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| Title: | **Cranial Reconstruction Using A Polycaprolactone Implant After BurrHole Trephination** |
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## Study Design, Objectives, and Methodology

- The aim of this study is to present a 10-year experience (2006–2015) of using PCL implants in 174 consecutive patients, which includes a variety of different uses of burr holes, and a retrospective review of all PCL implants in terms of their safety.
- Patients who underwent burr hole craniotomies and reconstruction with a 12-mm diameter, 5-mm thickness PCL implant (Osteoplug® and Osteoplug®-C) 2015 were included.
- Outpatient clinical assessments were conducted at postoperative 1-month, 3-month, 6-month and 12-month, in the first postoperative year.
- Safety end points included the incidence of localized and disseminated intracranial infections related to the surgical wound (e.g., wound infection and meningitis), incidence of re-operations and incidence of any deaths, which could possibly be attributable to the implant.
- Two cases of radiological results after 3 and 9 years of implant insertion are reported.
- Histological results demonstrating tissue morphology and bony infiltration of an implant harvested from an 89-year-old male patient who had repeated burr hole surgery for recurrent chronic subdural hemorrhage is reported.

## Results

- 275 burr holes in 174 patients were closed using Osteoplug® .
- Mean age was 64.63 ± 17.18 years. Mean follow-up was 248.1 ± 435.3 days. Longest follow-up included in the study was 9.5 years.
- 41% of our patients presented with chronic subdural hematoma (CSDH), which was the majority indication. Acute on chronic subdural hemorrhage and subacute SDH formed another 30%. There were also 24 cases (14%) of intracerebral hemorrhage. Stereotactic biopsy and shunts for hydrocephalus were other clinical scenarios in which burr hole covers were used. (*See Table 1)*
- In the acute and subacute SDH groups, there were six re-operations that were all related to recurrence of SDH. There were no cases of infection.

- The recurrence rate of CSDH postoperative with the burr hole cover is comparable with the rate reported without the burr hole cover.
- Visible radio-opacity suggesting tissue regeneration was observed within the reconstructed burr hole region for two patients with long-term follow-up CT scans at postoperative 15 months and 8 years. *(See Figure 1)*
- Histological findings of a single case of an Osteoplug® explanted from an 89-year-old male patient who underwent re-operation for recurrent CSDH at 3.5 months after the initial surgery suggested that extensive tissue ingrowth and filling of the burr hole was achieved. There was evidence of minor calcification inside the Osteoplug® and homogenous blood vessel infiltration throughout the harvested tissue. *(See Figures 2 & 3).*

## Conclusions

- No increase in infection rate or complications rate by using Osteoplug®. This demonstrates the safe use of the Osteoplug® as a burr hole cover in a variety of procedures.
- No extra risk added to the discussed procedures by Osteoplug® .
- Postoperative recurrence rate of CSDH with the burr hole cover is comparable with the rate reported without the burr hole cover. Osteoplug® /Osteoplug®-C did not increase the recurrence rate of CSDH.
- Additionally, the rate of wound infection (0.36%, 1 out of 275 implants or 0.57%, 1 outof 174 patients) did not increase with the use of either of the implants, as compared with the literature
- Osteoplug® does not increase the risk of complications in VP shunt surgery.
- In this study Osteoplug® did not increase any of the risks associated with stereotacticbrain biopsy procedures.
- Histological and radiological findings suggest tissue regeneration.
- Although no cortical bone-like radiological findings were observed, our patients recovered well and there were no cosmetic complaints such as scalp depressions or softening of the implant-regenerated area in the observed period.
- Several limitations of this study are lack of control group, no randomization, and no quantitative comparison for cosmetic benefits of the implant.Several limitations of this study are lack of control group, no randomization, and no quantitative comparison for cosmetic benefits of the implant.

## Key Messages for Sales Reps

- This is a retrospective case series of 174 patients and 275 implants. These larger case numbers allow more robust conclusions to be derived.
- Restoration of the cranial contour allows the patient to regain their quality of life andto prevent unintended clinical complications.
- PCL burr hole cover implants might be stable on a relatively long-term follow-up with minimal risk of infection.
- Osteoplug® was used in burr holes created for different conditions. Most common indication for a burr hole in this study was chronic subdural hematoma.
- This study demonstrated safe application with only 0.36% wound infection.
- Use of the implant did not increase the surgical risk or rate of surgical complications significantly compared with the reported rate in literature.
- Radiological evidence of bone formation can be seen in as early as 3 months.

## When to discuss this publication

- Show clinical evidence/experience to answer questions regarding long term safety and prove low complication rates.
- Show clinical evidence to demonstrate Osteoplug® applications for different indications.
- Show radiological and histological evidence of bone growth *(See Fig. 1,2 & 3)*

Preliminary Communication

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# Cranial reconstruction using a polycaprolactone implant after burr hole trephination

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**Aim:** This retrospective study evaluated the safety of using polycaprolactone (PCL) burr hole covers over a 10-year period. **Materials & methods:** Patients with PCL burr hole cover implants inserted between 1 April 2006 and 31 September 2015 were identified and included in this study. Burr hole covers were used in surgery for chronic subdural hematoma, hydrocephalus and tumor biopsy. **Results:** 174 patients with a total of 275 implants inserted were included in the study. Overall, the use of PCL implants was safe and did not increase the rate of surgical complications. The radiology study of two cases and histology study of a removed PCL implant demonstrated evidence of soft tissue regeneration. **Conclusion:** PCL burr hole covers demonstrated safety in use for craniotomy burr hole reconstruction.

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**Keywords:** burr hole • chronic subdural hemorrhage • implant • polycaprolactone • trephination

Burr hole surgery is used for creating access to the cranial cavity. The burr hole is a small opening that traverses the full thickness of the calvarium and may be created as a prelude to hematoma evacuation, brain biopsy, construction of a craniotomy flap or placement of intracranial devices (e.g., drain, catheter and endoscope). The size of burr holes has generally decreased over the years, in tandem with concept of reducing the size of surgically created defects to reduce site morbidity. Therefore, cranioplasty following burr hole trephination may not be routinely performed. However, Im *et al.* reported recently the high occurrence of patients developing inferiority complexes (74%) and/or experiencing cosmetic and functional handicaps during activities of daily life such as combing and hairdressing (64%) due to noticeable scalp depressions (tactile, visual) [1]. A study by Vasella *et al.* also shows that the aesthetic outcome of patients is improved after burr hole cover placement [2]. This suggests a need to reconstruct burr holes in order to prevent non-neurological medical complications. Reconstructing the burr hole may alleviate the symptoms of scalp depression and prevent the development of other medical complications.

To this end, efforts have been made to prevent or minimize scalp depression through the use of material such as gelatin foam (gelfoam) andmethylmethacrylate. However, these materials appear to have a clinically negligible effect on reducing trephination-associated skin indentation, as evidenced by a study which found that 91% of patients who underwent gelfoam packing complained of cosmetically troubling scalp indentations over their burr holes at a mean follow-up of 21 weeks [1]. Various bone grafts and bone substitute materials have also been developed to address the cosmetic and functional issues posed by burr hole with limited success [3–10]. Among syntheticmaterials, a variety of resorbable and nonresorbable polymers, titanium and ceramics have been tested and shown to provide adequate cosmesis at least in the short-term; but long-term outcomes have not been reported [3–10]. In recent years, there has been growing advocacy for the use of bioresorbable, biomimetic and osteoconductive implants on the basis of their ability to encourage tissue regeneration.

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Table 1. Summary of patient demographics.

| Characteristics | Number | % |
|---|---|---|
| Gender | | |
| Males | 123 | 70.7 |
| Females | 51 | 29.3 |
| **Age (years)** | 64.63 ( ± 17.18) | |
| **Indications for burr hole surgery** | | |
| Chronic subdural hematoma | 72 | 41.4 |
| Acute on chronic SDH | 38 | 21.8 |
| Subacute SDH | 14 | 8.0 |
| Intracerebral hematoma | 24 | 13.7 |
| Brain tumor | 15 | 8.5 |
| Hydrocephalus | 8 | 4.5 |
| Encephalitis | 1 | 0.6 |
| Subarachnoid hemorrhage | 1 | 0.6 |

SDH: Subdural hematoma

Our institution had earlier reported on the short-term outcomes of using a 3D-printed bioresorbable polycaprolactone (PCL) as burr hole implants, in two studies involving five and 12 patients [3,4]. The outcomes of those studies suggested that the PCL implants (Osteoplug®, Osteopore International Pte Ltd, Singapore) were stably anchored in the osseous environment with no detectable fluid collection. Postoperative recovery was uneventful. Radiographical evidence of bone formation into the defect area was also seen on follow-up computed tomography (CT) scans at 12 months after implant. Outpatient follow-up at 16 months also demonstrated good host–material compatibility, with no signs of infection. In this study, we aim to present a 10-year experience (2006–2015) of using PCL implants in 174 consecutive patients, which includes a variety of different uses of burr holes, and a retrospective review of all PCL implants in terms of their safety.

## Materials & methods

This retrospective study was approved by the Institutional Review Board of the institute, with waiver of written informed consent.We identified patients who underwent burr hole craniotomies and reconstruction with a 12-mm diameter, 5-mm thickness PCL implant (Osteoplug® and Osteoplug®-C; Osteopore International Pte Ltd) between 1 April 2006 and 30 September 2015 at our institute. The implants are made from the material PCL and printed using 3D printing. Both the Osteoplug® and Osteoplug®-C are designed as burr hole covers. They act as scaffold with osteoconductive properties and have microstructures similar to cancellous bone. They are identical in porosity, which is maintained at 70%. PCL scaffolds have a degradation time of approximately 2 years, as reported by previous *in vivo* studies [9].

Outpatient clinical assessments were conducted at postoperative 1-month, 3-month, 6-month and 12-month, in the first postoperative year. All patient records were retrieved from an electronic data registry maintained by the hospital, and the last follow-up date was taken as the date of the latest clinic visit or demise.

Safety end points included the incidence of localized and disseminated intracranial infections related to the surgical wound (e.g., wound infection and meningitis), incidence of re-operations and incidence of any deaths, which could possibly be attributable to the implant.We reported two cases of radiological results after 3 and 9 years of implant insertion. Additionally, we evaluated tissue morphology and bony infiltration of an implant harvested from an 89-year-old male patient who had repeated burr hole surgery for recurrent chronic subdural hemorrhage. The histology study used hematoxylin and eosin staining, Masson's trichrome staining and micro-computed tomography.

Descriptive statistics such as frequency and percentages for categorical variables were used for this study.

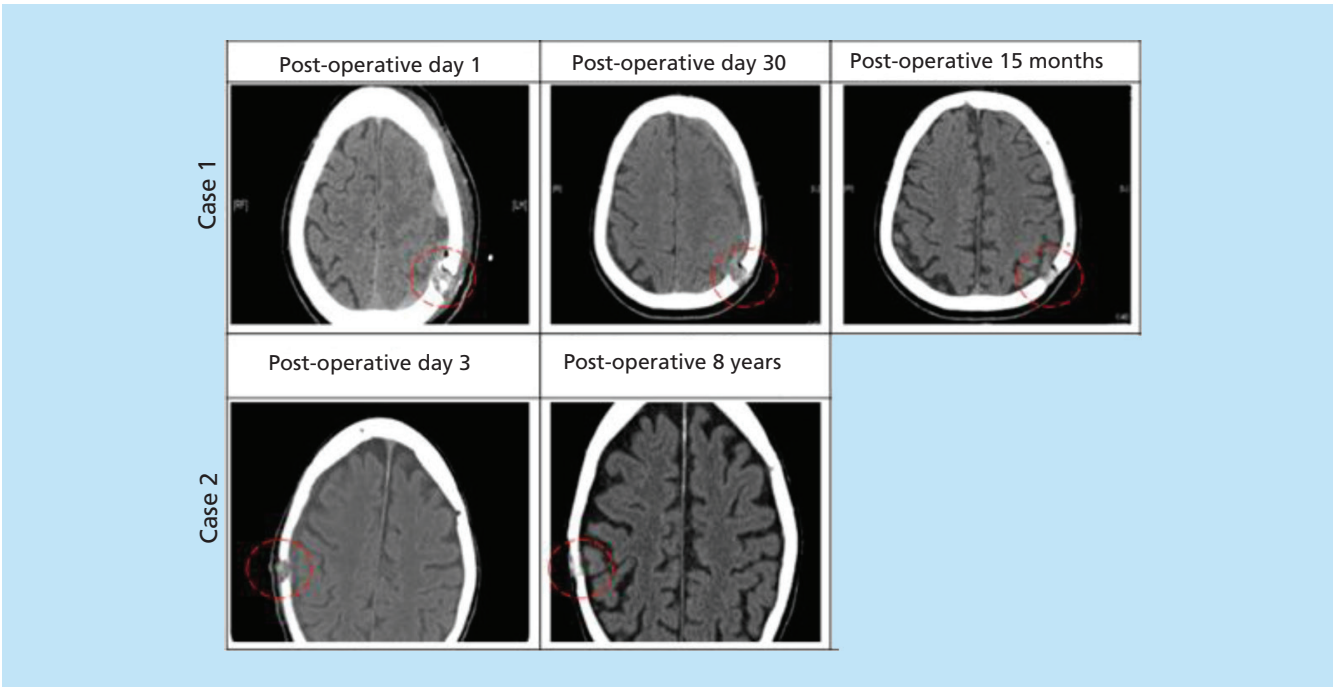


**Figure 1. Examples of serial postoperative computed tomography images at various stages of the implantation history in two cases.** In both cases, tissue ingrowth is observed to cover the burr hole sufficiently.

## Results

174 consecutive patients who underwent burr hole trephination had it reconstructed using the PCL implant during this 10-year period,mean follow-up of 248.1 (±435.3) days. The follow-up period was 1 day (early removal) to 9.5 years (at the time of data collection). Baseline characteristics and indications for burr hole surgery are summarized in Table 1. And detailed information regarding the initial surgery are shown in Supplementary Table 1. Based on the data collected, 41% of our patients presented with chronic subdural hematoma (CSDH), while acute on chronic subdural hemorrhage and subacute SDH formed another 30%. There were also 24 cases (14%) of burr hole trephination for intracerebral hemorrhage where the PCL implant was used as part of the closing procedure. Beyond SDH/intracerebral hemorrhage, other indications where the PCL implants were used included burr holes performed for stereotactic biopsy (for tumor biopsy, etc.) (8.5%), and shunt/drain for hydrocephalus (4.5%).

In the majority indication of CSDH, there were a total of ten re-operations out of 72 cases, of which nine were due to the recurrence of CSDH (recurrence rate 12.5%), and one was due to wound infection by methicillinresistant *Staphylococcus aureus* (0.57% of total patient population). A total of 65% of the CSDH was unilateral, 35% bilateral. In the acute and subacute SDH groups, there were six re-operations that were all related to recurrence of SDH. There were no cases of infection.

Stereotactic biopsy and shunts for hydrocephalus were other clinical scenarios in which we used the PCL burr hole covers. For hydrocephalus, ventriculoperitoneal (VP) shunts were inserted with a variation of the burr hole cover implant known as Osteoplug®-C, which catered for an access hole that facilitated the placement of the ventricular catheter. The same type of Osteoplug®-C cover could be used for subduroperitoneal shunt for persistent CSDH. One patient with this indication was re-operated upon due to a delayed shunt infection from *Pseudomonas aeruginosa.* The infection is unlikely to be directly related to the implant based on the clinical scenario. There were no infections reported from the stereotactic biopsy group.

Two patients with long-term follow-up CT scans are illustrated here (Figure 1). These are selected illustrative cases as no routine long-term follow-up scans are normally done for patients with burr hole covers. As baseline, both patients had CT scans taken within the first postoperative week. Follow-up CT was conducted at various time intervals postoperatively: 30 days and 15 months for the first case, and 8 years for the second case. Visible radio-opacity was observed within the circled regions, suggesting tissue regeneration. Case 1 showed signs of tissue ingrowth from the viable bone edge as early as day 30 postoperative. Case 2 demonstrated tissue ingrowth at 8 years. Both patients recovered with no postoperative complications and no documented skin depressions.

Additionally, we report the histological findings of a single case of an Osteoplug® explanted from an 89-year-old male patient who underwent re-operation for recurrent CSDH at 3.5 months after the initial surgery (Figures 2 & 3). The analysis of hematoxylin and eosin and Masson's trichrome staining by a histopathologist suggested that extensive tissue ingrowth and filling of the burr hole was achieved (Figure 3). The harvested tissue featured a predominantly adipose-like morphology, with some loose connective tissue forming around the scaffold filaments, along with minor calcification. Importantly, there was evidence of homogenous blood vessel infiltration throughout the harvested tissue.

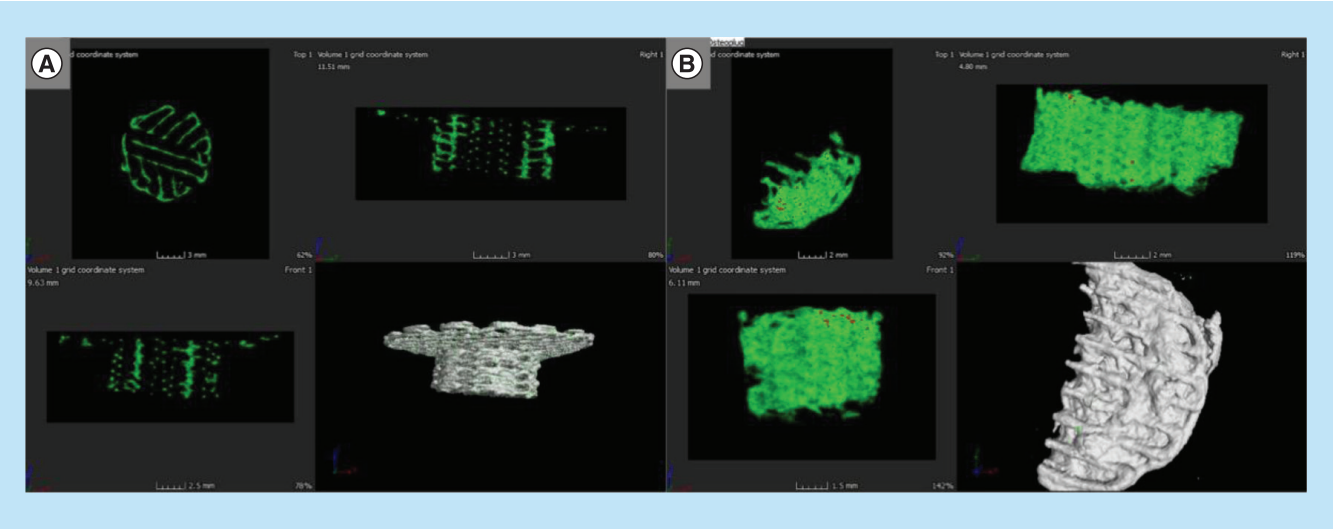


**Figure 2. Micro-computed tomography reconstructions of PCL burr hole cover implant Osteoplug®. (A)** A PCL implant (not implanted) and **(B)** the single-case explanted PCL implant Osteoplug®. Threshold levels were at the same brightness intensity to facilitate comparisons. Soft tissue components were highlighted green, while calcification signs were highlighted in red. PCL implant material also had the same brightness intensity as that of soft tissue, and was thus also highlighted in green. In comparison, there was significant tissue infiltration into the PCL implant in **(B)**. There was some minor calcification observed also.
PCL: Polycaprolactone.

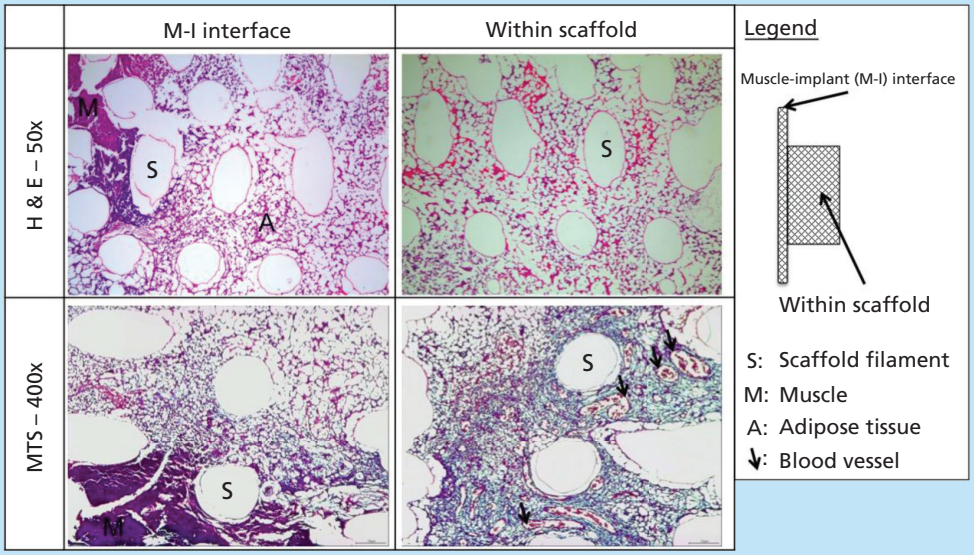


**Figure 3. Hematoxylin and eosin and Masson's trichrome staining of extracted polycaprolactone implant from an 89-year-old patient after 3.5 months of implantation.** The polycaprolactone implant was implanted in the patient for 3.5 months before being explanted. Tissue morphology was predominantly adipose like (labeled with A), while infiltration of blood vessels was evident (labeled with arrows).

## Discussion

Burr hole trephination is a ubiquitous procedure in the field of neurosurgery, but a limited repertoire of reconstruction procedures is currently available to alleviate the issue of scalp depression postoperatively. As aforementioned, this leads to non-neurological complications that can significantly impact patient quality of life. As such, it necessitates the restoration of the cranial contour to allow the patient to regain their quality of life and to prevent unintended clinical complications. Our institution developed and utilized the PCL burr hole cover implant Osteoplug® and Osteoplug®-C (Osteopore International Pte Ltd) for this purpose.

From a safety perspective, the results show that there is no increase in infection rate or complications rate by using the PCL implant. This demonstrates the safe use of the PCL implant as a burr hole cover in a variety of indications. We did not observe any extra risk added to the discussed procedures during the addition of the PCL implant.

### Comparison between Osteoplug® & Osteoplug®-C

The Osteoplug® and Osteoplug®-C are identical in porosity, which is maintained at 70%. In the design of Osteoplug®-C, there is a hole on the cover which allows for the insertion of a drainage catheter and for the residual fluid to flow out toward the drain. There is no direct data comparing the clearance of CSDH with and without the cover. However, the recurrence rate of CSDH postoperative with the burr hole cover is comparable with the rate reported without the burr hole cover. It suggests an insignificant effect on the clearance. This is consistent with our clinical experience. We recommend further study on this topic.

### *Chronic subdural hematoma*

In our institution, majority of the patients (72 patients, 41%) that received the PCL implants had burr hole made for evacuation of CSDH [3]. This group of patients was predominantly of the older generation with an average age of 71.8 years old. The rate of CSDH recurrence requiring re-operation was 15% in our cohort.Within the re-operated group, 77.8% patients were above 60 years old. This data corroborated the report by Qian *et al.*, who reported advanced age as one of the independent risk factors of CSDH recurrence that was statistically significant [11]. This recurrence rate of 15% is similar to what has been reported in other studies (Ko *et al.*: 9.4%; Liu *et al.*:8.0–14.1%) [12,13]. The recurrence rate of CSDH in our study appears to be comparable to the published series. It indicates the use of Osteoplug®/Osteoplug®-C did not increase the recurrence rate of CSDH, as compared with the rate reported by literature [11–13]. Additionally, the rate of wound infection (0.36%, 1 out of 275 implants or 0.57%, 1 out of 174 patients) did not increase with the use of either of the implants, as compared with the literature [11–13].

### *Shunt for hydrocephalus*

Complications of VP shunt procedure include infection, shunt malfunction, blockage etc. [14]. In this cohort, PCL implant Osteoplug®-C models were used to cover the burr holes in the cranium. The ventricular catheter passed through access hole at the edge of the cover. The results showed that using the Osteoplug®-C cover implant did not result in any new complications or increased the complication rates. It suggests that it does not increase the risk of complications in VP shunt surgery.

### *Stereotactic biopsy for brain tumor*

Stereotactic biopsy is a procedure that facilitates the extraction of tissue samples suspicious for tumor or other pathology. It is generally a low-risk procedure with intracranial hemorrhage reported as the most frequent complication (5.8%) after a data review of 7514 patients [15]. In our institution, using the PCL implant did not increase any of the risks associated with stereotactic brain biopsy procedures.

### *Tissue engineering & regenerative medicine*

The neurological effects of not filling the burr hole were clinically insignificant. However, the report by Im *et al*. hinted at an unintended medical consequence of the scalp; a loss in quality of life for the patient [1]. This is further discussed by Vasella *et al.* who reported improved aesthetic outcome of patients following placement of burr hole covers, determined by an aesthetic numeric analog scale [2]. A study by Velz *et al.* states that approximately three-quarters (76%) of the neurosurgeons surveyed indicated that their patients complained about skin depressions and/or unfavorable aesthetic outcome after burr hole trepanation for CSDH at clinical follow-up [16]. As such, it may be a reasonable consideration for burr holes to be filled at the end of surgery for more than just purely cosmetic reason. The selection of a suitable implant is therefore critical. Titanium burr hole covers have long been developed and used for this purpose, but there have been cases which have cited palpability, visibility, infection, exposure and pain associated with using titanium plates and screws that have necessitated removal [17,18]. In addition, postsurgical complications related to use of titanium implants have been reported in other neurosurgical applications, such as in cranioplasty [19]. Hence, while the usage of titanium implants is well established and safe, there is a concern that its safety may be compromised by the surrounding soft tissue coverage, particularly in areas where skin coverage is thin, or where vascular supply is limited.

To avoid such issues, our institution realized the concept of tissue engineering and regenerative medicine (TERM) by creating and evaluating an implant made from 3D-printed PCL, which allows natural tissue and vascular ingrowth [20]. Through a multitude of animal studies, the ability of such an implant to facilitate tissue ingrowth and regeneration has been established. Our early clinical findings also confirmed that bone ingrowth healing could occur with these bioresorbable burr hole implants [4]. The single-case Osteoplug explant histology confirmed vascular ingrowth, which is critical to the success of any regenerative therapy. Additionally, there was evidence of abundant stromal cell and blood vessel infiltration. Adipocytes, which are the most abundant stromal cell types in the adult bone marrow, featured

prominently in the explant, and therefore likely indicates ongoing soft tissue regeneration. The formation of bony tissue is dependent on the ability of the surrounding bone to integrate with the implant. It is noted that in the two long-term follow-up cases with radiological results presented here, structures resembling cortical bone were not observed, in contrast to our previous findings [4]. In earlier studies, a fibrin sealant was applied with the PCL implant. However, bone wax was used in the majority of the later cases. Bone wax is a nonregenerating material that is applied to stop the bleeding of diploic veins in the skull. Therefore, when bone wax is used, it appears to attenuate the bone regeneration capability, which is an expected outcome, because TERM requires the involvement of a scaffold, cells and biological factors. In this case, PCL implant is the scaffold; cells and biological factors are to be derived from the surrounding bone tissue and from blood. From our results, although we do not observe cortical bone-like radiological findings, our patients recovered well and there were no cosmetic complaints such as scalp depressions or softening of the implant-regenerated area in the observed period.

As compared with previous clinical investigations, a highlight of the current study is its considerably larger case numbers, allowing more robust conclusions to be derived.

### 3D-printed bioresorbable implant used as a burr hole cover

The burr hole cover (Osteoplug® and Osteoplug®-C; Osteopore International Pte Ltd) uses the material PCL, a biodegradable polyester that was first used as a long-term contraceptive device [21]. It is 3D-printed using fused deposition modeling, an additive manufacturing process. This method offers great ease and flexibility in material handling [22]. The bioresorbable scaffolds which are produced have high levels of interconnectivity and a controlled degradation and resorption to match cell/tissue growth [23].

## Study limitations

This study is a retrospective observational study on the clinical follow-up result of using a PCL burr hole cover. There are several limitations on the study, being lack of control group, no randomization, no measurable data on the cosmoses to comment on the cosmetic benefit. There are two cases presented for illustrative purposes, as there is no routine long-term follow-up scan indicated for patients with burr hole covers, in consideration toward risk versus benefit. As general awareness of the relevance of burr hole cover placement is increased, as is seen by the emerging trend described by various authors, more opportunities for measurement of clinical outcome of burr hole cover placements will become available.

## Conclusion

In conclusion, this work suggests that the PCL burr hole cover implants might be stable on a relatively long-term follow-up with minimal risk of infection. Use of the implant did not increase the surgical risk or rate of surgical complications significantly compared with the reported rate in literature. Notwithstanding the absence of a control group, the present study appears to support the safety of this PCL implant. While our study uses the fused deposition modeling method during scaffold production, presently there are different rapid prototyping technologies that have been reported on fabrication of bioresorbable scaffolds. We anticipate that following the increase in awareness and interest in TERM, more studies will be performed to evaluate the biocompatibility, safety and efficacy of 3D-printed bioresorbable implants.

## Supplementary data

To view the supplementary data that accompany this article please visit the journal website at:
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## Financial & competing interests disclosure

N Chou is a shareholder for Osteopore International Pte Ltd. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

## Ethical conduct of research

This retrospective study was approved by the Institutional Review Board (IRB) of the institute, with waiver of written informed consent.

## Summary Points

- Here we describe a 10-year retrospective study that evaluates the safety of using polycaprolactone (PCL) burr hole covers for cranial reconstruction in a total of 174 patients, with a total of 275 implants inserted.
- The implants are made from the material PCL, a bioresorbable polymer. They are 3D printed using fused deposition modeling, which is an additive manufacturing process.
- There is very little literature reporting the importance burr hole covers, and fewer reporting bioresorbable burr hole covers.
- The end points for evaluation of safety include infection rate, incidence of re-operation and incidence of death.
- Clinical scenarios which the burr holes were created and the burr hole covers used include chronic subdural hematoma, hydrocephalus requiring shunt placement and stereotactic biopsy.
- Results show that there is no increase in infection rate, incidence of re-operation and incidence of death when the PCL burr hole covers are used in the clinical scenarios discussed.
- Additionally, the CT scans of two patients are presented, together with the histology of one implant that was explanted due to re-operation. These data show evidence of tissue growth in the burr holes in tandem with implant bioresorption.
- We present the principles of tissue engineering and regenerative medicine, and how it is applied to this study.
- Limitations for this study include a lack of control group and no measurable data on the cosmoses to comment on the cosmetic benefit.

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