



The RESCUE_{icp} study

Randomised **E**valuation of **S**urgery with **C**raniectomy for
Uncontrollable **E**levation of **I**ntra-**C**ranial **P**ressure

This study has been approved by the
UK Multi Centre Research Ethics Committee (Eastern Region)

A randomised control trial comparing the efficacy of decompressive craniectomy versus optimal medical management for the treatment of refractory intracranial hypertension following brain trauma

The RESCUE_{ICP} study is a multi-centre trial organised as a collaboration between the University of Cambridge Departments of Neurosurgery / Neuro-intensive Care and the European Brain Injury Consortium.

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Introduction – the problem to be addressed

Head injury is a major cause of morbidity and mortality worldwide. Trauma is the leading cause of death in the first four decades of life with head injury being implicated in at least half the number of cases.¹ In the UK , 1500 per 100 000 of the population (total one million) attend Accident and Emergency Departments with a head injury ², 300 per 100 000 per year are admitted to hospital, 15 per 100 000 per year are admitted to Neurosurgical Units and 9 per 100 000 per year die from head injury.^{3;4}

Recent advances in the management of head injury have occurred at several levels including prevention, pre-hospital care, immediate hospital care (trauma teams, advanced trauma life support courses), acute hospital care (neuro-intensive care units with protocol driven therapy) and post-acute hospital care (rehabilitation). Recently, recommendations have been produced by the Royal College of Surgeons, including the transfer of all patients with severe head injury to regional neurosurgical units.² Despite improvement in outcome during the 1990s as shown in the data from the UK East Anglian Regional Audit of Head Injury ⁵ (table 1), mortality and morbidity remain high and controversy continues both about the fundamental concepts of treatment and about specific techniques.

The fundamental pathophysiological process following head injury is the development and propagation of an escalating cycle of brain swelling, increase in intra-cranial pressure (ICP), reduction in blood supply and oxygen delivery, energy failure and further swelling, enhancing brain injury and poor outcome (figure 1). The aim of this trial is to determine the effectiveness of an operation (decompressive craniectomy) to intercept this cycle, treat brain swelling and improve outcome.

Hypotheses – the principle research questions to be answered

The application of decompressive craniectomy to head-injured patients with raised intra-cranial pressure (ICP) refractory to medical treatment results in improvement in outcome

- (1) Decompressive craniectomy results in an improvement in the Extended Glasgow Outcome Score compared to optimal medical treatment
- (2) Decompressive craniectomy results in an improvement in surrogate endpoint measures (including specific outcome measures (SF-36 questionnaire), control of ICP, time in intensive care and time to discharge from the neurosurgical unit) compared to optimal medical treatment.

Rationale for a study – why is a trial needed now?

Cerebral ischaemia secondary to injury and brain swelling within the tight confines of the skull precipitates a cascade of adverse metabolic events which culminate in a cycle of further swelling, reductions in blood flow and in oxygen and glucose supply. Therapy to reduce ICP following acute brain injury is the cornerstone to the management of these patients. The introduction of protocol driven therapy with a number of stages to reduce ICP has been one of the factors leading to potential improvements in outcome.^{6,7} Two surgical manoeuvres can be employed to reduce ICP:-

- (1) The application of external ventricular drains to drain cerebro-spinal fluid
- (2) Decompressive craniectomy (removal of a large area of skull with opening of the dura to increase the volume of the cranial cavity, facilitating a reduction in ICP; figure 2).

Several reports in the literature investigate the role of decompressive craniectomy in traumatic brain injury⁸⁻²⁰. These studies demonstrated a wide range of clinical outcome, with no clear consensus regarding the indication for the operation. The generally accepted way to resolve the role of any therapy

for neurotrauma is to obtain class I evidence by performing prospective randomised trials. We are therefore proposing a multi-centre European trial, co-ordinated by the University of Cambridge, Department of Neurosurgery, in collaboration with the European Brain Injury Consortium (EBIC). Such a trial should be performed for the following reasons:

1. Severe head injury is common and severe disability and persistent vegetative state has profound social and economic consequences
2. The current data (small studies, class II and III evidence, poor follow up) are inconclusive
3. A randomised study has the potential to address the concerns that the operation does not influence the favourable outcome of good prognosis patients and that it shifts outcome from death to vegetative state / severe disability in poor prognosis patients.
4. To establish the incidence of complications resulting from this procedure e.g. post-operative haematoma, infection.

The proposed trial

The study will be a randomised trial comparing optimal medical management with surgery (decompressive craniectomy) for the management of intra-cranial hypertension following head injury, refractory to first-line treatment.

The trial will recruit from centres experienced in the intensive care management of head injury. The target study group will be ventilated ICP-monitored patients with refractory intracranial hypertension. The two arms will be the continuation of optimal medical management versus surgery (decompressive craniectomy).

The study has evolved as a result of discussions between potential study centres with the aim of providing flexibility in terms of the intensive care management of the patients yet sufficient protocol discipline to enable the hypotheses to be addressed.

Inclusion criteria

The inclusion criteria will be patients with head injury, age 10-65 years with an abnormal CT scan requiring ICP monitoring (Brain Trauma Foundation Guidelines) with raised ICP (>25mmHg >1 – 12 hours) refractory to initial medical treatment measures. Patients may have had an immediate operation for a mass lesion but not a “decompressive” craniectomy.

Exclusion criteria

The exclusion criteria will be bilateral fixed and dilated pupils, bleeding diathesis, devastating injury not expected to survive for 24 hours and follow up not possible. Patients treated by the Lund protocol are also not eligible.

Approval, consent and randomisation

Approval for the study will be obtained from the relevant local and national ethics committees. Consent for the study will be obtained from next of kin on admission to the neurosurgical unit with randomisation performed after stage 2 to avoid delays in treatment.

The principle of randomising neurosurgical patients to medical treatment versus craniotomy has already been proven with the successful implementation of the STICH trial (Surgical trial of intracerebral haemorrhage).²¹

The protocol

Patients with head injury requiring ventilation and intra-cranial pressure monitoring will be considered for the trial. Entry will be determined using the above inclusion and exclusion criteria and following consent for the next of kin. Patients will be managed on intensive care units using a standard protocol (figure 3). The major objective of this protocol is to maintain ICP<25 mmHg by applying treatment measures in a number of stages.

Stage 1 – initial treatment measures

Patients will be sedated, analgesed and ventilated. Patients may or may not be paralysed but this must be noted. They will be nursed head up with no venous obstruction. Invasive monitoring (central venous pressure and arterial lines as a minimum will be applied). Targets for physiological parameters will be cerebral perfusion pressure > 60 mmHg (central venous pressure 6-10), oxygen saturation >97%, arterial CO₂ 4.5-5.0 kPa, temperature <37°C, blood sugar 4-7 mmol/l.

The ICP will be assessed at this stage. If the ICP<20mmHg, the above medical treatment will continue. If the ICP>20mmHg, a repeat scan will be considered to investigate the presence of an evolving mass lesion and stage 2 will be applied.

Stage 2 – advanced treatment measures

In stage 2 the following measures can be considered, all of which are *optional*:

An external ventricular drain - depending on the size of the lateral ventricles

Mannitol

Inotropes to increase the mean arterial pressure to maintain a cerebral perfusion pressure of >60 mmHg

Arterial carbon dioxide 4.0-4.5 kPa (can be monitored with jugular venous oxygen saturation sensors maintaining SjvO₂ >55%)

Hypertonic saline

Moderate cooling (35-36°C) but not severe hypothermia <35°C

Loop diuretics

Barbiturates are not implemented as part of stage 2, but are reserved as part of continued medical treatment following randomisation. This clause enables a direct comparison between the efficacy of decompressive craniectomy and extended medical treatment including the introduction of barbiturate coma.

If despite stage 1 and 2 measures, the ICP remains above 25mmHg for 1 to 12 hours then patients will be randomised to either continued medical treatment stage 2 but also including barbiturates (e.g. thiopentone boluses + infusion 4-8 mg/kg/hr) or to surgical treatment (decompressive craniectomy). Treatment following randomisation should be implemented within 4-6 hours.

The surgical treatment will comprise

- (a) for unilateral hemisphere swelling / a large unilateral fronto-temporo-parietal craniectomy

or

- (b) for bilateral diffuse hemisphere swelling a large bilateral fronto-temporo-parietal craniectomy from the frontal sinus anteriorly to the coronal suture posteriorly and pterion laterally with a wide dural opening (pedicles based on the superior sagittal sinus medially and division of the falx anteriorly).

If continued medical treatment is drawn no decompressive surgery will be performed at the time of randomisation, but decompressive surgery may be performed later at the clinician's discretion if the patient subsequently deteriorates (for example prolonged and unacceptably high ICP >40mm Hg with compromised CPP). This clause is required if a situation arises whereby the treating physician feels that withholding surgery is acting against the best interest of the individual – "the interests of the patient always prevails over those of science and society". The same principle applies to barbiturates in the decompressive craniectomy group.

Imaging

CT scans will be read centrally and include the following:

- (a) Presentation CT scan
- (b) Pre-randomisation CT scan after stage 1 / 2 to check no evolving mass lesion
- (c) CT scan 72 hours post-randomisation

Power

The total number of patients will be 600 (300 in each arm of the study) for a 10% difference in outcome (increase in favourable outcome from 45% to 55%) (power=80%, p=0.05).

Outcome measures

1. The primary endpoint will be assessment of outcome at discharge (Glasgow Outcome Score) and 6 months (Extended Glasgow Outcome Score²²).
2. Secondary endpoints will be
 - a. Assessment of outcome using the SF-36²³ and SF-10 (children below 16 years of age) questionnaires.
 - b. Assessment of ICP control
 - c. Time in intensive care
 - d. Time to discharge from the neurosurgical unit.
 - e. Detailed health-economic analysis
3. Additional assessment of outcome using the above measures will be performed at 1 year and 2 years after the injury.

For patients undergoing decompressive craniectomy, it is recommended that the bone flap is replaced within six months of the initial injury.

Acknowledgements

This protocol has evolved as a result of discussions between representatives of the University of Cambridge and the European Brain Injury Consortium including the participants of the intra-dural lesion study.

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Table 1. Results of the East Anglian Regional Audit of Head Injury

Head injury	% * p<0.05	Favourable	Severe disability/PVS	Dead
All	1991-1993	56	21	23
	1994-1997	66	13	20
Severe	1991-1993	40*	32	28
	1994-1997	60*	21	22

Figure 1. Escalating cycle of brain swelling resulting in increase in brain injury and poor outcome

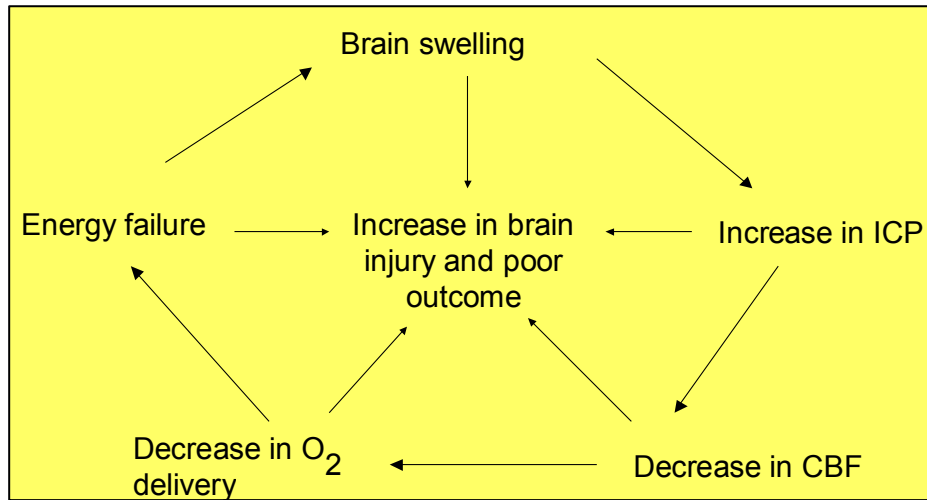
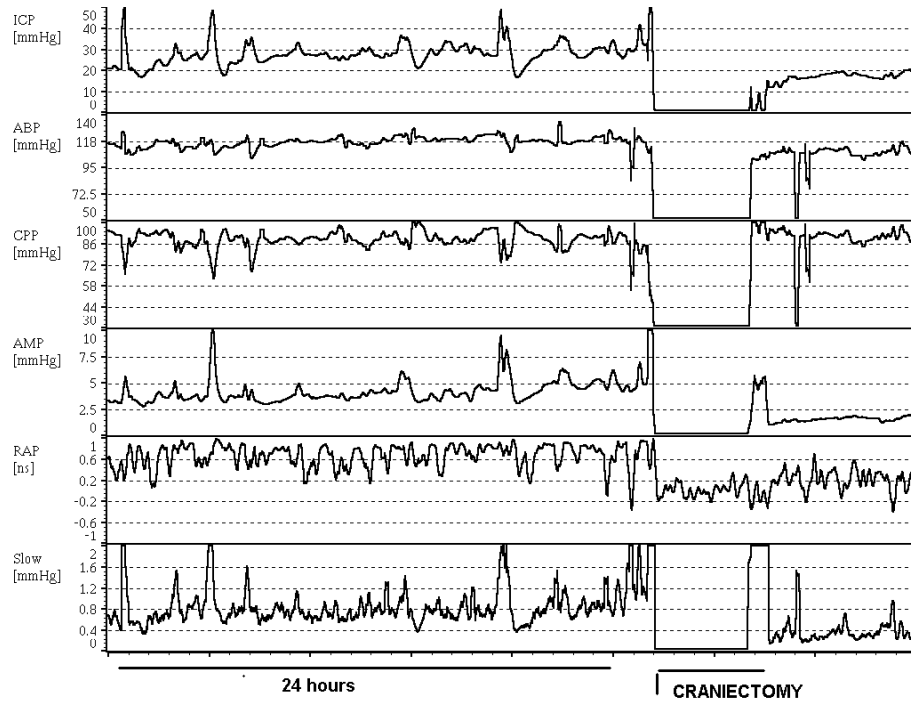
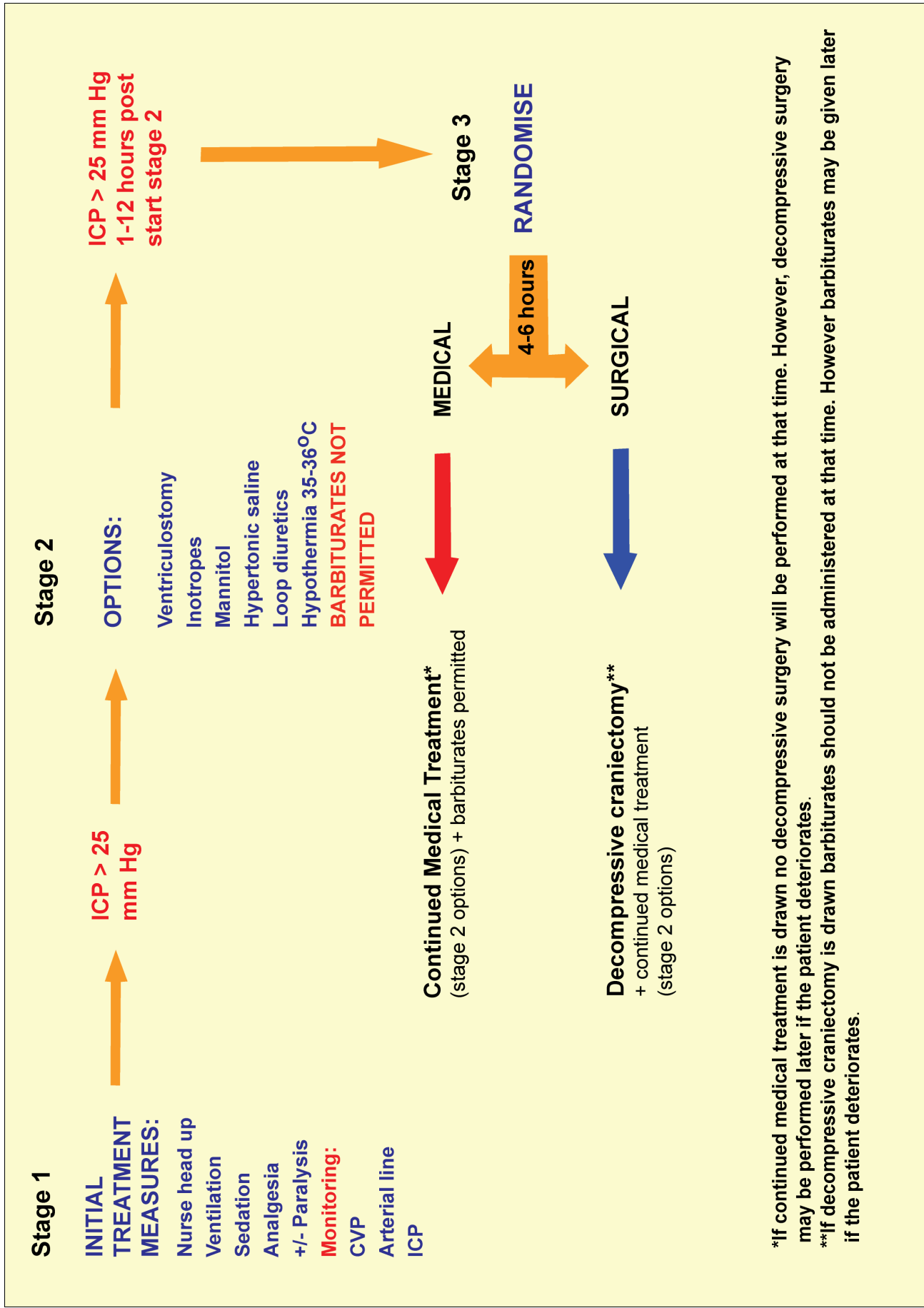


Figure 2. Effect of decompressive craniectomy on ICP appearances (from Whitfield et al)





*If continued medical treatment is drawn no decompressive surgery will be performed at that time. However, decompressive surgery may be performed later if the patient deteriorates.

**If decompressive craniectomy is drawn barbiturates should not be administered at that time. However barbiturates may be given later if the patient deteriorates.