in vivo *36*: 1267-1273 (2022)
doi:10.21873/invivo.12826

Enchondromas of the Hand: Curettage With Autogenous Bone *vs*. Bioactive Glass S53P4 for Void Augmentation

NINA LINDFORS[1*], ELIAS KUKKONEN[1*], ANTTI STENROOS[2], PANU H. NORDBACK[1], TURKKA ANTTILA[1] and SAMULI ASPINEN[1]

[1]*Department of Hand Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland;*
[2]*Department of Orthopaedics and Traumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*

Abstract. *Background/Aim Enchondroma is the most common primary bone tumour of the hand. When surgery is indicated, curettage with or without void augmentation has been described. However, only few comparative studies exist. The aim of this study was to compare the outcomes of hand enchondromas treated with autologous bone graft (AG) and bioactive glass S53P4 (BAG). Patients and Methods: A retrospective comparative analysis was conducted among patients surgically treated for hand enchondromas at a tertiary referral centre during a 17-year period. Results: A total of 190 patients (116 AG vs. 74 BAG) with 205 enchondromas were included. No statistically significant differences in outcome measures were observed. A reoperation was performed in five patients in the autologous bone-graft group; one patient presented a rare malignant transformation from enchondroma to chondrosarcoma after the primary operation. No reoperations were performed in the BAG group. Conclusion: Although AG is the gold standard for filling bony cavities, bone-graft retrieval can cause complications and postoperative pain. Our results suggest that S53P4 BAG is a safe and effective bone-graft material alternative for filling of enchondroma-evacuated cavities.*

*These Authors contributed equally to this study as first authors.

Correspondence to: Samuli Aspinen, Department of Hand Surgery, University of Helsinki and Helsinki University Hospital, Topeliuksenkatu 5 B, 00260 Helsinki, Finland. Tel: +35 80406360546, e-mail: samuli.aspinen@hus.fi

Key Words: Bioactive glass, bone graft, bone tumour, enchondroma.

Enchondroma is the most common primary bone tumour of the hand. While most enchondromas are asymptomatic, they may present with swelling, pain, deformity, or a pathological fracture. Malignant transformation of hand enchondromas is exceedingly rare – only a few well-documented case reports of pre-existing benign solitary hand enchondromas exist (1, 2).

Treatment of enchondromas varies between centres and surgeons. Conservative treatment may be preferred for incidentally discovered small and asymptomatic tumours (3). Operative treatment is recommended for symptomatic lesions, to prevent pathological fractures, and to allow for definitive diagnosis (4, 5).

Curettage is a well-accepted surgical treatment of enchondromas (6). Some surgeons employ simple curettage, while others recommend void augmentation with autogenous graft (AG); allogenous, xenogenous or synthetic bone; demineralized bone matrix; or bioactive glass (BAG) (7-9). BAG is a synthetic bone substitute with documented osteoconductive, bone bonding, and osteostimulative properties. Implanted in the bone cavity, a cascade of reactions occurs at the glass surface that promote osteoconduction. BAG-S53P4 (53% SiO_2, 23% Na_2O, 20% CaO, and 4% P_2O_5) is used for bone cavitary filling in bone tumour surgery, and especially in infected cavitary defects due to its antibacterial properties (8, 10-13).

The aim of this study was to evaluate surgical outcomes using BAG *versus* AG in the treatment of enchondromas in the hand region in a tertiary hand surgery unit.

Patients and Methods

The study was approved by the Hospital Institutional Review Board (379/2020). Ethical Review Board approval was not sought as this study was a retrospective analysis of data without patient interaction.

Patients. A medical chart review was performed for all adult patients (>18 years) who were treated operatively between 1 January 2003 to 31 December 2019 for a bone or soft-tissue tumour at our Institute. Data were extracted from the hospital database by combining use of

the International Statistical Classification of Diseases and Related Health Problems (10th revision, ICD-10; codes D16.0&, D16.1&, D17*, D18.1 and R22.3) (14) and the Nomesco (Nordic Medico-Statistical Committee) procedural classification (codes NDR*, NDQ*, NDK*, and ZZH*) (15). An additional search was conducted of the Department of Pathology archives using histopathological diagnosis for "enchondroma" and "chondroma" to ensure all patients with enchondroma were included in the study.

A total of 692 patients with an operatively treated hand tumour were identified. Of these, 443 patients were excluded due to soft-tissue or bone tumours other than enchondromas. We excluded a total of 60 patients with enchondromas; 11 patients were minors (<18 years), nine patients had recurrent enchondromas (primarily treated in another hospital or prior to 1 January 2003), and 40 patients had their enchondroma treated with curettage alone or curettage and void augmentation with demineralized bone matrix, calcium phosphate cement (Norian®), or calcium sulphate paste (Miig®). Five patients in the final dataset had no confirmation of diagnosis by tissue sample collection but were not excluded from the study due to typical clinical presentation at surgery. In total, 205 enchondromas in 190 patients were included in this study (Figure 1). The patients were followed-up from a national database for a minimum of 2 years. The median active follow-up (time between surgery and the last enchondroma-related hospital visit) was 9 weeks (BAG: range=4-76; AG: range=4-136), and the median number of follow-up visits was one in both groups (BAG: range=1-10; AG: range=1-8).

The indications for the primary procedure were pain or restriction in range of motion (or both) (n=54, 28.4%), pathological fracture (n=94, 49.5%), and risk of fracture or close relation to joint line (n=35, 18.4%). The indication was not clearly defined in the patient records for 17 patients (8.9%). Most patients with a pathological fracture underwent operative treatment after the fracture had healed; only one patient was considered to benefit from primary treatment of the fracture (rotational malalignment). All patients completed at least the first follow-up and were therefore included in the analysis.

The following data regarding the primary procedures were collected: Age, sex, hand dominance, height, weight, associated condition, number, and size of tumours diagnosed on each side, operated side, tumour histology, operative technique, autograft or bone substitute type, other simultaneous surgeries, and postoperative complications.

Radiological evaluation. We evaluated the retrieved preoperative X-rays by measuring the tumour volume (cm^3). Tumour width was measured from an antero-posterior view, depth from a lateral view, and length from both antero-posterior and lateral views using the mean value for final calculation of the tumour volume. The tumour was interpreted as consolidated when the tumour cavity was filled, and no radiolucency was seen. In the case of BAG-filled cavities, an appearance of fully consolidated bone was not anticipated, however, remodelling of the bone without any dissolving of the BAG were considered as indicating consolidation.

Anaesthesia and surgical technique. All procedures were performed under general anaesthesia (n=76) or regional anaesthesia (n=114) using brachial plexus block (n=99), intravenous regional anaesthesia (n=12), or digital block (n=3). We were unable to determine the type of incision (*e.g.*, dorsal, mid-lateral, or volar) in most cases, therefore, the type of incision was not included in our report. All enchondromas were approached through a cortical window and a thorough manual curettage was performed.

In the BAG group of 74 patients, the following types of BAG were used: granules of 1-2 mm size (Bonalive® granules (BonAlive Biomaterials Ltd, Turku, Finland), in 20 cases) or a putty formula (BonAlive® putty (BonAlive Biomaterials Ltd) consisting of 48% by weight of BAG S53P4 0.5-0.8 mm granules mixed with 12% by weight of spherical BAG S53P4 0.09-0.425 mm granules and 40% by weight of a synthetic binder mix of glycerol and three chain lengths of polyethylene glycol, in 26 cases). The type of BAG used (*i.e.*, granules or putty) was undefined in 28 patients in the BAG group. In the AG group of 116 patients, an autograft from the distal radius (n=46), the iliac crest (n=71), or trapezium (n=1) with simultaneous trapezoidectomy in the treatment of pantrapezoidal osteoarthrosis was used for bone void filling. The choice of augmentation material was at the surgeon's discretion.

A total of 96 (50.6%) patients were operated on by consultant-level hand surgeons, 48 (25.2%) by consultant-level orthopaedic surgeons (tumour surgeons), and 46 (24.2%) by surgeons in training (either hand or orthopaedic) supervised by a senior surgeon.

Statistical analysis. Results are presented as medians and range (minimum to maximum) or means and standard deviation for continuous non-skewed variables. Ninety-five percent confidence intervals were calculated for the mean difference. Levene's test was used to examine the homogeneity of variance between groups. The frequency distribution of the categorical variables was compared between groups with the chi-square test and Mann–Whitney *U*-test for continuous variables. The statistical significance level was set to $p<0.05$. (two-sided). All *p*-values are reported to three decimal places.

Results

The baseline demographic characteristics were similar for the two groups (Table I). The median tumour volume was 1.2 cm^3 (range=0.01-12.4 cm^3) for the BAG group and 0.8 cm^3 (range=0.01-18.1 cm^3) for the AG group. The fifth ray was the most affected ray and proximal phalanges were the most common location for the lesion.

The median number of follow-up visits was one for both groups (BAG: range=1-10 and AG: range=1-8) and the median time for the final follow-up was 9 weeks (BAG: range=4-76 weeks and AG: range=4-136 weeks). Fifty percent of patients were followed-up until full bony consolidation was reached (52.6% in BAG and 48.2% in AG), whereas the situation was considered as "consolidation in progress" in 47.4% of patients (43.2% in BAG and 50.0% in AG), *i.e.*, the filled cavity had not yet remodelled to the appearance of fully consolidated bone. No notable consolidation was observed when follow-up was discontinued in four patients (two in each group).

Eight procedure-associated complications were reported (BAG group: 4/74, 5.4%; AG group: 4/116, 3.4%) (Table II). No complications associated with the bone harvest procedure, either at the region of the distal radius or at the iliac crest, were observed. Case presentations are shown in Figure 2 and Figure 3.

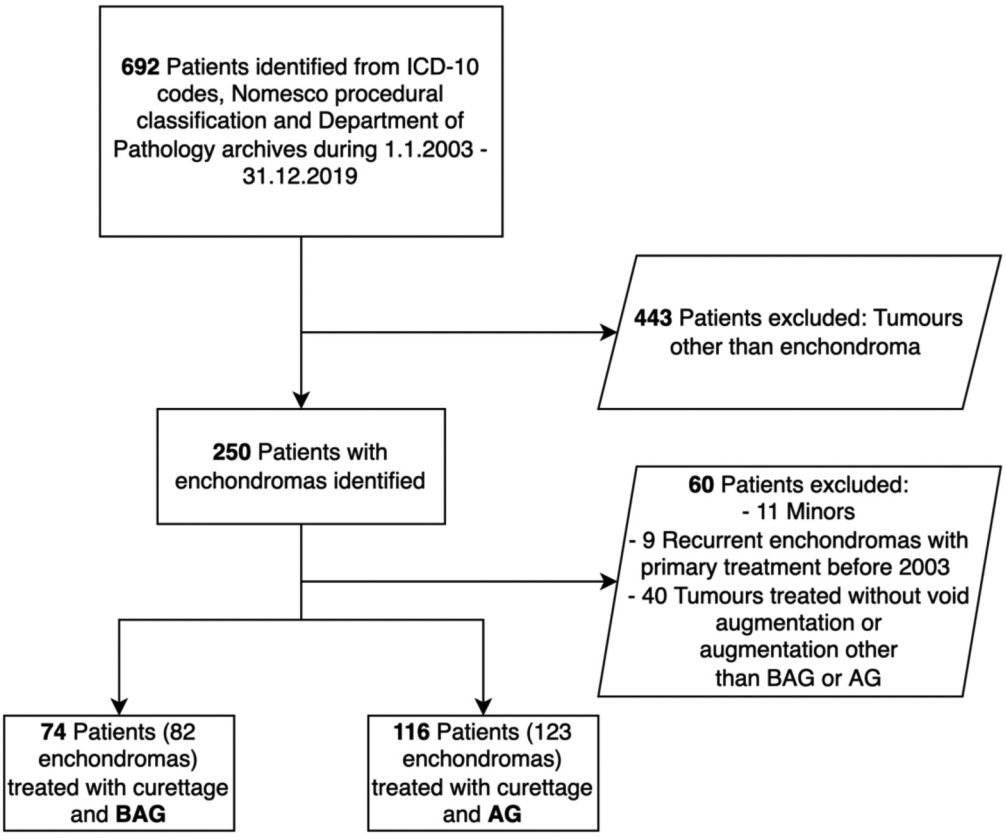

Figure 1. *Flowchart of the patient data-retrieval process. AG: Autologous bone graft; BAG: bioactive glass; ICD-10 codes: International Statistical Classification of Diseases and Related Health Problems, 10th revision (14).*

Reoperations for a recurrent tumour or growth of a residual tumour were rare. In the BAG group, there were no reoperations. In the AG group, five patients underwent reoperation, of whom one patient underwent two re-operations – final consolidation of the tumour was achieved after the second operation with a BAG filling. One patient primarily treated in 2009 presented with a recurrent tumour in 2020 and was treated with re-curettage and a BAG filling in 2021. The third patient's distal phalanx enchondroma was treated with curettage and AG fill. Later, the patient developed pain and a recurrent tumour was suspected and treated with recurettage and AG without complications. The fourth patient had a metacarpal bone enchondroma, which was treated with curettage and AG in 2017. The patient returned in 2019 due to pain and a recurrent tumour was detected on magnetic resonance imaging (MRI). The recurrent tumour was treated with recurettage and BAG fill in 2021.

The fifth reoperated patient presented a rare malignant transformation of a pre-existing solitary enchondroma. The primary tumour was treated with curettage and an AG filling in 2011 and diagnosis of an enchondroma was confirmed by postoperative histological examination. Consolidation of the void was progressing 5 weeks after the operation and thus further follow-up was ceased. One year after the initial treatment, the patient was re-examined because of increasing pain and swelling at the base of the operated digit and reduced finger flexion. MRI showed a soft-tissue mass protruding from the bone, raising suspicion of a chondrosarcoma, which was confirmed with an open biopsy and histological examination. The patient was treated with ray amputation and histological examination showed grade III chondrosarcoma. A re-evaluation of the histological samples from the primary operations did not change the primary histological diagnosis of enchondroma. No metastasis was found in a thorough assessment and the patient has been disease-free for 7 years.

Discussion

Enchondroma is the most common primary bone tumour in the hand. Symptomatic lesions and asymptomatic lesions with a highly increased risk of fracture (large, expanding tumour with cortical thinning) should be considered for surgical treatment. In such cases, curettage is a well-described operative method. Although several studies report

Table I. *Baseline demographic characteristics of the study groups.*

Characteristic		All (n=190)	Bioactive glass (n=74)	Autograft bone (n=116)
Age, years	Mean±SD	40.5±12.2	43.5±12.4	38.6±11.9
Cigarette smoking, n (%)	Yes	36	16 (22%)	20 (17%)
Associated condition, n (%)	None	189	74 (100%)	115 (99%)
	Ollier	1	0 (0%)	1 (1%)
	Malfucci	0	0 (0%)	0 (0%)
Symptoms, n (%)	None	35	17 (23%)	18 (16%)
	Pain/restriction of motion	54	15 (20%)	39 (34%)
	Fracture	94	38 (51%)	56 (48%)
	Other	7	4 (5%)	3 (3%)
Lesions treated in one operation, n (%)	1	181	71 (96%)	110 (95%)
	2	6	1 (1%)	5 (4%)
	>3	3	2 (3%)	1 (1%)
Lesion size	Median (range), cm^3	1.0 (0.01-18.1)	1.2 (0.01-12.4)	0.8 (0.01-18.1)
Subgroup, n (%)	<1 cm^3	74	32 (43%)	42 (36%)
	1-3 cm^3	64	25 (34%)	39 (34%)
	>3 cm^3	51	17 (23%)	34 (29%)
Location, n (%)	Distal phalanx	29	6 (8%)	23 (20%)
	Middle phalanx	44	17 (23%)	27 (23%)
	Proximal phalanx	78	41 (55%)	37 (32%)
	Metacarpal	38	11 (15%)	27 (23%)
	Radius	1	0 (0%)	1 (1%)
Ray, n (%)	I	21	7 (9%)	14 (12%)
	II	28	12 (16%)	16 (14%)
	III	38	13 (18%)	25 (22%)
	IV	45	19 (26%)	26 (22%)
	V	57	23 (31%)	34 (29%)

SD: Standard deviation.

the outcomes after simple curettage, there is a paucity of high-quality evidence that would support the use of this technique over another. In fact, these trials have methodological shortcomings, such as small sample size, considerable risk of selection bias, and incomplete outcome reporting. Moreover, most reports on simple curettage are not uniform in terms of operative technique, and the role of surgical adjuncts (*e.g.*, alcohol, phenol, laser) may have influenced the outcomes in these studies (6, 15, 16).

A question in treating enchondromas with simple curettage is the size of the tumour. While it might be convenient to treat small, monocentric, and non-expanding tumours with simple curettage, in the case of larger, multicentric, or expanding tumours, the bone may benefit from increased strength to resist fractures (18). In fact, most of the studies reporting on the results of simple curettage lack information on tumour size or included patients with small lesions (9, 19-21). As most of these studies are retrospective case series, the surgeons may have preferred to treat smaller lesions with simple curettage, thus causing selection bias.

Moreover, differentiating between a residual tumour and insufficient void filling or scanty bone formation after simple curettage may be difficult when assessing postoperative radiographs. Despite complete tumour removal, the resulting full bony consolidation varied from 58% to 82% in simple curettage series (6, 9, 16, 17, 20, 21). Small residual tumours may also be missed in routine radiograph follow-up. MRI scanning is required to distinguish between incomplete bone formation, a true recurrent tumour, and growth of a residual tumour. Thus, we believe that curettage with meticulous void augmentation will allay concerns of the treating surgeon when assessing postoperative radiographs.

Table II. *Procedure-associated complications in patients treated with autologous bone graft (AG) and those treated with bioactive glass (BAG).*

Complication	BAG group (n=74)	AG group (n=116)
Superficial infection	1	1
Permanent stiffness	1	1
Swan neck deformity	1	-
Hypertrophic scarring	1	-
Digital nerve injury	-	2

Various materials have been used for filling of bone defects (*e.g.*, autogenic, allogenic, xenogenic, and synthetic bone substitutes) (22). The ideal material to replace bone tissue

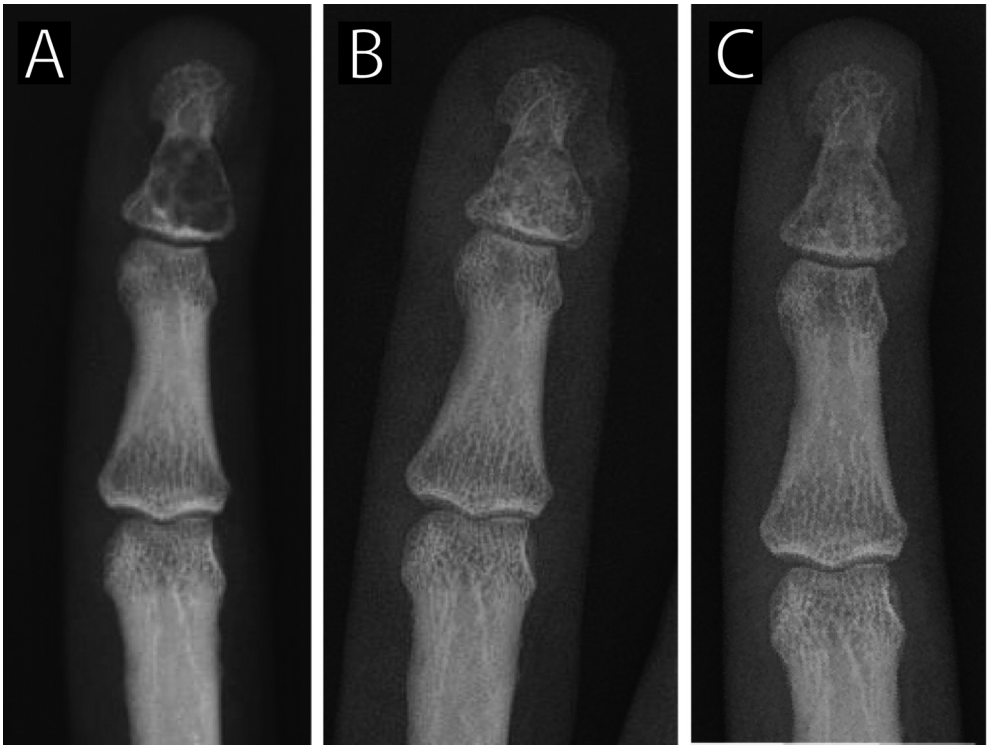

Figure 2. *Plain radiographs from the case of a 35-year-old female with distal phalanx enchondroma at presentation (A), and at 3 months (B) and 1 year (C) after treatment with curettage and autogenous bone grafting.*

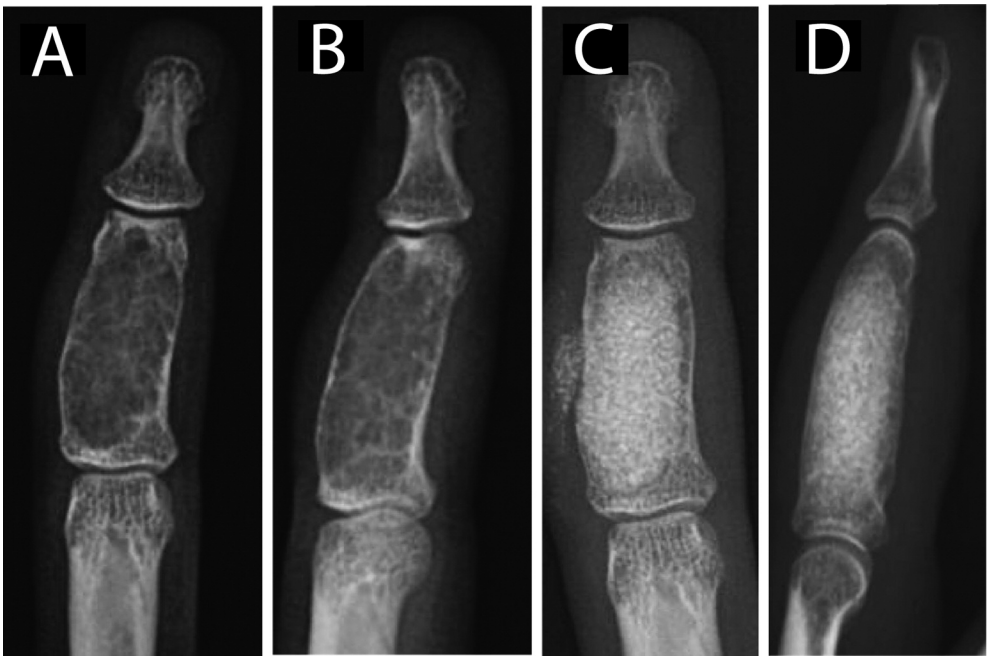

Figure 3. *Plain radiographs from the case of a 19-year-old female with middle phalanx enchondroma at presentation (A and B), and at 6 months after treatment with curettage and bioactive glass filling (C and D). A small amount of the bioactive glass can be seen to have drifted outside of the cavity without any clinical relevance (C).*

should meet precise criteria, such as being biocompatible, bioresorbable, osteoconductive, structurally similar to bone, porous, mechanically resistant, easy to use, safe, and cost-effective (23). Among bone-graft materials, AG represents the gold standard. Regarding the criteria above and compared with allograft bone, AG can be considered the ideal bone-graft replacement material, as any immunogenicity or rejection problems or disease transmission risks can be avoided (22). However, the risk of comorbidity associated with the donor site is inevitable. Although major complications are rare, a third of all complications occur at the site of harvest (6). Moreover, larger defects necessitate general anaesthesia and iliac crest bone harvesting.

BAG-S53P4 is a safe and well-tolerated bone-graft material and has successfully been used in the treatment of bone cysts and cavities, including treatment of those arising from infection. Bone formation in experimental *in vitro* and *in vivo* bone defect models of BAG-S53P4 has been well documented (24, 25).

In a prospective randomized study comparing BAG-S53P4 and AG in the treatment of benign bone tumours in 21 patients, BAG-S53P4-filled cavities appeared dense on X-rays and MRI showed a mainly fatty bone marrow at the 14-year follow-up. Moreover, increased cortical thickness was observed on enchondromas that were filled with BAG-S53P4 (12). Following bone remodelling in cavitary defects, repair of the BAG-S53P4-filled cavities has been shown to start from the periphery into the deeper parts of the defects. Plain films and computed-tomography have not revealed resorptive changes at the BAG-S53P4–bone interface (8).

Clinically, BAG-S53P4 can be used either as granules or as a more mouldable putty. The difference between the two is that the granules possess an antibacterial property, which is lost due to the glycerol (to improve mouldability properties) included in the putty formula. The bone-forming qualities for the putty were at least as good as bone-graft expanders in an interbody spinal fusion study (26).

The present study is thus far the largest report on enchondroma curettage comparing AG and a bone substitute. In our study, both BAG and AG were safe and effective in the treatment of hand enchondromas. The number of complications was low and was equally distributed between the study groups. There were no reoperations in the BAG group compared to five in the AG group. However, no conclusions regarding the preferability of BAG over AG can be made. The indication for reoperation should be based on clinical symptoms and radiographic growth, as small recurrent or residual tumours, or insufficient void filling may persist in radiographs without causing any symptoms or risk of pathological fracture.

In conclusion, void augmentation with BAG is a good alternative to the well-established use of AG in curettage-treated bone. BAG obviates the need for general anaesthesia and harvesting of autologous bone grafts. However, high-quality research on operative treatment is warranted.

Conflict of Interest

The Authors declare no potential conflicts of interest with respect to the research, authorship, and publication of this article. Nina Lindfors is a clinical advisor for BonAlive Biomaterials.

Authors' Contributions

SA conceived the study. All Authors contributed to designing the study. SA, EK, TA, and PN acquired the data. SA and AS performed the data analysis. NL, EK, and SA drafted the article. All Authors contributed to refinement and approval of the final article.

References

1 Nelson DL, Abdul-Karim FW, Carter JR and Makley JT: Chondrosarcoma of small bones of the hand arising from enchondroma. J Hand Surg Am *15(4)*: 655-659, 1990. PMID: 2199571. DOI: 10.1016/s0363-5023(09)90032-6

2 Wu KK, Frost HM and Guise EE: A chondrosarcoma of the hand arising from an asymptomatic benign solitary enchondroma of 40 years' duration. J Hand Surg Am *8(3)*: 317-319, 1983. PMID: 6875237. DOI: 10.1016/s0363-5023(83)80169-5

3 Tang C, Chan M, Fok M and Fung B: Current management of hand enchondroma: a review. Hand Surg *20(1)*: 191-195, 2015. PMID: 25609298. DOI: 10.1142/S0218810415300028

4 Liodaki E, Kraemer R, Mailaender P and Stang F: The use of bone graft substitute in hand surgery: a prospective observational study. Medicine (Baltimore) *95(24)*: e3631, 2016. PMID: 27310946. DOI: 10.1097/MD.0000000000003631

5 Lubahn JD and Bachoura A: Enchondroma of the hand: evaluation and management. J Am Acad Orthop Surg *24(9)*: 625-633, 2016. PMID: 27454024. DOI: 10.5435/JAAOS-D-15-00452

6 Bachoura A, Rice IS, Lubahn AR and Lubahn JD: The surgical management of hand enchondroma without postcurettage void augmentation: authors' experience and a systematic review. Hand (N Y) *10(3)*: 461-471, 2015. PMID: 26330779. DOI: 10.1007/s11552-015-9738-y

7 Henderson M, Neumeister MW and Bueno RA Jr: Hand tumors: II. Benign and malignant bone tumors of the hand. Plast Reconstr Surg *133(6)*: 814e-821e, 2014. PMID: 24867740. DOI: 10.1097/PRS.0000000000000178

8 Lindfors NC, Heikkilä JT, Koski I, Mattila K and Aho AJ: Bioactive glass and autogenous bone as bone graft substitutes in benign bone tumors. J Biomed Mater Res B Appl Biomater *90(1)*: 131-136, 2009. PMID: 18988277. DOI: 10.1002/jbm.b.31263

9 Tordai P, Hoglund M and Lugnegård H: Is the treatment of enchondroma in the hand by simple curettage a rewarding method? J Hand Surg Br *15(3)*: 331-334, 1990. PMID: 2230500. DOI: 10.1016/0266-7681(90)90013-t

10 Geurts J, van Vugt T, Thijssen E and Arts JJ: Cost-effectiveness study of one-stage treatment of chronic osteomyelitis with bioactive glass S53P4. Materials (Basel) *12(19)*: 3209, 2019. PMID: 31574970. DOI: 10.3390/ma12193209

11 Lindfors NC, Hyvönen P, Nyyssönen M, Kirjavainen M, Kankare J, Gullichsen E and Salo J: Bioactive glass S53P4 as bone graft

substitute in treatment of osteomyelitis. Bone *47(2)*: 212-218, 2010. PMID: 20624692. DOI: 10.1016/j.bone.2010.05.030

12 Lindfors NC, Koski I, Heikkilä JT, Mattila K and Aho AJ: A prospective randomized 14-year follow-up study of bioactive glass and autogenous bone as bone graft substitutes in benign bone tumors. J Biomed Mater Res B Appl Biomater *94(1)*: 157-164, 2010. PMID: 20524190. DOI: 10.1002/jbm.b.31636

13 Peltola M, Aitasalo K, Suonpää J, Varpula M and Yli-Urpo A: Bioactive glass S53P4 in frontal sinus obliteration: a long-term clinical experience. Head Neck *28(9)*: 834-841, 2006. PMID: 16823870. DOI: 10.1002/hed.20436

14 ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision, Second Edition. World Health Organization, 2004. Available at: https://apps.who.int/iris/handle/10665/42980 [Last accessed on March 30, 2022]

15 NOMESCO Classification of Surgical Procedures (NCSP), version 1.16. Nomesco, Nordclass, 2009. Available at: https://norden.diva-portal.org/smash/get/diva2:970547/FULLTEXT01.pdf [Last accessed on March 30, 2022]

16 Giles DW, Miller SJ and Rayan GM: Adjunctive treatment of enchondromas with CO2 laser. Lasers Surg Med *24(3)*: 187-193, 1999. PMID: 10229149. DOI: 10.1002/(sici)1096-9101(1999)24:3<187::aid-lsm3>3.0.co;2-v

17 Wulle C: On the treatment of enchondroma. J Hand Surg Br *15(3)*: 320-330, 1990. PMID: 2230499. DOI: 10.1016/0266-7681(90)90012-s

18 Pianta TJ, Baldwin PS, Obopilwe E, Mazzocca AD, Rodner CM and Silverstein EA: A biomechanical analysis of treatment options for enchondromas of the hand. Hand (N Y) *8(1)*: 86-91, 2013. PMID: 24426900. DOI: 10.1007/s11552-012-9476-3

19 Goto T, Yokokura S, Kawano H, Yamamoto A, Matsuda K and Nakamura K: Simple curettage without bone grafting for enchondromata of the hand: with special reference to replacement of the cortical window. J Hand Surg Br *27(5)*: 446-451, 2002. PMID: 12367544. DOI: 10.1054/jhsb.2002.0843

20 Hasselgren G, Forssblad P and Törnvall A: Bone grafting unnecessary in the treatment of enchondromas in the hand. J Hand Surg Am *16(1)*: 139-142, 1991. PMID: 1995672. DOI: 10.1016/s0363-5023(10)80031-0

21 Morii T, Mochizuki K, Tajima T and Satomi K: Treatment outcome of enchondroma by simple curettage without augmentation. J Orthop Sci *15(1)*: 112-117, 2010. PMID: 20151260. DOI: 10.1007/s00776-009-1419-7

22 Fernandez de Grado G, Keller L, Idoux-Gillet Y, Wagner Q, Musset AM, Benkirane-Jessel N, Bornert F and Offner D: Bone substitutes: a review of their characteristics, clinical use, and perspectives for large bone defects management. J Tissue Eng *9*: 2041731418776819, 2018. PMID: 29899969. DOI: 10.1177/2041731418776819

23 Faour O, Dimitriou R, Cousins CA and Giannoudis PV: The use of bone graft substitutes in large cancellous voids: any specific needs? Injury *42(Suppl 2)*: S87-S90, 2011. PMID: 21723553. DOI: 10.1016/j.injury.2011.06.020

24 Björkenheim R, Jämsen E, Eriksson E, Uppstu P, Aalto-Setälä L, Hupa L, Eklund KK, Ainola M, Lindfors NC and Pajarinen J: Sintered S53P4 bioactive glass scaffolds have anti-inflammatory properties and stimulate osteogenesis *in vitro*. Eur Cell Mater *41*: 15-30, 2021. PMID: 33389745. DOI: 10.22203/eCM.v041a02

25 Eriksson E, Björkenheim R, Strömberg G, Ainola M, Uppstu P, Aalto-Setälä L, Leino VM, Hupa L, Pajarinen J and Lindfors NC: S53P4 bioactive glass scaffolds induce BMP expression and integrative bone formation in a critical-sized diaphysis defect treated with a single-staged induced membrane technique. Acta Biomater *126*: 463-476, 2021. PMID: 33774197. DOI: 10.1016/j.actbio.2021.03.035

26 Saarenpää I, Hirvonen J, Rinne J, Frantzén J: Novel bioactive glass putty (S53P4) as bone graft expander in minimally invasive lumbosacral interbody fusion. J Minim Invasive Spine Surg Tech *3*: 52-58, 2018. DOI: 10.21182/jmisst.2018.00332

Received March 9, 2022
Revised April 6, 2022
Accepted April 8, 2022