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# Clinical case series describes a contraindication for SerenoCem Granules™ in mastoid obliteration: Our experience in sixty-four patients.

Running title: Contraindication for SerenoCem Granules™

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Key Points

- SerenoCem Granules™ are a pre-set glass ionomer cement and are associated with abnormal resorption of bone adjacent to the site of implantation when used in mastoid obliteration
- This was a completely new clinical situation with erosion occurring in asymptomatic patients. Advice was sort from the MHRA leading otologists and radiologists. The MHRA advised that patients should be recalled, examined and CT scanned to determine the nature of the problem.
- SerenoCem Granules™ contain a trace of aluminium but are pre-set, which means that the vast majority of aluminium is released in the setting phase and should not constitute a neurotoxicity risk
- Lack of progression on CT findings suggests erosion occurs early on and stabilizes
- Regulatory standards of the 1990s were perhaps not sufficiently robust and nowadays a more exacting clinical trial would be needed

Introduction

Mastoid obliteration has been performed with various materials including muscle, fat, cartilage, musculoperiosteal flaps, chips and pâté[1]. Biocompatible materials used since the 1960s, have a number of potential advantages over autologous tissue. They are sterile, available off the shelf without the need for harvest and have a low risk of implanting cholesteatoma.

SerenoCem Granules™ (Corinthian Medical Ltd, Nottingham,UK) are a pre-set version of SerenoCem™ ionomeric cement, which is a bone-bonding and bioactive material released on the market since 1999. Extensive in-vitro and in-vivo studies have demonstrated that specific Glass Ionomer Cement(GIC) compositions have excellent biocompatibility using both bone cells and

tissues[2,3]. Furthermore, when first adopted for use in bone repair, early examples of set cement granules showed desirable bony integration when implanted into the rat femur[8]. This early work led in time to their clinical use and they were eventually marketed as ideal material for use in mastoid obliteration.

SerenoCem Granules™ have been sold in the UK only and employed in approximately 1500 cases. The SerenoCem™ cement formulation on which the granular bone graft substitute was based has a CE mark for mastoid surgery, with no adverse events reported for this cement. This paper reports our experience with SerenoCem Granules™ in mastoid obliteration and associated bony erosion.

## Methods

### Ethical Considerations

At the time of each procedure SerenoCem Granules™ were an established product licensed for use therefore no ethical approval was required.

### Patients

This is a retrospective review conducted as the senior authors became aware of abnormal resorption of bone adjacent to SerenoCem Granules™. Patients with open cavities were initially selected for mastoid obliteration due to chronic otorrhoea. Those with closed cavities were obliterated at a combined approach tympanoplasty Stage-2 procedure. Furthermore, no SerenoCem™ granules were placed directly on dura.

### Radiological classification

A classification system for CT findings was devised to quantify the amount of bony erosion across three subsites (tegmen, posterior fossa (sigmoid notch and medial to the notch) and the otic capsule)(Figure1a,1b). The number of subsites for each patient was then recorded(table1).

## Results

### CA results

45 (25 males,20 females) cases were performed between 2001-2010, with a mean age of 28.8 years(range,6-73). Seventeen cases were performed on open mastoid cavities and 28 as part of a stage-2 combined approach tympanoplasty.

Median post-operative follow-up for this cohort was 85 months,range(1-192). Four patients developed an immediate post-operative infection, in two of these patients the SerenoCem Granules™ extruded.

Overall, 13 patients underwent revision surgery including two patients with recurrent disease and one with residual disease.

IB results

19 (14 males,5 females) cases were performed between 2001-2015 with a mean age of 43.9 years,range(21-77). All obliterations were performed on open mastoid cavities in this group. Median post-operative follow up was 140.21months,range(14-182). None of the patients had residual or recurrent disease and revision surgery was performed for wet mastoid cavities. The average number of subsites showing bony erosion in IB's results was 0.74(table1).

Two patients within this series underwent obliteration with SerenoCem Granules™ on one side and obliteration with bone pâté alone on the contralateral side. Interestingly, they only displayed bony erosion on the side where the SerenoCem Granules™ were used(figure2). Interval scans on two patients suggest bony erosion occurs early on and does not progress.

During revision surgery both surgeons noted that the granules were surrounded by soft tissue with no evidence of bony integration. For both obliteration as part of a stage-2 combined approach tympanoplasty and obliteration of an open cavity the average number of subsites showing bony erosion was 1.38(table1).

Histology

Histological review of tissue sampling adjacent to the site of SerenoCem Granules™ revealed local inflammation, giant cell reaction and fibrous tissue encapsulation without evidence of bone regeneration or osseointegration(figure3).

Discussion

Synopsis of key findings

In 2015, CA operated on a patient with a small recurrent cholesteatoma and removed SerenoCem Granules™ from the mastoid cavity. Extensive bony erosion was noted adjacent to the SerenoCem Granules™ , but unrelated to the cholesteatoma. In particular, the tegmen tympani, tegmen mastoideum, posterior external auditory canal wall, and the bone over the posterior fossa, facial canal and lateral semicircular canal were widely eroded. Following these observations, patients in whom SerenoCem Granules™ had been used were recalled for review and bony erosions were identified on CT imaging.

Comparisons with other studies

Currently, there is one paper in the literature supporting the use of SerenoCem™ granules for mastoid obliteration. The authors reported a post-operative improvement on the Glasgow Benefit Inventory score as well as a reduction in aural care visits, however, authors also reported that the granules failed to osseointegrate[4].

Several animal studies have been performed using GIC bone substitutes. To date, there are no animal studies where SerenoCem Granules™ were implanted into the mastoid. A previous commercial formulation (the Ionogran™ prototype) has been inserted into the mid-shaft of a rat femur in-vivo, which at four weeks demonstrated increased osteoid formation compared to hydroxyapatite granules. There was no associated chronic inflammatory response at 4 weeks[5]. Whilst the laboratory rat femur is a sterile site, in mastoid obliteration, the granules are inserted into a potentially infected and inflamed cavity. This raises the possibility of a biofilm reaction, being the causative factor in the development of bony erosion described in this series.

SerenoCem™ Granules differ from other GIC preparations, such as Ionocem

(aluminium-calcium-fluorosilicate,Ionocem®IONOS-D8031 Seefeld/Obb,Germany), in that they are a dried granular preparation. However, other studies have shown a high risk of extrusion with ionomeric cement[6].

There have been four cases of subacute aluminium myoclonic encephalopathy following closure of a skull base defects with Ionocem™ cement. Two of these patients developed refractory status epilepticus leading to brain failure and subsequent death. It was suggested that high concentrations of aluminium in CSF and plasma led to encephalopathy as a result of aluminium leaching from the cement[7],[8].

SerenoCem Granules™contain a trace of aluminium, which may be of concern in those where the granules become adjacent to the dura. GICs in their cement form are generally contraindicated in situations where they will come into contact with neural tissue or nerves.

Excessive aluminium ion exposure has been implicated in a number of diseases in particular it exerts direct genotoxicity in neural cells[9]. SerenoCem Granules™ are pre-set, which means the setting phase is already complete at the point of sale and it is also washed out during the manufacturing process. Aluminium ions will therefore not leach out in large amounts compared to known cases of aluminium toxicity, and over time aluminum release from implanted SerenoCem Granules™ will effectively cease.

The relationship between the aluminium content, ion release, and biocompatibility is undoubtedly complex. Brook et al reported no correlation between the aluminum content, ion release and biocompatibility[2]. Furthermore, the dura is also a strong barrier protecting neural tissue. While relatively little data is available regarding the long term release of aluminium ions from set glass-ionomers in general or SerenoCem Granules™ specifically, this information suggested that after 12 months the amounts of aluminium that may be released are in the parts per million range where they are difficult to detect and would not constitute a risk to human health[10].

## Clinical applicability of the study

Our detection of bony erosions associated with SerenoCem Granules™ presents a dilemma for asymptomatic patients. All patients included in the study have been informed of the association between SerenoCem Granules™ and potential loss of bone. Advice was sought from the Medicines and Healthcare Products Regulatory Agency (MHRA), leading otologists and radiologists. All affected patients were subsequently recalled. In liason with the manufacturer, Corinthian Medical Ltd, and on review of glass ionomer cement use, we have developed a management strategy for these patients. Furthermore, Corinthian Medical Ltd, has voluntarily withdrawn the product from the market.

Establishing the low risk of potential concerns such as the leaching out of aluminium from the granules and progression of bony erosion has been paramount in quantifying the risk associated with SerenoCem Granules™. Lack of progression on CT in those with implanted SerenoCem Granules™ suggests erosion occurs early following implantation, and the implant sites appear to stabilise in the longer term.

In patients with bony erosion on CT scanning it was felt the benefits of removing the granules was outweighed by the risks of surgery, and therefore it was suggested patients should be clinically reviewed annually with a repeat CT scan after two years. If at this point there was evidence of progressive erosion then the patient would be advised to have the granules removed.

## Conclusion

Currently, those that have purchased SerenoCem Granules™ have been instructed not to use them and they have also been withdrawn from the market. The regulatory environment of the 1990s was not sufficiently robust, and with current standards any new bone graft substitute, even one based on an otherwise biocompatible material, would be subjected to a more exacting clinical trial before use. This is because biocompatibility is specific to a given clinical practice or procedure, rather than an intrinsic property of the actual biomaterial. We hypothesize that either a foreign body reaction or a biofilm-mediated response may be taking place, and this may have become a chronic adverse event due to the action of inflammatory cells and cytokines.

## Conflict of Interest

None declared

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| | Open/closed cavity | Tegmen mastoidium | Posterior fossa | Otic capsule | Total |
|---|---|---|---|---|---|
| Radiological classification scores in those with obliteration of a stage 2 combined approach tympanoplasty and open cavities (CA results) | | | | | |
| 1 | Stage 2 CAT | 1 | 1 | 0 | **2** |
| 2 | Stage 2 CAT | 1 | 0 | 0 | **1** |
| 3 | Stage 2 CAT | 0 | 0 | 0 | **0** |
| 4 | Stage 2 CAT | 1 | 0 | 0 | **1** |
| 5 | Stage 2 CAT | 1 | 1 | 0 | **2** |
| 6 | Stage 2 CAT | 1 | 0 | 0 | **1** |
| 7 | Stage 2 CAT | 1 | 0 | 0 | **1** |
| 8 | Stage 2 CAT | 0 | 0 | 0 | **0** |
| 9 | Stage 2 CAT | 1 | 1 | 1 | **3** |
| 10 | Stage 2 CAT | 1 | 1 | 1 | **3** |
| 11 | Stage 2 CAT | 1 | 1 | 0 | **2** |
| 12 | Stage 2 CAT | 1 | 1 | 0 | **2** |
| 13 | Stage 2 CAT | 1 | 0 | 0 | **1** |
| 14 | Stage 2 CAT | 1 | 1 | 0 | **2** |
| 15 | Stage 2 CAT | 0 | 0 | 0 | **0** |
| 16 | Stage 2 CAT | 1 | 0 | 0 | **1** |
| 17 | Open cavity | 1 | 0 | 0 | **1** |
| 18 | Open cavity | 1 | 1 | 1 | **3** |
| 19 | Open cavity | 1 | 1 | 0 | **2** |
| 20 | Open cavity | 0 | 0 | 0 | **0** |
| 21 | Open cavity | 1 | 1 | 0 | **2** |
| 22 | Open cavity | 0 | 0 | 0 | **0** |
| 23 | Open cavity | 0 | 1 | 0 | **1** |
| 24 | Open cavity | 1 | 1 | 0 | **2** |
| 25 | Open cavity | 1 | 1 | 0 | **2** |

| | | | | | |
|---|---|---|---|---|---|
| 26 | Open cavity | 1 | 0 | 1 | **2** |
| 27 | Open cavity | 1 | 0 | 0 | **1** |
| 28 | Open cavity | 0 | 0 | 1 | **1** |
| 29 | Open cavity | 1 | 0 | 0 | **1** |
| 30 | Open cavity | 0 | 0 | 0 | **1** |
| Radiological classification scores in those with obliteration of only open cavities (IB results) | | | | | |
| 1 | Open Cavity | 0 | 0 | 0 | **0** |
| 2 | Open Cavity | 0 | 0 | 0 | **0** |
| 3 | Open Cavity | 1 | 0 | 0 | **1** |
| 4 | Open Cavity | 0 | 0 | 0 | **0** |
| 5 | Open Cavity | 1 | 1 | 0 | **2** |
| 6 | Open Cavity | 1 | 1 | 1 | **3** |
| 7 | Open Cavity | 0 | 0 | 0 | **0** |
| 8 | Open Cavity | 0 | 0 | 0 | **0** |
| 9 | Open Cavity | 0 | 0 | 0 | **0** |
| 10 | Open Cavity | 0 | 0 | 0 | **0** |
| 11 | Open Cavity | 0 | 0 | 0 | **0** |
| 12 | Open Cavity | 1 | 0 | 0 | **1** |
| 13 | Open Cavity | 1 | 0 | 0 | **1** |
| 14 | Open Cavity | 1 | 0 | 0 | **1** |
| 15 | Open Cavity | 1 | 0 | 1 | **2** |
| 16 | Open Cavity | 1 | 0 | 0 | **1** |
| 17 | Open Cavity | 0 | 0 | 0 | **0** |
| 18 | Open Cavity | 1 | 1 | 0 | **2** |
| 19 | Open Cavity | 0 | 0 | 0 | **0** |

Table 1. Subsites associated with bone resorption on CT scanning.