STUDY PROTOCOL

Assessing use of vancomycin powder in craniotomy: randomized controlled trial (AVIC) [version 1; peer review: awaiting peer review]

Sirajeddin Belkhair¹, Muhammad Mohsin khan², Younis Baregzai², Khalida Walizada², Ahmed Eid², Ahmed Taha², Saleh Safi², Amr Mohammad², Abdullah Illeyyan², Tarek Ben Zabih², Ali Raza², Adnan khan², Firas Hammadi², Raed Jarir², Ali Ayyad², Talal Alrabayah²

¹Professor, Qatar University, Doha, Qatar
²Neurosurgery, Hamad General Hospital Surgical Specialty Center, Doha, 3050, Qatar
³Professor, Cornell University, Doha, Qatar

Abstract

Background: Surgical-site infections (SSIs) can lead to greater postoperative morbidity, mortality, and health care costs. Despite current prophylactic measures, rates of SSIs have been reported in up to 5% of patients post craniotomy. Intrawound vancomycin powder has been studied extensively in spinal fusion surgeries and been found to reduce rates of surgical site infections (SSIs) significantly. Despite its success in spinal surgeries, topical vancomycin has not been extensively studied with respect to cranial neurosurgery.

Methods: Our study is Prospective Randomized clinical trial. Patients will be divided in this Trial into two groups, first group (intervention arm) they will receive the drug (vancomycin) in the wound before the closure of the skin at the end of the surgical procedure. The second group (control arm) they will not receive the drug, otherwise both groups they will receive identical measure to decrease the postoperative SSI. The primary outcome variable will be SSI rate factored by cohort. Secondary outcome will be to monitor the safety and any complication related to the use of vancomycin. SSI found to be around 0.49% when vancomycin was used, while SSI in standard care found to be 5%, to get power of study 80% and level of significance 5%. Sample size will be 250 in each group using sample size calculator.

Discussion: This study is designed to evaluate the efficacy of vancomycin compared to standard method in neuro-surgical cases undergoing craniotomy. Additionally, safety of vancomycin will be assessed in these patients.

Open Peer Review

Approval Status  AWAITING PEER REVIEW

Any reports and responses or comments on the article can be found at the end of the article.
Keywords
vancomycin, craniotomy, infection, brain, surgery

This article is included in the Sidra Medicine gateway.

Corresponding author: Muhammad Mohsin khan (Mmkyousafzai@gmail.com)

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Abbreviations
CI: Confidence interval
CRM: Clinical Research Monitor
Hmc: Hamad medical corporation
ICMJE: International Committee of Medical Journal Editors
MRC: Medical Research Centre
OR: Odds ratio
RCTs: Randomized controlled trials
SPSS: Statistical Package for Social Sciences

Trial registration
ClinicalTrials.gov Identifier: NCT04917627, registered on June 8, 2021

Introduction
Background and rationale
SSI after Craniotomy is a significant cause of morbidity and mortality besides its high health care cost.

In each hospital, all measures are taken to decrease SSI.\(^1\) Despite current prophylactic measures, SSI rates have been reported in up to 5% of patients post-craniotomy. Intrawound vancomycin powder has been studied extensively in spinal fusion surgeries and has been found to reduce rates of surgical site infections (SSIs) significantly. Despite its success in spinal surgeries, topical vancomycin has not been extensively studied concerning cranial neurosurgery.\(^2\)

Using vancomycin powder during spinal fusion surgery can significantly lower the likelihood of postoperative infections\(^3\) and reduce medical costs associated with those infections. Godil et al., in their study, suggest that the use of vancomycin powder for high-risk patients in spinal fusion surgery is a cost-effective option that can save up to $438,165 for every 100 spinal fusions performed.\(^4\)

Topical vancomycin is safe, effective, and cost-effective in preventing SSIs.

Following Craniotomy.\(^5\)

Objectives
I. **Primary objective:** to assess the effectiveness of vancomycin in Craniotomy on the surgical site infection rate compared to controls.

II. **Secondary objective:** to assess the complications of intrawound vancomycin like seroma, long-term benefit, and cost-effectiveness of vancomycin use on hospital stay and patient recovery.

Trial design
Our study is a Prospective Randomized Clinical Trial, parallel-group allocation with an equal number of patients. We will do block randomization by a biostatistician through SAS software and determine the superiority of intervention to the control group. Patients will be divided in this Trial into two groups, first group (intervention arm) will receive the drug (vancomycin). The second group (control arm) will not receive the drug; otherwise, both groups will receive identical measures to decrease the postoperative SSI.

Methods
Study setting
The Hamad General Hospital in Qatar, a government-run health facility and the main center for neurosurgery in Qatar was selected as the primary location for recruiting participants in this study. This hospital is very accessible and affordable for the majority of the country’s population, making it a good representation of the community as a whole. Plus, the hospital provides continuous healthcare services for the people of Qatar free of cost.
Eligibility criteria
Patient inclusion and exclusion criteria:

Inclusion criteria:

1) Any Craniotomy, whatever the cause
2) Age more than 18 years
3) Patient with no evidence of any source of infection

Exclusion criteria:

1) Any evidence of infection
2) Age less than 18 years
3) Previous and multiple craniotomies

Who will take informed consent?
The consent will be taken by investigators of the study that MRC approves.

Additional consent provisions for the collection and use of participant data and biological specimens
No biological specimen is required in the study.

Interventions
The explanation for the choice of comparators
In our study, not to cause any potential bias in the selection process, the comparative arm of the study is chosen from the same hospital setting where all patients are admitted. Our study’s inclusion and exclusion criteria are applied to ensure that the selection process is fair and unbiased.

Intervention description
After the surgery, we will be performing a thorough irrigation, a single vial of vancomycin powder containing 1000 mg of the drug will be applied post-op to the surgical bed and wound at the end of the surgery.

Criteria for discontinuing or modifying allocated interventions
This intervention is only a one-time occurrence; participants can leave the study at any point and withdraw their consent. In our study, there are no specific criteria for discontinuing or modifying the interventions that have been allocated to them.

Strategies to improve adherence to interventions
Data collectors will provide phone reminders regarding their follow-up appointments to ensure that our study participants in both groups adhere to the study protocol.

Relevant concomitant care permitted or prohibited during the Trial
If a participant develops any other extra-cranial infection or disease during the study, they will be referred to urgent emergency care based on the Hamad Medical Corporation (HMC) guidelines. The participant will receive appropriate treatment free of cost.

Provisions for post-trial care
All necessary treatments for cancer and other conditions will be provided to the participants free of charge at the Hamad Medical Corporation following their guidelines and the patient’s diagnosis.

Outcomes
In trial in addition to assessing the effectiveness of using intra-wound topical vancomycin to prevent surgical site infections (SSIs) after open craniotomies, this study will also examine the incidence of meningitis as well as morbidity and mortality rates.
Primary outcome: surgical site infection.

Secondary outcome: complications of intrawound vancomycin, hospital cost.

Participant timeline

<table>
<thead>
<tr>
<th>TIMEPOINT**</th>
<th>STUDY PERIOD</th>
<th>ENROLMENT</th>
<th>Allocation</th>
<th>Post-allocation</th>
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<tbody>
<tr>
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<td>Enrolment</td>
<td>Allocation</td>
<td>Post-allocation</td>
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<td>ENROLMENT:</td>
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<tr>
<td>Eligibility screen</td>
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<td>Informed consent</td>
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<td>Randomization</td>
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<td>INTERVENTIONS:</td>
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<td>Vancomycin application</td>
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<td>ASSESSMENTS:</td>
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<tr>
<td>1. Chronic illnesses</td>
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<td>2. Chemotherapy</td>
<td>X</td>
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<td>3. Smoking</td>
<td>X</td>
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<td>4. Hypertension</td>
<td>X</td>
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<td>5. Diabetes</td>
<td>X</td>
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<tr>
<td>6. 2 weeks wound assessment</td>
<td>X</td>
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<tr>
<td>7. 6-12 weeks wound assessment</td>
<td>X</td>
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</tbody>
</table>

-t₁: before enrolment, assessment for eligible and exclusion criteria; 0: after randomization and allocation, it is the baseline; t₁: the intervention; t₂: 2 weeks wound assessment; t₃: 6-12 weeks wound assessment.

Sample size
SSI was found to be around 0.49% when vancomycin was used, while SSI in standard care was 5%, to get the power of study 80% and level of significance 5%. The sample size will be 250 in each group using a sample size calculator.

The statistical formula used in the computation of the required and adequate sample size because of the primary outcome, i.e.,

SSI rate between the two groups:

The sample size was computed using the following statistical formula and sample size determination equation:

\[ n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times (p_1(1 - p_1) + p_2(1 - p_2))}{(p_1 - p_2)^2} \]

Where \( Z_{\alpha/2} \) is the critical value of the Normal distribution at \( \alpha/2 \) (e.g., for a confidence level of 95%, \( \alpha = 0.05 \) and the critical value is 1.96), \( Z_{\beta} \) is the critical value of the Normal distribution at \( \beta \) (e.g., for a power of 80%, \( \beta = 0.2 \), and the critical value is 0.84) and \( p_1 \) and \( p_2 \) are the expected sample proportions of the two groups (SSI rate between the two groups, i.e., vancomycin and control groups).


Recruitment
After assessing the eligibility and exclusion criteria, it was done through the patients presenting to hamad general hospital for Craniotomy.
Assignment of interventions: allocation

Sequence generation

Before the study randomization list was generated with a coded file with each code randomized to either arm (intervention arm or control arm), the patient will be assigned to the subsequent arm according to the code. The code was blinded to the rest of the team doing wound assessment on follow-up.

Concealment mechanism

The participants in our study will be randomly allocated into either the intervention or control group to minimize selection bias. Concealment of group allocation will also be performed to prevent potential bias. Before the intervention, an investigator who will not be involved in patient follow-up will allocate eligible participants into the two groups according to the randomization list. The investigators approved by MRC who will be following up with the patients will be blinded to the randomized group to prevent any potential bias in the study.

Implementation

One investigator is assigned to generate the allocation list, enrol participants, and assign patients to one of the groups according to the randomization list.

Assignment of interventions: Blinding

Who will be blinded?

To minimize performance and ascertainment bias in our study, blinding will be implemented for the data analyst. The data entry process will also be blinded by providing each subject with a unique code before entering the data for analysis. Plus, the team responsible for following up with the patients’ wounds will be blinded to the randomization of the patients.

Procedure for unblinding if needed

One investigator will have access to both the coded and randomization lists, and unblinding will only occur after a team meeting and approval.

Data collection and management

Plans for assessment and collection of outcomes

In our study, data will be collected using a data sheet approved by the MRC (Medical Research Council). At the initial assessment, data on demographics will be collected, and at later follow-up visits, data on wound condition will be collected by two separate investigators in our study. Both investigators and data sheets will be blinded from each other and the rest of the research team to prevent potential bias.

Plans to promote participant retention and complete follow-up

All patients in our study would be required to follow up regularly as per the hospital’s policy for assessment after surgery. The investigators responsible for following up with the patients will proactively contact them in case of missed appointments. Patients who are lost to follow-up will be noted in the study records.

Data management

The data collected from our study will be entered and analysed using the Statistical Package for Social Sciences SPSS® V22.0. Both electronic and paper-based data will be stored in HMC for a maximum of 10 years and destroyed afterward.

Confidentiality

To ensure patient confidentiality in our study, all patient-related information will be coded on separate sheets. Validity-checked data will be transferred to the study statistician in the same secure manner, with identifiable patient information being password-protected. The code identification list that links the subject’s identity will be kept confidential and stored separately in a sealed envelope, locked in a cabinet, along with the study files with limited access. The team will maintain a screening/enrolment and randomization log to record screening, enrolment, and randomization details.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use

Does not apply.

Statistical methods

Statistical methods for primary and secondary outcomes

In data analysis for our RCT, Quantitative variables will be presented as mean and standard deviations. On the other hand, categorical variables will be reported as frequencies with percentages, the intervention and control groups will be
described in a table with all their characteristics, and percentages of categorical variables will be compared using the Chi-square test. Following the analysis, Regression analysis will be conducted to stratify the data and eliminate potential confounders and effect modifiers. in our RCT, a p-value of 0.05 (two-tailed) would be considered the threshold for statistical significance.

**Interim analyses**
We will do the interim analysis of our study when we reach 250 research participants, with 125 in each group.

**Methods for additional analyses (e.g., subgroup analyses)**
Subgroup and regression analyses will be conducted to investigate the effects of age, chemotherapy, and chronic illness on the outcome of RCT; this analysis will aim to understand better how these variables may influence the efficacy of intrawound topical vancomycin for preventing surgical site infections after open craniotomies.

**Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data**
In our RCT, the intention-to-treat principle will be applied during the study analysis, meaning that all participants will be analysed in the randomized group, regardless of whether they completed the study or not. Early discontinuation of the study will be treated as an independent right censoring in the primary analysis. Since all patients will undergo regular follow-ups for wound care and stitch removal, we do not anticipate any lost-to-follow-up cases during the study.

**Plans to give access to the complete protocol, participant-level data, and statistical code**
Yes, on request.

**Oversight and monitoring**

**Composition of the coordinating center and trial steering committee**
Institutional Review Board (IRB) will ensure human research participants’ protection, safety, and welfare under its supervision. The HMC IRB monitors and assigns this duty to Clinical Research Monitor(s) (CRM). The HMC IRB office designates the CRM, which takes responsibility for site initiation and monitoring visits. The IRB’s risk assessment of the study determines the monitoring schedule.

Before conducting visits, the monitor(s) must be well-versed in the study protocol and all related procedures. Throughout the study, initial site training, routine monitoring, and close-out monitoring will be carried out. The initial monitoring visit will occur after enrolling the first 20 subjects, with subsequent visits occurring midway through and at the study’s conclusion. The research will adhere to the principles of the “Declaration of Helsinki,” Good Clinical Practice, and the laws and regulations set forth by Qatar’s Ministry of Public Health, emphasizing autonomy, justice, informed consent, and fast-track ethical approval under protocol number (MRC-01-18-220). Participation or non-participation will not impact the standard care received by patients.

**Composition of the data monitoring committee, its role, and reporting structure**
The MRC ethical committee will conduct formal external independent monitoring. This monitoring process involves site visits to the research location in order to review informed consent forms, as well as remote inspections of Cerner’s database and related documentation.

**Adverse event reporting and harms**
During our study, adverse effects and reporting will always adhere to the HMC (MRC) policy. Our research indicates minimal risk, vancomycin’s safety profile is well-established, and its low application poses even fewer risks. In compliance with HMC’s policy, any patient experiencing an adverse effect will receive an immediate referral for evaluation by the neurosurgery team in the emergency department.

**Frequency and plans for auditing trial conduct**
After enrolling the initial 20 subjects, the first monitoring visit will occur. Subsequent visits are scheduled for the middle and conclusion of the study. During these visits, the monitor(s) will examine 50% of the data collection sheets and consent forms. Following each visit, the CRM will provide feedback to the study team, commending them on aspects executed well and identifying areas requiring improvement. At the final visit, the monitor(s) will confirm that all questions have been addressed, the study product has been accounted for and either returned or disposed of, and all study documents have been appropriately archived.
Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees)
Obtaining approval for any protocol modifications or amendments will be required from the HMC ethical committees. All alterations will be documented in the study registration.

Dissemination plans
The study protocol and its findings will be published in prominent journals to share the results. Individuals involved in the study will be granted authorship following the International Committee of Medical Journal Editors (ICMJE) guidelines. Professional writers and those not directly involved in the writing process will not be considered for authorship.

Discussion
In neurosurgical procedures, Craniotomy is the backbone of all procedures. That is used to operate multiple cases. There are different kinds of Craniotomy. It involves the removal of the bone flap and gives you access to the brain. Postoperative wound infections in neurosurgery can be lethal and devastating. Our study includes vancomycin to decrease this postoperative risk of infection.

Moreover, to see if it helps decrease wound infection rates in craniotomy patients, vancomycin is a safe drug and can be used for local applications on the wound. Moreover, its safety has been well documented in the literature.

Trial status
We are recruiting patients at present.

Data availability
No data are associated with this article.

Reporting guidelines

References
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