BEST TBI

Bactericidal External ventricular drainS in paTients with Traumatic Brain Injury

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CONFIDENTIAL

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Table of Contents

1 Management committee authorisation page

We the undersigned members of the management committee have read the protocol attached herewith and authorize it as the official protocol for the study entitled, “Bactericidal external ventricular drains in patients with traumatic brain injury”.

_____	___/___/_____
Justin Moore	Date
_____	___/___/_____
Piers Thomas	Date
_____	___/___/_____
Dashiell Gantner	Date
_____	___/___/_____
Nicholas Maartens	Date
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Shirley Vallance	Date
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Meredith Young	Date
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Owen Roodenburg	Date
_____	___/___/_____
Allen Cheng	Date
_____	___/___/_____
Jeffrey Rosenfeld	Date

2 Background and rationale

External ventricular drain (EVD) catheters are integral to the management of treating patients with head trauma, subarachnoid haemorrhage and other neurosurgical conditions that necessitate cerebro-spinal fluid (CSF) diversion. However, as with all interventions the possible benefits must be weighed against the possible complications of the intervention. A common and potentially devastating complication of an EVD insertion is catheter infection leading to ventriculitis and meningitis. Infection rates ranging from 3.4%-21.9% have been reported[1-7]. These infections appear to stem from microorganism colonization of the EVD catheter. Development of ventriculitis not only has the potential to cause significant morbidity (with poor functional outcome), but also significantly raises the cost of health care for these patients, as a consequence of increased lengths of intensive care unit (ICU) and hospital stays, ongoing antibiotics and additional medical interventions[13,14].

In order to overcome this problem of bacterial colonization and subsequent infection, EVD and shunt catheters, which have been impregnated with antibiotics, have been used with varying degrees of success. A recent meta- and economic analysis focusing on the use of antibiotic impregnated shunts in a mixed population of paediatric and adult patients, found a significant reduction in infections when using these systems with an associated cost saving[18]. These catheters are significantly more expensive than standard catheters. To date, a number of studies have looked into the effect of using antibiotic impregnated catheters on EVD infection rates. An initial study which obtained data from 288 patients found that rifampicin and minocycline impregnated catheters were half as likely to be colonized as non-impregnated catheters and more importantly, the authors reported that CSF positive cultures were 7 times less frequent when using antibiotic catheters (1.3 vs 9.4%, p=0.002)[8]. However, less than 20% of these enrolled patients were trauma patients.

Another contemporary study, from New Zealand, compared infection rates in 60 patients with clindamycin and rifampicin impregnated catheters with 60 historical controls. The results suggested that impregnated catheters reduced the risk of ventriculitis (defined as positive CSF culture or raised WCC count) from 15% to 5% and CSF positive results dropped from 6.6% to 1.3%[9]. However, the indications for the insertion of the EVD were not provided[9]. Recently a large international, prospective, randomized trial found that of an initial sample size of 434 patients, 176 received an impregnated catheter and 181 a standard catheter[10]. This trial failed to find a significant benefit to the use of antibiotic impregnated catheter with a 2.3% for impregnated catheters compared to a 2.8% infection rate (positive CSF gram stain and culture) for standard catheters[10]. Suspected infection rate (positive CSF culture but negative gram stain or leucocytosis) was 17.6% versus 20.4%

and again was not significant. Unfortunately this study did not provide any information of whether any of the patients had suffered a traumatic head injury[10].

The most recent double blind, prospective randomised controlled trial conducted by Keong et al (2012) comparing silver impregnated catheters with standard catheters found a significant reduction in EVD infection rates (21.4% vs 12.3%)[11]. These authors also found that patients with EVD infections had twice the risk of shunt placement. However, again in this cohort of 278 patients, only 20% had traumatic brain injury[11]. Winkler et al. have recently found that infection rates between antibiotic-coated EVD catheters and silver impregnated catheters were not significantly different[12]. Numerous studies have found a reduced rate of blood stream infections from use of central venous catheters (CVC) impregnated with antibiotics, which has resulted in a significant reduction in CVC related costs[15,16,17].

To summarise the contemporary literature, the role of antibiotic impregnated catheters remains unsettled; in particular, the trauma setting is underrepresented within these studies.

In our experience patients suffering traumatic head injures often suffer multiple injuries in addition to their head injury and often require prolonged stays in ICU. It is in this cohort of patients that impregnated catheters might be most useful, as we suspect the altered physiological conditions and presence of concomitant (often contaminated) injuries enhance the global risk of catheter infection beyond that of other patient cohorts requiring EVD insertion.

3 Objectives

3.1 Aim

This study aims to determine whether, compared to standard EVDs, insertion of antibiotic-impregnated Bactiseal™ EVDs reduces the incidence of catheter-associated central nervous system (CNS) infection in patients with TBI.

3.2 Study hypothesis

It is our hypothesis that patients suffering traumatic head injuries requiring insertion of EVD may benefit from reduced rates of ventriculitis by the use of antibiotic impregnated catheters. We propose to test this hypothesis by undertaking a prospective randomized trial comparing antibiotic impregnated EVD catheters to standard catheters in patients suffering TBI.

4 Study outcome measures

4.1 Primary endpoint

- Incidence of ventriculitis in TBI patients with Bactiseal™ EVDs compared with standard EVDs

4.2 Secondary endpoints

- Indications for EVD insertion
- Duration of placement
- Shunt placement
- Rates of complications: CSF leaks around EVD/Infections of EVD wound
- ICU and hospital lengths of stay
- Estimated health care costs associated with acute care.
- Extended Glasgow Outcome Scale (GOSE) at 6 months

5 Overall study design

5.1 Study design

BEST TBI is a prospective, multi-centre, randomized, controlled trial comparing the effect of antibiotic-impregnated Bactiseal™ EVDs on incidence of ventriculitis when compared with standard EVDs in patients with TBI.

5.2 Study population

Sequential adult (≥16 years old) patients with TBI of any severity who require insertion of an EVD for any reason, who meet all inclusion criteria and have no exclusion criteria.

5.3 Inclusion criteria

- ≥16 years old
- TBI requiring EVD insertion

5.4 Exclusion criteria

- Known or suspected CSF infection at time of EVD insertion
- Any other indication for ongoing antibiotics at the time of EVD insertion
- Prior EVD insertion (last 30 days)
- Sepsis, ventriculitis, meningitis, skin infection at implantation site.
- Allergy to Rifampicin and Clindamycin
- Multiple EVDs required con-currently

6 Study procedures

6.1 Investigational product

EVDs are routinely used for the management of hydrocephalus and intracranial hypertension, and for intracranial pressure monitoring in TBI. Standard and antibiotic (rifampicin and clindamycin) impregnated (Bactiseal™) catheters are currently both in use at participating study sites , without clear guidelines for which patients should receive either type.

6.2 Eligible patients

Patients with TBI will be screened in the emergency department, operating theatre and intensive care by the neurosurgical and intensive care research teams for their potential eligibility.

6.3 Enrolment and randomisation

Eligible patients will be transferred to the operating theatre for EVD insertion. Sealed, sequentially numbered, opaque, randomization envelopes will be placed in the operating theatre and will be opened by the neurosurgeon while the patient is being prepared for the procedure. The scrub nurses will then provide the EVD as per the randomly allocated treatment arm for the surgeon to insert. In rare cases EVD insertion may occur in the ICU, in which case the next envelope will be opened and treatment allocation identified prior to transfer of appropriate equipment to the ICU.

Randomisation will be on a 1:1 ratio, stratified by study site. The study statistician will develop a randomised schedule.

6.4 Blinding

The catheters are different colours; hence the surgeon placing the catheter and other theatre staff will not be able to be blinded. However, potential treatment differences will be minimised by exclusion of patients with other indications for antibiotics, thereby reducing the potential for early ad hoc antibiotic administration. Study group allocation will not be revealed to the treating ICU medical team. In the post-insertion ICU period, ICU teams and research coordinators will be blinded to the type of catheter inserted by application of opaque dressings. Redressings will be undertaken by nursing staff unaware of treatment allocation. Inadvertent recognition of catheter type by nursing staff is highly unlikely to lead to differences in patient management.

In the event of an adverse event suspected to be causally related to this study, blinding may be broken.

6.5 Discontinuation of treatment

The EVD will be removed once it is no longer required according to current practice, and as determined by the treating neurosurgical and ICU teams. Trial participation will have no bearing on the decision to remove the EVD.

6.6 Laboratory sampling and testing

Surveillance CSF samples will be collected from the patient every 72 hours post EVD insertion. Additional samples will be drawn if signs of infection are present (febrile, change in mental status, raised WCC, signs of meningitis).

At the time of EVD removal, the catheter will be removed aseptically and tip sent for culture/colonization.

6.7 Antibiotic usage

Prophylactic antibiotic administration at the time of EVD insertion is recommended. In the absence of hypersensitivity, a first-generation cephalosporin (cephazolin) is routinely given at the trial sites. Ongoing antibiotic prophylaxis is not recommended in the absence of suspected or confirmed CNS infection; patients who have other indications for ongoing antibiotics at the time of EVD insertion will be excluded from the trial, preventing the early, ad hoc use of antibiotics.

During the study participants may develop loci of infection outside the CNS for which courses of antibiotics are indicated. The use of, type and indication for ongoing antibiotics, will be recorded to enable comparison between groups.

6.8 Outcome assessments

6.8.1 Ventriculitis

Meningitis or ventriculitis must meet at least 1 of the following criteria:

1. Patient has organisms cultured from cerebrospinal fluid (CSF).

2. Patient has at least 1 of the following signs or symptoms: fever (>38°C), headache*, stiff neck*, meningeal signs*, cranial nerve signs*, or irritability*

   AND at least 1 of the following:

   a. increased white cells[$], elevated protein, and decreased glucose in CSF

   b. organisms seen on Gram's stain of CSF

   c. organisms cultured from blood

   d. positive laboratory test of CSF

   e. diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen

AND if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy.

* With no other recognized cause

[$] For increased White cells: WBC: RBC ratio of greater than 0.02

6.8.2 Glasgow Outcome Scale

The extended Glasgow Outcome Scale (GOSE) is routinely obtained for all trauma patients in Victoria by the Victorian State Trauma Registry (VSTR). This data will be obtained for BEST TBI participants and compared between groups. Participating non-Victorian sites will obtain this data via their local Trauma outcome follow up.

7 Ethics

This study is to be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000 and Note of Clarification 2002, 2004, 2008), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated

with Therapeutic Goods Administration comments and NHMRC National Statement on Ethical Conduct in Human Research (2007 – updated May 2013).

7.1 Ethical issues of the study

Patients will not have the capacity to consent for themselves. However, this study is low risk, comparing two treatments in current accepted care without any additional sample collection beyond that which would already be undertaken; hence an opt-out approach will be used.

7.2 Ethics committee approval

This protocol will be submitted to each participating hospital's Human Research and Ethics Committee (HREC). Approval of the protocol and related documents will be obtained prior to the start of the study at each site.

It is the Principal Investigator's responsibility to ensure that all conditions for the approval of the study are met and that amendments to the protocol or serious adverse events are also reported to the HREC as required by that committee.

7.3 Confidentiality of patient data

Following enrolment, patients will be identified by their unique study number. A log will be kept with patient details and the corresponding unique identifier. The patient log will be kept in a secure locked office.

Study data will be entered into a secure, password-protected database. Identifiable data will not be divulged to any third parties outside of the study.

7.4 Informed consent

This project involves emergency care research; recruitment has to be achieved rapidly as the treatment (EVD insertion) is urgent. The NHMRC National Statement on Ethical Conduct in Human Research acknowledges (4.4.6) that where the research involves emergency treatment a waiver for consent may be provided. The Statement also outlines the conditions when an opt-out approach may be granted (2.3.6 and 4.4.13). The reasons we believe such an approach may be granted to this project include: it carries no more than low risk as defined by the National Statement (2.1.6 and 2.1.7); the research supports a reasonable possibility of benefit over standard care; it is impractical to obtain consent given the emergency nature of the treatment; there is an adequate plan to protect the confidentiality of data; both arms of treatment are within current practice, and there is no known reason for thinking the participants would not have consented if asked.

Once the diagnosis of TBI has been made, there is frequently an urgent need for EVD insertion in the operating theatre. Frequently the patient's next of kin is not readily contactable, and the procedure is performed on the basis of emergency lifesaving treatment. As soon as is practical following recruitment the participant and/or their legally authorised representative will be informed of their inclusion in the study, and of the option to withdraw without any reduction in quality of care. Written information including contact information for research staff will be provided. If they choose to withdraw, permission will be asked to use the data collected up to that time (4.4.14).

Any interaction between research staff, participants and their person responsible will take into consideration the stress or emotional factors associated with critical illness and ensure that the dependency of potential participants and their relatives on medical personnel providing treatment does not compromise the freedom of the decision to continue participation (4.4.11).

8 Data management

8.1 Data collection methods

Data will be entered into a secure, password-protected database. Data entry and data management will be coordinated by the Chief Investigator. Data will be checked at the time of entry and queries referred back to the relevant sites.

Initial data collection will be by the treating surgeon who has placed the EVD. Data variables are listed below. Subsequent data will then be collected by the ICU research coordinators, including clinical and laboratory findings, patient outcomes and adverse events.

Additionally patients will be reviewed one-week post EVD removal (the vast majority of these patient will be either in ICU or on the ward) to ensure there is no evidence of delayed ventriculitis / meningitis. This will be a clinical review conducted by the treating neurosurgical team, with the aide of diagnostic tests as appropriate (which is the current practice).

The patients GOS at 6 months will then be reviewed. This data is routinely collected by the Victorian State Trauma Outcomes Registry (VSTORM) for all trauma patients in Victoria. Permission to access this data will be requested from the VSTORM principal investigator and project co-ordinator. Non-Victorian sites will obtain this data from their local trauma outcome follow up service.

8.2 Data variables collected

8.2.1 Demographic data

- Initials
- Date of birth
- Gender
- Australian and New Zealand Intensive Care Society Adult Patient Database identifier

8.2.2 Injury data

- Mechanism of injury
- GCS on scene and on arrival in ED
- Trauma severity scores
- Open skull fracture
- Contaminated head wounds
- Head CT appearance:
    - Trauma with Haemorrhage
    - Intraventricular haemorrhage
    - Diffuse traumatic head injury
    - Hydrocephalus

8.2.3 Procedure

- Number of attempts to pass EVD.
- Mean length tunnelled.
- Place of insertion: OT/ICU
- Type of catheter (AI vs. Standard).
- Procedure time (minutes- skin to skin))

- Associated neurosurgical procedures (Craniotomy/Craniectomy)

8.2.4 Hospital and ICU data

- Hospital admission and discharge dates
- ICU admission and discharge dates
- Infection: Categorized
    - CNS
    - EVD insertion site
    - Chest
    - Wound
    - Other
- Timing and type of systemic antibiotic therapy
- EVD colonization: species.
- Time to infection
- Insertion site shaved.
- Length of time EVD inserted (days)
- Any CSF leaks from around drain site or other locations, during the period of insertion
- Development of CDC/NHSN criteria for ventriculitis (see below)

8.2.4.1 CDC/NHSN Definition for Ventriculitis

- Clinical signs:
    - fever (>38°C)
    - headache*
    - stiff neck*

- meningeal signs*
- cranial nerve signs*
- irritability*

***With no other recognized cause**

- Microbiology
    - increased white count, elevated protein, and decreased glucose in CSF
    - organisms seen on Gram's stain of CSF
    - organisms cultured from blood
    - positive laboratory test of CSF
    - diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen

8.2.5 Follow up

- GOSE at 6 months
- Shunt placement at 6 months

8.3 Data management

Patients will be identified by a unique identifier. A log will be kept with patient details and the corresponding unique identifier. The patient log will be kept in the secure locked offices of the research staff.

Information will be stored in the form of paper CRFs archived in accordance with the standard operating procedure of the local HREC. Only the research staff will have access to this data. The log of patients involved in the study which permits identification of the information will be retained in the ICU Research Office and will be accessible only by the research staff. De-identified data will then be entered into a secure, password-protected computer database which will only be accessible by the research team.

8.4 Monitoring

Recruitment, data collection, result analysis and general conduct of the trial will be monitored by the Chief Investigator with the aide of the co-investigators. Any concerns, particularly those concerned with breaches of confidentiality will be reported to the HREC, investigated and managed according to hospital practice.

9 Statistical considerations

9.1 Power calculations and sample size

The baseline incidence of ventriculitis is estimated to be 9%. Our sample size is based on an absolute decrease of 8%, to 1%. This effect size would be highly clinically relevant (number needed to treat [NNT] to prevent one case of ventriculitis = 13). This relative decrease is equivalent to or less than observed in previous trials. With a type 1 error of 0.05 and type II error of 0.2 (power 80%), the required number is 140 patients per group, or 280 patients in total.

The estimated time to complete patient recruitment is 1.5 – 2.5 years.

9.2 Analysis of results

This study will be analysed on an intention to treat basis. All analyses will be undertaken by the Chief Investigator with the aid of a biostatistician. Baseline comparisons will be performed using chi-square tests for equal proportion, student t-tests for continuous normally distributed variables and Wilcoxon rank sum tests otherwise. The primary outcome will be analysed using a chi-square test with results reported as frequencies and percentages per arm. A two-sided p-value of 0.05 will be considered to be statistically significant.

9.3 Minimising bias

Data collectors, the treating ICU team and outcome assessors will be blinded to the type of EVD used. It is not possible to blind the operating surgeon who places the EVD, but they will not know the EVD allocation until the time of insertion, thus minimising potential selection bias.

10 Safety

10.1 Adverse events

Foremost, it should be noted that the trial poses no more of a risk than is inherent in the patient's condition and alternative treatment, as all of these patients currently would receive an EVD and many of them would be antibiotic impregnated.

However, it should be noted that critically ill patients in the intensive care unit are at increased risk of a number of deleterious events. A large portion of these will be related to the physical state of the patient, and some will be related to the routine interventions that occur in ICU. Any adverse events will be managed by the treating clinicians at their discretion and according to standard ICU protocols.

Whilst the patient is in ICU, routine daily data recording will include daily clinical examination and all relevant biochemical and haematological parameters and measures of organ dysfunction. This routine data recording is designed to assess patient progress and monitor adverse events of therapy including complications of an EVD.

The nature of the pathology (severe TBI, often associated with multi-system injuries) and by being in the intensive care and requiring acute therapies, include intervention for raised intracranial pressure there will be inherent risks. If any participant has an adverse event to either standard or antibiotic impregnated catheters whether it be foreseen or unforeseen, then the patient will be reviewed by the treating intensive care physician and if necessary the neurosurgical team, which is currently the standard practice.

Treatments, hospitalizations or events related to the natural history of the underlying health problem will not be considered SAE's that require reporting to the hospital ethics committee.

10.2 Serious adverse events

Principal Investigators will report any serious and unexpected adverse event they consider possibly, probably or definitely related to study treatment where the adverse event is not already captured by routine data collection. These will be reported to the HRECs within 72 hours. Predictable complications of therapy such EVD infections will not be reported to HRECs as these events are recognised complications and recorded as study outcomes.

11 Funding

This study has been supported by an unconditional grant from the Brain Foundation.

12 Timelines

HREC approval: Alfred Hospital: August 2014

Recruitment: Begins December 2014.

Recruitment should be complete in approximately 1.5-2.5 years (280 patients).

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Appendix 1 – Schedule of events

Data collection / Procedures	Hospital admission	Operating theatre	Daily ICU admission	Hospital discharge	6-month follow up
Screening log	**X**				
Inclusion & exclusion criteria		**X**			
Baseline characteristics		**X**			
Procedure data		**X**			
Clinical and laboratory markers of infection			**X**	**X**	
Adverse events		**X**	**X**	**X**	**X**
Glasgow outcome score					**X**

Appendix 2 – CRF

Part A (initial data collection) To be completed at time of EVD insertion

Name Unique Identifier

Age Sex

GCS: On Scene In ED Intubated: Y/N

Open skull fracture: Y/N Contaminated Head wound: Y/N

Type of ED Placed: Standard/Antibiotic Impregnated (Circle)

Insertion site shaved (Circle): Yes/No

Number of EVD pass attempts: 1 2 3 4 5 or more (please circle)

Mean length EVD tunnelled from wound (cm)

CT findings: Focal Extra axial collection (EDH/SDH)

(please circle) Diffuse Axonal Injury

Contusions/Intracranial haematoma

Intraventricular haemorrhage

Hydrocephalus

Additional operation: Evacuation of Haematoma/Decompressive craniectomy

Place of EVD insertion: Operating theatre/Emergency department/Intensive care unit (circle)

Procedure Time (Minutes): 0-30min, 30-60 min, 1-2 hours, Greater than 2 hours.

To be completed within 48 hours

Trauma: Single/Multi-trauma Trauma severity score:

Part B (To be completed on day 1 of admission, and then every 3rd day or when CSF sample sent).

Unique identifier:

CSF Culture: Positive Y / N

If yes: Type of bacteria and sensitivities

Microbiology

CSF Gram stain: Positive/Negative Type of Organism seen

CSF biochem:

White Cells Red Blood Cells Protein Glucose

Blood culture results: Positive/Negative Type of Organism seen

Clinical Signs (Please circle)

Fever (>38) Headache Stiff neck

Meningeal signs Cranial nerve signs Irritability

If the patient is not assessable (due to sedation/agitation) please place N/A

Current antibiotic therapy: None

Currently on systemic antibiotics: regime.

Indication:

Any CSF leaks: Yes/No Site: EVD drain site/EVD wound/other sites

Part C Follow up

Unique identifier

Length of time EVD *in situ* (days)

Length of time between EVD insertion and diagnosed infection (days)

EVD tip colonisation: No/Yes If yes: Species:

1 week post EVD follow up: Signs of ventriculitis/Meningitis: Yes/No

If yes: CSF confirmed: Yes/No

Length of stay in ICU

Length of stay in Hospital

GOS 6 months