Treatment of benign bone lesions with an injectable biphasic bone substitute

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Abstract

Background  Injectable biphasic ceramic bone substitutes (BCBSs) represent a modern alternative to conventional options for bone defect filling, as they further open the possibilities for percutaneous cavity reconstruction. Although recent studies have shown good surgical outcomes after treatment with BCBSs, mid-term follow-up data are still missing.

Patients and methods  Between 2013 and 2017, 18 patients were [1] treated with BCBS [2] for benign bone lesions and [3] had a complete set of retrospective information, including surgical protocols, imaging, patient dismissal letters and outpatient clinic protocols, [4] with a minimum follow-up time of one year. Eleven patients received percutaneous surgery, while 7 patients had open curettage and BCBS filling. The median follow-up time was 36.5 (range 12–80) months.

Results  Local recurrence was reported in four patients. A distinctive bone remodelling pattern was noted on follow-up X-ray and magnetic resonance imaging showing a double-line phenomenon and continuously increasing cortical thickness one year after treatment in nine of thirteen patients. Regarding surgical complications, one patient suffered from a septic complication that required BCBS removal and lavage. One patient experienced superficial surgical site inflammation with redness and swelling, while two other patients had prolonged wound secretion.

Conclusion  In a limited case series, the studied BCBS demonstrated acceptable surgical outcomes. Initial wound leakage and recurrence seemed to be associated with percutaneous injection. Further studies are needed to compare recurrence and bone graft resorption after open and percutaneous bone cyst surgeries and to further evaluate postoperative surgical site inflammation, which appears self-limiting in most cases.

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Introduction

In many institutions, the standard therapeutic approach for the operative treatment of benign bone tumours and tumour-like lesions consists of open surgical intralesional curettage with or without the application of adjuvant treatment methods, such as cavity burring with a mechanical burr, phenolization, sclerotherapy or cryotherapy, to further reduce potentially remaining tumour cells. [1–4] The remaining bone cavity is usually filled and impacted with either autograft bone, with iliac crest autograft as a widely accepted gold standard, or an allograft, such as bone chips or bone substitute materials, to circumvent the possible donor site morbidities and quantity limitations associated with autograft bone retrieval. Calcium phosphates and calcium sulfates are widespread bone substitute materials for defect reconstruction. [5–8] Calcium phosphates, such as hydroxyapatite (HA), serve as osteoinductive porous scaffolds to enhance cell migration and bone formation while providing structural support. HA can be optionally ground to powders and combined with other bioactive materials to further improve bone mineralization. [8] In this context, faster dissolving calcium sulfates are known for their osteoinductive behaviour and can serve as resorbable carriers for calcium phosphates. [9, 10] A general trend towards minimally invasive procedures can be observed in all surgical disciplines to diminish the risks of open surgical treatment, such as surgical site infections, pain and functional impairment. In some benign bone tumours, this trend has resulted in the implementation of biopsies with an intention to cure ("curopsy"), percutaneous needle aspiration, or even noninvasive treatments, such as medication with bisphosphonates or denosumab. [11–18] Although these minimally invasive techniques have shown acceptable results regarding recurrence in recent literature, there remains a postoperative bone cavity of variable dimensions.

Novel galenic formulations have been introduced to accommodate the surgical needs of defect reconstruction. In this context, biphasic ceramic bone substitute (BCBS) powders consisting of HA and calcium sulfate have a potential application in the minimally invasive treatment of benign and borderline bone tumours, as BCBSs can be moulded and injected into tumour cavities after the treatment of cystic lesions. BCBSs have been successfully used in the reconstruction of bone defects after the surgical treatment of benign bone tumours or to fill the defects of depressed metaphyseal or comminuted fractures. [19–23]

Although earlier studies showed that BCBSs had a good remodelling effect, follow-up data regarding bone graft resorption and consolidation after BCBS treatment are sparse. Additionally, there are no magnetic resonance imaging (MRI) follow-up data describing BCBS ingrowth aside from a single case report. [24] We therefore asked:

1) What is the treatment failure rate after surgical treatment with a BCBS?
2) How does the cavity morphology change in the postoperative course?
3) What are the treatment-specific complications?

Patients and methods

After receiving approval from the local ethics committee, a retrospective analysis of the data in the in-house software system (“AKIM”, Siemens) identified 21 patients. After application of the inclusion criteria, the included patients [1] received treatment with a BCBS [2] for benign bone tumours or tumour-like lesions 3) and had a complete set of retrospective information, including surgical protocols, X-rays, patient dismissal letters and outpatient clinic protocols, [4] with a minimum follow-up of one year; two patients were excluded because they were followed up for less than one year, and one patient was excluded because of an inconclusive histological report. Thus, the analysed population consisted of 18 patients. Thirteen patients were male, and 5 patients were female. The median patient age was 14 (range 6–25) years. Histologically, the tumour entities were unicameral bone cysts (UBCs, n=13), aneurysmal bone cysts (ABCs, n=2), secondary ABC (n=1), and nonossifying fibroma (NOF, n=2). The bone tumours were primarily treated with a BCBS in 7 cases, and in 11 cases, a BCBS was used to treat recurrent bone tumours. The median follow-up time was 36.5 (range 12–80) months. Further basic demographic information is depicted in Table 1.

In the first postoperative year, clinical check-up visits with X-ray imaging were performed after 6 weeks, 3 months, 6 months and 12 months and every 6 months thereafter. The X-ray images were screened for contrast levels, BCBS residua in the soft tissue, recurrent bone tumours and the “double line” phenomenon in cortical bone. This double line phenomenon consisted of a duplication of the cavities’ border shadow and was typically observed on postoperative X-ray images. (Fig. 1) Morphologic cavity changes were graded according to the modified Neer classification. [25] MRI was primarily used for patients with suspected recurrence, incomplete cavity consolidation or BCBS resorption. Twelve patients received a first MRI with a median of 12.5 (range 6–45) months after surgery, while four of these patients received a follow-up MRI 29.5 (range 13–44) months after surgery.
Surgical procedure

Either percutaneous or open surgery was performed before filling with a CERAMENT Bone Void Filler (BONESUPPORT, Lund, Sweden); these procedures were conducted by seven orthopaedic surgeons in this study. In percutaneous treatment, cyst localization was confirmed with mobile X-ray image intensifier before stab incision and preparation to the bone. Cystic lesions were opened with two Jamshidi needles. The first Jamshidi needle was placed in the distal portion of the tumour, while the second needle, which served as a “ventilation needle”, was placed in a more proximal cyst localization and at a different angle. The cysts were then washed with saline before the cyst walls were scraped with K-wires, which were inserted over the Jamshidi needles. This technique was further promoted by Kaczmarczyk et al., who showed that cyst wall scraping was sufficient to allow for bony ingrowth in the allograft composite. [23] An adequate amount of BCBS was prepared and applied over the distal needle under an X-ray image intensifier. The proximally placed needle was closed when the BCBS filling was performed after a standard ten-minute interval to await BCBS hardening, the wound was closed. The follow-up duration was calculated from the date of surgery with BCBS filling to the date of the last follow-up visit. Revision intervals were calculated from the date of surgery with BCBS filling to the date of revision surgery. The median preoperative cavity volume was calculated using preoperative MRI. Statistical calculations were made using SPSS version 26 (IBM).

Results

Recurrent bone tumours were observed in 4 patients who underwent percutaneous treatment. The recurrent lesions were one ABC, one secondary ABC and two UBCs. Revision surgeries due to recurrent bone tumours were performed after a median time of 9 months (range 4–51) after initial BCBS treatment. Three of these four patients were treated with open curettage and filling with allograft bone chips, while one patient received percutaneous sclerotherapy. (Table 2) Percutaneous surgeries were performed in 11 patients, while open curettage and filling were performed in 7 patients. The median BCBS filling volume was 18 ml (range 10–38) ml. No pathologic fractures occurred after BCBS treatment.

Twelve months after treatment, 2 out of 17 cavities showed full resolution (Neer I), and 7 cavities showed partial resolution (Neer II). Persisting lesions (Neer III) were observed in three patients, while three other patients suffered from recurrences (Neer IV) in the first postoperative year. One patient underwent BCBS extraction prior to completing a twelve-month follow-up period. X-ray examinations revealed BCBS leakage in 6 patients, with the BCBS residua in the soft tissue completely vanishing in the first postoperative year in all cases. (Fig. 2) Nine out of thirteen patients showed an increased cortical bone thickness on imaging one year after treatment. The modified Neer score decreased accordingly, with nine out of thirteen lesions classified as “healed” or “healing with defect” and a median Neer score of 2 (range 1–4) one year after surgery. BCBS insertion masses and septa via curettage. As adjuvant treatments to open surgery, one patient received cavity burring with a mechanical burr, while another patient received additional phenolization using phenol-soaked swabs after curettage. Thereafter, the inside of the cavity was filled with BCBS. After a standard ten-minute interval to await BCBS hardening, the wound was closed.

Statistical analysis

Statistical analyses focused on treatment outcomes after BCBS insertion. Descriptive statistics were applied to depict frequencies, means and ranges of relevant parameters. Revision surgeries included those for recurrences, defined as progressive lesions in a previously obliterated area as described by the modified Neer classification system, and surgical site complications. [25] The follow-up duration was calculated from the date of surgery with BCBS filling to the date of the last follow-up visit. Revision intervals were calculated from the date of surgery with BCBS filling to the date of revision surgery. The median preoperative cavity volume was calculated using preoperative MRI. Statistical calculations were made using SPSS version 26 (IBM).

Table 1  Demographic parameters

| Parameter                          | Patients (n = 18) |
|------------------------------------|------------------|
| Median age at index surgery        | 14 years (range 6–25) |
| Median follow up time              | 36.5 months (range 12–80) |
| Median time to recurrence after index surgery | 9.5 months (range 4–51) |
| Sex                                | Male/Female 13/5 |
| Localization                       | Humerus 13 |
|                                    | Femur 4 |
|                                    | Tibia 1 |
| Imaging                            | Median cyst volume 27 ml (range 10–63) |
|                                    | Soft tissue leakage 6 |
| Tumor entities                     | Unicameral bone cyst 13 |
|                                    | Aneurysmal bone cyst 2 |
|                                    | Non-ossifying fibroma 2 |
|                                    | Secondary aneurysmal bone cyst 1 |
|                                    | Recurrent lesion 11 |
| Surgical procedure                 | Percutaneous treatment 11 |
|                                    | Curettage 7 |
|                                    | Median amount BCBS delivered 18 ml (range 10–38) |

In open surgery, after approaching the bone, either an adequately sized bone flap was lifted off the cyst wall or, when osteosynthesis removal was indicated, the recurrent cyst was approached over the remaining screw tunnel. Afterwards, the cavity was cleared of tumour
resulted in a characteristic radio-opaque “double line” around the border of the bone cavity on early X-rays. The double-line phenomenon was observed in fourteen of fifteen patients three months after surgery and vanished in all but two patients by 18 months after surgery. A radiopaque fluid in the distal part of the cavity, corresponding to the mixture of the iohexol contrast agent with the
BCBS, was visible in twelve of fifteen patients six weeks after surgery and quickly vanished thereafter. (Fig. 3) On initial MRIs acquired 12.5 (range 6–45) months after surgery, a T2 hyperintense and T1 hypointense cavity signal with sclerotic cavity borders and a central filling material core were typically seen. This observation corresponded to the status of the bone substitute before full remodelling. Progressive bony consolidation was

| Patient | Localisation | Histology | Percutaneous | Indication | Treatment | Time |
|---------|--------------|-----------|--------------|------------|-----------|------|
| 1       | Humerus      | ABC       | 1            | Recurrence | Curettage, Phenolization, Allograft | 4 months |
| 2       | Humerus      | UBC       | 0            | Septic revision | Filling material extraction | 2 weeks |
| 3       | Humerus      | sABC      | 1            | Recurrence | Curettage, filling with allograft | 9 months |
| 4       | Femur        | UBC       | 1            | Recurrence | Curettage, filling with allograft, osteosynthesis | 51 months |
| 5       | Humerus      | UBC       | 1            | Pain       | Material removal (Titanium elastic nail) | 21 months |
| 6       | Humerus      | UBC       | 1            | Recurrence | Percutaneous sclerotherapy | 10 months |

ABC = aneurysmal bone cyst, UBC = unicameral bone cyst, FD = fibrous dysplasia, sABC = secondary aneurysmal bone cyst
Revisions after surgical treatment

The treatment failure rate was acceptable, with 5 out of 18 patients experiencing surgical revision due to treatment failure and four of these patients suffering from recurrent lesions. We found that all patients suffering from local recurrences underwent percutaneous surgery. Percutaneous and open surgery is established surgical strategies for the treatment of benign lytic bone lesions. Open curettage can lead to acceptable recurrence rates through manual tumour cell removal and cyst lining disruption, as well as potential access to growth factors and stem cells by entry into the medullary cavity. [26, 27] However, because of the invasiveness and associated complications of open procedures, some authors do not recommend initial open surgery for some benign bone lesions. [28] In percutaneous treatment approaches, various sclerosants, such as polidocanol, ethanol or doxycycline, may be used in addition to mechanical cyst membrane disruption. [29, 30] In a larger case series, Rastogi et al. observed a lesion size reduction of 76.6% after a mean of 3 injections in 72 patients with ABCs treated with polidocanol [31], while Marie-Hardy et al. reported a lesion size reduction in 85% in 55 ABCs treated with 96% ethanol in a mean of 1.7 injections. [32] We think that additional cavity reconstruction using injectable bone void fillers may be of particular benefit for minimally invasive treatments of recurrent benign bone lesions to further promote bone healing.

To put our findings into context with studies using the same BCBS, Kotrych et al. showed a very low recurrence risk with no reported recurrence in 33 patients after open curettage and filling of benign bone tumours, although the short median follow-up of 10 months needs to be mentioned. [10] In a prospective case series of 14 patients with solid and cystic benign bone tumours, Kaczmarczyk et al. reported no recurrence at the 12-month follow-up after treatment. [23] To date, studies analysing bone remodelling and recurrence after the treatment of benign bone lesions with BCBS suffer from high heterogeneity in surgical approaches and tumour entities. Larger and more homogenous case series are needed to evaluate the clinical value of these novel filling materials.

Bone remodelling behaviour

On postoperative X-ray and MRI, the BCBS showed a characteristic remodelling behaviour, with a distinctive double-line phenomenon at the cavity borders and progressively increasing cortical bone thickness in the months after treatment. (Fig. 1) In this context, the inherent microporosity of the material allows for direct penetration of tissue fluids and thus cells and growth factors after implantation, which promotes the natural bone healing process. [23] However, the material properties also allow for postoperative soft tissue leakage, which was observed in six patients in this case series. Although the shrinking of the residual BCBS in the soft tissue should be monitored by X-ray, there is no evidence of a higher chance of postoperative soft tissue inflammation in these patients. [22]
MRI was used in cases of suspected recurrence or incomplete lesion consolidation in this study. In these cases, we did not find full bony consolidation but instead a central bone substitute core with an inhomogeneous T2 hyperintense transformation zone at the cavity borders. Further X-ray examinations at regular follow-up intervals showed complete cavity remodelling 9–18 months after surgery. This gradual degradation is a known feature of different multiphasic injectable bone substitutes, which may show barrier-like structures at the surface that control connective tissue ingrowth into the central regions of the implantation bed. [33, 34] This characteristic may allow for guided bone regeneration with bone formation directed from the defect barriers into the central defect regions. [33]

A previous case series on BCBS demonstrated the healing process on follow-up X-ray and computed tomography images, showing peripheral reactive zones, trabecular bone bridging and improved cortical bone thickness one year after surgery. [22, 23] We think that both MRI and computed tomography have different advantages in evaluating bone healing and suspected recurrences, but MRI avoids radiation exposure and thus should be recommended, especially in a presumably young patient population.

**Surgical complications**

Complications after BCBS application mainly consisted of superficial inflammation and secretion. One patient needed revision surgery due to wound breakdown and secretion. A primarily sterile inflammatory response is a known complication of calcium sulfate grafting. [35–37] Although it may be assumed that the inflammatory processes are caused by rapid graft resorption and thus calcium-rich fluids in surrounding soft tissue, which lead to a decrease in the local pH value and an invasion of inflammatory cells [38, 39], Nilsson et al. showed that carbonated HA precipitates on the implant surface, which may allow for a more gradual dispersion and resorption of calcium sulfate in a calcium sulfate and HA biocomposite. [40] This gradual resorption is a desirable trait for bony ingrowth, as residual HA provides stability to the newly mineralizing tissues. [41]. The presence of a local inflammatory response and secretion after BCBS insertion is inconsistently described in the literature. McNally et al. observed fewer prolonged wound leakages and lower recurrence rates with a ceramic biphasic bone substitute with gentamicin than with a collagen fleece with gentamicin or calcium sulfate with tobramycin pellets for dead space filling after resection of chronic osteomyelitis. They attributed their results to higher antibiotic levels in the defect and the controlled release profile of the biphasic bone substitute. [42] McNally et al. further reported that only 6 of 100 patients suffered from self-limiting white wound drainage, which had the appearance of liquefied calcium sulfate residue, in a prospective case series. [43] In a review of ceramic biocomposites, Ferguson et al. linked this potential reduction of wound ooze to a smaller volume of calcium sulfate and a larger percentage of less soluble HA. [37] In contrast, Hofmann et al. reported a very low complication rate in a detailed list of adverse events, with only one out of 62 patients each suffering from seroma, prolonged wound healing and implant site inflammation; Horstmann et al. observed soft tissue inflammation in 7 out of 35 patients treated with BCBS. [19, 22] Although this condition generally does not seem to require further surgical intervention, surgeons need to be aware of the possibility of soft tissue inflammation and secretion after the application of BCBS and carefully monitor the resulting surgical wounds.

**Limitations**

A possible treatment bias needs to be reported, as treatment and indications, especially when choosing percutaneous surgery over open surgery, were not standardized. In general, open surgery was performed for solid tumours or recurrent cysts when metal removal surgery was additionally indicated, while percutaneous surgery was performed for cystic lesions.

As the bone cavity after BCBS treatment undergoes a constant transformation until one year after surgery, it was difficult to differentiate early recurrences and tumour progression from residual material in the postoperative cavity on X-ray and MRI. It cannot be ruled out that revision surgeries might have been undertaken, although BCBS ingrowth was not fully completed. Consequently, surgical treatment decisions were postponed to at least one year after surgery in cases of unclear or borderline cavity appearances.

Due to the heterogeneity of the underlying lesions, no direct comparisons of recurrence-free survival can be made. However, the restriction to benign bone lesions should provide a safe basis for the use of injectable synthetic allografts, especially in cases of recurrence and confirmed histology.

**Conclusion**

BCBS opens further possibilities for cavity filling in percutaneous and open treatments for bone cysts as it showed good bone remodelling features in the postoperative course. However, initial wound leakage and recurrence seemed to be associated with percutaneous injection. This information helps treating surgeons identify indications for minimally invasive therapy and raises awareness for surgical site inspections. Further studies are needed to compare the recurrence and adverse
event rates of open and minimally invasive bone lesion surgeries.

Abbreviations

HA: Hydroxyapatite
BCBS: Biphasic ceramic bone substitute
UBC: Unicameral bone cyst
ABC: Aneurysmal bone cyst
sABC: Secondary aneurysmal bone cyst
NOF: Non-ossifying fibroma
MRI: Magnetic resonance imaging

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Authors’ contributions

Conceptualization, K.D., CR., SP., RW., CC.; methodology, K.D., CR., SP., RW., CC.; validation, K.D., CR., AK., JP., SP., RW., CC.; investigation, K.D., CR., AK., JP., SP., RW., CC.; data curation, KD., CR., AK., SP., CC.; writing—original draft preparation, K.D., CR.; writing—review and editing, A.K., JP., SP., RW., CC.; project administration, K.D., CC.; All authors read and approved the final manuscript.

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Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the Medical University of Vienna (protocol code 1218/2016). Written informed consent was obtained from all subjects and/or their legal guardian(s).

Consent for publication

Not applicable.

Competing interests

RW reports grants from De Puy Synthes, personal fees from Johnson & Johnson Medical Limited, grants from Johnson & Johnson Medical Limited, grants from Medacta, personal fees from Stryker European Operations Limited, grants from Zimmer Biomet outside the submitted work. All the other authors, excluding RW, declare no other conflict of interest.

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References

1. Manikin HJ, Horinick EJ, Ortiz-Cruz E, Villafuerte J, Gebhardt MC. Aneurysmal bone cyst: a review of 150 patients. J Clin Oncol. 2005;23(27):6756–62.
2. Erol B, Onay T, Çalışkan E, Aydemir AN, Topkar OM. Treatment of pathological fractures following pathological fractures involving benign bone tumors. J Surg Oncol. 2015;112(3):846–52.
3. Carvalho P, Griffin AM, Ferguson PC, Wunder JS. Salvage of the proximal femur following pathological fractures involving benign bone tumors. J Orthop Traumatol Surg Res. 2016;102(2):213–6.
4. Mavčič B, Saraph V, Gilg MM, Bergovec M, Brecelj J, Leithner A. Comparison of three surgical treatment options for unicameral bone cysts in humerus. J Pediatr Orthop B. 2019;28(1):51–6.
5. Shiels WE 2nd, Mayerson JL. Percutaneous doxycycline treatment of aneurysmal bone cysts with low recurrence rate: a preliminary report. Clin Orthop Relat Res. 2010;468(4):731–45.
6. Kuemmerle C, Menon J, Patto D, K. Calcium sulfate as bone graft substitute in the treatment of osseous bone defects, a prospective study. J Clin Diagn Res. 2013;7(12):2926–8.
7. Tamai N, Myoui A, Kudawara I, Ueda T, Yoshikawa H. Novel fully interconnected porous hydroxyapatite ceramic in surgical treatment of benign bone tumor. J Orthop Sci. 2010;15(4):560–8.
8. Ramesh N, Moratti SC, Dias GJ. Hydroxyapatite-polymer biocomposites for bone regeneration: A review of current trends. J Biomed Mater Res B Appl Biomater. 2018;106(5):3046–57.
9. Baldwin P, Li DJ, Auston DA, Mir HS, Yoon RS, Koval KJ. Aneurysmal bone cyst: results of an off label treatment with Denosumab. BMC Musculoskeletal Disord. 2019;20(1):456.
10. Mavčič B, Saraph V, Gilg MM, Bergovec M, Brecelj J, Leithner A. Comparison of three surgical treatment options for unicameral bone cysts in humerus. J Pediatr Orthop B. 2019;28(1):51–6.
11. Durr HR, Graheins F, Baur-Melniky A, Knöbel T, Birkenmaier C, Janss V, et al. Aneurysmal bone cyst: results of an off label treatment with Denosumab. BMC Musculoskeletal Disorders. 2019;20(1):456.
12. Reddy K, Sinnaeve F, Gaston CL, Grimer RJ, Carter SR. Aneurysmal bone cysts: do simple treatments work? J Pediatr Orthop B. 2014;23(6):1901–10.
13. Kurucu N, Akyuz C, Ergen FB, Yalcin B, Kosemehmetoglu K, Ayaz M, et al. Denosumab treatment in aneurysmal bone cyst: Evaluation of nine cases. Pediatr Blood Cancer. 2018;65(4).
14. Batisse F, Schmitt A, Vendeuvre T, Herbreteau D, Bonnard M. Aneurysmal bone cyst: A 19-case series managed by percutaneous sclerotherapy. Orthop Traumatol Surg Res. 2016;102(2):213–6.
15. Döring K, Puchner S, Vertesich K, Funovics PT, Hobusch G, Sulzbacher I, et al. Autologous Iliac Bone Graft Compared with Biphasic Hydroxyapatite and Calcium Sulfate Cement for the Treatment of Bone Defects in Tibial Plateau Fractures: A Prospective, Randomized, Open-Label, Multicenter Study. J Bone Joint Surg Am. 2020;102(3):179–93.
16. Yeo QY, Kee Kwek EB. Use of a biphasic cement bone substitute in the management of metaphyseal fractures. J Clin Orthop Trauma. 2019;10(4):789–91.
17. Iundusi R, Gasbarra E, D’Arienzo M, Piccioli A, Tarantino U. Augmentation of metaphyseal bone defects, prospective study. J Bone Joint Surg Am. 2010;92(8):1901–10.
18. Döring K, Puchner S, Vertesich K, Funovics PT, Hobusch G, Sulzbacher I, et al. Comparison of three surgical treatment options for unicameral bone cysts in humerus. J Pediatr Orthop B. 2019;28(1):51–6.
19. Kaczmarczyk J, Sowinski P, Goch M, Katulska K. Complete twelve month experience with a Ceramic Bone Graft Substitute in the Treatment of Benign Bone Tumors and Tumor-like Lesions. Open Med (Wars). 2018;16:115.
20. Rosario MS, Hayashi K, Yamamoto N, Takeuchi A, Miwa S, Tanguchi Y, et al. Functional and radiological outcomes of a minimally invasive surgical approach to monostotic fibrous dysplasia. World J Surg Oncol. 2017;15(1):1.
21. Hofmann A, Gorbulev S, Gueringh T, Schulz AP, Schupfer R, Raschke M, et al. Autologous Ilac Bone Graft Compared with Biphasic Hydroxyapatite and Calcium Sulfate Cement for the Treatment of Bone Defects in Tibial Plateau Fractures. Bone. 2021;113:115794.
22. Yeo QY, Kee Kwek EB. Use of a biphasic cement bone substitute in the management of metaphyseal fractures. J Clin Orthop Trauma. 2019;10(4):789–91.
23. Kaczmarczyk J, Sowinski P, Goch M, Katulska K. Complete twelve month bone remodeling with a bi-phasic injectable bone substitute in benign bone tumors: a prospective pilot study. BMC Musculoskeletal Disorders. 2015;16:369.
24. Guarnieri G, Vassallo P, Muto M, Muto M. Percutaneous treatment of symptomatic aneurysmal bone cyst of LS by percutaneous injection of osteoconductive material (Cerament™). BMU Case Rep. 2013;2013.
25. Neer CS 2nd, Francis KC, Marcove RC, Ting CL, Carbonara PN. Treatment of unicameral bone cyst: A follow-up study of one hundred seventy-five cases. J Bone Joint Surg Am. 1966;48(4):731–45.
26. Wang EH, Marfori ML, Serrano MV, Rubio DA. Is curettage and high-speed burn sufficient treatment for aneurysmal bone cysts? Clin Orthop Relat Res. 2014;472(11):3483–8.
27. Döring K, Puchner S, Vertesich K, Funovics PT, Hobusch G, Sulzbacher I, et al. Results in the surgical treatment of aneurysmal bone cysts - A retrospective data analysis. Orthop Traumatol Surg Res. 2022;108(4):103095.
28. Hou HY, Wu K, Wang CT, Chang SM, Lin WH, Yang RS. Treatment of unicameral bone cyst: a comparative study of selected techniques. J Bone Joint Surg Am. 2010;92(8):655–62.
29. Shields WE 2nd, Mayerson JL. Percutaneous doxycycline treatment of aneurysmal bone cysts with low recurrence rate: a preliminary report. Clin Orthop Relat Res. 2013;471(8):2675–83.
30. Canavese F, Wright JG, Cole WG, Hopyan S. Unicameral bone cysts: comparison of percutaneous curettage, steroid, and autologous bone marrow injections. J Pediatr Orthop. 2011;31(1):50–5.

31. Rastogi S, Varshney MK, Trikha V, Khan SA, Choudhury B, Safaya R. Treatment of aneurysmal bone cysts with percutaneous sclerotherapy using polidocanol: a review of 72 cases with long-term follow-up. J Bone Joint Surg Br. 2006;88(9):1212–6.

32. Marie-Hardy L, El Sayed L, Alves A, Brunelle F, Ouchrif Y, Naggara O, et al. Percutaneous alcohol-based sclerosis in aneurysmal bone cyst in children and adolescents. Orthop Traumatol Surg Res. 2020;106(7):1313–8.

33. Barbeck M, Jung O, Smeets R, Gosau M, Schnettler R, Rider P, et al. Implantation of an Injectable Bone Substitute Material Enables Integration Following the Principles of Guided Bone Regeneration. In Vivo. 2020;34(2):557–68.

34. Ghanaati S, Barbeck M, Hilbig U, Hoffmann C, Unger RE, Sader RA, et al. An injectable bone substitute composed of beta-tricalcium phosphate granules, methylcellulose and hyaluronic acid inhibits connective tissue influx into its implantation bed in vivo. Acta Biomater. 2011;7(11):4018–28.

35. Friesenbichler J, Maurer-Ertl W, Sadoghi P, Pirker-Fruehauf U, Bodo K, Leitner A. Adverse reactions of artificial bone graft substitutes: lessons learned from using tricalcium phosphate geneX®. Clin Orthop Relat Res. 2014;472(2):767–8.

36. Nilsson M, Wang JS, Wielanek L, Tanner KE, Lidgren L. Biodegradation and biocompatibility of a calcium sulphate-hydroxyapatite bone substitute. J Bone Joint Surg Br. 2004;86(1):120–5.

37. Hatten HP Jr, Voor MJ. Bone healing using a bi-phasic ceramic bone substitute demonstrated in human vertebralplasty and with histology in a rabbit cancellous bone defect model. Interv Neuroradiol. 2012;18(1):105–13.

38. McNally M, Ferguson J, Kendall J, Dudareva M, Scarborough M, Stubbs D. A COMPARATIVE STUDY OF THREE BIOABSORBABLE ANTIBIOTIC CARRIERS IN CHRONIC OSTEOMYELITIS: 313 PATIENTS WITH MINIMUM ONE-YEAR FOLLOW-UP. Orthopaedic Proceedings. 2015;97-B(SUPP_16):21.

39. McNally MA, Ferguson JY, Lau AC, Diefenbeck M, Scarborough M, Ramsden AJ, et al. Single-stage treatment of chronic osteomyelitis with a new absorbable, gentamicin-loaded, calcium sulphate/hydroxyapatite biocomposite: a prospective series of 100 cases. Bone Joint J. 2016;98-b(9):1289–96.

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