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The surgical management of the cavity and bone defects in enchondroma cases: A prospective randomized trial

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ABSTRACT

Background: We compared the curettage/bone grafting and the curettage/bone graft substitutes surgical techniques in their relation to functional outcomes, oncologic outcome (recurrence, malignant transformation), the rate of postsurgical complications, durations of surgery and of postsurgical immobilization for hand-localized cases of solitary and multiple enchondromas.

Methods: The current prospective randomized trial analyzed 200 adult patients (2012–2017) with enchondroma who underwent surgical intervention. The cases were randomly divided into Group 1 (n = 100; F 56, M 44) for surgeries with curettage and autogenous bone grafting, and Group 2 (n = 100; F 55, M 45) for surgeries with curettage and bone graft substitutes. The placebo control Group 3 consisted of cases operated by curettage only (n = 56; F 31, M 25). The follow-up period was set at 30 months.

Results: The duration of surgery was 51 ± 4 min in Group 1 and 27 ± 1 min in Group 2 (p = 0.008). In Group 1, the rate of recurrence was 6% against 1% in Group 2 (p = 0.005). No other statistically significant differences in postsurgical outcomes between three involved groups were noted.

Conclusion: In cases of enchondroma of the hand, postsurgical functional outcomes, the rate of postsurgical complications, the duration of immobilization, and the time to complete recovery are not influenced by the type of chosen grafting material. The implementation of HAp-collagen bone substitutes in granules instead of autogenous bone grafting reduces the duration of surgery. The implementation of autogenous bone grafting may increase the rate of tumor recurrence.

1. Introduction

Enchondroma is a benign hyaline cartilage tumor arising within the medullary cavity of a bone and is a relatively common skeletal neoplasm. The most frequent site for the tumor is the hand. While benign and slow-growing, enchondroma may lead to pathological fractures of the involved bones. Malignant degeneration of enchondroma into chondrosarcoma or fibrosarcoma, while extremely rare, is well-documented [1–3]. Therefore, an improvement of the operative technique for such cases is important both from surgical and oncological viewpoints.

Two topics have been discussed in this connection for decades: 1) simple curettage versus curettage with subsequent filling of the bone defect and 2) human bone grafting versus other filling materials as bone substitutes. The simple curettage approach had a small number of partisans [4–6]. The majority of the researchers expressed the opinion that the postoperative bone defects are to be filled [7–24]. Numerous materials and approaches were suggested for this filling: filling of the cavity with “bone meal” [12], corticalis-graft plasty [13], cortico-cancellous allograft obtained from cadaveric banked bone [14], bone cement and intramedullary hardware [15], injectable phosphocalcic cement [16], just to name a few. Finally, the opinion was expressed that autogenous

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cancellous bone graft should be counted as the gold standard [7,10,16–18]. This statement, however, has remained under question up-to-date. The autologous bone graft technique, when the graft is usually harvested from the iliac crest, may be difficult to apply in some pediatric cases when the skeleton is still developing, in gerontology cases with demineralized and fragile bones, in cases when comorbidities may stimulate donor site complications, and in cases of multiple (polyfocal) enchondroma when significant amounts of the graft may be needed. The donor site complication rates are low, but such complications are possible [10,19].

The efforts to develop various synthetic bone substitutes continued. Currently, bone cement (PMMA), osteoconductive ceramics, injectable calcium phosphate cement, and some other synthetic calcium phosphate bone substitutes such as hydroxyapatite (HAp) and beta-tricalcium phosphate particles (beta-TCP) were suggested as alternatives to autogenous bone grafts [10,20–22]. It was reported that implementation of bone graft substitutes in general and calcium phosphate bone substitutes in particular provides surgery success rate equivalent to that of autografts [20–24]. As early as in the 1990s, these reports were supported by a randomized control trials but they were performed only for long bone fractures [25,26]. The oncology-related and the hand surgery-related randomized control trials were not performed.

The authors aimed to compare the curettage/bone grafting and the curettage/bone graft substitutes surgical techniques in their relation to functional outcomes, oncologic outcome (recurrence rate, the rate of malignant transformation to chondrosarcoma), the rate of postsurgical complications, the duration of surgery, and the duration of postsurgical immobilization for hand-localized cases of solitary enchondroma and multiple enchondroma.

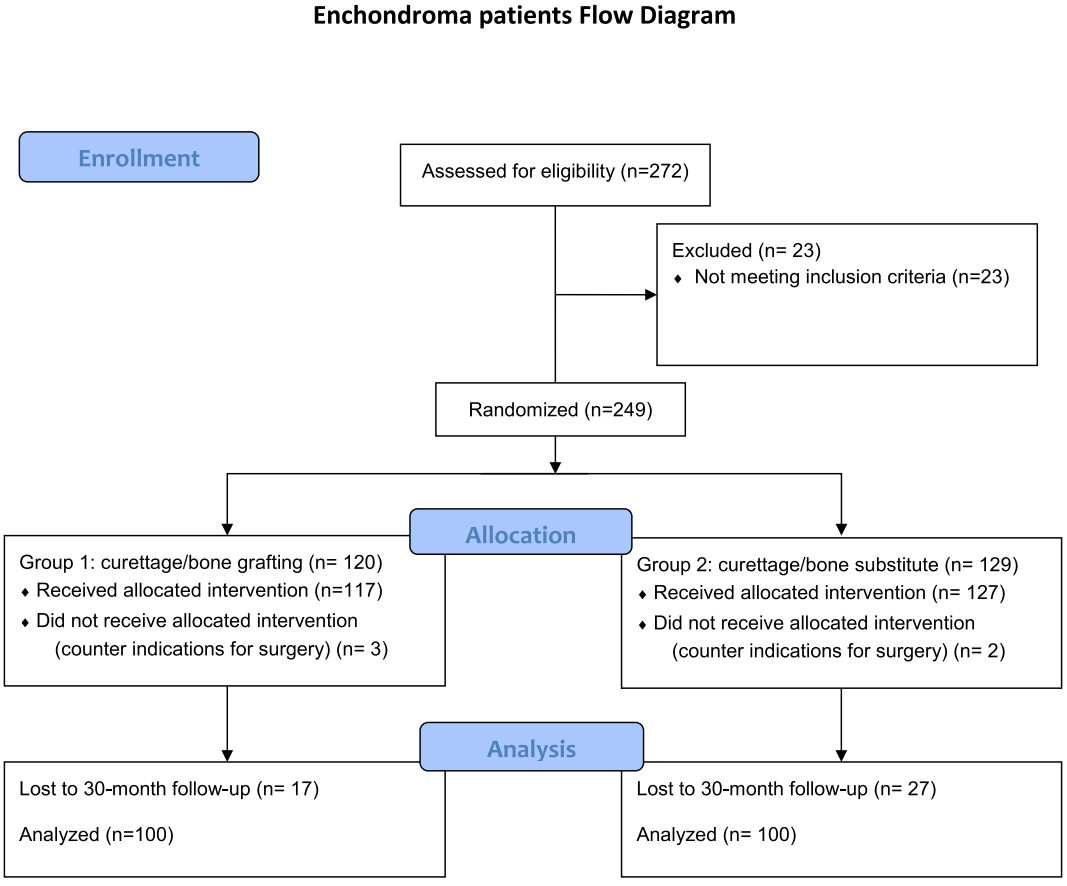
2. Methods

The current prospective randomized trial analyzed 200 patients (November 2012–December 2017 with follow-up to June 2020) diagnosed with enchondroma of the hand bones to whom a surgical intervention was performed. The patients were referred to two tertiary referral hospitals by secondary care outpatient or inpatient medical centers or private practitioners who suspected or diagnosed the cases of hand enchondroma and forwarded the patients for further management to specialized hand surgery departments. In all cases, the diagnosis was confirmed by X-ray or CT and MRI (in uncertain cases) investigation and post-surgical histological examination. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (amended 2013) as reflected a priori after approval by the institutions' Ethical Committees as a "prospective single-blinded randomized study".

The inclusion criteria were the hand-located cases of solitary enchondroma and multiple (polyfocal) enchondroma not related to Ollier disease. The cases of osteochondroma, multiple osteochondromatosis, multiple enchondromatosis (Ollier Disease), periosteal chondroma, extraskeletal (soft tissue) chondroma, chondroblastoma, chondromyxoid fibroma, and chondrosarcoma were excluded. Patients with type 2 diabetes mellitus were not involved in the study. The cases with the follow-up less than 30 months (five six-month follow-up meetings) were excluded from the study.

The patients were randomly chosen among adult hospital patients according to a predetermined randomization code. The standard Randomization and Enrollment form and sealed envelope method were used. The patients flow is presented in Table 1. The cases were randomly divided into two groups: Group 1 (n = 100; 110 tumor sites; F 56, M 44;

Table 1
The patients' flow diagram.



mean age 43 ± 9.5 years) for surgeries with curettage and autogenous bone grafting, and Group 2 (n = 100; 116 tumor sites; F 55, M 45; mean age 37 ± 11.5 years) for surgeries with curettage and bone graft substitutes. There were four multiple enchondroma cases in Group 1 and six cases in Group 2. The placebo control Group 3 consisted of cases operated by curettage only (n = 56; 56 tumor sites; F 31, M 25; mean age 38 ± 12.5 years). The patients for this group were not randomized because the decision to operate by curettage only was made primarily for the cases in which the distal phalanx or carpal bones were involved. Three different surgeons experienced in hand surgery operated on these patients. All surgeries were performed at tertiary referral hospitals with fully functioning surgical units, including a separate hand surgery unit, and proper imaging facilities. The external control Group 4 consisted of 40 non-hands no grafting cases that were retrospectively collected. In these cases, the surgical intervention was performed for chondromas located within the maxillofacial and head-and-neck areas that were managed without any grafting. These cases could not be compared to the hand cases for functional outcomes or the duration of surgery but we aimed to have an additional reference group for assessment of oncologic outcome and the rate of postsurgical complications. The study was terminated when we collected 100 cases for each of two main groups no matter how many cases were collected for Group 3.

Functional outcomes, the rate of postsurgical complications, the duration of surgery, the duration of immobilization, the time to complete recovery, and the rate of malignant transformation to chondrosarcoma were taken for comparison between two main groups as well as incidence of tumor recurrence. The Disability of the Arm, Shoulder, and Hand (DASH) function scale (0–100, no disability – full disability) and the Takigawa criteria assessing appearance, the active range of motion, the patients' grip strength, and radiographic evidence of healing without shortening, deformity, osteoarthrosis, or tumor recurrence (4–0, excellent - poor) [27] were used to evaluate the function of the operated hand.

2.1. Surgical techniques

The indication for the surgical intervention was the clinical manifestation of the disease with the following possible symptoms in various combinations: local pain, a deformity or palpable formation at the bone level, an impaired function of the limb or a nearby joint, and pathological fracture. The X-ray investigations were carried out on digital low-dose and analog X-ray devices with standard cartridges. Analyzing the X-ray diffraction patterns, the shape, size, contours of the bone, the morphology of the surrounding soft tissues, the presence of an endosteal and periosteal reaction, the localization of the process, and the internal structure of the focus were evaluated. (Fig. 1). To compare the structure of the bone, as required, the radiographs of the contralateral section of the study area were also evaluated. When assessing the revealed pathological formations, the size, shape, contour, extent, topographic localization, and destructive changes were used as the criteria for the differential diagnosis between benign tumor and tumor-like diseases of limb bones.

In both groups, all surgeries were performed under local anesthesia if the distal or the middle phalanx was involved. In cases when the proximal or the metacarpal phalanx was involved, regional (brachial plexus block) anesthesia was applied. For all 10 cases of multiple enchondroma, general anesthesia was applied. All patients in Groups 1 and 2 underwent surgical treatment using minimally invasive access under the X-ray control. An angled curette and/or a sharp spoon were used for curetting the cavity. A tumor was enucleated, the cavity was coagulated, and then it was cleansed with 3% hydrogen peroxide and bone wax. For Group 1 patients, the surgery ended with filling of the bone defect with cancellous bone harvested from the ipsilateral iliac crest and the cortical window was used for reconstruction. Group 2 patients underwent plastic surgery with filling the bone defect with Calcium orthophosphate-based bioceramic granules consisting of hydroxyapatite (HAp, $Ca_{10}(PO_4)_6(OH)_2$) and collagen as the main components (Collagraft, NeuColl Inc., USA; Collapan L, Intermedapatite, Russia; Collapat, Symatese, France). (Fig. 2). The trimmed pieces (Collapat) or granule sizes were selected according to the size of the cortical window and the volume to be filled. The wounds were closed after hemostatic revision.

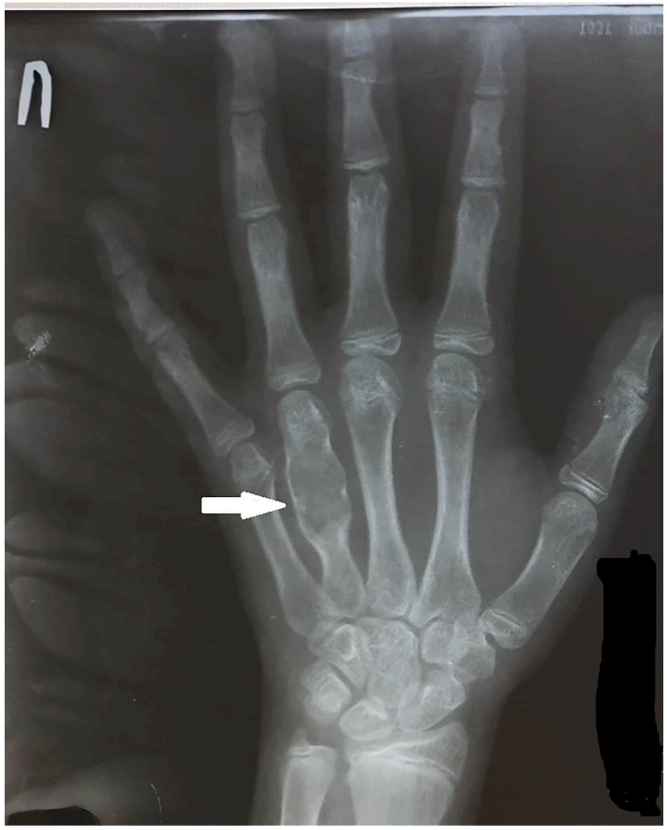


Fig. 1. The left-hand X-ray of a 34-y-old patient shows the image of a metacarpal bone enchondroma in the fourth finger. The lesion widened the anteroposterior diameter of the bone and thickened the cortices. A surgical intervention was suggested.

2.2. Follow-up

All X-ray studies were carried out in dynamics: at the initial examination, on the third day after surgery, after the end of the immobilization period - one month or somewhat earlier after surgery, two and three months after surgery to determine signs of bone marrow formation, and six and 12 months after surgery to detect bone remodeling defect. (Fig. 3). The follow-up meetings were scheduled accordingly. The subsequent follow-ups were carried out in a six-month periods checking functional outcomes and possible tumor recurrence.

The range of movement of the involved finger joints was evaluated by comparing it with the healthy contralateral side. An active range of motion of >80% in comparison with the contralateral side and grip strengths of ≥80% in comparison with the contralateral side were counted as indications of complete recovery. Radiologic outcomes were measured via X-ray imaging using the Tordai classification system [5]: 1) normal cortical and cancellous bone or presence of a bone defect ‹ 3 mm in diameter; 2) bone defect of 4–10 mm with no clear-cut recurrence; and 3) bone defect › 10 mm with the characteristics of an enchondroma. Grade 1 obtained after the three-month or six-month X-ray investigation was counted as an indication of complete recovery.

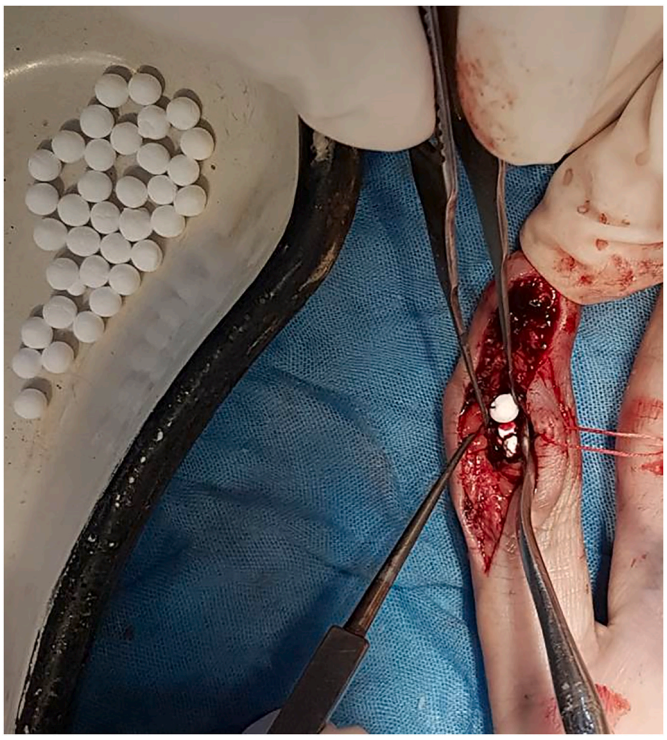


Fig. 2. The 30-y-old male patient from Group 2 underwent plastic surgery with filling the bone defect with Calcium orthophosphate-based bioceramic granules (in this case, Collapan L). The complete recovery was noted at the two-month follow-up meeting.

2.3. Statistical analysis

A standard sample size calculation determined that a minimum of 66 subjects per group with a total of 132 subjects were required for the difference between Group 1 and Group 2 values to be statistically significant when $\alpha = 0.05$, the power of the study set at 80% (null hypothesis as equivalence design, $\alpha = 0.05$; $\beta = 0.20$). However, taking into account between-center heterogeneity for two unequally sized study centers, a sample size was recalculated as 92 subjects per group. As a 15% loss to follow-up was assumed, the number of subjects per group to reach the objectives was indicated as 106 per group. Finally, applying a Chi-Square test with a two-sided 0.05 significance level and with 80% power, a hundred full-follow-up-period patients per group convenience sample was used as this was believed to provide adequate data to inform the surgical outcomes.

A Chi-Square test was used for the statistical analysis of demographic data, time-related variables, and complications after surgery between groups. One-way ANOVA was selected to compare the differences between groups in the follow-up outcomes (SPSS ver. 19.0). Data were expressed as mean ± standard deviations. Statistical significance was considered at the p‹0.05 level.

3. Results

In all groups, 282 tumors were operated in 256 patients. The size of the tumors ranged from 0.2 cm^2 to 5.9 cm^2, with a mean size of 1.8 ± 1.1 cm^2, and there was no significant difference between Group 1 and Group 2 in the distributions of the sizes of the tumors and their location among specific hand bones ($p = 0.74$ for sizes; $p = 0.32$ for the most frequently affected bones in Group 1 vs. Group 2; $p = 0.14$ for the less frequently affected bone in the group comparison). There were 34 cases of enchondroma with pathological fractures (out of 110 tumor sites) in Group 1 and 37 cases with pathological fractures (out of 116 sites) in Group 2 ($p = 0.69$).

The duration of surgery was 51 ± 4 min (range 45–60 min) in Group 1 and 27 ± 1 min (range 25–30 min) in Group 2 ($p = 0.008$). There were no cases of intraoperative fractures in our cohort. The duration of postsurgical immobilization was almost similar in all three groups: Group 1–25 ± 3 days, Group 2–26 ± 3 days, and Group 3–22 ± 3 days (Group 1 vs. Group 2 $p = 0.92$). The time to complete recovery also was almost similar and occurred mostly between the one-month and two-month follow-ups: Group 1–93/100 patients, Group 2–95/100, and Group 3–53/56. Among the remaining 15 patients, in four cases complete recovery was noted already at the one-month follow-up. In 11 cases, the patients also showed signs of complete recovery between the one-month and two-month follow-ups but later they underwent secondary surgery because of recurrence and/or fracture and, therefore, their complete recovery was delayed.

Functional outcomes results are presented in Table 2. The rates of postsurgical complications are presented in Table 3 and the rate of recurrence in Table 4. For the whole cohort of 256 patients, the rate of recurrence was 3.1% but the distribution of the recurrence cases among the groups was uneven. Six secondary operations for the whole cohort (n = 256) were performed because of tumor recurrence, three operations were performed because of fractures, and two cases of tumor recurrence associated with fracture were reoperated. The subsequent

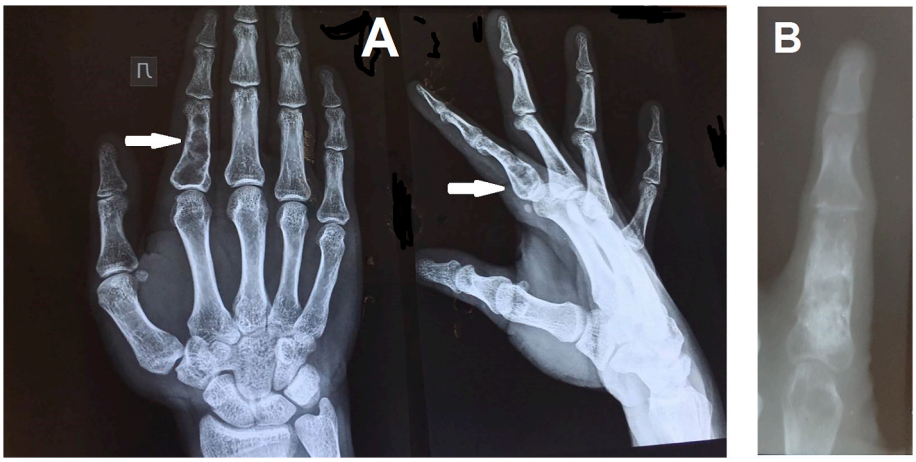


Fig. 3. A. Plain radiographs of a 41-u-old patient show a radiolucent lesion of the proximal phalanx of the right index finger with a thinned cortex. The patient was diagnosed with solitary enchondroma and randomly assigned to Group 2.
B. The 12-month postoperative radiograph demonstrates bone union and no tumor recurrence.

Table 2
Postsurgical functional outcome results as presented during the follow-up period. P1 – p-value for Group 1 vs. Group 2 comparison; P2 - p-value for Groups 1/2 vs. Group 3 comparison.

Outcomes	Group 1	Group 2	Group 3	P1	P2
Presurgical DASH score	52 ± 8	54 ± 9	45 ± 6	0.88	0.08/0.06
1 month *follow-up*					
motion range >80% (ptnts)	73/100	70/100	39/56	0.32	0.54/0.47
grip strengths ≥80% (ptnts)	72/100	75/100	45/56	0.45	0.51/0.54
DASH score	16 ± 4.1	17 ± 4.2	10 ± 3.3	0.92	0.05/0.04
Takigawa criteria score	3.2 ± 0.6	3.3 ± 0.6	3.5 ± 0.6	0.94	0.32/0.38
6 months *follow-up*					
range of motion of >80%	92/100	94/100	51/56	0.88	0.73/0.82
grip strengths of ≥80%	95/100	96/100	53/56	0.92	0.92/0.94
DASH score	9 ± 2.2	8 ± 3.2	5 ± 1.4	0.86	0.05/0.07
Takigawa criteria score	3.7 ± 0.5	3.6 ± 0.4	3.8 ± 0.2	0.87	0.93/0.82
Tordai X-ray score	1.2 ± 0.2	1	1	0.95	0.95/1
30 months *follow-up*					
range of motion of >80%	93/100	95/100	55/56	0.90	0.72/0.86
grip strengths of ≥80%	93/100	97/100	56/56	0.83	0.69/0.92
DASH score	4.5 ± 1.1	3 ± 1	2 ± 0.5	0.07	0.05/0.07
Takigawa criteria score	3.5 ± 0.5	3.7 ± 0.4	3.8 ± 0.2	0.87	0.93/0.82
Tordai X-ray score	1.5 ± 0.2	1.1 ± 0.2	1	0.90	0.90/0.96

Table 3
The rates of postsurgical complications in Groups 1-4 that were developed during the first postoperative month. P-value is presented for Group 1 vs. Group 2 comparison.

Complication	Group 1	Group 2	Group 3	Group 4	P
Infection	3	2	1	2	
Donor site infection	2	N/A	N/A	N/A	
Hematoma	0	0	0	0	
Persistent pain	2	3	1	0	
Finger joint stiffness	2	2	1	N/A	
Fracture/refracture	2	3	0	N/A	
TOTAL	11	10	3	2	0.95

Table 4
The rate of malignant transformation to chondrosarcoma and the incidence of enchondroma recurrence detected during the 30-months follow-up period. P1 - p-value is presented for Group 1 vs. Group 2 comparison. P2 - p-value is presented for Group 1 (n=100) vs. Groups 3 and 4 (n=96) comparison.

Recurrences	Group 1	Group 2	Group 3	Group 4	P1	P2
Enchndorma	5	1	0	1		
Chondrosarcoma	1	0	1	0		
TOTAL (%)	6 (6%)	1 (1%)	1 (1.8%)	1 (2.5%)	0.005	0.05
Time since surgery	9 mo ± 3 mo	18 mo ± 4 mo	12 mo ± 3 mo	24 mo ± 4 mo		

results obtained from these 11 cases were not included in the above-mentioned tables but in all these cases functional outcomes, while delayed, were good and complete recovery was achieved after the second surgery that was noted during the rescheduled follow-ups.

4. Discussion

Our results demonstrate that in cases of enchondroma of the hand, postsurgical functional outcomes, the rate of postsurgical complications, the duration of immobilization, and the time to complete recovery are not influenced by the type of chosen grafting material.

The most intriguing finding within our set of results was a significant difference in the rate of recurrence between Group 1 and Groups 2, 3, and 4. The problem of enchondroma recurrence after surgical removal and its malignant degeneration into chondrosarcoma or fibrosarcoma has been discussed at least since the 1970s [1]. In the emerging literature, the rate of recurrence was reported from 0% [14,15,19,20,28] to 11%–13.3% [1,17,29]. The generally accepted (Green's operative hand surgery, 2010) recurrence rate is 4.5% [30]. It was also pointed out in another manual that when enchondroma recurred, "it can be low-grade chondrosarcoma" [31]. It was also reported that "most recurrences occur early after initial surgery" [32] and we confirm this statement. We did not perform the literature meta-analysis on the subject and no direct statement is possible, but within our reference list of hand-related enchondroma surgeries, while the rate of recurrence after surgeries that ended with autogenous cancellous bone grafting was reported to be from 0% to 13.3% [29], the highest reported recurrence rate for surgeries with synthetic bone substitutes was 7% [33]. In fact, the highest reported recurrence rate for surgeries with autogenous cancellous bone grafting was reported as 14.3% [34], but for this cohort, the follow-up period was up to 11–17 years. It does not mean that synthetic bone substitutes inhibit the tendency for recurrence because in our placebo Groups 3 and 4, in which no grafting was performed, the rate of recurrence was similarly low. Whether the iliac crest bone cells may somehow interact with the hand bone cells or any other hypothesis is possible, is the subject for a separate cell-biology-specific research.

In addition to the low rate of recurrence, another statistically significant benefit of the usage of HAp-collagen granulated bone substitutes was the reduction of the duration of surgery. The hand surgery combined with the bone harvesting from the iliac crest is a time-consuming operation. Similarly, while injectable calcium phosphate cement is probably the most widely used bone substitute to-date, its preparation in a special sterile kit and subsequent application require from 15 min to 20–25 min setting time according to the established cement preparation protocols for various types of cement [35]. The HAp-collagen materials that we used were previously investigated in a rabbit and dog femoral condyle models and were used for treatment of long tubular bone fractures, false joints, and maxillo-facial defects [22,36–39]. To our knowledge, they were never used in the hand surgery before. Being supplied in granules or easily trimmed sponges, they do not require any preparation protocol and their application significantly shortens the duration of surgery. While porous bioceramics, a good mechanical fixation is guaranteed in addition to providing sites on the surface that allow chemical bonding between them and bones and they are colonized easily by cells and bone tissues [40,41]. In addition, both bone grafts and cement fillings may require an additional fixation with a screw or a plate [19,42] and we never felt such a necessity in our cases with the HAp-collagen granules.

We also were satisfied with hydrogen peroxide usage during our surgeries. Our motif to choose this specific adjuvant treatment was based on its simplicity in handling and on previously reported good results. It was recently demonstrated that hydrogen peroxide provides an adequate anti-infection effect and reduces the risk for tumor recurrence [43,44].

Patients with type 2 diabetes mellitus were not involved in our study because diabetes is understood as a risk factor for postsurgical infection [45,46]. Diabetes may affect bone quality and bone metabolism [47,48], increase risk for bone fragility [49], and risk of bone surgery postoperative complications in general [50]. In cases when an urgent surgical intervention is required for such patients (pathological fracture of the bone, for example), an in-depth surgical and endocrinological

investigation should be performed prior to surgical intervention.

4.1. Limitations

Our placebo control Group 3, while consisting of hand enchondroma cases, was not fully identical to our main Groups 1 and 2 in sizes of the tumor. We, however, were forced to use this control group because, by the hospital protocol, only small bone defects were treated without grafting. Some reports on the subject provided results obtained from longer follow-up periods, up to 12 years. While our 30-month follow-up period is acceptable, the longer period of follow-up may change the rate of recurrence.

5. Conclusion

In cases of enchondroma of the hand, postsurgical functional outcomes, the rate of postsurgical complications, the duration of immobilization, and the time to complete recovery are not influenced by the type of chosen grafting material. The implementation of HAp-collagen bone substitutes in granules instead of autogenous bone grafting reduces the duration of surgery. The implementation of autogenous bone grafting may increase the rate of tumor recurrence.

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