CONTEMPORARY NEUROLOGICAL DILEMMAS

Decompressive surgery for malignant middle cerebral artery territory infarction

A case of complete middle cerebral artery territory infarction associated with some haemorrhagic transformation at 36 hours post onset, and at one day after decompressive surgery. Note the effect of surgery on midline shift and ventricular compression. The patient survived with a Modified Rankin Score of 3. But would the patient have done as well without surgery? Here we present the two opposing views.

Yes, I would do it

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INTRODUCTION: THE SYNDROME AND ITS PROGNOSIS

Early death after acute ischaemic stroke is most frequently caused by space occupying ischaemic brain oedema. With complete middle cerebral artery (MCA) territory infarction, including the basal ganglia, and occasionally additional infarction of the anterior cerebral artery or the posterior cerebral artery territories, the large post ischaemic oedematous infarct may cause mass effect, raised intracranial pressure (ICP), and so herniation and brain death (Hacke *et al.* 1996; Frank 1995; Ropper 1984; Berrouschot *et al.* 1998). Clinically, the patients present with dense hemiplegia, head- and eye-deviation, progressive deterioration of consciousness over the first 24–48 h and reduced ventilatory drive. Herniation occurs between day 2 and day 5 after onset. Because older patients tend to have more brain atrophy, this condition is more frequently seen among patients under 60 years of age.

Brain oedema formation depends on the size of infarct, location of vessel occlusion and state of the collaterals (Hacke *et al.* 1996). Whether recanalization of the occluded artery also contributes to space occupying oedema is still a matter of debate. Prognosis of large MCA or hemispheric infarctions is poor: about 80% die from herniation despite maximum conservative therapy including artificial ventilation, hyperventilation, osmotherapy, barbiturates or tris-buffer solution (Hacke *et al.* 1996; Frank 1995; Ropper 1984). Of the 20% who survive, the outcome is better than one might expect given the large area of infarction: very few patients remain completely dependent, perhaps because they are relatively young (Hacke *et al.* 1996).

With the advent of thrombolytic treatment and the improved organization of stroke services, these patients are more frequently encountered. Severe hyperacute strokes are admitted as possible candidates for thrombolysis, but some are not treated because of early signs of

major infarction (Berrouschot *et al.* 1998). The question is, what to offer patients with this life threatening condition?

NON-INVASIVE MEDICAL INTERVENTION

General measures to treat increased ICP after acute ischaemic stroke include raising the head to a 30 ° angle to improve venous drainage, and avoiding both hyperthermia and hyperglycaemia. Blood pressure should be kept under 200 mm of mercury systolic. Specific antioedematous pharmacological treatment to reduce brain oedema includes osmotherapy with glycerol, mannitol, or hyperotonic saline solutions (Schwab *et al.* 2001; Hacke *et al.* 1994; Schwarz *et al.* 1998; Norris and VC 1986). All these substances work by lowering ICP, but only for a limited time. The same is true for barbiturates. Steroids have not been shown to be beneficial for oedema following ischaemic stroke (Kalia & Yonas 1993).

In my unit, stroke patients requiring artificial ventilation are treated on an intensive care unit (ICU) and receive ventilatory support but there is still debate whether such patients, in particular those with ischaemic stroke, should be treated on an ICU at all. There are also differences in the indication for intubation and ventilation between countries and regions.

DECOMPRESSIVE SURGERY

Decompressive surgery for malignant MCA infarction is not new. In fact, the first studies date back to as early as 1935. Over the past decades, several case reports and smaller retrospective case series have suggested that decompressive surgery is a possible treatment option for massive hemispheric ischaemic stroke. However, no controlled data support its superiority. The rationale of decompressive surgery is to allow extracranial expansion of the oedematous brain tissue and so avoid ventricular compression and horizontal, as well as vertical, brain tissue shifts. This concept is supported by experimental studies showing a dramatic decrease in mortality and substantial tissue salvage (Forsting *et al.* 1995; Dörfler *et al.* 1996). Hemicraniectomy may also reduce intracranial pressure, enhance perfusion pressure and preserve remaining cerebral blood flow.

It was not until 1995, that a large case series was published and, although it included a concurrent control group, sadly enough this was

not a randomized controlled trial (Rieke *et al.* 1995). Nevertheless, in this control group the well-known 80% mortality with maximum conservative treatment was demonstrated, while the mortality in the surgically treated group was only 34%. Among the survivors, the quality of survival was surprisingly good with a median modified Rankin score of 2.6.

Technical details

In a geometrical model it has been shown that the craniectomy should have a diameter of at least 12 cm to allow a significant proportion of brain tissue to shift outside the skull. In addition to this extended craniectomy, a duraplasty is performed. Many surgeons resect the temporal bone down to the skull base. It is still controversial whether infarcted tissue should also be removed. Complications of this surgery include infection, subdural or epidural haematoma and subdural CSF hygroma. All these complications are easily recognizable on the ICU and do not contribute to perioperative mortality in my unit.

When to operate

This is probably the most important question for those who support this treatment. In the past, surgery was frequently only offered in patients who were already herniating – it is no surprise that the outcome wasn't very good. In our first case series, we waited for the first signs of reversible herniation, and a major mid-line shift on brain CT, before surgery was considered (Rieke *et al.* 1995). But, over the past 7 years, our treatment protocol has been substantially changed to allow early recognition of candidates who may be at risk for malignant MCA infarction. We do not wait any more for the first signs of herniation, or for raised ICP readings, before intervening (Schwab *et al.* 1996a; Schwab *et al.* 1998a). Early repeated CT scanning and, more recently, immediate diffusion and perfusion MRI studies, allow us to identify the size of the infarct very early on and, combined with the clinical syndrome of complete MCA infarction, the diagnosis may be made long before any life-threatening swelling occurs. It is true that this policy of pre-emptive intervention may mean that some patients who would have survived anyway undergo surgery. It is the same problem with therapeutic thrombolysis within the 3 h time window where there may be transient ischaemic attack patients who would have recovered without treatment.

Using the strategy of early identification of patients at risk for malignant MCA infarction, a second series of 32 patients has been published, in which the intervention took place on average within the first 24 h of stroke onset (Schwab *et al.* 1998a). Mortality in this cohort was down to less than 20%, and quality of survival was even better with a mean Barthel score of 80 and a median modified Rankin Scale of 2.4. That and the as yet unpublished continuation of the Heidelberg treatment protocol includes early MRI imaging supports the idea of very early intervention with a mortality that is currently less than 20% (Steiner *et al.*, in prep.)

Unfortunately, neither our second study nor the ongoing third study has a control group. Therefore, comparison of outcomes is difficult, as we are dealing with a historical control group that was assembled 7–8 years ago. There may also have been improvement in our general ICU practice leading to a higher survival rate without decompressive surgery. However, there are good reasons to believe that conservative treatment cannot reduce mortality down to as low as 20%, especially if artificial ventilation is not offered.

THE CALL FOR RANDOMIZED TRIALS

In the USA, the NIH is sponsoring a prospective, randomized controlled trial called HEAD-FIRST (hemicraniectomy and durotomy upon deterioration for massive hemispheric infarcts). Presently, although funding has been granted some months ago, to my knowledge no patients have been recruited. I am aware of attempts in other parts of the world to test hemicraniectomy prospectively. For example, in the Netherlands a trial has been proposed that will compare treatment on a normal ward, and in an ICU with decompressive surgery. I am very supportive of randomized trials, although with our own experience of more than 110 surgically treated patients, I would myself find it hard to randomize patients anymore. However, in hospitals where, at the present time, no special treatment is given to the victims of malignant MCA infarction, randomization would offer at least 50% of the patients a chance of receiving treatment that allows decent survival. I completely agree that mortality is important, but it is not the only issue in a trial. Everyone is concerned about allowing poor quality survival in a completely dependent, non-communicative

tive state. But our experience does not support this concern, and that is why over time we have even operated on dominant hemisphere patients – about 25% of our patients are left hemispheric.

If a trial of decompressive surgery in malignant MCA infarction is to be started, we would strongly recommend a case adjudication committee to check that in every randomised patient the infarct syndrome was appropriate, early infarct signs had been detected properly, and that the timing and technique of the intervention was correct. All these are extremely important issues. For example, the surgical results will be massively influenced with bad timing or bad technique (craniectomy too small, no duraplasty, etc.). The knowledge and experience that some centres have now accumulated must be considered in the design of any trial.

However, I am afraid that the same will happen as has already happened with intra-arterial thrombolysis for basilar artery thrombosis. For decades, several groups around the world have been trying to get together a randomized controlled trial, but no one has succeeded in finding enough patients. Meanwhile, in many centres where an acute active stroke programme is run, thrombolytic therapy for basilar artery occlusion is considered the treatment of choice, despite the lack of any randomized data. The same is true for decompressive surgery for cerebellar-space-occupying infarction, although no randomized data are there to support it.

What should physicians do, meanwhile, while waiting for controlled trials to start? First, if a centre has not yet performed decompressive surgery for malignant MCA infarction, they should send neurologists and neurosurgeons to institutions who have experience, get trained, and randomize. However, in centres in which 30 or more patients have been treated successfully, they should continue with their treatment efforts and help others get the experience required

for a good study. By the way, this same approach is also appropriate for another interesting option for the treatment of malignant MCA infarction: controlled moderate hypothermia of 32 °C over three days with slow rewarming (Schwab et al. 1998b; Schwab et al. 1996b).

THE IDEAL STUDY DESIGN?

In my opinion, the ideal design for a randomized trial for the treatment of malignant MCA infarction in a setting where until now even ICU treatment of patients with large infarct was not considered an option, would be a three arm trial – maximum medical treatment on a stroke unit without ventilation vs. complete ICU treatment including ventilation vs. ICU treatment with early decompressive surgery. To allow as many patients as possible to benefit from one of the active treatments, I would prefer a 1-2-2 randomization. One would probably not need more than 15–20 patients per arm to show superiority in mortality in an ICU, with or without surgery, over non-ICU treatment without ventilation. At that point, the conservative treatment arm could be stopped, and the randomization should continue, comparing decompressive surgery and standard ICU treatment with ICU alone.

Since the first draft of this opinion statement was written, and after many decisions taken with my co-workers in Heidelberg and several colleagues from other experimental hospitals in Germany, we have now decided to enter a randomized trial, despite all ethical problems that we may have. We believe that by doing it in an experienced, high-volume centre, a result can be achieved much faster, and this, in the end, beats all ethical concerns.

I am very supportive of randomized trials, although with our own experience of more than 110 surgically treated patients, I would myself find it hard to randomize patients anymore

No wait, more evidence is required!

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The high early case fatality among patients with large, space-occupying cerebral infarctions calls for new, effective treatments. The poor prognosis is, at least in part, a consequence of cerebral oedema, which may cause raised intracranial pressure, herniation, and death (Frank 1995). It is therefore a rational approach, as described by Werner Hacke, to release the restriction of the

dura mater and cranial vault and allow the infarcted brain tissue to swell.

Any new treatment should result in net benefits compared with the old (or 'standard') treatment. However, to find out whether surgical intervention is superior to medical intervention (or even conservative treatment), we need to answer three questions:

- 1 how can we make a valid comparison between surgical intervention and standard medical treatment?
- 2 how do we define and measure 'net benefits'?
- 3 can we generalise the results to the majority of patients with large, space-occupying cerebral infarcts?

HOW DO WE COMPARE THE EFFECTS OF DIFFERENT INTERVENTIONS?

To compare the effects of decompressive surgery and 'standard' medical treatment, we performed a Cochrane systematic review (Morley *et al.* 2002). The search strategy retrieved about 8000 references, of which 27 represented descriptive, non-controlled studies (Table 1). We also found four observational studies involving a comparison between surgical and standard medical treatment (Holtkamp *et al.* 2001; Mori *et al.* 2001; Schwab *et al.* 1998c; Steiger 1991) (Table 2), but no completed randomised controlled trials. Unfortunately, because of variable methodological quality, the four observational studies were inconclusive, and could not give a clear answer to whether decompressive surgery is more effective, equally effective, or less effective than standard medical treatment. We will discuss, in general terms, the limitations of such studies, and encourage clinicians to enter their patients into the on-going randomised controlled trials (Frank *et al.* 1999; Hofmeijer *et al.* 2001).

Bias and systematic error

For a comparison between two treatments to be valid (i.e. whether the observed difference in treatment effect reflects a true difference, and not a spurious one), the comparison must be unbiased and unconfounded, and the play of chance must be ruled out as an alternative explanation for any observed difference (Hennekens & Buring 1987). If some aspect of the design or conduct of a study has introduced a systematic error into the results, bias is said to be present. In the observational studies patients

Table 1 Descriptive studies (without control groups)

Study*	No. of patients	Average age†	No. of survivors	No. with Glasgow Outcome Scale score 4–5‡
Kjellberg 1971	1	—	0	—
Ivamoto 1974	1	49	1	1
Kakita 1976	2	66	0	—
Mracek 1978	2	38	1	1
Rengechary 1981	3	31	3	—
Fujita 1982	10	—	8	7
Young 1982	1	59	1	1
Ueno 1984	7	67	3	—
Saito 1987	7	—	4	—
Kondziolka 1988	3	40	2	—
Ojemann 1988	2	2	—	—
Delashaw 1990	8	56	7	3
Jourdan 1993	7	46	5	5
Kalia 1993	4	34	4	4
Martins 1993	8	62	6	—
Tsuruno 1993	15	63	10	4
Carter 1997	14	49	11	8
Kristensen 1998	1	45	1	—
Mori 1998	4	61	4	1
Sakai 1998	24	64	16	—
Cristofori 1998	2	45	1	—
Koh 1999	8	47	7	4
Lindegaard 1999	1	28	1	1
Sollid 1999	1	61	1	—
Manai 2000	20	17	13	—
Oro 2000	2	34	2	2
van Leusen 2001	3	41	3	1
Total	161	47	121 (75%)	56 (35%)

*Details of the studies can be found in (Morley *et al.* 2002); †Average age is calculated as the sum of the ages known, divided by the number of cases where the age is known; ‡Favourable outcome

	Surgical treatment N (%)	Medical treatment N (%)
Mori 2001		
No. of patients	19	15
Average age (years)*	63	72
No. of survivors	16 (84)	5 (33)
No. with Glasgow Outcome Scale 4–5†	3 (16)	0 (0)
Holtkamp 2001		
No. of patients	12	12
Average age (years)*	65	73
No. of survivors	8 (67)	2 (17)
No. with Glasgow Outcome Scale 4–5†	0 (0)	0 (0)
Schwab 1998		
No. of patients	63	55
Average age (years)*	50	56
No. of survivors	47 (75)	12 (22)
No. with Glasgow Outcome Scale 4–5†	17 (27)	–
Steiger 1991		
No. of patients	8	7
Average age (years)*	–	–
No. of survivors	6 (75)	0 (0)
No. with Glasgow Outcome Scale 4–5†	4 (59)	0 (0)

Average age is calculated as the sum of the ages known, divided by the number of cases where the age is known; †Favourable outcome.

Table 2 Observational studies (with non-randomised control groups)

may have been (unintentionally) selected differently for surgical and 'standard' treatment. Indeed, in many studies there was explicit selection of patients for surgery on the basis of age, stroke severity, and lack of comorbidity (Holtkamp et al. 2001; Mori et al. 2001; Schwab et al. 1998c; Steiger 1991). If these differences are related to outcome (e.g. younger and fitter patients being selected for surgery), then a 'selection bias' exists. Similarly, if the manner in which information is obtained, reported, or interpreted is different between the groups in the study, an inaccurate impression of the true difference in effect may be obtained (i.e. 'observation bias'). The investigators in the studies performed to date have not been blinded to the allocated treatment. They may therefore (unintentionally) have elicited or interpreted information differently in the surgery and non-surgery groups.

Confounding

An alternative explanation that must be considered is that an observed difference in effect (or lack of one) is in fact due to a mixing of effects (i.e. interaction) between the intervention, the outcome, and a third factor that is associated with the intervention and independently affects

the risk of developing the outcome. For example, when two series of patients are compared (e.g. a series receiving surgical intervention, and a group of historical controls receiving standard medical treatment) the groups are likely to be different in respects other than just the intervention under study (e.g. age, stroke severity, or more subtle patient characteristics). If these differences are related to outcome, confounding is present, and the true effect of the intervention may be difficult to identify.

Confounding will also result if surgically-treated patients receive more careful monitoring and better pre- or post-operative care in an intensive care unit than patients treated in a medical ward. It is difficult to disentangle the effects of surgery itself, and the effects of the pre- and post-operative care, but this may not always be desirable. In 'pragmatic' studies the aim is to compare 'surgical management' with 'standard management', which is more relevant from a clinical point of view. To establish the impact of intensive care units would require another treatment arm involving intensive care unit care, but without surgery, as suggested by Werner Hacke.

The play of chance

A principal assumption underlying the com-

parison between groups receiving different interventions is that we can use the result to draw an inference about the effect of the intervention in the entire population. One of the major problems in drawing such an inference is that the play of chance may affect the results observed simply because of random variation from sample to sample. In other words, because of chance variation, it is very unlikely that the proportion of patients with a good outcome (e.g. survival) will be identical in any two samples drawn from the same total population, and the difference in effect between the two groups will always reflect, to some extent, the play of chance.

One of the major determinants of the degree to which chance affects the findings in any particular study is the sample size. The observational studies of surgical decompression are small (up to 20–30 participants in each group), and the resultant difference in effect might differ substantially from the true treatment effect, simply as a result of chance. If we had obtained data from more patients, there would be less variability in the effect estimates, and we would be much more likely to draw a valid inference about the experience of the total population.

THE IDEAL STUDY DESIGN FOR COMPARING DIFFERENT INTERVENTIONS

The effects of bias, confounding and the play of chance can be substantial, and every measure should be taken in the design and conduct of a study to minimize or eliminate their occurrence. Randomization offers many unique advantages compared with the methods of allocation used in the observational studies. Firstly, if randomization is done properly, nobody involved in deciding whether a patient is eligible to enter the study will know in advance the assigned treatment group. Thus, the potential for selection bias is removed. If the patients and the investigator performing the outcome assessments are denied knowledge of the patients' treatment allocation ('blind-

ing', 'masking'), observation bias can also be avoided. Blinding patients to the allocated treatment is obviously near impossible, but blinded assessment of outcome is possible using telephone or postal follow-up, or by giving all patients special hats to wear, as in one of the on-going randomised controlled trials (Frank *et al.* 1999). Blinding is simple for 'hard' outcomes, such as death.

Another unique advantage of randomization is that, on average, the study groups will be comparable with respect to all variables except for the intervention being studied, so that confounding is reduced or eliminated. 'On average' implies that the larger the sample size, the more successful the randomization process will be in distributing these variables equally among the groups. This feature of randomization is important because any baseline characteristic that affects risk and differs in the treatment groups could potentially confound the relationship between treatment and outcome. Thus, randomization provides a degree of assurance about the comparability of the study groups which is simply not possible in any observational study design.

WHAT IS THE VALUE OF TREATMENT BENEFITS AND ADVERSE OUTCOMES?

Before we can conclude that surgical decompression is beneficial, we must also decide how to measure the 'net benefits' of treatment. It is often the case that treatment success for some patients is achieved at the 'expense' of adverse outcomes for other patients. It is possible, for example, that surgical intervention reduces the number of deaths, but increases the number of patients who survive in a dependent, severely disabled state (Fig. 1). If these outcomes had equal weights, the net benefit could be calculated as the sum of the positive and negative outcomes. In real life, however, patients assign different values to different outcomes (i.e. death, survival in a dependent state, and survival in an independent state) and the size

Medical treatment	Dead	Dependent	Independent
Surgical treatment	Dead	Dependent	Independent

Figure 1 Hypothetical study result: surgical treatment reduces the proportion of dead patients, but increases the proportion of disabled, dependent patients. What is the size of the net benefit?

patients need to trade off the chance of treatment success against the risk of an adverse outcome, and the patient's preferred choice of treatment will depend, not only on the risks, but also on the values that he or she assigns to the different outcomes

of the net benefit must be adjusted to reflect these values. On the individual level, patients need to trade off the chance of treatment success against the risk of an adverse outcome, and the patient's preferred choice of treatment will depend, not only on the risks, but also on the values that he or she assigns to the different outcomes ('utility values').

Interventions that produce worthwhile benefits often carry definite risks (e.g. thrombolysis for acute ischaemic stroke, or endarterectomy for carotid stenosis), and it may well be that the effect of reducing the number of patients who die will be to increase the number of severely disabled patients. The increase in the number of disabled patients may not only represent a reduction in dead patients, but may also a shift of patients from the independent to the dependent state (Fig. 2). Surgical treatment of critically-ill patients is an additional trauma to the stroke itself, and may be associated with severe pre- or post-operative complications (Wagner *et al.* 2001). The 'cost' of increased survival may therefore be substantial and the size of the 'net benefit' will depend on how patients value the different health outcomes after stroke.

Figure 2 Hypothetical study result: surgical treatment reduces the proportion of dead patients, but increases the proportion of dependent patients and reduces the proportion of independent patients.

WHAT ARE THE EFFECTS IN DIFFERENT CATEGORIES OF PATIENTS?

The studies to date have mainly been performed among younger patients, and it may not be possible to generalize the results to typical stroke patients, who are older (Tables 1 and 2). Due to brain atrophy in older patients, the natural course of oedema may be more benign, and surgical treatment may therefore be less effective. Older patients may also be at higher risk of complications of surgery, and they may have different attitudes towards the risk of various adverse outcomes. Interestingly, Holtkamp reported a poorer quality of life following decompressive surgery in an older group of patients than had been described in younger patients (Holtkamp *et al.* 2001).

The effect of decompressive surgery may also depend on the timing of the intervention, as Werner Hacke emphasizes. Early surgery, before the symptoms of oedema develop, may be more beneficial for those who will go on to develop symptomatic brain oedema. However, some of the patients treated early may never have gone on to develop the 'malignant middle cerebral artery syndrome'. If the predictions are anything less than 100% specific, some patients may achieve a 'favourable outcome', not as a result of treatment, but because they had a good prognosis in the first place. Patients considered for early surgical treatment, before symptomatic oedema has developed, may therefore have a better natural prognosis than patients who have developed symptoms, and any indirect comparison between the outcomes in the two groups is potentially biased and misleading.

SHOULD SURGICAL INTERVENTION BE RECOMMENDED FOR CLINICAL PRACTICE?

Given the uncertainty surrounding the effectiveness of decompressive surgery, the unresolved issues of how to define and measure net benefits, and the problems of generalizing

Given the uncertainty surrounding the effectiveness of decompressive surgery, the unresolved issues of how to define and measure net benefits, and the problems of generalizing from small subsets of patients to the majority of stroke patients, it is premature to introduce decompressive surgery into routine clinical practice

Editor's comment

from small subsets of patients to the majority of stroke patients, it is premature to introduce decompressive surgery into routine clinical practice. Instead, patients with large, space-occupying infarctions should be included in one of the on-going randomised controlled trials (Frank *et al.* 1999; Hofmeijer *et al.* 2001). Patients who are included in these trials may also benefit from the detailed information, monitoring and follow-up, which are features of participation in randomised controlled trials and which may account for the outcome advantage of patients enrolled in trials compared with those who are not (Braunholtz *et al.* 2001).

There are certainly difficulties in performing randomised controlled trials of complex interventions such as decompressive craniotomy. Centres with experience of the procedure might be able to enrol a large number of patients, but some clinicians – like Werner Hacke – may feel ethically unable to randomise patients because they are convinced that surgical treatment is more effective than medical treatment. Although they may be correct, they may also be misled by their apparent success (for all the reasons given above). They do not believe that there is equipoise between the alternative treatment regimens in the randomised controlled trials.

The effectiveness of decompressive surgery may be less in a randomised controlled trial that includes inexperienced centres. However, participation in a randomised controlled trial offers a unique opportunity to gain experience and learn new procedures, and increases the likelihood that new, effective interventions are later implemented in routine practice (Ketley & Woods 1993); and even if 'pragmatic' trials including a wide range of centres may underestimate the efficacy of decompressive surgery (compared with trials including only the 'best centres'), they will allow one to predict the impact of introducing decompressive surgery into routine clinical practice.

It is very simple really, because both groups agree that randomised trials should be done, so let's get on and do them! There is a logic, there is experience of decompressive surgery, the results of the intervention are promising, not everyone gets it, there is uncertainty, acute stroke units are

The problems will be numbers and funding, but surely they are not enough to overwhelm the international stroke community

springing up everywhere, and both groups have run acute stroke trials for years. The problems will be numbers and funding, but surely they are not enough to overwhelm the international stroke community.

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