients underwent DCE; 13 patients were included in the BMT group.

Three patients underwent DCE surgery during the period of the study, but were not included in the trial due to a time frame violation (they were

operated on later than 100 hours from onset). None of them survived.

There was 1 patient who had a parenchymal ICP monitoring gauge implanted, but no signs of herniation or elevated intracranial pressure developed. Since initially the patient was included in the DCE group, but did not receive decompression surgery, he was observed separately from both groups.

The mean age of the patients in the DCE group was 57.2 years (range, 49 to 67 years) and in the BMT group was 65 years (range, 49 to 81) ($P=0.02$). The mean interval between infarction and surgery was 21 hours (range, 8 to 36) in the DCE group, and the mean interval between infarction and inclusion into the trial was 19 hours (range, 6 to 34) in the BMT group. The mean NIHSS scores were 21.2 (range, 16 to 28) and 20.8 (range from 17 to 24) in the DCE and BMT groups, respectively ($P>0.05$). The mean CIV in the DCE group was 366 cm³ (range, 165 to 623) and 367 cm³ (range, 145 to 598) in the BMT group ($P>0.05$). There was no significant difference in the mean GCS score comparing the DCE and BMT groups (mean, 8.8; range, 6 to 12, versus mean 8.7; range, 7 to 12; $P>0.05$).

The overall survival rate in the DCE group was 45.5% ($n=5$, none of the patients was older than 60 years) and 7.69% in the BMT group ($n=1$) (2-tailed $P=0.03$ by the chi-square test without a Yates correction [$\chi^2=4.531$, $df=1$] and $P=0.06$ by the Fisher exact test). In both the groups, none of the patients with CIV of more 390 cm³ survived (3 patients in the DCE group and 6 in the BMT group) ($P=0.05$). In the subgroup of patients with CIV of 390 cm³ or less, the survival rate was 62.5% and 14.3% in the DCE (5 of 8) and BMT groups (1 of 7), respectively ($P=0.1$).

There was no significant difference in the NIHSS and GCS scores between the groups and survivors/nonsurvivors ($P>0.05$).

Outcome among the survivors in the DCE group was favorable in all cases (3 patients with a mRS score of 3 and 2 with a MRS score of 2). The only survived patient in the BMT group one year after ictus was moderate-to-severe disabled (mRS of 4).

The majority of nonsurvivors in the DCE group died from the typical complications of stroke (pneumonia, urinary tract infections, bedsores, pulmonary embolism, etc.) (10), which were not directly related to brain herniation. The average length of life from onset to death was 26 days in the DCE group and 7.7 days in the BMT group with a statistically significant difference ($P=0.009$).

Discussion

From nowadays internationally available literature focusing on surgical treatment of malignant MCA stroke (case series and published data from randomized controlled trials), it is well known that

decompressive surgery in some patients can be effective in terms of both survival and quality of life (2–5). Despite the efforts made over the last decades in search of the best indications for decompressive surgery, the question whether DCE will be effective or not for a concrete patient is still far from being clear. The analysis of data from the recently done RCTs suggests that decompressive surgery increases the probability of survival to nearly 80% (2–4, 6) and increases the number of patients with a favorable functional outcome after a malignant MCA stroke, at least if they are aged 60 years or less, surgery was undertaken within 48 hours from stroke onset and patient had no significant coexisting diseases (2, 3, 6).

In our trial, the patients aged 60 years and more were also included, and the overall survival rate in the DCE group was much lower (45.5%) than in RCTs (nearly 80%). The benefit of surgery comparing with the best medical treatment in terms of survival in our trial appears to be statistically significant when the standard chi-square test is employed ($P=0.03$), but taking into account small sample size of our trial, the Fisher exact test ($P=0.06$) still highly suggests a benefit of surgery in selected patients. Nonetheless, the study is still ongoing, and hopefully, the benefit of surgery in selected patients will become statistically proven with more patients involved.

Among the survivors in the DCE group, none was older than 60 years (the oldest survivor, 57 years). The survival rate in the DCE subgroup of patients younger than 61 years was 62.5%. Slightly worse results in the DCE subgroup of patients younger than 61 years can be possibly explained by a small number of patients involved.

The difference in age between the groups is recognized as one of the weaknesses of this trial so far. Nonetheless, our results tend to agree with the previous findings from uncontrolled series suggesting that the age of more than 60 years is likely to be a predictor of bad outcome (5). Despite the fact that at the moment there is no evidence from RCTs exploring the impact of DCE on patients aged more than 60 years and age is most likely one of the most powerful predictors of bad outcome (several uncontrolled series demonstrated improved outcomes in patients aged 50 or 60 and less (5, 6), still there is no doubt that DCE can be useful also for very selected patients older than 60 years if they are without significant comorbidities that could limit their survival and/or rehabilitation potential. In general, the effectiveness of DCE in the elderly subpopulation remains questionable, and more data from randomized trials are needed to address this question in the future.

Two patients who did not underwent DCE survived: 1 patient initially assigned to the DCE group, who did not develop the signs of elevated intracranial

pressure or herniation, and a 72-year-old woman in the BMT group, and their survival can be easily explained by the fact that not every patient with an MCA infarct develops fatal brain edema (6, 11) and relatively small CIV (159 and 146 cm³), which is just a little above the widely accepted threshold of 145 cm³ to be considered as a “malignant” MCA stroke (2).

Data from internationally available literature indicate that the mortality rate after a “malignant” MCA stroke if treated only medically is about 80% (1–4, 6, 7, 12–14). In our trial, the mortality rate in the BMT group was even higher (92.31%), which actually is not controversial to the international data, but a slightly higher mortality rate in our study can be explained by a relatively small number of the patients included that does not allow us to make clear conclusions.

In internationally available literature, an MCA stroke is defined as “malignant” if CIV is 145 cm³ or more (2). CIV as an independent criterion whether to perform DCE or not is not discussed in literature. In our trial, we found that in both the groups, none of the patients survived with CIV of more than 390 cm³. The *P* value of this finding (*P*=0.05) is of borderline significance and highly suggests that patients with CIV of >390 cm³ may be bad candidates for DCE (they die due to complications that develop on the background of extremely devastating disease), and surgery done on them only leads to more pain and suffering. More data are needed to support this finding.

However, most of colleagues agree that mortality

alone is not the only important issue; the concern is not only about survival, but also rather about a clinical outcome and quality of life. There is still ongoing discussion about the cutoff of mRS score to be used to distinguish “favorable” outcome from “unfavorable.” The answer to this question becomes even more difficult because our understanding of what patients view as an acceptable outcome may be poor. However, in most of the literature, a favorable outcome is defined as survival without a disastrous outcome, e.g., complete dependency or permanent vegetative state (mRS score of 5) (1–3, 6). Data from RCTs showed that DCE in the selected patients increases the probability of survival without increasing the number of very severely disabled survivors (2, 3, 6). Our findings support the international data – all the survivors in the DCE group had favorable outcomes.

Conclusions

Decompressive surgery in the selected patients is very likely to increase the probability of survival with a favorable outcome without increasing the number of severely disabled survivors. Patients with CIV of more than 390 cm³ may be bad candidates for DCE, and the prognosis is likely to be bad regardless the treatment strategy. Initial NIHSS and GCS scores did not prove any prognostic value in outcome by now. More data from RCTs are needed to support these findings.

Statement of Conflict of Interest

The authors state no conflict of interest.

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