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Research Article

Evaluating the Safety and Efficacy of Semi-Synthetic Dural Substitutes in Cranial Surgery: A Combined Retrospective and Prospective Study

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Abstract

Introduction: The use of semi-synthetic dural substitutes in cranial surgery has garnered attention due to its potential in reducing complications, particularly Cerebrospinal Fluid (CSF) leakage. However, there is a lack of extensive research, especially in the form of randomized studies, to validate its efficacy and safety.

Methods: Our study was divided into two parts: a retrospective analysis of 30 patients who received semi-synthetic dural replacements from December 2022 to March 2023, and a prospective study of another 30 patients from March 2023 to September 2023. The inclusion criteria were patients over 18 undergoing neurosurgical procedures requiring dural replacement. The primary outcome measured was the rate of CSF leakages, with secondary outcomes including clinical and radiographic parameters to assess signs of infection or inflammation.

Results: Both the retrospective and prospective studies successfully included 30 patients each, with no adverse events reported in either group. No evidence of CSF leakage or inflammation was observed in the postoperative period. The average age of patients was 63.2 years in the retrospective group and 61.2 years in the prospective group, with a balanced distribution of male and female patients.

Discussion: The results indicate that semi-synthetic dural replacement is a safe and effective option in cranial surgery, aligning with findings from other studies in the field. However, the variability in CSF leakage rates in existing literature underscores the need for larger, randomized studies for a more definitive conclusion.

Conclusion: Our study supports the use of semi-synthetic dural substitutes as a safe and low-risk option in neurosurgery. While our results are encouraging, further large-scale randomized studies are necessary to conclusively determine its effectiveness in preventing CSF leakage.

INTRODUCTION

The dural closure represents a critical step in cranial surgeries, often relegated to assistant physicians due to its underestimated importance. Despite its significance, there is a lack of clear guidelines and pivotal studies addressing this procedure. This oversight becomes even more pronounced in surgeries involving the posterior cranial fossa. Highlighting this issue, a comprehensive review article was published by Achinger in 2023 [1]. This paper underscores the evolving understanding and the critical need for more focused research on the impact of dural closure techniques in neurosurgery.

BACKGROUND

The absence of clear, randomized studies in the field of cranial surgery, particularly regarding dural closure, presents a significant gap in medical knowledge. The most severe complication in these procedures remains the Cerebrospinal Fluid (CSF) leak. Persistent CSF leakage poses a substantial risk of infection, potentially jeopardizing the success of the entire surgical operation. Additionally, the use of allogeneic dural replacement materials remains a topic of considerable debate within the medical community.

A notable study contributing to this conversation is by Azzam D, et al. [2] which was published in World Neurosurgery in 2018. This study underscores the need for further research to evaluate the safety and efficacy of dural substitutes in larger, prospective patient cohorts.

In light of these findings and ongoing debates, we at the

University Hospital Augsburg have initiated a bifurcated study focused specifically on the use of allogeneic dural replacement. This study aims to provide more detailed insights into the implications of using allogeneic materials for dural closure in cranial surgeries, addressing a critical gap in current medical research.

METHODS

This study was designed as a two-part investigation, comprising both retrospective and prospective components. The research was approved by the Ethics Committee of Ludwig-Maximilian University Munich.

We used the STROBE statement as a reporting guideline [3].

Study design and patient selection

This study was designed as a combined retrospective and prospective analysis focusing on patients who underwent neurosurgical procedures involving semi-synthetic dural replacements. It was conducted in two distinct phases:

Retrospective analysis (December 2022 - March 2023): This phase involved analyzing data from the last 30 patients who received semi-synthetic dural replacements during the specified period. Inclusion criteria were patients aged 18 and above who had undergone allogeneic dural replacement, with the primary exclusion criterion being a history of prior craniotomy.

Prospective analysis (March 2023 - September 2023): The prospective phase involved the active enrollment and monitoring of 30 new patients undergoing similar procedures. The inclusion and exclusion criteria were consistent with those of the retrospective phase. This phase aimed to collect real-time data for a more current understanding of the outcomes.

FOLLOW-UP PERIOD

In both retrospective and prospective phases, patients were followed for a duration of 30 days post-surgery. This follow-up period was chosen to effectively monitor immediate and short-term postoperative outcomes, such as complications, recovery progress, and early signs of infection or inflammation.

Data collection and management

Data were comprehensively collected from patient medical records, surgical reports, and follow-up notes. Key information included:

- Demographic details of the patients
- Specifics of the neurosurgical procedures
- Immediate and short-term postoperative outcomes
- Follow-up data within the 30-day postoperative window

Surgical approach and procedure

The surgical approach in this study was meticulously designed to prioritize the integrity and functionality of the dural replacement. A key objective in each procedure was to achieve a watertight suture, critical for preventing Cerebrospinal Fluid (CSF) leakage and ensuring optimal patient outcomes.

DURAL SUTURING TECHNIQUE

- Each neurosurgical procedure involved careful handling of the semi-synthetic dural replacements.
- The primary aim during suturing was to establish a watertight seal. This was considered a critical step in the procedure, as a watertight suture significantly reduces the risk of CSF leakage and related complications.
- Surgeons were given the discretion to decide on the suturing technique. They could opt for a pure suture approach or enhance the suture line using additional materials like adhesive patches or fibrin glue. This flexibility allowed surgeons to tailor the procedure based on the specific surgical scenario and patient's condition.

USE OF ADHESIVE ENHANCEMENTS

- In situations where additional security was deemed necessary, surgeons could employ adhesive patches or fibrin glue.
- The use of these materials was at the surgeon's discretion and was based on factors like the size of the dural opening, the patient's medical history, and intraoperative findings.
- These adhesive enhancements were applied to reinforce the suture line, ensuring a more robust and reliable seal.

Final Water Test

- The culmination of the dural suturing process involved a critical water test.
- This test was conducted to ensure the suture's integrity and confirm its watertight nature.
- During the test, the surgical area was irrigated with sterile water, and the suture line was closely inspected for any sign of leakage.
- This step was mandatory for all procedures, serving as a quality control measure to verify the success of the suturing technique.

ENDPOINTS

Primary Endpoint

- Incidence of CSF leakage within the 30-day follow-up period.

Secondary Endpoints

- Clinical assessments for signs of infection or inflammation during the follow-up.

- Radiographic evaluations within the follow-up period.
- Recovery and quality of life metrics assessed at the end of the 30-day follow-up.

Ethical Considerations

The study was conducted in compliance with ethical standards, with approval from the relevant ethics committee. Patient confidentiality and data privacy were a top priority.

The study protocol was approved by the ethic committee of the Ludwig-Maximilian-University Munich (Bavaria / Germany) at 12.03.2023 with the ID: 22-1112.

Study limitations

Recognized limitations included potential selection bias, limited follow-up duration impacting the assessment of long-term outcomes, and non-randomized patient selection influencing results.

Study design

This research utilized a single-center study design to investigate the phenomenon under investigation. The decision to conduct a single-center study was based on logistical and resource constraints. While this design offers specific advantages, such as control over experimental conditions and consistent data collection protocols, it may limit the generalizability of the findings to a broader population.

Blinded evaluation

The evaluation of study outcomes was not conducted in a blinded manner. Due to practical considerations, the evaluators were aware of the treatment allocation for each participant during the data analysis phase. This lack of blinding introduces the potential for bias in the interpretation of the results. To minimize potential bias, we employed absolute analysis criteria (such as assessing whether the patient was alive or required re-operation). While blinding was not feasible in this study, efforts were made to minimize bias through rigorous data collection and analysis.

Non-simultaneous treatment allocation

The treatment allocation for the study groups did not occur simultaneously. This may introduce confounding variables associated with temporal changes or external factors that could impact the outcomes of the study. While efforts were made to minimize these potential confounders through rigorous participant selection criteria and data analysis techniques, it is important to acknowledge the possibility of temporal influences on the observed results.

Statistical analysis

Comprehensive statistical methods were employed. Techniques included descriptive and inferential statistics to analyze patient outcomes during the 30-day follow-up period. Significance was set at $p < 0.05$.

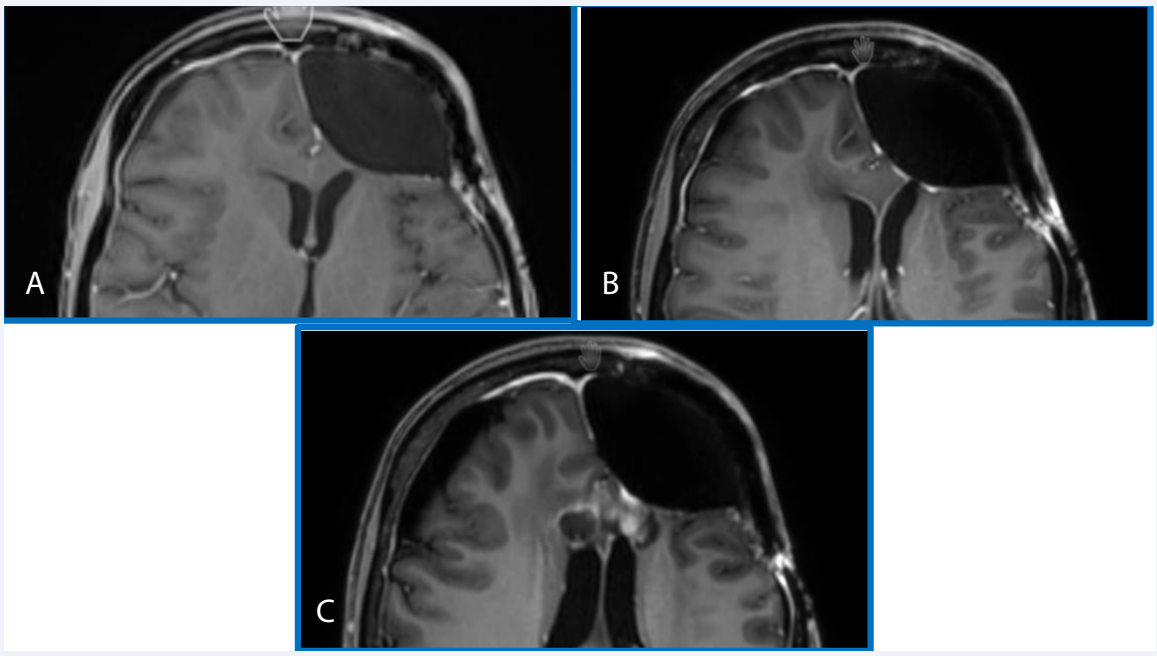

Figure 1 Follow-up series.
1A: 48h postoperative; 1B: 30 days postoperative; 1C: 3 Months postoperative

The collected data were subjected to rigorous statistical analysis to examine the research hypotheses. Descriptive statistics, inferential tests (e.g., t-tests, chi-square tests), and regression analyses were conducted as appropriate based on the nature of the variables and research questions.

Statistical software (GraphPad PRISM 9; GraphPad Software Boston (MA) USA) was employed for data analysis, and the significance level was set at $p < 0.05$.

Values were reported using median and one standard deviation (+/- 1SD). We checked Gaussians distribution using the Shapiro-Wilk test. Statistical differences of metric variables (blood loss, duration of surgery, length of hospital stay) were calculated using either the Student´s t-test or the Wilcoxon test for paired samples and the Mann-Whitney-U test for unpaired samples.

Data quality and integrity

Data quality and integrity were ensured through rigorous training of data collectors, double-data entry, and validation checks.

RESULTS

Retrospective study

In the retrospective study, we successfully included 30 patients as planned. The cohort comprised 43% female patients, with an average age of 63.2 years. The semi-synthetic dural replacement was used in 7 cases of benign conditions, such as infiltrative meningiomas, and in 23 cases of malignant tumors, including Glioblastoma Multiforme (GBM) and metastases. The surgeries were distributed as 10 on the left side and 20 on the right side of the brain. The size of the dural substitute used was consistently 6x8 cm. No adverse events occurred intraoperatively or in the 30-day postoperative period. Notably, there was no evidence of CSF leakage. Postoperative MRIs, conducted within 72 hours, showed no signs of inflammation, and humoral inflammatory parameters remained within normal ranges throughout the study period.

Prospective study

Similarly, in the prospective study, 30 patients were enrolled as per the study plan, with 46% female patients and an average age of 61.2 years. The dural replacement was used in 13 cases of benign conditions, such as infiltrative meningiomas, and in 15 cases of malignant tumors like GBM and metastases. Additionally, dural replacement was used in one case of cranioplasty and one case of decompression surgery for Arnold-Chiari Malformation. The surgeries were distributed as 11 on the left side, 17 on the right side, and 2 strictly in the midline. The size of the dural substitutes varied, ranging from 6x8 cm to 8x12 cm. Similar to the retrospective study, no adverse events were observed intraoperatively or in the 30-day postoperative period. There was no evidence of CSF leakage, and postoperative MRIs performed within 72 hours showed no signs of inflammation. The humoral inflammatory parameters consistently remained within normal limits.

DISCUSSION

Our study, both in its retrospective and prospective parts, demonstrated that semi-synthetic dural replacement is a safe and effective product in clinical practice. Across 60 cases involving significant cranial surgeries, we observed no adverse side effects or complications, particularly no instances of CSF leakage.

The work of Achinger and Williams in their systematic review "Trends in CSF Leakage Associated with Duraplasty in Infratentorial Procedures over the Last 20 Years" highlighted varying incidences of CSF leakage, with rates ranging from 0% to 25%, and larger studies reporting incidences between 3% and 15%. Their analysis underscored the complications associated with animal-derived substitutes, particularly bovine endocard and collagen matrix [1].

In contrast, the meta-analysis by Azzam et al. in "Dural Repair in Cranial Surgery" compared 462 cases of dural replacement and found no significant difference between autologous and allogeneic dura, although without detailed case analysis or match-pair analysis [2].

Hutter et al.'s randomized study on the efficacy of fleece-bound tissue sealing versus dural suturing alone in preventing postoperative CSF leaks and Surgical Site Infections (SSI) revealed a significant reduction in both CSF leakage and SSI with the use of TachoSil [4].

Khan, Pervez, and Sharafat's evaluation of a semi-synthetic dural substitute noted no difference in complication rates compared to autologous fascia lata, but highlighted a time-saving benefit of 40 minutes with the semi-synthetic substitute [5].

Lee et al. compared porcine and bovine collagen dural substitutes in posterior fossa decompression, noting a higher complication rate with porcine materials [6].

Mekonnen et al. reported a low complication profile with the use of DuraMatrix-Onlay(®) in cranial surgery, suggesting its safety for neurosurgical use [7].

Mohammed et al.'s observational case series highlighted extensive foreign body reactions to synthetic dural replacements. In contrast, our study with a semi-synthetic dura detected no such radiographic or laboratory changes [8].

Sánchez Fernández and Rodríguez-Arias' retrospective comparison of primary dural sutures with and without a sealant hemostatic patch showed a significantly lower CSF leakage rate in the patch-assisted group [9].

Sanpakitwattana et al. explored an innovative Cefazolin-loaded dural substitute, showing constant Cefazolin release and potential for new dural replacement technologies [10].

Earlier studies in 2016 and 2018 demonstrated promising

results with absorbable dural substitutes. However, a large 2022 study analyzing patients post-decompressive hemicraniectomy indicated that nonabsorbable dura is superior to absorbable dura in terms of complications and prognosis [11-13].

Other research groups, like Shimizu et al., have developed techniques to reduce the need for allogeneic duraplasty, though few have reached publication status [14].

In Summary our publication contributes significantly to the ongoing efforts to reduce postoperative complications following craniotomies that involve opening the dura. Techniques that add layers of security, such as patch plasties, are showing promising results in clinical practice. Specifically, our study highlights the safety and utility of semi-synthetic dura mater, demonstrating its extremely low risk profile in neurosurgical procedures(Figure 1).

In addition to these findings, it's important to discuss why semi-synthetic meninges are effective in preventing CSF leaks, a major concern in such surgeries:

Standardized surgical protocol for dural closure

- A key element in our approach was the implementation of a standardized protocol for dural closure. This protocol was meticulously designed and rigorously followed across all surgeries.
- Standardization ensured consistency in the handling and suturing of the dural material, which played a significant role in reducing the incidence of postoperative CSF leaks.
- By adhering to this protocol, surgeons were able to apply best practices uniformly, ensuring the highest quality of care and minimizing variability in surgical outcomes.

Properties of Semi-Synthetic Material:

- The semi-synthetic dura mater used in our study was selected for its excellent suture handling and overall manageability.
- Its properties, such as ease of suturing and adaptability to the surgical site, contributed significantly to achieving watertight closure.
- The material's compatibility with the human body and its ability to integrate well into the surgical site without causing irritation or rejection also played a crucial role in its effectiveness.

CONCLUSION

Our study demonstrated that the semi-synthetic dura offers a safe and low-risk option for cranial surgery applications. While our findings are promising, it is imperative to conduct larger randomized trials to accurately determine the effectiveness of semi-synthetic dura in preventing CSF leakage. The encouraging results from our research contribute to the evolving understanding of dural substitutes in neurosurgery and lay the groundwork for future studies in this critical area of medical science.

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AUTHOR CONTRIBUTIONS

MNB: Responsible for study design, conducting analyses, and manuscript drafting.

XZ: Provided scientific support and manuscript revision.

CW, MC, CM, AB, BS: Contributed to the study through data collection

DISCLOSURE STATEMENT

Maximilian Niklas Bonk (MNB): Received travel expense reimbursement from the sponsor.

Zhang X (XZ): Employees of the sponsor, involved in Research and Development.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of LMU Munich (approval number: 22-1112).

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