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## TREATMENT OF MALIGNANT MCA INFARCTION

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*Space-occupying malignant middle cerebral artery infarction is one of the most devastating forms of ischemic stroke. Several case series suggested decompressive hemicraniectomy as a life saving therapy, but until recently there has been no proof for this procedure from randomized controlled trials. Recent findings from 2007, and results from pooled analyses of three European trials in 2009 revealed evidence for the benefit of hemicraniectomy. This review focuses on the clinical syndrome, provides information on pathophysiology and imaging modalities, and describes therapeutic options with special regard to decompressive surgery.*

**Key words:** stroke, malignant MCA infarction, hemicraniectomy, decompressive surgery.

*Злокачественный инфаркт мозга в бассейне средней мозговой артерии, сопровождающийся объемным эффектом, является одной из наиболее деструктивных форм ишемического инсульта. Несколько исследований серий случаев предложили декомпрессию гемикраниэктомию в качестве сохраняющей жизнь операции, но до недавнего времени не было доказательств пользы данного вмешательства, полученных в рандомизированных контролируемых испытаниях. Данные, опубликованные в 2007 году и результаты объединенного анализа трех европейских испытаний за 2009 год установили факты в пользу гемикраниэктомии. Данный обзор посвящен клиническому синдрому, содержит информацию по патофизиологии и способам визуализации, а также описывает лечебные подходы с особым вниманием по отношению к декомпрессионной хирургии.*

**Ключевые слова:** инсульт, злокачественный инфаркт СМА, гемикраниэктомия, декомпрессионная хирургия.

### History

The first indication of prehistoric trepanations was provided in 1865 when Squier and colleges discovered skulls of individuals of the pre-Columbian time in whom the surgical removal of part of the cranium had been performed [27]. The survival of patients who underwent even multiple "trephinations" – despite a lack of antibiotics and anesthesia – was based on evidence of callus formation in patients from Cuzco, the capital of the Inca Empire around 1400 AD [2] (Fig. 1). Half a millennium afterwards, in 1894 Annandale first introduced the term "decompressive surgery", and in 1905 Cushing reported on findings of subtemporal and suboccipital decompression to alleviate increased intracranial pressure (ICP), mainly as a palliative procedure in inoperable brain tumors. Cushing predicated this «subtemporal decompressive operation» an usefulness in severe head injury which leads to fatal outcome otherwise [13]. Another thirty years later, Greco for the first time used decompressive surgery for successful treatment of a patient with a space-occupying cerebral infarction [31], and it took until 1968 before the first case series of 9 patients receiving decompressive surgery (yet 67% surviving) was published from Greenwood [32].

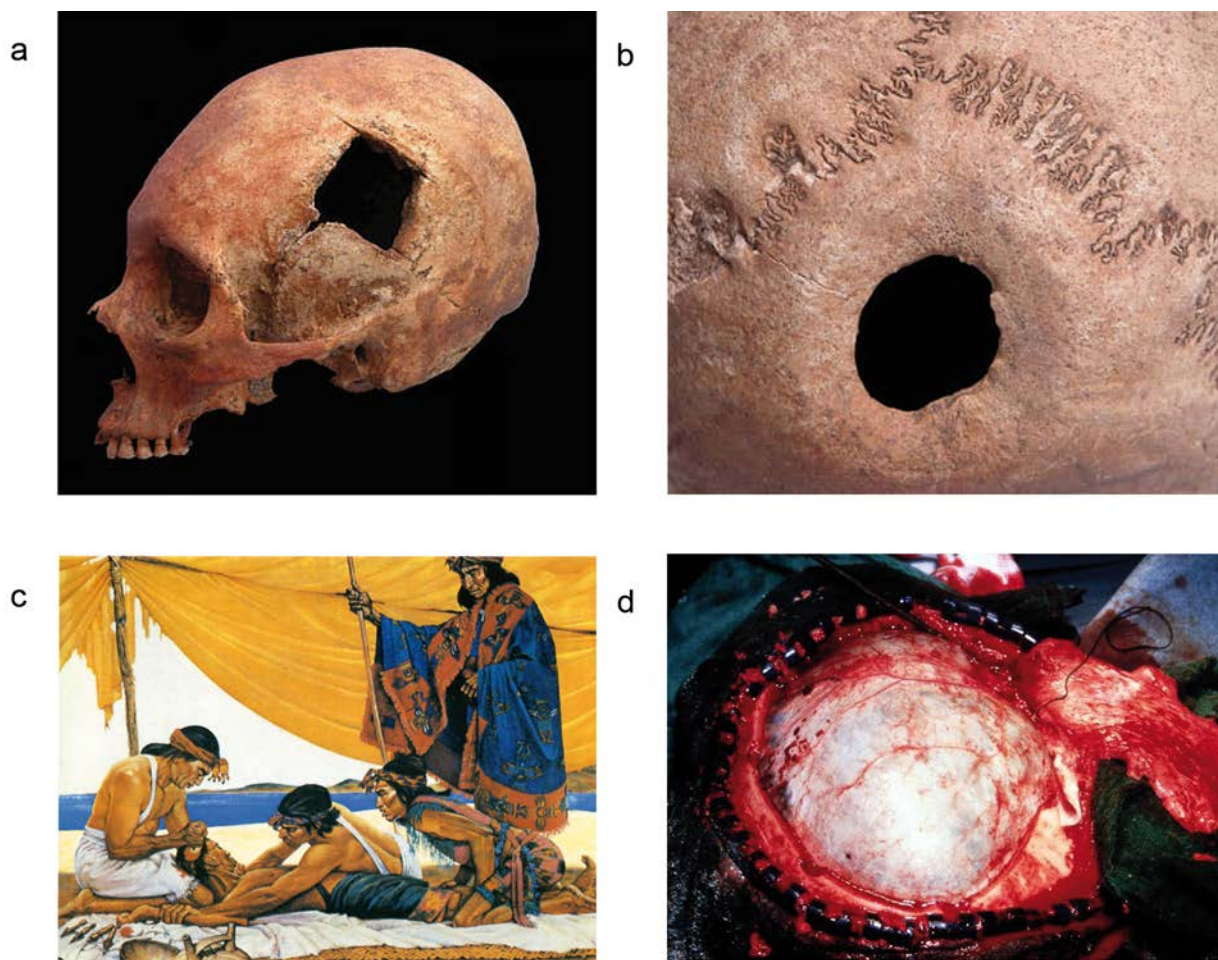
### Clinical syndrome

Patients with subtotal or complete middle cerebral artery (MCA) infarctions typically present with hemiparesis, severe sensory deficits, head- and eye-deviation, hemi-inattention, and, if the dominant hemisphere is involved, global aphasia [36, 63]. Within 24-48 hours patients usually continuously deteriorate in their level of consciousness based on the commonly associated serious brain swelling evolving within 1-5 days after stroke [18, 28]. The resulting increased ICP leads to further destruction of formerly healthy brain tissue that is why the term "malignant MCA infarction" was proposed [39]. These large cerebral infarctions often result in severe shifting of midline structures with subsequent uncal or even transtentorial herniation [58] and were attributed an extremely poor prognosis in over 80% of cases [45, 48, 52, 69]. Over decades the treatment of malignant MCA infarction remained a major unsolved problem in

neurocritical care [28, 57]. Several pharmacological treatment approaches such as osmotic therapy, steroids, hyperventilation, barbiturates, and buffers have been proposed to reduce cerebral edema formation, but up to now none of these therapeutic strategies was supported by adequate evidence of efficacy from clinical trials [4, 10, 35]. Finally, between 2006 and 2009 data from randomized trials were published providing a clear evidence of a dramatic reduction in mortality of patients who underwent decompressive surgery (so-called hemicraniectomy) for treatment of space-occupying MCA infarction.

### Pathophysiology

The pathophysiological processes that lead to a malignant MCA infarction are not yet completely discovered. Generally, a critical reduction of the cerebral blood flow of less than 40% of regular values results in a collapse of membrane potential with consecutive loss of electric functionality of neurons [65]. Brain tissue with perfusion levels below the threshold for structural integrity will irreversibly die. The discontinuation in supply of oxygen and substrate leads to metabolic-based reduction of adenosine-triphosphate (ATP) levels, latter being already completely exhausted after ~10-20 minutes. As a consequence of loss of energy, on one hand the reuptake of the excitatory amino-acid glutamate into the presynaptic astrocytes is deranged, and on the other hand its release into the extracellular space increased because of cell depolarization based on dysfunctional ATP-dependent ion pumps. Scientific approaches using microdialysis identified this raised glutamate to be a very early mediator of ischemia [6, 49, 61]. Moreover, cortical spreading depression and depolarization of peri-ischemic brain tissue may occur and further leads to imbalances of glutamate levels [16]. The elevated glutamate level itself accounts for an increased influx of potassium by activation of voltage-dependent potassium channel and glutamate-NMDA/AMPA receptors. A hyperexcitatory snowball effect of *vice versa* induced glutamate release and potassium overload leads to further calcium-dependent harms and deregulation of the neuronal NO-synthesis resulting in both raised levels of free radicals and



**Figure 1. From history to modernity.**

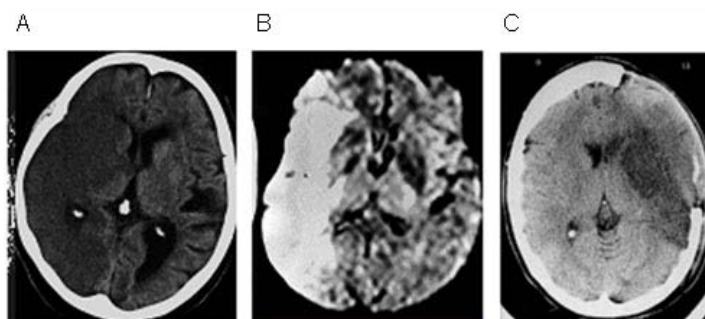
*(A) Rectangular incised trepanation observed in an old adult Inca woman. The cutmarks did not show signs of healing such as remodeling or reactive bone, leading to the conclusion that the individual did not survive the trepanation procedure. (B) Example of an Inca individual who underwent circular trepanation with signs of healing thereafter. (C) Picture of Inca trepanation. (D) Intra-operative view on strained dura after removal of the bone flap during hemispherectomy.*

pathological genes expression and DNA fragmentation [23, 37]. The intracellular calcium-burst activates calpains that destruct the cytoskeleton, the structural protein spectrin, and the microtubule [42]. Taken together, the ischemic cascade mainly constitutes of (i) excitatory phase, followed by (ii) peri-ischemic depolarizations that lead to (iii) inflammation, and finally (iv) apoptosis [17].

#### CT and MR imaging

Cranial computed tomography (CT) is widely used for diagnosis and monitoring of patients with malignant MCA infarction [11, 46, 63] (Fig. 2). However, as repeated CT imaging within the first days may be necessary to demonstrate the definite area of infarction, various studies concentrate on identification of parameters for an early prediction of a malignant course using multi-slice CT, CT-angiography and -perfusion [1, 46]. In this regard, magnetic resonance imaging (MRI) may be of advantage especially in earlier stages of the disease [50, 51]. Generally, a neuroradiological definition of a malignant MCA infarction assumes that at least two thirds of the MCA territory are affected. Other authors predict a severe edema formation even if more than 50% of the rostral MCA territory with involvement of the basal ganglia show ischemic alterations [16, 51]. Additionally, infarctions of the ipsilateral anterior or

posterior cerebral arteries may occur. The definite infarction volume on MRI is evident as hyper-intense lesions on FLAIR sequences, however, in the hyper-acute stages even diffusion-weighted sequences (DWI) reliably predict a malignant MCA infarction if the lesion volume exceeds 145 cm<sup>3</sup> [67].



**Figure 2. Brain imaging findings before and after hemispherectomy in malignant MCA infarction**

*(A) Axial cranial computed tomography 24h after symptom onset. (B) Axial diffusion-weighted magnetic resonance tomography in the acute phase of malignant MCA infarction. (C) Axial computed tomography of another patient with left-sided malignant MCA infarction 2 days after hemispherectomy showing outward swelling of the ischemic brain tissue.*

### Conservative treatment

Patients with large space-occupying MCA infarctions require immediate intensive care in a specialized neurocritical care unit. Sedation, intubation and mechanical ventilation appear indicated early and even electively once the malignant course of the disease has been verified to prevent aspiration and to start invasive treatment [4, 41]. There is a wide variety of pharmacological treatment approaches for prevention and management of the developing brain edema [4]. Administration of osmotic agents, mannitol, glycerol, and hypertonic saline reduces increased ICP and seems to be likely to impact outcome but their efficacy has not been proven in randomized clinical trials yet [4, 10]. Unfortunately, all other approaches, such as barbiturates, hyperventilation, head elevation, THAM (Trishydroxymethylaminomethane) buffer, indomethacin, steroids, and furosemide were not supported by adequate evidence of efficacy and may even be detrimental [3, 4, 62, 66]. Case series on outcome of patients with malignant MCA infarctions who received maximum conservative treatment did not report significant clinical impact of those procedures [39, 45].

Moderate hypothermia, achieved with endovascular catheters and target temperatures between 33-35°C, represents a promising approach for neuroprotection in patients with large MCA infarctions [7, 60]. Hypothermia reduces the cerebral metabolic rate and stabilizes the blood-brain barrier. Reduction of free radicals formation and release of excitatory neurotransmitters results in less brain edema formation, and attenuates the postischemic inflammatory response and apoptosis [30]. Besides various encouraging animal studies that confirmed these findings, clinical observational studies demonstrated a reduced mortality and a good outcome of the surviving patients [21, 26, 29, 30, 43, 47, 59, 70]. In light of a strong association of fever and poorer outcome after stroke [8], these encouraging data on hypothermia however, have to be considered as preliminary findings as up to now there is no evidence from randomized trials on cooling in treatment of malignant MCA infarction.

### Hemicraniectomy

*Surgical techniques and observational clinical studies.* Key idea of decompressive surgery is to remove part of the cranium to allow outward swelling of ischemic brain tissue without compromising healthy brain areas by midline shift and ventricular compression [15, 22]. The consecutive "normalizing" of increased ICP levels results in raised cerebral blood flow and improved cerebral perfusion pressure that leads to better oxygenation of yet healthy brain tissue [5, 10, 38]. Decompressive surgery is based on a hemicraniectomy in combination with a duraplasty [22]. A question mark-shaped skin incision is followed by removal of a bone flap that at least has a diameter of 12 cm including parts of the frontal, parietal, temporal, and occipital squama [9, 56]. After opening of the dura a dural patch is inserted which usually consists of homologous periost or of a temporal fascia. Ischemic brain tissue is not resected. An ICP probe may be inserted for further monitoring. After 6 weeks and up to 6 months the stored or an artificial bone flap is used for reconstituting cranioplasty [34].

A wide majority of clinical observational studies were able to confirm the experimental data on a reduced mortality of patients who underwent decompressive surgery. Admittedly, some trials compared their results to historical patients and lots of the control patients suffered from severe co-morbidity or were of older age. The findings regarding functional outcome and quality of life remain arguable. Several risk factors that predict mortality and poor functional

outcome were identified, age being the strongest one, followed by a low Glasgow coma scale score on admission, involvement of other than the MCA territory, presence of anisocoria, early clinical deterioration, presence of coronary artery disease, and internal carotid artery occlusion [14, 20, 24, 25, 33, 40, 44, 48]. Unfortunately, there are only few data on the long-term outcome and quality of life of patients who received hemicraniectomy [12, 53-55, 68].

*Randomized clinical trials on hemicraniectomy.* Three European trials (i) Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY) [16], (ii) Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarcts (DECIMAL) [67], and (iii) Hemicraniectomy After Middle Cerebral Artery Infarction with Life-threatening Edema Trial (HAMLET) [64] have been published recently. In addition, in 2007 a pooled analysis of DECIMAL, DESTINY, and 23 patients of the ongoing at that time HAMLET trial were published [19]. An updated meta-analysis after completion of HAMLET in 2009 was published [64].

The German DESTINY trial was an open, controlled, prospective, randomized, multicenter study that included patients with a malignant MCA infarction younger than 60 years of age and within 36 hours after symptom onset. Patients were randomized to either surgical plus best medical treatment or to best conservative treatment alone excluding hypothermia. DESTINY was based on a sequential design: as a first endpoint mortality after 30 days was assessed, and randomization was planned to go on until a statistical significance for this endpoint was reached. Patient enrollment would then be interrupted until data of the primary endpoint (dichotomized 6-months functional outcome according to the modified Rankin Scale (mRS) 0-3 versus 4-6) had been collected. Depending on the observed difference in functional outcome, the final sample size would be recalculated for a second explorative trial stage. As a secondary endpoint dichotomization of patients into those who reached mRS 0-4 after one year versus those who showed a mRS of 5-6 was planned. A statistically significant difference in mortality was seen after inclusion of 32 patients. The "Intention to treat"-analysis revealed that the 30 days-mortality was 12% (2/17) in the hemicraniectomy arm and 47% (7/15) in the conservative treatment group ( $p=0.02$ ). The consecutive functional outcome analysis did not show significant differences (47% of the patients in the surgical arm versus 27% in the conservative treatment group reached a mRS of 0-3;  $p=0.23$ ). Indeed, the secondary outcome comparison revealed a significant difference in favour of surgical treatment (76.5% in the surgical arm versus 33.3% of conservatively treated patients reached a mRS of 0-4;  $p=0.01$ ), as did the distribution of the mRS scores ( $p=0.04$ ). After calculation of a sample size for attaining the primary endpoint (necessity of at least 188 randomized patients), DESTINY was stopped because of ethical concerns [16].

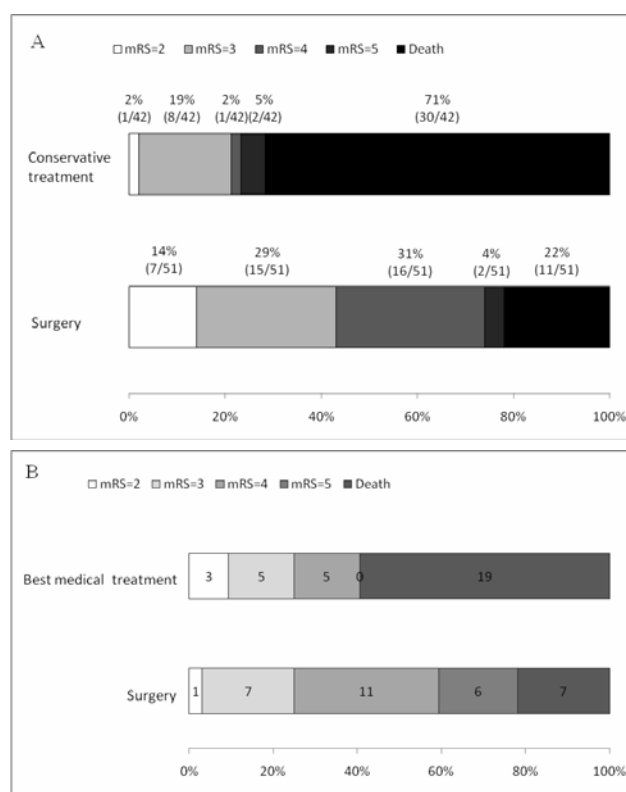
The French DECIMAL trial was similarly resigned and included patients younger than 55 years of age within 30 hours after symptom onset. The primary endpoint in DECIMAL was functional outcome based on the score on the mRS, dichotomized 0-3 versus 4-6 and interim analyses after every four patients. Secondary endpoints included survival and mRS at 6 and 12 months. After randomization of 38 patients the data safety monitoring committee recommended discontinuation of the study because of a planned pooled analysis with the other European trials. At that time-point there was a significant difference in survival (5/20 patients (25%) who received hemicraniectomy versus 14/18 patients (78%) treated conservatively ( $p<0.01$ ) had

died, reflecting an absolute risk reduction of more than 52%). The functional outcome analysis failed to reach significance both in the 6- (mRS  $\geq 3$  in 25% versus 5.6%;  $p=0.18$ ) and 12 months follow-up examination (mRS  $\geq 3$  in 50% versus 22.2%;  $p=0.10$ ) [67].

The Dutch HAMLET trial included patients younger than 60 years of age within 96 hours after symptom onset. The primary endpoint was the functional outcome after 12 months, dichotomized according to the mRS (0-3 versus 4-6). Besides others, secondary endpoints were case fatality and a dichotomized functional outcome analysis (mRS 0-4 versus 5-6). After obtaining the 1-year follow-up outcome data of 50 patients (at that time 64 patients had been recruited), the data monitoring committee recommended discontinuation of the trial as it appeared unlikely to reach significance for the primary outcome measure. Also the secondary outcome measure was negative with respect to functionality on the mRS. However, surgical decompression showed a clear reduction in mortality (21.8% versus 59.3%;  $p=0.002$ ) with an absolute risk reduction of 38% [64].

**Pooled analysis and meta-analysis of DECIMAL, DESTINY, and HAMLET.** In 2007 the results of a pooled analysis of the three European trials (DESTINY, DECIMAL, and 23 patients from HAMLET) were published [10]. For this prospectively planned pooled analysis a maximum "time window" from stroke onset to treatment of 48 hours was adopted. Outcome measures were mortality and functional outcome (mRS) at one year, dichotomized into a mRS of 0-3 versus 4-6, and 0-4 versus 5-6, respectively. Of 93 patients analyzed 51 had received hemicraniectomy and 42 had been assigned to conservative treatment. There was a significantly lower case fatality rate in the surgical group than in the conservative treatment arm (29% versus 78%;  $p<0.01$ ) with an absolute risk reduction of 50%. Regarding the functional outcome, the pooled analysis demonstrated that patients who underwent decompressive surgery significantly more often reached both a mRS  $\leq 3$  (43% versus 21%;  $p=0.014$ ; absolute risk reduction of 23%), and a mRS  $\leq 4$  (75% versus 24%;  $p<0.01$ ; absolute risk reduction of 51%). These data were the basis of a calculation of the numbers needed to treat (NNT). (i) the NNT for survival was 2, irrespective of functional outcome, (ii) the NNT for a mRS  $\leq 3$  was 4, and (iii) the NNT for a mRS  $\leq 4$  was 2. This positive effect of surgery was moreover highly consistent across the three trials. However, there was no difference in the benefit of surgery for neither of predefined subgroups (i) age (above and below 50 years), (ii) presence of aphasia, and (iii) time to randomization (within or beyond 24h) [10].

After completion of HAMLET in 2009, an updated meta-analysis including all patients of DESTINY, DECIMAL, and HAMLET who were randomized within 48 hours after stroke onset focussed on case fatality rate and functional outcome after 12 months [68]. Of altogether 109 patients analyzed, 58 had been assigned to surgery and 51 to conservative treatment. With respect to mortality, the absolute risk reduction achieved with surgical decompression compared to conservative treatment alone was 49.9% (95%-confidence intervals (CI): 33.9-65.9), confirming the previously reported NNT of 2 for prevention of death. There was an absolute risk reduction of 41.9% (CI: 25.2 to 58.6) for an outcome measure mRS  $>4$  when being treated with hemicraniectomy, reflecting a NNT of 2. Yet, the functional outcome analysis of those patients who reached a mRS of three and less revealed a non significant benefit of surgical decompression (23/58 (39.6%) versus 12/51 (23.5%); absolute risk reduction of 16.3% (-0.1-33.1), corresponding to a NNT of 6 patients) (Fig. 3).



**Figure 3. Comparison of outcome after malignant MCA infarction as distributions of the scores on the mRS. Best medical treatment versus hemicraniectomy. (A) Long-term outcome after 12 months according to the pooled analysis of DESTINY, DECIMAL and 23 patients of HAMLET as published in 2007 [19]. Distributions of the scores on the mRS (see text). (B) Long-term outcome after 12 months of the 64 patients of HAMLET [64] (for interpretation see text).**

### Open questions and conclusion

Despite the dramatic improvement in the survival rate of patients who received surgical decompression instead of conservative treatment, there remain some important issues that need to be addressed in the future. They include (i) a potential age limit for surgical decompression (currently analyzed in the DESTINY II trial), (ii) whether patients with involvement of the dominant hemisphere should be operated on, (iii) and the exact time-point of surgery, and accordingly whether a cut-off time exists after which surgery would not be beneficial any longer. Taken together, the three European prospective randomized trials and the pooled-analyses revealed a dramatic increase in survival by decompressive surgery. However, several clinical and ethical questions remain that need to be resolved in future studies.

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