Brain and Spine 3 (2023) 102677

Contents lists available at ScienceDirect

Brain and Spine

journal homepage: www.journals.elsevier.com/brain-and-spine

Study protocol for a multicenter randomized controlled pilot study on decompressive laparotomy vs. decompressive craniectomy for intractable intracranial pressure after traumatic brain injury: The SCALPEL study

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ARTICLE INFO

Handling Editor: Dr. W. Peul

Keywords:
Traumatic brain injury
Intracranial pressure
Decompressive craniectomy
Decompressive laparotomy

ABSTRACT

Introduction: Decompressive craniectomy (DC) is the ultimate intervention to lower intracranial pressure (ICP) following severe traumatic brain injury (TBI). However, this intervention is associated with considerable adverse events and a higher proportion of survivors with poor functional outcomes.
Research question: In a multicompartment system ICP is associated with intraabdominal pressure (IAP) due to cerebral venous outflow from the brain. This is the rationale for decompressive laparotomy (DL) to control ICP after TBI as reported by experimental and retrospective clinical data. The safety profile of DL is superior to DC. This study aims to randomly assign patients with intractable high ICP after severe TBI to DL or DC.
Material and methods: Among other inclusion criteria, ICP must be above 20 mmHg (1–12 h) despite sedation and all other measures according to current guidelines. The primary outcome is the Extended Glasgow Outcome Scale assessed after twelve months. Further secondary outcome measures are compartmental pressure values, complications, etc. After 20 initial patients, results will be reviewed by the ethics committees and safety monitoring board to decide on the enrolment of 80 additional patients.
Results: The study is designed to provide not only high-quality prospective data for the first time on this treatment approach, its two-stage design (20 + 80 pts) also provides maximum patient safety. This protocol conforms with the SPIRIT 2013 Statement. Ethics approval was granted by our but also 5 other university ethics committees (registration 473/18S).
Conclusion: Registration was performed prior to study initiation in November 2021 (registration number NCT 05115929).

1. Introduction

Traumatic brain injuries (TBI) are held responsible for about half of the trauma related death rate (Wilson et al., 2014) and they are a leading cause of loss of quality adjusted life years worldwide (QALY) (Fountain et al., 2017). This applies to medical systems of the western world as well as to those of resource limited countries or in armed conflicts (Langlois et al., 2006; Bruns and Hauser, 2003; Lindquist et al., 2017).

The avoidance of secondary injuries is the focus neurocritical care after TBI. As severe brain swelling within the confined skull will impair brain tissue oxygenation and brain perfusion, ICP after TBI must be controlled although there remains some uncertainty about the goals of

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https://doi.org/10.1016/j.bas.2023.102677
Received 7 July 2023; Received in revised form 5 September 2023; Accepted 17 September 2023
Available online 26 September 2023

therapy. Different authors argue for thresholds not greater than 20 mmHg or 25 mmHg as a surrogate for impaired brain tissue perfusion with further decompensation from this point (Balestreri et al., 2006; Bratton et al., 2007; Lazarus et al., 2018).

Medical interventions for raised ICP in TBI include elevation of the head 30–45° to optimize venous outflow, adequate sedation, analgesia, and vasopressors to optimize cerebral perfusion pressure. Coagulopathy contributes to the severity and mortality of TBI and tranexamic acid proved to be effective in selected patients according to the CRASH-3 protocol (Effects of tranexamic acid on, 2019).

Although the evidence remains debatable for those therapies, centers might have local protocols including ventriculostomy, mannitol or hypertonic saline infusions, temperature control or deep barbiturate sedation (Carney et al., 2017).

DC has shown to be a lifesaving surgical intervention for diffuse TBI within the RESCUEicp trial, at the cost of those additional survivors being distributed over the functional neurological spectrum, resulting in patients with favorable neurological outcome after DC, as well as additional survivors with poor functional outcomes or in vegetative state after DC (Kolias et al., 2016). The negative effect of DC on functional outcome in some patients might partly be explained by the severe inherent morbidity of the DC or the consecutive cranioplasty in itself. Various studies have shown surgical complications post cranioplasty and DC in around one third of the cases including reoperation for hematoma expansion, hydrocephalus, seizures, and graft infections (Gopalakrishnan et al., 2018; Honeybul and Ho, 2011; Sauvigny et al., 2021; Stiver, 2009; Zanaty et al., 2015).

Our literature review for alternative treatment options showed a highly informative case series conducted by the Shock Trauma Center at John's Hopkins Medical Center in Baltimore. The group performed decompressive laparotomies in 24 patients with intractable ICPs in spite of maximal medical therapy including decompressive craniectomy, and reported considerable treatment effects and outcomes in their endpoints "overall survival", as well as "survival with good neurological outcome" (Joseph et al., 2004).

The sequence of decompression was not standardized in that protocol, so that there have been patients with DL before DC and patients with DC before DL. Nonetheless ICP fell reproducible in those patients independently from the treatment sequence, with no patients having clinical signs of intraabdominal compartment syndrome prior to DL (Scalea et al., 2007).

The rationale for the relationship between intraabdominal, intrathoracic and intracerebral pressure, is thought to be via the venous outflow from the brain in a multicompartment system (Bloomfield et al., 1997; Citerio et al., 2001; Malbrain et al., 2006; Scalea et al., 2007; Wilson, 2016). This has for example been shown in a porcine model by Bloomfield et al. (1997) Citerio et al. induced an ICP increase in neurotrauma patients by temporarily increasing abdominal pressure with an externally placed waterbag (Citerio et al., 2001). Others studied the effect of pneumoperitoneum as a model of intraabdominal hypertension during laparoscopic surgery on ICP (Kamine et al., 2016; Montorfano et al., 2020; Yashwashi et al., 2020). Additionally there might be a vasopressin-related pathway for the correlation between ICP and intraabdominal hypertension (Montorfano et al., 2020).

The concept of ICP is based on the over 200 years old Monro-Kellie-Doctrine, which says that the intracranial volume is constant and the sum of brain tissue volume, volume of cerebro-spinal fluid (CSF), and blood both arterial and venous (Mokri, 2001). Brain swelling due to TBI, and brain contusions occupies space and therefore requires other components to be reduced in their intracranial volume. Therefore, initial compensating mechanisms comprise of outflow of intracranial CSF and cerebral blood volume, predominantly in the venous side of circulation. Concerning the volume-pressure-relationship, intracranial pressure increases exponentially around 20–25 mmHg of ICP with further expansion of intracranial volume. Vice versa, if ICP is in that critical range, small reductions of intracranial volume can lower ICP significantly (Bouma et al., 1992; Czosnyka and Pickard, 2004; Wilson, 2016).

Decompressive laparotomy (DL) is thought to increase venous outflow from the brain via the jugular and vertebral veins and vertebrovenous plexus which reduces the intracranially present amount of venous blood and therefore ICP.

We are hypothesizing that DL may have the benefit of lowering the ICP, without the inherent risks and complications caused by a large craniectomy and its influence on long-term outcome.

We consider DL to be less invasive than DC, but still literature on adverse events (AE) during DL and open abdomen therapy (OAT) include entero-atmospheric fistulas, volume depletion, surgical site infections, abscesses or ventral hernias which can require extensive abdominal wall reconstructions later in the patients course (Cristaudo et al., 2017).

The rate of AE is primarily determined by the underlying abdominal disease process, thereby we are confident that we will see a very low number in this specific cohort without intraabdominal pathologies (Karhof et al., 2021). This is supported by literature showing low rates of AE in trauma victims after non-therapeutic explorative laparotomies (Weigelt and Kingman, 1988). Within the above mentioned DL case series from John's Hopkins the abdominal facia has been left open as a planned hernia with a skin only closure. This left the patient with a significant morbidity and made extensive abdominal reconstructions necessary such as the component separation technique (Scheuerlein et al., 2018).

But using vacuum-assisted wound closure and mesh-mediated fascial traction (VAWCM) as a measure to dynamically approximate and close the rectus abdominis fascia with staged surgical procedures and a visceral protective layer to the vacuum dressing to avoid entero-atmospheric fistulas, morbidity of that procedure will be much lower than 20 years ago (Beltzer et al., 2016; Coccolini et al., 2018; Schaaf et al., 2020; Weigelt and Kingman, 1988; Willms et al., 2015, 2020, 2022).

In conclusion it remains unclear whether DL has a comparable benefit on long-term functional outcomes after TBI, but if the results of this study indicate non-inferiority, decompressive laparotomy has the potential to become an alternative surgical treatment option which is readily available to benefit TBI patients worldwide.

2. Methods and analysis

2.1. Primary objectives

Building on this evidence and rationale, we plan to study the effects of DL vs. DC on the long-term functional outcome after severe TBI.

2.2. Secondary objectives

Additionally, we will study mortality rate, complications, life quality and several physiological parameters.

2.3. Study design

SCALPEL is an international, pragmatic, allocation concealed, open label, randomized, controlled, multicenter, pilot clinical study. It has a two-stage design: An initial phase will recruit 10 patients per study arm to test for clinical recruitment and safety before enrolment of another 80 patients in the main study. After 20 initial patients, results will be reviewed by the ethics committees and safety monitoring board to decide on the enrolment of 80 additional patients. The study will include at least 10 German level 3 hospitals and is open to be expanded to other countries. It will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP). The study protocol has been designed to include researchers, statisticians, and experienced clinicians in the fields of neurosurgery, trauma surgery, general surgery and neurocritical care. The pragmatic best practice

guidelines for DL, DC and neurocritical care within this trial reflect the current standard of care to ensure clinical quality and clinician engagement.

2.4. Screening

All patients admitted with severe traumatic brain injuries will be screened by hospital or research staff, regardless of time and date. Screened patients will be documented in the centers' screening log. Reasons for non-enrolment of eligible patients need to be named to establish an unbiased population.

2.5. Inclusion criteria

To be eligible for the clinical study there must be:

- Age between 18 and 65 years.
- TBI with abnormal CT scan.
- Invasive ICP monitoring in place.
- ICP >20 mmHg for 1–12 h after conventional therapies step I and step II before study (refer to Fig. 1).
- Written informed consent, by study participant or legal representative, enrolment possible by peer-proxy process according to study protocol.

2.6. Exclusion criteria

Inclusion of the patient is impossible if any of the following is present:

- Bilateral fixed and dilated pupils.

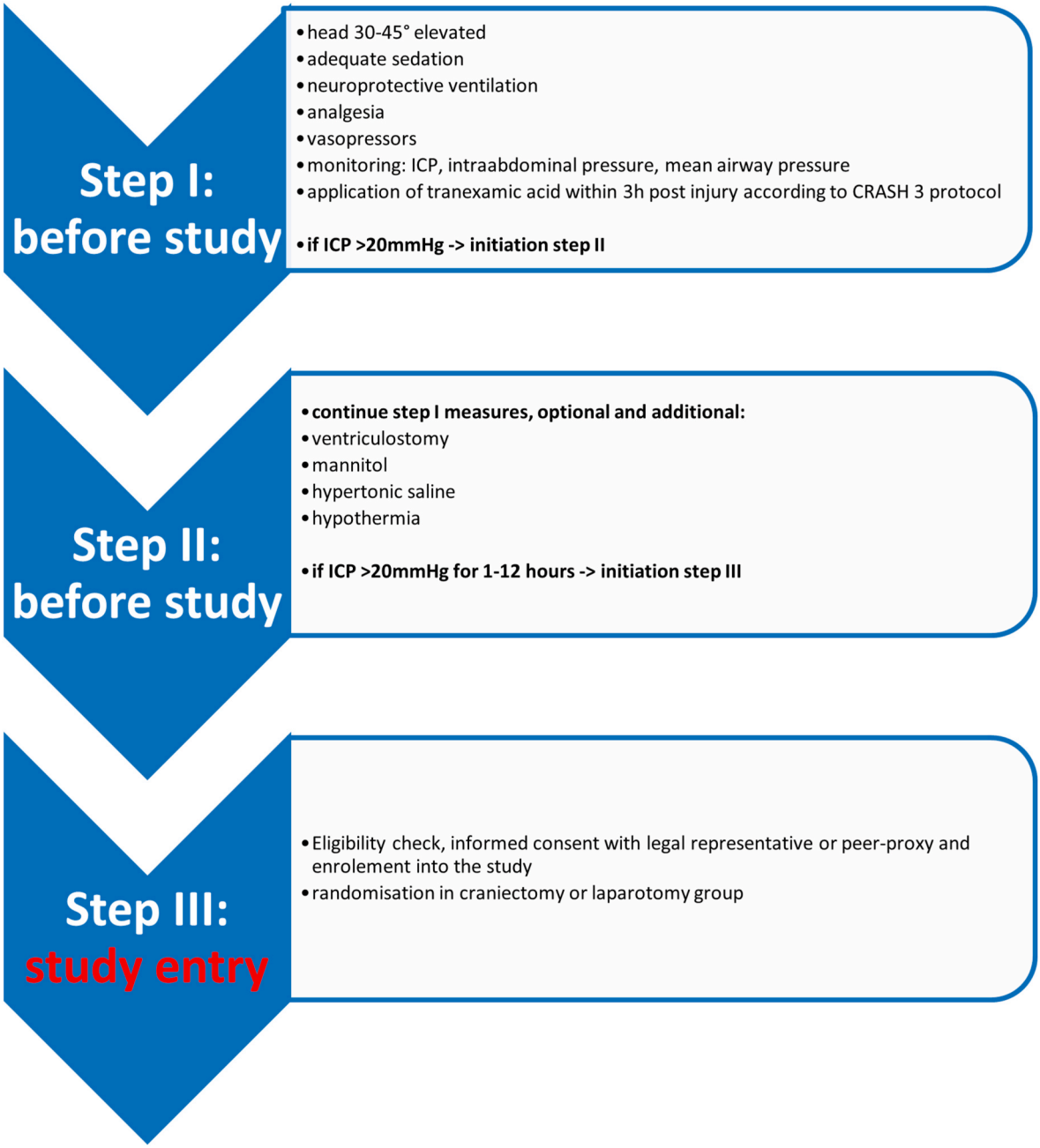

Fig. 1. Flow Chart: Interventions and medical procedures before and at study entry.

- Limitation of therapies due to poor prognosis as decided by the local team.
- Withdrawal of consent.
- Severe pre-existing physical or mental disability or co-morbidity which would lead to a poor outcome even if the patient made a full recovery from the head injury or would interfere with the assessment of functional outcome.
- Intracranial injury mandating craniotomy or craniectomy in itself (decompression of hematoma before indication to DC is not excluding from the study).
- Intraabdominal injury mandating laparotomy in itself.

Consent

As the study participants will be initially unable to give consent by themselves, there is a hierarchy of informed consent in the SCALPEL study:

1) If next of kin is known, available and the necessary discussion can be done safely prior to enrollment.Only enrollment if the next of kin accepts written consent.
2) If next of kin is known and available, but the necessary discussion would unduly delay the immediately needed intervention and consequently jeopardize the patient's safety or next of kin is unknown and an independent nominated consultant cannot be reached (e.g., out of hours).

The responsibility for enrollment will then be taken by a peer-review process, including a physician who is not involved in the patient's care (for example radiologist or medical resident on call) and gives written consent if the following conditions are met and documented:

- Immediately life-threatening situation.
- Both laparotomy and craniectomy are well-established procedures in the treating center.
- A neurosurgeon and general/trauma surgeon are involved.

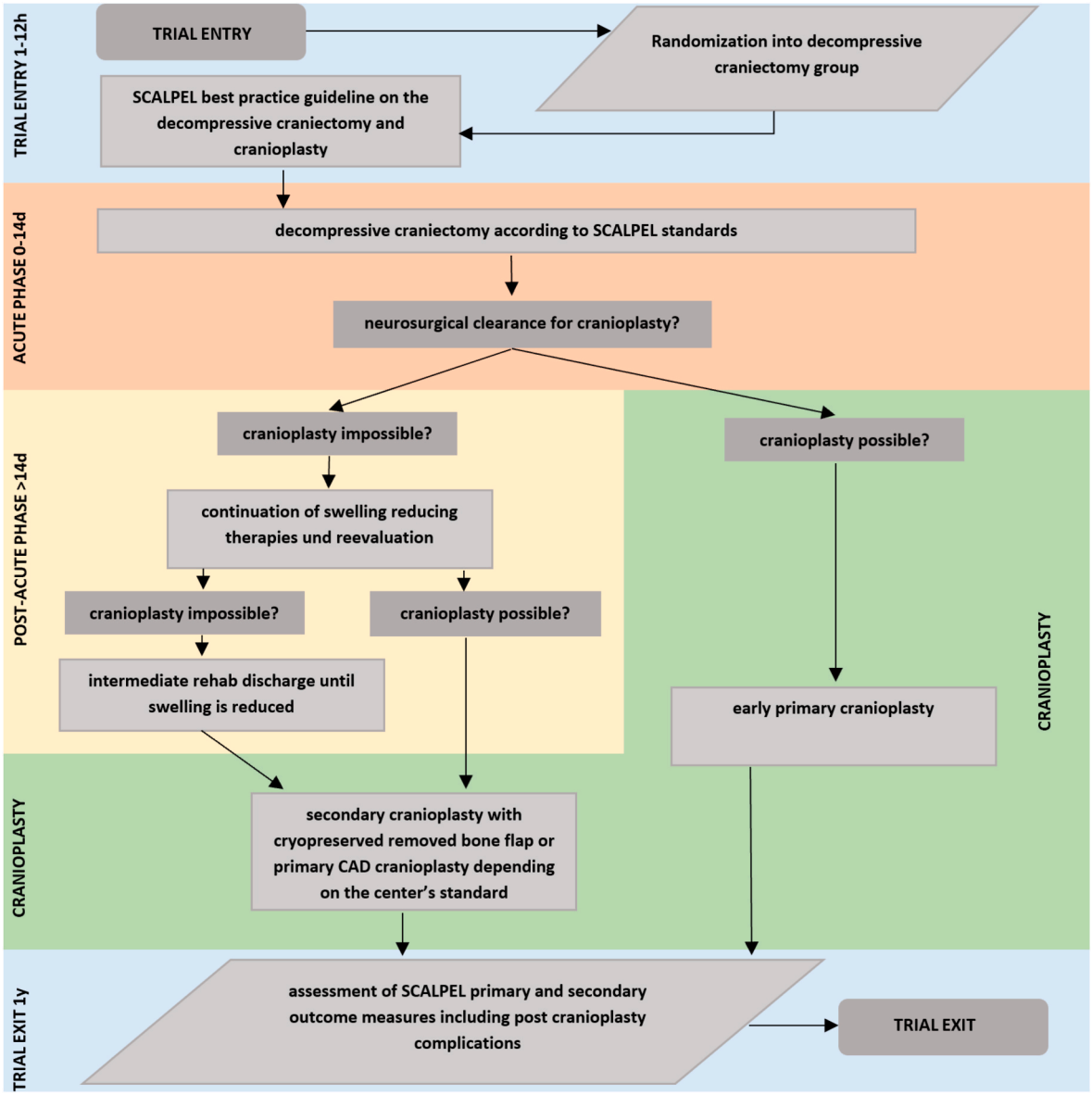

Fig. 2. Decompressive craniectomy arm flowchart for the SCALPEL trial (SCALPEL=Standard Craniectomy Against Laparotomy for the treatment of traumatic rise in intracranial Pressure and the Effect on Long-term outcome, DC = decompressive craniectomy, CP = cranioplasty, ICP = intracranial pressure, CAD = 3D computer assisted, designed, and manufactured implant.

If given consent is retrospectively withdrawn by next of kin or patient, the patient will be excluded from the study.

We adapted this from current practice in most interventional stroke trials. In different centers, we ask the neuroradiologist on-call or the stroke call for the peer-proxy process. Those are mostly attending-level staff members or senior residents, depending on the center. All these physicians and their whole departments were officially informed about the study prior to the enrolment of the study center. Thus, we make sure that the independent peers and their supervisors are fully aware of the study in advance. They are not bound to directives by the study's treatment teams, and participation in the peer-proxy process is voluntary.

3) If the patient regains consciousness after surgery, detailed information will be given as soon as possible, and consent will be documented in written form. If the patient wishes to be withdrawn, all documented data will be deleted.

2.7. Study interventions

Providing the patient meets the criteria for eligibility above, they will be randomly assigned to either:

- DC: It is discretionary to the treating neurosurgeon if a bifrontal vs. frontotemporoparietal hemicraniectomy is performed, depending on the clinical situation and local standards. The bone flap should be generous. Secondary to the decompression, there will be the necessity for a cranioplasty after resolving of the brain swelling 2–20 weeks after craniectomy (Fig. 2).
- DL: A long median laparotomy (from xiphoid to symphysis) will be performed in the laparotomy group. The skin and fascia are left open as a laparostomy. The laparostomy is temporarily closed by a negative pressure dressing or other adequate laparostomy dressings according to the local protocols. The interposition of a traction-free mesh is allowed for bridging the gap between the fascial edges (Fig. 3).

ICP is monitored for 1 h in the OR after the surgical intervention with optimal neurocritical care according to current guidelines, as a key procedure for patient safety within this protocol. If ICP does not decrease adequately under 20 mmHg, crossover is advised. As this is a pragmatic trial and with respect to the treating team's expertise, we decided against a single mandatory ICP cutoff for crossover in this pilot study.

2.8. Primary outcome measure

The primary endpoint is functional outcome measured by the extended Glasgow-Outcome-Scale Extended (GOS-E) 12 months post-injury. It will be evaluated via a structured interview with the patient or caregiver by a physician not involved in the initial treatment.

2.9. Secondary outcome measures

1. Mortality rate 12 months after surgery.
2. GOS-E at 6 months post-injury.
3. Detailed comparison of serious adverse events and surgical complications measured by the Clavien-Dindo Scale (Grade I: "any deviation from the normal postoperative course without the need for pharmacological treatment" up to grade V: death; with several gradings for treatment and long-term consequences).
4. Frequency and severity of organ failure measured by the Clavien-Dindo Scale.
5. EQ-5D life quality at 6- and 12-months post-injury.
6. GCS at discharge from the ICU and acute care facility compared to baseline.
7. Length of stay at the ICU, neurosurgical unit, and rehabilitation unit.
8. Cross-over rate between the two groups.
9. ICP, IAP, and mean arterial pressure (MAP) at visit II & III.

IAP will be measured in all patients eligible for randomization and documented every 10 min after DL or DC and afterwards every 8 h during the first 7 d of neurocritical care within the eCRF. Concerning ICP we leave it to the participating centers to decide between intraventricular catheters, epidural or intraparenchymal probes. IAP is usually measured via urinary catheters.

Our outcome measures focus on ICP decrease and functional status, which are mostly influenced by the amount of ICP decrease in the immediate period of treatment. The closure timing and sequelae do not affect ICP, so we are very positive that there is no bias. We need to leave the closure to the clinical status and treatment, but this also means that we will obtain valuable data on the actual variability of closure.

2.10. Sample size

Sample size estimation is based on the primary endpoint of the study, the functional outcome measured by the extended Glasgow-Outcome-Scale (GOS-E) 12 months post-injury and dichotomized into favorable (GOS-E $\geq$ 4)/unfavorable (GOS-E $\leq$ 3) outcome. When the sample size is 43 patients per group (total of 86 patients), a two-sided 95% confidence interval for the frequency of unfavorable outcomes will extend 0.15 from the observed proportion for an expected proportion of 0.546 in each group (assumptions based on RESCUEicp). Assuming a drop-out rate of 14%, we would need to include 100 patients in the study (50 per treatment arm).

2.11. Randomization

If the local team (neurosurgery and general surgery) agrees on the eligibility of the patient and no exclusion criteria are present, the patient can be randomized using a paper-based application with sealed envelopes.

Treatment allocation will be performed based on pre-defined computer-generated listings. Randomization will be 1:1, stratified by treatment center and with varying block sizes.

2.12. Blinding

Patients and local clinicians cannot be blinded due to the obvious differences in post-operative treatments, dressings, and secondary interventions.

If it is necessary to perform face-to-face interviews, they will be performed by staff not involved in the primary care process of the patient. Statistical analyses using the actual treatment group, including summary statistics per group, will only be produced after database closure to minimize bias.

2.13. Data collection

The documentation of the study data is the responsibility of the local investigators but closely monitored via remote and on-site visits. Original data (source documents) remains at the respective study site. Medical record and information on the eCRF must be traceable and consistent with the original data. No information in source documents about the identity of the patients will be disclosed on the eCRF. All data collected in this study and relevant for analysis must be entered in the eCRF which has to be completed by the investigator or authorized study personnel and signed by the investigator. This also applies for those patients who do not complete the study. In case of premature discontinuation, the reason must be recorded on the eCRF. The site investigators are responsible for ensuring the accuracy, completeness, and timeliness of all data reported to the study leadership in the eCRFs over

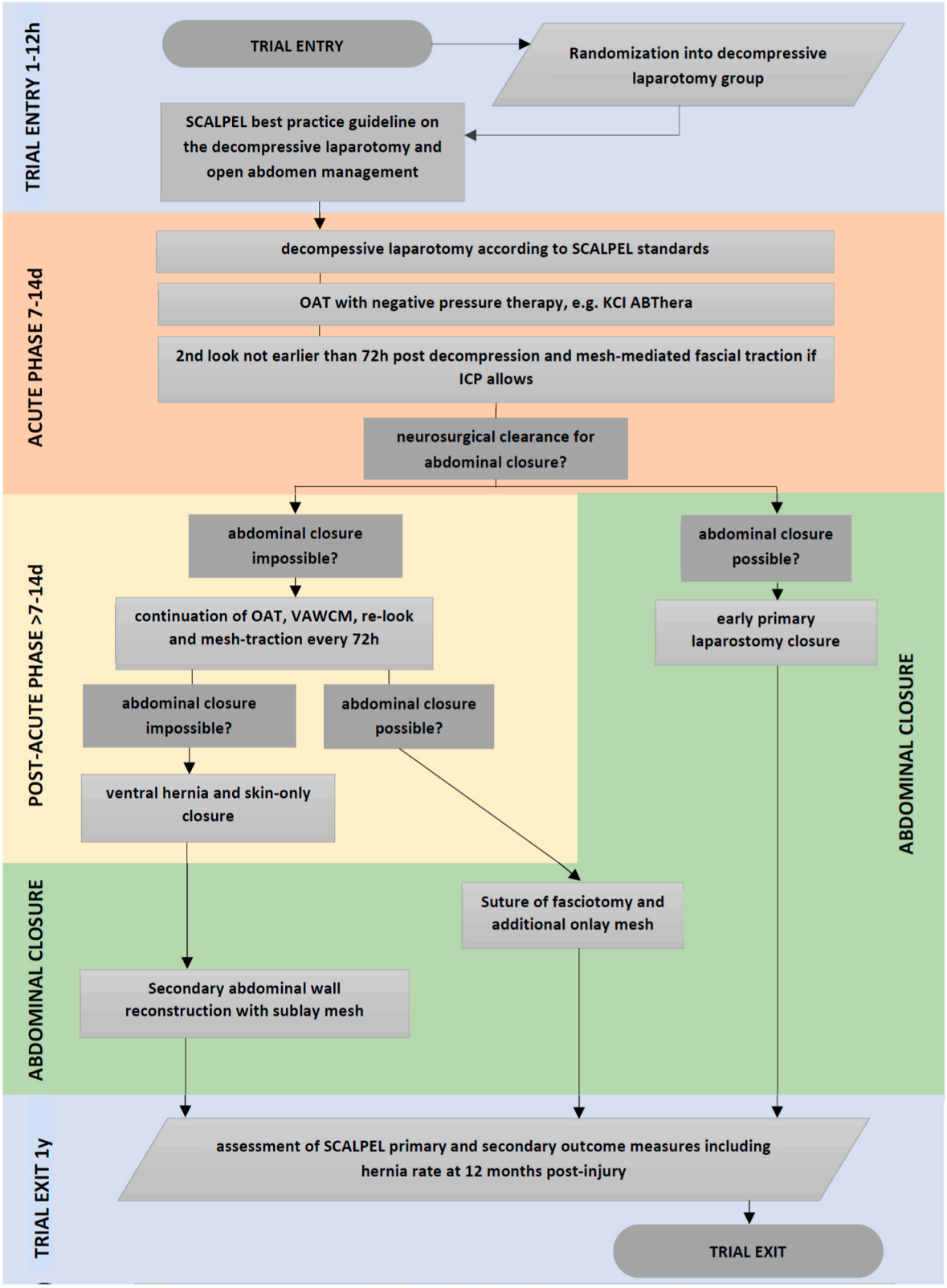

Fig. 3. Decompressive laparotomy arm flowchart for the SCALPEL study (SCALPEL=Standard Craniectomy Against Laparotomy for the treatment of traumatic rise in intracranial Pressure and the Effect on Long-term outcome, OAT = open abdominal treatment, KCI=Kinetic Concepts Inc. ABThera® Sensa T.R.A.C.®, ICP = intracranial pressure, VAWCM = vacuum-assisted wound closure and mesh-mediated fascial traction).

multiple visits during the 12 month study period (Fig. 4).

2.14. Safety interim analysis

An interim analysis on safety data only will be performed after 10 patients have been recruited in each group of the clinical study and completed 14 days of study participation. Recruitment will not be stopped unless there is an increase of harm, seen in the mortality and GCS data at that point in time. Safety data will be discussed, and decisions made by the Safety Monitoring Board, ethics committee and the Study Leadership.

This analysis has no influence on the efficacy analysis at the end of the study in terms of multiple looks at the data and alpha-spending.

2.15. Final statistical analysis

The full analysis set (FAS) consists of all patients with correct informed consent process, who were randomized into the study and received surgical treatment. All efficacy analyses will be performed on the FAS as randomized, regardless of cross-over (analysis "as randomized").

The per-protocol set (PPS) consists of all patients in the FAS, who did not cross over to the other arm and delivered GOS-E values 12 months post-surgery (analysis "as treated"). This analysis set will be used in the non-inferiority analysis only.

The cross-over set (COS) consists of all patients in the FAS who delivered GOS-E values 12 months post-surgery. The study arms will be increased to 4, so that each cross-over direction is analyzed in a separate study arm "as treated" (A, B, AB, BA, where A and B stand for the initial two therapies). This analysis set will be used for sensitivity analysis of the primary endpoint.

The safety analysis set (SA) consists of all patients who received a study-related procedure and did not withdraw consent. We expect that the FAS and the SA will contain the same patients. All safety analyses will be done on the SA "as treated".

The primary endpoint of the study is the functional outcome at 12 months post injury, measured with the GOS-E. GOS-E takes values between 1 and 8, where higher values correspond to better recovery, ranging from dead (GOS-E = 1) to upper good recovery (GOS-E = 8). The GOS-E will be dichotomized into favorable outcome (GOS-E 4 and above) and unfavorable outcome (GOS-E 3 and below) as described in the RESCUE-ICP trial. The frequency of unfavorable outcomes will be calculated in each treatment group including a 95%CI. The study is not powered to show non-inferiority, nonetheless we define a non-inferiority margin of 5%, so that in case at the end of the study the lower end of the 95%CI for the difference between decompressive craniectomy and decompressive laparotomy (DC-DL) in terms of frequency of unfavorable outcomes is higher than −0.05 on the FAS and on the PP

	Visite 0 Screening (while step I and II)	Visit I Baseline while step III	Visit II At admission to ICU after surgical intervention	Visit III 48 h after surgical intervention	Visit IV at discharge from ICU	Visit V at discharge from acute care facility	Visit VI At 6 months post injury	Visit VII at 12 months post injury
Socio-demographic details		X						
Preceding trauma therapy		X						
Injury related events		X						
Initial Glasgow Coma Scale		X			X	X		
Neurological assessment	X	X	X	X	X	X		
Eligibility, Informed consent	X	X			X			
Randomization		X						
Surgery related data			X	X				
Concomitant injuries		X						
Intracranial pressure (ICP)		X	X	X				
Intraabdominal pressure (IAP)		X	X	X				
Mean airway pressure (MPAW)		X	X	X				
Mean arterial pressure (MAP)		X	X	X				
Quality of life (EQ-5D)							X	X
Extended Glasgow Outcome Scale (GOS-E)							X	X
Length of stay at ICU, Neurosurgical unit, rehabilitation unit					X	X	X	X
Adverse events			X	X	X	X		
End-of-study								X

Fig. 4. Overview of assessment parameters and visits.

set, then we can conclude non-inferiority of decompressive laparotomy over decompressive craniectomy.

Secondary endpoints will be analyzed using appropriate descriptive statistics. Between-group comparisons will be performed using appropriate two-sided statistical tests for independent samples at the 5% significance level. No adjustment will be made for multiple testing.

2.16. Missing data

Missing values will not be estimated except for the primary endpoint on the FAS. Here drop-outs from both treatment arms will be with an unfavorable outcome. A sensitivity analysis will include only the complete case primary endpoint on the FAS.

2.17. Data monitoring

According to the principles of Good Clinical Practice (GCP) and the monitoring plan, there will be on-site and remote monitoring visits to ensure protocol adherence, recruitment, and follow-up. The responsible monitor will contact the investigator and will be allowed, on request, to inspect the various records of the study (eCRF and other pertinent data) if patient confidentiality is maintained in accordance with local requirements. The monitor will have access to patient records, any information needed to verify the entries in the eCRF and all necessary information and essential study documents.

3. Safety, ethics, and dissemination

3.1. Adverse outcomes

As this is the first randomized controlled study on decompressive laparotomy for TBI, secondary endpoints address the specific complications in both treatment groups. We will rate the severity of the complications using the Clavien-Dindo Complication Scale (Clavien et al., 2009).

4. Regulatory and ethics approvals

The study protocol was reviewed and accepted by the ethics committee at Technical University Munich (registration number 473/18 S). Participating centers will each require review by their local ethics committee depending on local regulations.

Protocol amendments: Necessary changes of the study protocol (amendments) will be presented to the ethics committees for review.

The study was registered prior to initiation at clinicaltrials.gov with the code NCT 05115929.

4.1. Confidentiality

The applicable regulations of data privacy protection will be followed. The patients and legal representatives will be informed that any patient-related data and materials will be appropriately pseudonymized and that these data may be used for analysis and publication purposes. Furthermore, the patients will be informed that their data may be inspected by monitors or other authorized personnel. Patients who do not provide consent for transmission of their data, according to the consent form, will not be included in the study.

4.2. Dissemination

Study results will be reported no matter what the outcomes are in a reputable peer-reviewed scientific journal in accordance with the CONSORT statement. German Department of Defence will be acknowledged as funder in all publications and presentations.

The author sequence will be discussed transparently depending on participation and contribution (recruitment numbers) to the study. The results will be published in a free and open accessible fashion.

Authors' contribution

BK, AN, UM and SK conceived the study. AW provided the open abdomen management algorithm for the study. VK is the study statistician. BK and SK wrote the first draft of the manuscript, and all authors critically revised the manuscript and gave final approval of the version to be published.

Funding

This study is supported by the German Department of Defence. The funder did not have a role in the design or conduct of the study and the authors have ultimate authority over study activities. The content is solely the responsibility of the authors and does not necessarily represent the official views of the German Armed Forces Medical Services on the topic.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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