Factors predictive of positive response to steroid therapy in simple bone cysts: an old trick that still works

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Abstract

Purpose The aim of the study was to identify clinical, demographic and radiological factors predicting a positive response to steroid treatment in simple bone cysts (SBCs).

Methods A retrospective study was conducted on 62 patients. The mean follow-up period was 9.2 years after the final steroid injection. Recurrences were defined according to Neer's scale as modified by Chang et al.. To identify predictive factors, the group of patients who positively responded to treatment (Neer stages I and II, $n=39$, 62.9 %, group 1) were compared with the group in which recurrences occurred (Neer stages III and IV, $n=23$, 37.1 %, group 2).

Results Recurrences were experienced by 37.1 % of the patients ($n=23$). Cyst location, numbers of cavities (uni- or multilocular), the area of the cyst and its Enneking stage differed significantly between the groups ($p<0.05$).

Conclusions Steroid therapy may be of benefit in patients with unilocular, small-sized, humeral cysts, classified as Enneking stage IA.

Introduction

Simple bone cysts (SBCs) are rare, tumour-like osteolytic bone lesions which affect mainly children and adolescents. Spontaneous healing occurs only about 5–10 % of all cases [1, 2]. Treatment of cysts should be initiated promptly: either at the time of diagnosis or as soon as the fracture

heals. Pathological fractures and bone growth disturbances are observed in about 10–15 % of cases [3–6].

More than 20 methods of treating SBCs have been described in the literature, the most commonly used ones being:

- curettage and bone grafting [7]
- injections of steroids, autogenic bone marrow [8], various osteoinductive (demineralised bone matrix [9]) or osteoconductive materials (pastes containing calcium sulphate, calcium hydroxyapatite and tricalcium phosphate [10–12]) into the cysts
- multiple drilling of the cyst wall [13]
- flexible intramedullary nailing [14, 15]

Curettage and bone grafting were the most common procedures used for the treatment of cysts until the 1980s [7]. A study published by Scaglietti et al. reporting that methylprednisolone injections into the cyst resulted in a 96 % treatment success rate was a breakthrough [16]. However, more recent studies have suggested the results of steroid therapy may be significantly worse: in as many as half of the patients, the lesion relapses [6, 17–19]. These unsatisfactory results prompted a search for other biologically active substances which can stimulate osteogenesis and facilitate the healing process of the SBCs. Although steroid therapy has many advantages, such as its simplicity, low cost, high availability and lack of direct post-operative adverse effects, interest in their use for treating SBCs has waned since the introduction of other innovative biologically active materials. The aim of our study was to identify clinical, demographic and radiological factors predicting a positive response to steroid treatment.

Methods

A retrospective study was conducted on 62 patients referred to our clinic for SBC treatment during the period 1993–2008.

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The following study inclusion criteria applied: SBC diagnosed radiologically, subject age at the time of procedure less than 18 years, cyst treated with steroid injection and the procedure had been performed in the study site. Each patient received between one and six steroid injections (mean number 2.66) into the cyst by a single-needle technique after drilling the cyst wall with a Kirschner wire. The steroid dose ranged from 40 to 120 mg methylprednisolone (mean 80.01 mg, SD 21.1 mg) per procedure depending on the age and body weight of the child and the size of the cyst. The total dose administered during the whole therapy ranged from 40 to 760 mg (mean 216.8 mg, SD 132.3 mg). Treatment duration ranged from three months to six years and eight months (mean 17.5 months) and methylprednisolone was administered on average every four months. The demographic characteristics of the subjects enrolled for the study together with cyst locations are presented in Table 1.

After identifying the cyst on the X-ray the following radiological parameters were determined:

- number of cyst cavities (uni- or multilocular)
- cyst type, according to Enneking's scale for benign tumours (latent, active, aggressive) [20]
- longitudinal bone axis length to cyst length ratio (< 10 % group 1, 10–20 % group 2, >20 % group 3)
- cyst area
- cyst index of Kaelin and MacEwen [21] (i.e. the cyst area divided by diaphyseal diameter squared)
- cyst diameter ratio (i.e. the extent of the lesion on the longitudinal axis divided by the normal expected diameter of the long bone) [15]
- minimal cortical thickness
- ratio of the minimal cortical thickness to the cortical thickness in the unaffected part of the diaphysis adjacent to the lesion
- cyst activity (a cyst located ≤ 0.5 cm from the growth plate was considered active, whereas all cysts located >0.5 cm from the growth plate were considered latent) [7]
- occurrence of pathological fractures

Table 1 Demographic data for patients with SBCs

Sample size	62
Age at diagnosis, range (years)	3–17
Mean age (years)	9.64
Women (%)	27.42
Men (%)	73.58
Humerus, <i>n</i> (%)	37 (59.7)
Femur, <i>n</i> (%)	13 (21)
Tibia, <i>n</i> (%)	6 (9.7)
Fibula, <i>n</i> (%)	5 (8)
Calcaneus, <i>n</i> (%)	1 (1.6)

The mean follow-up period was 9.2 years after the final steroid injection (range three to 19 years). The outcomes were evaluated radiologically: X-rays of the affected limb were taken in standard positions every three months during the steroid therapy and once a year thereafter until complete cyst resolution. Recurrences were defined according to Neer's scale as modified by Chang et al. [22]. Stages I and II signified that the therapy was successful, whereas stages III and IV referred to therapy failure (recurrence or no response to treatment). Limb length was assessed according to the AO Foundation guidelines, with a 1.5-cm difference for the lower limbs and a 2-cm difference for the upper limbs considered clinically relevant [23].

The χ^2 test of independence was used to compare the number of qualitative parameters in the study groups and subgroups selected on the basis of different variables; Yates' correction was used for small samples. As most of the parameters analysed in the study were not normally distributed, the mean values were compared using non-parametric tests: the Mann-Whitney test for two groups and the Kruskal-Wallis test for several independent groups. The study was approved by the Institutional Review Board.

Results

Recurrences were experienced by 37.1 % of the patients ($n=23$). In response, eight of these patients underwent curettage with bone grafting, one patient underwent en bloc excision and four patients were reinjected with methylprednisolone. Sample follow-up X-rays of a case of recurrence are shown in Fig. 1. In ten cases, no treatment was resumed as no consent was received to continue the therapy. The follow-up revealed limb length discrepancy in six patients (9.68 %) and pathological fractures at the time of therapy in eight subjects (12.9 %).

To identify predictive factors, the group of patients who positively responded to treatment (Neer stages I and II, $n=39$, 62.9 %, group 1) were compared with the group in which recurrences occurred (Neer stages III and IV, $n=23$, 37.1 %, group 2). No statistically significant differences regarding age, sex, mean methylprednisolone dose per procedure or mean number of procedures performed per patient ($p>0.05$) were found. The results are presented in Table 2.

Table 3 shows the radiological and clinical characteristics of both groups. A statistically significant correlation between treatment result and cyst location was found ($\chi^2=11.299$, $p<0.05$). Steroid therapy was significantly more likely to be successful when the cyst was located in the humerus, while lesions located in the femur, tibia and fibula were significantly more likely to be associated with failure (group 2).

Fig. 1 Example of patient with SBC in the humerus. **a** X-ray view of the lesion, first steroid injection. **b** Follow-up X-ray at 3 months, second steroid injection. **c** Follow-up X-ray at 6 months, third steroid injection. **d** Follow-up at 16 months after fourth (at 9 months) and fifth (at 12 months) steroid injections. **e** Follow-up at 5 years from treatment initiation, curettage with allogenic bone graft. **f** Final result 1.5 years after operation

Table 2 Age, sex, mean methylprednisolone dose per procedure and mean number of procedures performed per patient in the study groups

	Positive response, Neer stages I and II	Recurrences, Nerr stages III and IV	Test value	<i>p</i> value
Sample size	39	23		
Mean age (SD)	9.67 (3.53)	9.61 (3.67)	$z=0.063$	$p>0.05$
Women (<i>n</i>)	12	5	$\chi^2=0.226$	$p>0.05$
Men (<i>n</i>)	27	18		
Mean methylprednisolone dose per procedure, mg (SD)	80.64 (16.58)	80.29 (26.47)	$z=0.098$	$p>0.05$
Mean number of procedures performed per patient (SD)	2.59 (1.57)	2.4 (1.19)	$z=0.493$	$p>0.05$

Unilocular lesions were more frequent in group 1 ($\chi^2=4.996$, $p<0.05$). This implies that a positive response to steroid therapy is more probable in uninocular than in multilocular lesions.

The area of the cyst and its Enneking stage differed significantly between the groups. Cyst area appeared to be significantly smaller in the group with positive treatment results than in the group who did not respond ($z=2.171$, $p<0.05$):

Table 3 Morphological and radiological cyst characteristics in the study group

	Positive response	Recurrence	Test value	<i>p</i> value
Sample size	39	23		
Cyst location				
Humerus, <i>n</i> (%)	30 (76.9)	7 (30.45)	$\chi^2=11.299$	$p<0.05$
Femur, <i>n</i> (%)	4 (10.3)	9 (39.1)		
Calf, <i>n</i> (%)	4 (10.3)	7 (30.45)		
Calcaneus, <i>n</i> (%)	1 (2.5)	0		
Cyst location: shaft/metaphysis				
Metaphysis, <i>n</i> (%)	26 (66.7)	17 (73.9)	$\chi^2=0.357$	$p>0.05$
Shaft, <i>n</i> (%)	13 (33.3)	6 (26.1)		
Cyst activity				
Active cyst, <i>n</i> (%)	16 (41)	12 (52.2)	$\chi^2=0.726$	$p>0.05$
Latent cyst, <i>n</i> (%)	23 (59)	11 (47.8)		
Number of cavities				
Uninocular, <i>n</i> (%)	25 (64.1)	8 (34.8)	$\chi^2=4.996$	$p<0.05$
Multilocular, <i>n</i> (%)	14 (35.9)	15 (65.2)		
Pathological fractures at the time of diagnosis				
Yes, <i>n</i> (%)	33 (84.6)	15 (65.2)	$\chi^2=3.114$	$p>0.05$
No, <i>n</i> (%)	6 (15.4)	8 (34.8)		
Enneking stage				
IA, <i>n</i> (%)	34 (87.2)	10 (43.5)	$\chi^2=10.173$	$p<0.01$
IB, <i>n</i> (%)	5 (12.8)	12 (52.2)		
IC, <i>n</i> (%)	0	1 (4.3)		
Longitudinal bone axis length to cyst length ratio				
$< 1/10$, <i>n</i> (%)	8 (20.5)	5 (21.8)	$\chi^2=0.072$	$p>0.05$
$1/10-1/5$, <i>n</i> (%)	15 (38.5)	9 (39.1)		
$> 1/5$, <i>n</i> (%)	16 (41)	9 (39.1)		
Radiological parameters				
Mean cyst area, cm ² (SD)	13.05 (7.38)	18.93 (13.58)	$z=2.171$	$p<0.05$
Mean cyst index of Kaelin and MacEwen (SD)	19.61 (10.89)	20.55 (13.05)	$z=0.300$	
Mean cyst diameter ratio (SD)	3.6 (1.54)	3.65 (1.74)	$z=0.116$	
Mean minimal cortical thickness, mm ² (SD)	0.17 (0.086)	0.16 (0.08)	$z=0.446$	
Mean ratio of the minimal cortical thickness to the cortical thickness in the diaphysis (SD)	0.42 (0.17)	0.38 (0.19)	$z=0.839$	

13.05 cm² vs 18.93 cm², respectively. The majority of cysts in the group with better response to steroid therapy were those classified as Enneking stage IA (i.e. benign inactive cysts) ($\chi^2=10.173$, $p<0.01$).

No significant differences ($p>0.05$) were found between the groups for the remaining analysed features: cyst location in the bone itself (diaphysis vs metaphysis), cyst activity, pathological fracture upon diagnosis, percentage of the affected bone, cyst index, cyst diameter ratio, thickness of the cortical layer in the lesion or the ratio of the thickness of the cortical layers. It can thus be concluded that steroid therapy may be of benefit in patients with unilocular, small-sized, humeral cysts, classified as Enneking stage IA.

Discussion

Steroid use in SBC management was first reported by Scaglietti et al., who administered doses of 40–200 mg of Depo-Medrol®, depending on cyst size and patient age, by means of a self-invented technique using two separate needles—one for temporary cyst decompression and the other to administer the drug [16]. The procedure described by the authors became standard practice in the treatment of SBCs. In this study, a different, single-needle technique was used, which involved first drilling the cyst wall with a Kirschner wire, followed by aspiration of the fluid and then methylprednisolone administration. During the drilling, care was taken to connect all the separate cavities of the lesion. In general, the methylprednisolone dose was slightly lower than the one reported by Scaglietti et al., reaching a maximum level of 140 mg per procedure (mean 80.01 mg) depending on the weight and age of the child and the size of the cyst, which is in accordance with other authors [6, 24]. Also the time to treatment initiation in our study—1.5–3 months from the diagnosis or pathological fracture—corresponds to figures presented in the pertinent literature [6, 22].

One of the most common problems with steroid therapy in SBCs is its long duration. This is due to the fact that usually more than one procedure is necessary to achieve complete lesion resolution. As the minimal interval between the injections allowing for proper bone healing is three to five months, the average treatment period is two years. In our study, the mean treatment period was found to be 17.5 months, and although the maximum number of procedures needed was six, three were enough (median of three) to achieve cyst healing in the majority of cases—all of which is similar to the experiences of other authors. Due to the strict rules that a child has to follow during the whole healing process (i.e. avoiding intensive physical activity due to high risk of pathological fractures) and fear of the potential adverse effects of repeated steroid injections and further

procedures, many parents are reluctant to follow this mode of therapy. Given the high percentage of pathological fractures (up to 20 %) and long bone rebuilding period, neither parents nor children are willing to continue the treatment—in this study the dropout rate was 16.1 % (ten patients).

In general, the results of steroid therapy in SBCs in our cohort were similar to those mentioned in the literature. Some authors report a treatment success rate as high as 75 % [5, 17, 18, 22]. However, they emphasise that a few procedures are required for the healing process to be completed and that in many cases (25–35 %) the bone remodelling at the site of the lesion is only partial. So far, none of the studies performed afterwards has been able to produce results anywhere close to the ones obtained by the inventor of this mode of treatment: 96 % of patients being recurrence-free after an 18-month follow-up observation period [16]. Nonetheless, more recent research shows a higher percentage of recurrences, even up to 60 % [19].

Few studies have attempted to evaluate factors predictive of response to different modes of SBCs treatment. Neer et al. were the first to carry out such an analysis [7]. In the group in which curettage was performed, a higher percentage of recurrences was observed in cysts located in the proximal parts of the humerus and distal part of the femur. Better results were seen with cysts in the tibia and fibula. In the cases of cysts located in the humerus, recurrences were related to the age of the patient. However, no correlation was found between recurrence rate and cyst activity. The results were not statistically analysed—the authors based their conclusions only on direct comparison of percentages of recurrences.

Campanacci et al. analysed factors predicting response to therapy in groups treated with curettage and with methylprednisolone [5]. In the cases of surgical treatment, recurrences were more common in active cysts, whereas the size and type of the grafts (autogenous vs allogenic) had no effect on the outcome. In patients treated with steroids the risk of recurrence was higher in multilocular, active and large-sized cysts. Neither the type of the affected bone nor the fact that it had been previously operated upon affected the response rate. However, the results were not analysed statistically.

Hashemi-Nejad and Cole, who assessed outcomes of steroid administration into SBCs, found no statistically significant correlations between radiological results of the treatment and the size of the cyst ($p=0.113$), its activity ($p=0.072$) and the child's age ($p=0.067$) [6]. On the other hand, Chang et al. confirmed a significant association between the size of the cyst and the patient's age but not gender, cyst site and type (active/latent) and presence or absence of a previous pathological fracture [22].

One study linked the venous outflow by cystography with the risk of recurrence. The authors have shown that better treatment results (i.e. no recurrences) were observed in cases when there was no venous outflow, while rapid venous outflow (under three minutes) was associated with a treatment failure rate of 21.9 % ($p < 0.05$). At the same time, no correlation was observed between the recurrences and age, sex and the number of cavities in the lesion ($p > 0.05$) [17].

In their study on modern methods of treating cysts (radiographically controlled curettage accompanied by opening of the bone marrow canal and the application of calcium sulphate), Mik et al. did not notice a significant correlation between the frequency of recurrences and age ($p = 0.055$), presence of pathological fracture ($p > 0.1$) and the activity of the cyst ($p = 0.41$). Although the difference in mean age (8.7 vs 11.3 years) did not reach the level of statistical significance, it was very close to it, so it is probable that younger children are more prone to recurrences [11].

Our observation was that poor response to steroid injections was associated with the following cyst characteristics: multilocular, benign active, large-sized and located in the lower limb. Some of the findings are similar to those reported by Neer et al. (cyst location), Campanacci et al. (number of cavities and cyst area) and Chang et al. (size of the cyst) [5, 7, 22]. As for multilocular cysts, unsatisfactory outcomes of steroid injections probably result from unequal distribution of the drug in cyst cavities. Another factor affecting drug distribution is the size of the cyst: in larger cysts, drug concentration may be too low to bring about therapeutic effects.

The advantage of this study is the number of subjects: both groups, with poor and good response to treatment, are large enough to allow for the presented differences to be statistically significant. Moreover, as many as 14 factors were compared; to our knowledge, no such detailed comparison has been previously reported.

Conclusions

Therapy with methylprednisolone may be of benefit to patients with simple unilocular, humeral and small-sized bone cysts, classified as benign inactive lesions. Otherwise, steroid therapy may result in a high recurrence rate and increased risk of pathological fractures. Therefore, in the latter case, other treatment modalities should be pursued: prophylactic stabilisation of the bone together with application of osteoinductive (bone marrow, demineralised bone matrix) or osteoconductive (pastes containing calcium phosphate) materials.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. Neer CS, Francis KC, Johnston AD, Kiernan HA Jr (1973) Current concepts on the treatment of solitary unicameral bone cyst. *Clin Orthop Relat Res* 97:40–51
2. Ahn JI, Park JS (1994) Pathological fractures secondary to unicameral bone cysts. *Int Orthop* 18:20–22
3. Stanton RP, Abdel-Mota'al MM (1998) Growth arrest resulting from unicameral bone cyst. *J Pediatr Orthop* 18:198–201
4. Glowacki M, Ignys-O'Byrne A, Ignys I, Wroblewska K (2011) Limb shortening in the course of solitary bone cyst treatment—a comparative study. *Skeletal Radiol* 40:173–179. doi:10.1007/s00256-010-0964-7
5. Campanacci M, Capanna R, Picci P (1986) Unicameral and aneurysmal bone cysts. *Clin Orthop Relat Res* 204:25–36
6. Hashemi-Nejad A, Cole WG (1997) Incomplete healing of simple bone cysts after steroid injections. *J Bone Joint Surg Br* 79:727–730
7. Neer CS, Francis KC, Marcove RC, Terz J, Carbonara PN (1966) Treatment of unicameral bone cyst. A follow-up study of one hundred seventy-five cases. *J Bone Joint Surg Am* 48:731–745
8. Lokiec F, Ezra E, Khmush O, Wientroub S (1996) Simple bone cysts treated by percutaneous autologous marrow grafting. A preliminary report. *J Bone Joint Surg Br* 78:934–937
9. Killian JT, Wilkinson L, White S, Brassard M (1998) Treatment of unicameral bone cyst with demineralized bone matrix. *J Pediatr Orthop* 18:621–624
10. Thawrani D, Thai CC, Welch RD, Copley L, Johnston CE (2009) Successful treatment of unicameral bone cyst by single percutaneous injection of alpha-BSM. *J Pediatr Orthop* 29:511–517. doi:10.1097/BPO.0b013e3181aad704
11. Mik G, Arkader A, Manteghi A, Dormans JP (2009) Results of a minimally invasive technique for treatment of unicameral bone cysts. *Clin Orthop Relat Res* 467:2949–2954. doi:10.1007/s11999-009-1008-2
12. Altermatt S, Schwöbel M, Pochon JP (1992) Operative treatment of solitary bone cysts with tricalcium phosphate ceramic. A 1 to 7 year follow-up. *Eur J Pediatr Surg* 2:180–182
13. Shinozaki T, Arita S, Watanabe H, Chigira M (1996) Simple bone cysts treated by multiple drill-holes. 23 cysts followed 2–10 years. *Acta Orthop Scand* 67:288–290
14. Givon U, Sher-Lurie N, Schindler A, Ganel A (2004) Titanium elastic nail—a useful instrument for the treatment of simple bone cyst. *J Pediatr Orthop* 24:317–318
15. Kanellopoulos AD, Mavrogenis AF, Papagelopoulos PJ, Soucacos PN (2007) Elastic intramedullary nailing and DBM-bone marrow injection for the treatment of simple bone cysts. *World J Surg Oncol* 5:111
16. Scaglietti O, Marchetti PG, Bartolozzi P (1979) The effects of methylprednisolone acetate in the treatment of bone cysts. Results of three years follow-up. *J Bone Joint Surg Br* 61:200–204
17. Ramirez A, Abril JC, Touza A (2012) Unicameral bone cyst: radiographic assessment of venous outflow by cystography as a prognostic index. *J Pediatr Orthop B* 21:489–494. doi:10.1097/BPB.0b013e328355e5ba
18. Hou HY, Wu K, Wang CT, Chang SM, Lin WH, Yang RS (2010) Treatment of unicameral bone cyst: a comparative study of selected techniques. *J Bone Joint Surg Am* 92:855–862. doi:10.2106/JBJS.I.00607

19. Canavese F, Wright JG, Cole WG, Hopyan S (2011) Unicameral bone cysts: comparison of percutaneous curettage, steroid, and autologous bone marrow injections. *J Pediatr Orthop* 31:50–55. doi:[10.1097/BPO.0b013e3181ff7510](https://doi.org/10.1097/BPO.0b013e3181ff7510)
20. Enneking WF (1986) A system of staging musculoskeletal neoplasms. *Clin Orthop Relat Res* 204:9–24
21. Kaelin AJ, MacEwen GD (1989) Unicameral bone cysts. Natural history and the risk of fracture. *Int Orthop* 13:275–282
22. Chang CH, Stanton RP, Glutting J (2002) Unicameral bone cysts treated by injection of bone marrow or methylprednisolone. *J Bone Joint Surg Br* 84:407–412
23. Ryf C, Weymann A (1999) Range of motion—AO ASIF neutral-O method. Thieme, Davos
24. Hagmann S, Eichhorn F, Moradi B, Gotterbarm T, Dreher T, Lehner B, Zeifang F (2011) Mid- and long-term clinical results of surgical therapy in unicameral bone cysts. *BMC Musculoskelet Disord* 12:281. doi:[10.1186/1471-2474-12-281](https://doi.org/10.1186/1471-2474-12-281)