A Randomized Clinical Trial Comparing Intralesional Bone Marrow and Steroid Injections for Simple Bone Cysts

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Background: Simple bone cysts are common benign lesions in growing children that predispose them to fracture and are sometimes painful. The purpose of this trial was to compare rates of healing of simple bone cysts treated with intralesional injections of bone marrow with rates of healing of those treated with methylprednisolone acetate.

Methods: Of ninety patients randomly allocated to treatment with either a bone-marrow or a methylprednisolone acetate injection, seventy-seven were followed for two years. The primary outcome, determined by a radiologist who was blind to the type of treatment, was radiographic evidence of healing. The cyst was judged to be either not healed (grade 1 [a clearly visible cyst] or grade 2 [a cyst that was visible but multilocular and opaque]) or healed (grade 3 [sclerosis around or within a partially visible cyst] or grade 4 [complete healing with obliteration of the cyst]). Patient function was assessed with use of the Activity Scale for Kids, and pain was assessed with the Oucher Scale.

Results: Sixteen (42%) of the thirty-eight cysts treated with methylprednisolone acetate healed, and nine (23%) of the thirty-nine cysts treated with bone marrow healed ($p = 0.01$). There was no significant difference between the treatment groups ($p > 0.09$) with respect to function, pain, number of injections, additional fractures, or complications.

Conclusions: Although the rate of healing of simple bone cysts was low following injection of either bone marrow or methylprednisolone, the latter provided superior healing rates.

Level of Evidence: Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

Although often resolving at skeletal maturity, simple bone cysts are a common benign lesion in growing children. They predispose children to fracture, are sometimes painful, and may restrict function because of concerns about refracture or a surgeon's recommendation to avoid physical activity.

Simple bone cysts seldom heal after fracture[1], so treatment is often used to speed resolution. Because curettage with bone-grafting is followed by a high rate of cyst recurrence[1,2], many minimally invasive methods have been proposed[3-6]. The reported rates of healing associated with traditional treatment—intralesional injection of methylprednisolone acetate—have been widely variable[3,7,8]. A newer treatment—injection of autogenous bone marrow—was initially reported to result in a 100% healing rate[9]. Subsequent studies have demonstrated

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Disclosure: In support of their research for or preparation of this work, one or more of the authors received, in any one year, outside funding or grants in excess of $10,000 from the Arthur Huene Award, Pediatric Orthopaedic Society of North America (POSNA) research grant, Salter Chair in Surgical Research, and Shriners Hospitals for Children. Neither they nor a member of their immediate families received payments or other benefits or a commitment or agreement to provide such benefits from a commercial entity. No commercial entity paid or directed, or agreed to pay or direct, any benefits to any research fund, foundation, division, center, clinical practice, or other charitable or nonprofit organization with which the authors, or a member of their immediate families, are affiliated or associated.

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lower rates of cyst healing after bone marrow injection(s)[10,11]. The purpose of this study was to compare the rates of healing of simple bone cysts following intralesional injection of bone marrow with those following methylprednisolone injection.

Materials and Methods

Design

This study was a multicenter, randomized clinical trial conducted at twenty-four centers across North America and India. It was the inaugural trial of the Pediatric Orthopaedic Society of North America Clinical Trials Network.

Study Participants

All children eighteen years of age or younger with a diagnosis of simple bone cyst were eligible, including those with previous fracture(s) or previous (failed) treatment but excluding those with a malignant tumor, bone marrow disease, chronic steroid use, chemotherapy, contraindications to steroid use, or pregnancy. This study received ethical approval from the institutional review board at each study site.

Baseline Information

We obtained data regarding the patients' age and sex and details of prior treatment(s) or fracture(s). Patients completed the Activities Scale for Kids (ASK)[12-15], a thirty-item scale focusing on children's abilities and the functional activities that they perform. It has an internal reliability of 0.90 (Cronbach alpha) and a test-retest reliability of 0.97 (intraclass correlation coefficient)[14]. Construct validity of the ASK has been demonstrated by a correlation of 0.81 ($p < 0.0001$) with the parent-reported Childhood Health Assessment Questionnaire (CHAQ) and a correlation of 0.92 ($p < 0.0001$) with clinicians' observations[15]. Patients also completed the Oucher Scale[16], which is used to measure pain in children and has a reported test-retest reliability ranging from 0.54 to 0.72 (correlation coefficients)[16]. Construct validity was demonstrated by gamma correlation coefficients ranging from 0.70 to 0.98 in comparisons with the Poker Chip Tool[17,18], and convergent validity was found in comparison with a visual analogue scale[19]. Discriminant validity ranged from 0.07 to 0.35 when the Oucher Scale was tested against standard fear measures, the Hospital Fears Rating Scale[20] and the Scare Scale[21].

Radiographic assessment of the lesion included determination of the cyst-healing grade with Cole's modification of Neer's criteria[3]. Grade 1 indicates that the cyst is clearly visible, grade 2 indicates that the cyst is visible but multilocular and opaque, grade 3 indicates sclerosis around or within a partially visible cyst, and grade 4 indicates complete healing with obliteration of the cyst[1,3,22]. The radiographs were also assessed to determine cyst activity (the distance from the physis in centimeters)[2], the cyst area (length by width by depth in cubic centimeters) based on two orthogonal plain radiographs[23], cyst loculation (present or absent)[23], location in the lower or upper extremity[3], and location within the bone (metaphyseal, epiphyseal, or diaphyseal). Magnetic resonance imaging was not routinely performed.

Randomization

Randomization was performed after patients were deemed eligible and had provided informed consent. Patients were randomly allocated to receive injection of either bone marrow or steroid (methylprednisolone acetate) in variable (two, three, or four-patient) random-size blocks stratified by prior fracture(s) (yes or no) and prior treatment (yes or no). An independent biostatistician created the randomization schedule with a computer. Treatment assignments, placed in sequentially numbered opaque envelopes, were assigned by one of two trial managers.

Interventions

Technique Common to Steroid and Bone Marrow Injections

Each patient received a maximum of three injections, with at least three months between injections. The indication for a second or third injection was based on the surgeon's judgment regarding whether the cyst was healing or not. Patients with a prior fracture were treated with the injection at least three weeks after the fracture, and patients with prior treatment were treated with the injection at least three months after the previous treatment. Injections were performed with the patient under general anesthesia. The diagnosis of a simple bone cyst was confirmed by needle aspiration of clear or straw-colored fluid[2,23,24]. Contrast medium (50% Hypaque [diatrizoate meglumine] and 50% sterile saline solution) was injected to visualize the extent of the cyst. After irrigation with the contrast solution, a needle (16 gauge for children older than five years of age and 18 gauge for children five years of age or younger) was used to break down loculations and scrape the cyst lining[4,9,10]. If the cyst was multilocular, each cavity was injected separately[3,10]. Radiographic assessment of venous outflow was not routinely performed.

Technique Specific to Bone Marrow Injections

With use of an 11-gauge needle (for patients weighing >75 lb [>34 kg]) or a 13-gauge needle (for patients weighing ≤75 lb), autologous bone marrow was aspirated from the iliac crest and into a plastic nonheparinized syringe[25-27]. Through a single skin-puncture site, the surgeon withdrew 2 to 3-mL aliquots of bone marrow from enough areas within the ilium to obtain 9 to 18 mL of bone marrow, which was then injected into the cyst[10,25,28,29].

Technique Specific to Steroid Injections

The total cyst volume was calculated as the maximum length by width by depth on the anteroposterior and lateral radiographs. Methylprednisolone acetate, 3 mg/cm^3 of cyst volume with a maximum dose of 180 mg, was injected into the cyst.

Study Outcomes

Two-Year Outcomes

The primary study outcome was the cyst-healing grade[1,3,22]. Secondary outcome measures included function (according to the ASK[15]), pain (according to the Oucher scale[16]), number of injections, subsequent fractures, and complications. The rela-

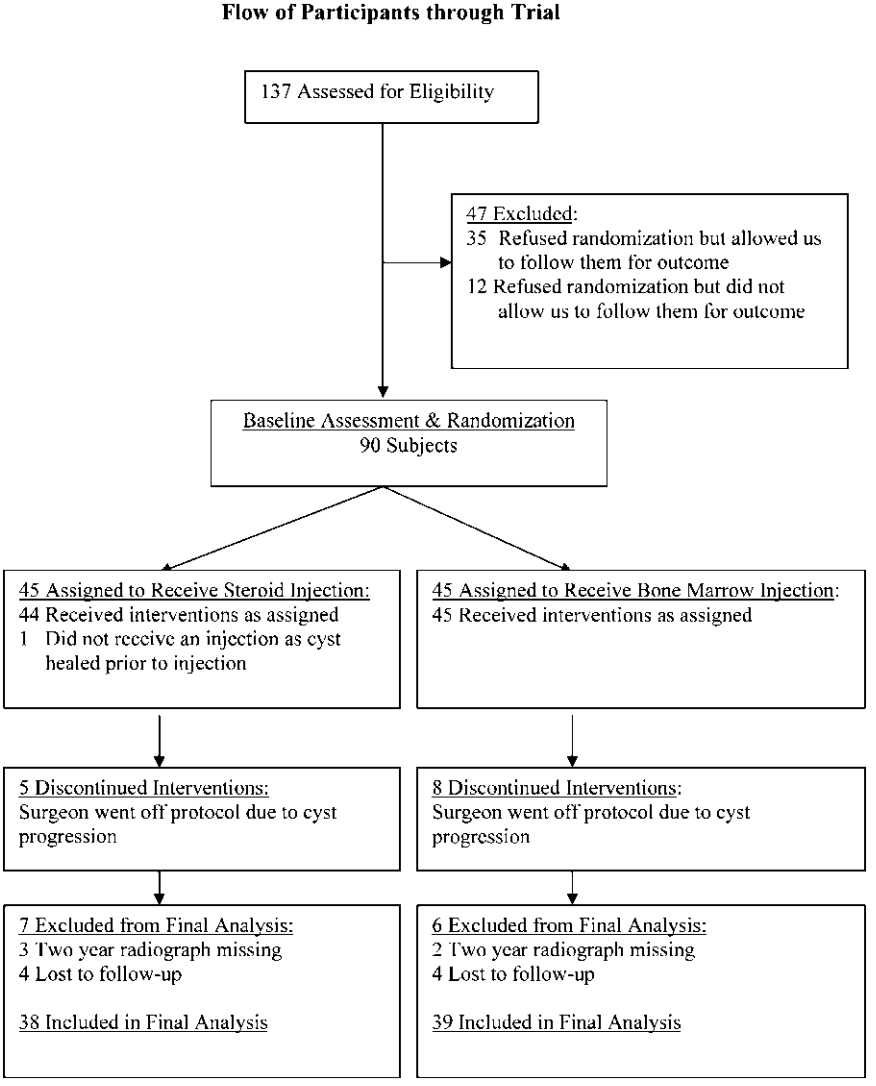

Fig. 1
Flow of participants through the trial.

tionship of the radiographic and clinical characteristics with subsequent fractures (yes or no) and healing (cyst grade 3 or 4) at two years was also evaluated.

The primary outcome was determined by two musculoskeletal radiologists who were blind to the type of treatment. The patients and families also were not informed of the treatment assignment. However, blinding was difficult because the bone-marrow-aspiration sites generally revealed puncture marks or mild bruising. The surgeons who administered the interventions were not blinded.

Statistical Analyses

Sample Size

On the basis of an anticipated rate of "satisfactory healing" (grade 3 or 4) of 80% in the bone marrow group and 50% in the steroid group[2,3,7,9-11,23,24,30], with an alpha of 0.05 and a beta of 0.2 the required sample size was forty patients in each treatment group. The sample size was increased by 10% to allow for an anticipated 10% loss to follow-up.

Primary and Secondary Outcomes

The primary analysis comparing cyst healing between the two groups was performed with use of the chi-square test. To adjust for differences between the two groups at baseline, analysis was performed with multiple logistic regressions and odds ratios were used to estimate the difference between the treatment groups. Additional analyses were performed with use of two-way or multiway tables, t tests, or analysis of variance, as appropriate. Continuous data were described by means, medians, and standard deviations and categorical data, by proportions. Where appropriate, 95% confidence intervals were calculated.

Statistical analyses were performed on an intention-to-treat basis so that patients were analyzed according to the

TABLE I Descriptive Baseline Data

	Steroid Group (N = 45)	Bone Marrow Group (N = 45)	Nonrandomized Patients (N = 35)
Continuous variables*			
Age *(yr)*			
At entry into trial	9.2 ± 3.6	9.7 ± 3.2	10.1 ± 3.3
At diagnosis	7.6 ± 3.1	8.5 ± 3.2	8.8 ± 3.3
Height *(cm)*	118.0 ± 25.1	137.3 ± 22.4	140.2 ± 21.7
Weight *(kg)*	32.4 ± 15.4	40.9 ± 16.2	45.4 ± 24.7
No. of previous fractures	2.4 ± 1.5	2.2 ± 1.6	2.2 ± 1.6
ASK function score (max., 100 points) (*points*)	86.9 ± 13.0	88.9 ± 17.3	86.2 ± 20.5
Oucher pain score (max., 100 points) (*points*)	5.7 ± 14.4	3.0 ± 7.6	11.9 ± 14.7
Cyst area *(cm^3)*	88.9 ± 69.8	63.0 ± 58.3	103.0 ± 59.8
Cyst activity (distance from physis) *(cm)*	1.2 ± 2.1	2.0 ± 2.6	0.7 ± 1.8
Aspirate amount *(mL)*	19.7 ± 18.1	20.0 ± 22.1	15.1 ± 18.3
Categorical variables†			
Male sex	31 (69%)	30 (67%)	25 (71%)
Upper extremity involved	30 (67%)	36 (80%)	20 (57%)
Involved bone			
Humerus	30 (67%)	36 (80%)	20 (57%)
Femur	13 (29%)	5 (11%)	12 (34%)
Other	2 (4%)	4 (9%)	3 (9%)
No. of previous fractures			
0	9 (20%)	9 (20%)	6 (17%)
1	16 (36%)	23 (51%)	18 (51%)
2	16 (36%)	8 (18%)	5 (14%)
3	3 (7%)	5 (11%)	4 (11%)
≥4 (2%)	0 (0%)	2 (6%)	
Previous treatment	9 (20%)	7 (16%)	11 (31%)
Radiographic grade			
Grade 1: clearly visible	32 (71%)	34 (76%)	24 (69%)
Grade 2: multilocular + opaque	7 (16%)	9 (20%)	5 (14%)
Grade 3: sclerosis + partially visible	0 (0%)	0 (0%)	0 (0%)
Grade 4: complete healing	0 (0%)	0 (0%)	0 (0%)
Missing from chart	6 (13%)	2 (4%)	6 (17%)
Cyst loculation			
Unilocular	18 (40%)	20 (44%)	5 (14%)
Multilocular	20 (44%)	23 (51%)	23 (66%)
Missing from chart	7 (16%)	2 (4%)	7 (20%)
Location within bone			
Metaphysis	23 (51%)	14 (31%)	17 (49%)
Epiphysis	0 (0%)	0 (0%)	0 (0%)
Diaphysis	13 (29%)	15 (33%)	3 (9%)
Metaphysis + diaphysis	2 (4%)	11 (24%)	7 (20%)
Metaphysis + epiphysis	0 (0%)	2 (4%)	0 (0%)
Metaphysis + epiphysis + diaphysis	0 (0%)	0 (0%)	2 (6%)
Missing from chart	7 (16%)	3 (7%)	6 (17%)
Aspirate appearance			
Clear	5 (11%)	7 (16%)	6 (17%)
Blood-tinged	26 (58%)	23 (51%)	16 (46%)
Bloody	10 (22%)	12 (28%)	11 (31%)
Missing from chart	4 (9%)	3 (7%)	2 (6%)

*The values are given as the mean and standard deviation. †The values are given as the number of patients with the percentage in parentheses.

TABLE II Primary and Secondary Outcomes by Treatment Group

Outcomes	Steroid Group (N = 38)	Bone Marrow Group (N = 39)	P Value (Unadjusted)	Effect Size* and 95% Confidence Interval (Adjusted)	P Value (Adjusted)
Healing†			0.07	4.9 (1.4 to 16.8)	0.01
Not healed: grades 1 + 2	22 (58%)	30 (77%)			
Healed: grades 3 + 4	16 (42%)	9 (23%)			
ASK function score (max., 100 points)‡ *(points)*	96.9 ± 8.7	96.0 ± 6.1	0.61	0.1 (−5.2 to 5.3)	0.97
Oucher pain score (max., 100 points)‡ *(points)*	3.1 ± 12.1	1.4 ± 6.7	0.44	2.3 (−3.9 to 8.4)	0.47
Cyst activity (distance from physis‡ *(cm)*	1.8 ± 2.7	2.9 ± 2.6	0.09	−0.4 (−1.9 to 1.1)	0.58
Cyst area (length × width × depth)‡ *(cm^3)*	96.2 ± 115.3	68.1 ± 53.4	0.21	18.3 (−12.5 to 49.2)	0.24
Cyst loculation†§			0.95	1.2 (0.1 to 15.1)	0.90
Unilocular	2 (6%)	2 (6%)			
Multilocular	31 (94%)	33 (94%)			
No. of injections‡	1.7 ± 1.0	2.1 ± 1.2	0.12	−0.5 (−1.1 to 0.2)	0.16
Additional fractures†			0.61	0.6 (0.2 to 2.2)	0.42
No	27 (71%)	30 (77%)			
Yes	11 (29%)	9 (23%)			
Complications†			0.80	0.3 (0.1 to 1.4)	0.12
Fracture or infection	10 (26%)	11 (28%)			
None	28 (74%)	28 (72%)			

*The effect size is given as the odds ratio for the categorical data and as the difference in proportions for the continuous data. †The values in the treatment-group columns are given as the number of patients with the percentage in parentheses. ‡The values in the treatment-group columns are given as the mean and standard deviation. §The data were missing for some patients.

treatment group to which they had been randomized. Patients whose parents refused to allow them to be randomized but permitted us to follow them to assess the outcome (nonrandomized patients) were compared with randomized patients in terms of subsequent fractures and two-year rates of healing. The few children who had been admitted to the trial and later found to have an aneurysmal bone cyst on the basis of biopsy and pathological findings, and hence were ineligible, were dropped from the analyses.

Results

Recruitment and Participant Flow

Recruitment took place between March 1998 and June 2003, with the two-year follow-up period extending to June 2005. The flow of participants through the trial is shown in Figure 1. There were 137 eligible patients; the parents of thirty-five of them refused treatment randomization but allowed us to follow their child to assess the outcome, and the parents of twelve refused to allow us to follow their child to assess the outcome. Thus, the consent rate was 66% (ninety of 137). All families who refused treatment randomization wanted to choose the treatment (either steroid or bone marrow injection) themselves. Of the forty-five patients assigned to receive steroid injection(s), one did not have an injection as the cyst healed prior to treatment and five did not complete the course of the intervention (three injections) as the surgeon discontinued the protocol because of cyst progression. All of the forty-five patients assigned to receive bone marrow injection(s) received the assigned treatment, but eight of them did not complete the course of intervention (three injections) as the surgeon discontinued the protocol because of cyst progression. Seventy-seven of the ninety patients enrolled in the trial (thirty-eight [84%] of the forty-five in the steroid injection group and thirty-nine [87%] of the forty-five in the bone marrow injection group) were included in the final analysis. Of the thirteen patients not included in the final analysis, eight were lost to follow-up and five did not have two-year radiographs.

Baseline Data

As detailed in Table I, the two treatment groups were comparable at baseline except with regard to body weight ($p = 0.03$) and the location of the cyst within the bone ($p = 0.02$). The randomized and nonrandomized patients (Table I) differed in terms of body weight ($p = 0.05$), cyst area ($p = 0.05$), types of previous treatment ($p = 0.02$), location of the cyst within the bone ($p = 0.02$), and loculation ($p = 0.03$).

Two-Year Outcomes

The difference in the two-year rates of healing between the treatment groups was 19% (odds ratio, 4.9; 95% confidence interval, 1.4 to 16.8) (Table II). Forty-two percent (sixteen) of

TABLE III Characteristics Associated with Nonhealing and Healing at Two Years

Characteristic	Nonhealing: Grades 1 + 2	Healing: Grades 3 + 4	P Value
Cyst activity (distance from physis)* *(cm)*	2.04 ± 2.7	2.9 ± 2.6	0.21
Cyst area (length × width × depth)* *(cm^3)*	94.6 ± 101.4	53.8 ± 51.3	0.03†
Cyst loculation†			0.89
Unilocular	3/49 (6%)	1/19 (5%)	
Multilocular	46/49 (94%)	18/19 (95%)	
Involved extremity†			0.79
Upper extremity	39/52 (75%)	18/25 (72%)	
Lower extremity	13/52 (25%)	7/25 (28%)	
Location within bone†			0.66
Metaphysis	17/49 (35%)	7/25 (28%)	
Epiphysis	0/49 (0%)	0/25 (0%)	
Diaphysis	22/49 (45%)	14/25 (56%)	
Metaphysis + diaphysis	10/49 (20%)	4/25 (16%)	
Fracture within 2-yr study period†			0.04‡
0	34/52 (65%)	23/25 (92%)	
1	17/52 (33%)	2/25 (8%)	
3	1/52 (2%)	0/25 (0%)	

*The values in the healing-group columns are given as the mean and standard deviation. †The values in the healing-group columns are given as the number of patients with the percentage in parentheses. ‡A significant difference.

the thirty-eight cysts treated with the steroid healed (grade 3 or 4), and 23% (nine) of the thirty-nine in the bone marrow group healed. Adjustment for baseline differences in body weight and the location of the cyst within the bone with use of binary logistic regression indicated that steroid injection was significantly better than bone marrow injection for bringing about healing of bone cysts ($p = 0.01$). A secondary analysis performed according to the treatment that was actually received provided similar results ($p = 0.09$).

There was no difference between the treatment groups at two years with regard to function (average difference in ASK scores, 0.1 point; 95% confidence interval, −5.2 to 5.3;

TABLE IV Associations with Fracture

Characteristic	No Fracture	Fracture	P Value
Cyst activity (distance from physis)* *(cm)*	2.5 ± 2.8	1.8 ± 2.3	0.28
Cyst area (length × width × depth)* *(cm^3)*	69.8 ± 59.3	118.0 ± 144.2	0.18
Cyst loculation†			0.84
Unilocular	3/48 (6%)	1/20 (5%)	
Multilocular	45/48 (94%)	19/20 (95%)	
Involved extremity†			0.18
Upper extremity	49/57 (86%)	17/20 (85%)	
Lower extremity	21/57 (37%)	3/20 (15%)	
Location within bone†			0.62
Metaphysis	18/55 (33%)	6/19 (32%)	
Epiphysis	0/55 (0%)	0/19 (0%)	
Diaphysis	28/55 (51%)	8/19 (42%)	
Metaphysis + diaphysis	9/55 (16%)	5/19 (26%)	

*The values in the fracture-group columns are given as the mean and standard deviation. †The values in the fracture-group columns are given as the number of patients with the percentage in parentheses.

p = 0.97) or pain (average difference in scores on Oucher scale, 2.3 points; 95% confidence interval, −3.9 to 8.4; p = 0.47). Other secondary outcomes (cyst activity, area, and loculation; number of injections; subsequent fractures; and complications) also did not differ between the treatment groups (p > 0.09) (Table II). A fracture occurred in eleven of the patients in the steroid group and nine in the bone marrow group, and an infection developed in no patient in the steroid group and in two in the bone marrow group. The rate of adverse events within the two-year study period did not differ between the treatment groups (p = 0.36). After adjustment for cyst area, the risk of fracture was lower in the methylprednisolone group, but the difference was not significant (p = 0.42).

Randomized and Nonrandomized Patients

Children whose parents refused to let them enter the trial but allowed us to follow them to assess the outcome (nonrandomized patients) were compared with the randomized patients in terms of the rates of healing and subsequent fracture at two years. There were no significant differences in these factors (rate of healing, p = 0.6; rate of subsequent fracture, p = 0.5) between the randomized and nonrandomized patients (with the analysis unadjusted for differences in baseline variables between the groups).

Associations with Healing and Subsequent Fracture

Both subsequent fracture (p = 0.04) and cyst area (p = 0.03) were significantly associated with cyst healing at two years (Table III). The mean baseline areas of the healed and nonhealed cysts were 53.8 and 94.6 cm^3, respectively (p = 0.03).

As shown in Table IV, there were no significant associations between fractures and cyst activity, cyst area, loculation, location in the upper or lower extremity, or location within the bone.

Discussion

Simple bone cysts are benign lesions in growing children. Some children with simple bone cysts sustain multiple fractures. Many children are fearful of subsequent fractures or are restricted from activity by their physicians. Families and surgeons would welcome a minimally invasive, low-risk treatment.

Treatment strategies for simple bone cysts include curettage and bone-grafting, intralesional injections, damage to the cyst wall and lining, decompression of the cyst, structural stabilization, or some combination of these methods. Substances that have been injected into cysts include methylprednisolone acetate[8], bone marrow[9], calcium sulphate pellets[5], demineralized bone matrix[6], and calcium-phosphate bone cement (Norian, Cupertino, California)[31]. Methods for damaging the cyst lining include scraping with needles or direct curettage. Decompression of the cyst can be performed with Kirschner wires[22] or cannulated screws[32]. Flexible intramedullary nails provide structural stability but also disrupt the cyst lining and may decompress the cyst[33]. Few comparative studies, however, have been done to directly evaluate treatment, and consequently treatment varies widely.

Injection of methylprednisolone acetate was the traditional form of treatment for simple bone cysts for many years[7,8]. An early study of bone marrow injection demonstrated a 100% rate of healing after one injection[9]. Although subsequent studies showed lower rates[4,10,11,30,34,35], bone marrow became the preferred substance for intralesional injection at many centers. The results of the present blinded, multicenter, randomized trial showed injection of either bone marrow or methylprednisolone acetate to have low rates of success, but methylprednisolone acetate provided superior rates. This study demonstrates the value of prospective comparisons with blinded evaluation of treatment outcomes. In contrast, case series often provide inaccurate or overly optimistic estimates of treatment effectiveness[36].

In this study, the rates of full or partial healing following both forms of treatment were lower than those reported in previous studies[3,7-11]. This difference can be attributed to several factors. First, blinded evaluation by radiologists who have no vested interest in the outcome provides a very objective measure of cyst healing. All too often, surgeons and parents want to interpret posttreatment radiographs, made with various techniques, as indicating cyst healing. Second, patients were followed for two years in our trial. Many cysts that appear to be healing at one year after injection look no different than they did before treatment when they are evaluated two years after the injection. Third, in the initial reports by Lokiec et al.[4,9], treatment included the combination of scraping the cyst, opening the medullary canal, and bone marrow injections. Although scraping the cyst was part of the trial protocol in our study, the completeness of this step by the participating surgeons is unknown. Fourth, patients in this study received only three injections. Although Hashemi-Nejad and Cole[3] found that more than three injections of steroid did not improve healing, it is possible that more injections may have resulted in higher healing rates in both groups.

An important issue for families of children with a simple bone cyst is the risk of refracture. None of the factors evaluated in this study were associated with fracture (Table IV). Thus, the parameters that we evaluated on plain radiographs did not provide significant prognostic information for families or surgeons. Quantitative computed tomography may be a more accurate modality for predicting fracture and evaluating healing in future studies[37]. The cyst area and fracture were the only variables found to be related to healing.

The main limitation of this study was that we evaluated only two forms of treatment, and we do not know how either of these treatments would fare against no treatment. This was the first multicenter trial of the Pediatric Orthopaedic Society of North America Clinical Trials Network. It showed that multicenter trials can provide useful and practical answers to some clinical questions. Authors of future studies will need to evaluate other treatments for simple bone cysts. A second potential limitation of this study was that Cole's modification of the Neer grading system[3] offers a liberal definition of healing (grade 3 or 4). However, using grade 4 only as the radiographic outcome of treatment would have resulted in

even lower rates of healing in both groups. A third limitation is that the study was not sufficiently powered to evaluate the fracture risk in the two treatment groups. Finally, concentrated bone marrow may have greater potential for achieving cyst healing than the unconcentrated bone marrow used in this study[38].

In conclusion, intralesional injections of methylprednisolone acetate are superior to injections of bone marrow to achieve cyst healing. Future trials are needed to compare other treatments for simple bone cysts in children and to develop new measures of cyst healing. ■

NOTE: The authors thank the trial radiologists, Dr. Crim and Dr. Murray, for their time and effort in reviewing and evaluating each radiograph in our study. They also thank the trial statistician, Mr. Derek Stephens, for his input regarding the design, statistical analysis, and interpretation of the results.

The centers participating in the clinical trial were Children's Hospital MLC, Cincinnati, OH, Children's Orthopedics of Hawaii, Honolulu, HI, Gillette Children's Specialty Healthcare, St. Paul, MN, Hospital for Joint Diseases, New York, NY, Kasturba Medical College, Manipal, India, Mayo Clinic, Rochester, MN, Medical College of Wisconsin, Milwaukee, WI, New England Medical Center, Boston, MA, Shriners Hospitals for Children, Chicago, IL, Shriners Hospitals for Children, Erie, PA, Shriners Hospitals for Children, Honolulu, HI, Shriners Hospitals for Children, Intermountain, Salt Lake City, UT, Shriners Hospitals for Children, Lexington, KY, Shriners Hospitals for Children, Los Angeles, CA, Shriners Hospitals for Children, Philadelphia, PA, Shriners Hospitals for Children, Sacramento, CA, Shriners Hospitals for Children, Shreveport, LA, Shriners Hospitals for Children, Spokane, WA, Shriners Hospitals for Children, St. Louis, MO, Shriners Hospitals for Children, Tampa, FL, Southern Illinois University School of Medicine, Springfield, IL, Texas Orthopaedic Hospital, Houston, TX, The Hospital for Sick Children, Toronto, ON, Canada, and Women and Children's Hospital of Buffalo, Buffalo, NY.

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References

1. Neer CS 2nd, Francis KC, Marcove RC, Terz J, Carbonara PN. Treatment of unicameral bone cyst. A follow-up study of one hundred seventy-five cases. J Bone Joint Surg Am. 1966;48:731-45.

2. Oppenheim WL, Galleno H. Operative treatment versus steroid injection in the management of unicameral bone cysts. J Pediatr Orthop. 1984;4:1-7.

3. Hashemi-Nejad A, Cole WG. Incomplete healing of simple bone cysts after steroid injections. J Bone Joint Surg Br. 1997;79:727-30.

4. Lokiec F, Ezra E, Meller I, Kollender I, Wientroub B. Percutaneous autologous marrow grafting in simple bone cysts—treatment considerations and efficacy. Read at the annual meeting of the Pediatric Orthopaedic Society of North America; 1998; Cleveland, Ohio.

5. Dormans JP, Sankar WN, Moroz L, Erol B. Percutaneous intramedullary decompression, curettage, and grafting with medical-grade calcium sulfate pellets for unicameral bone cysts in children: a new minimally invasive technique. J Pediatr Orthop. 2005;25:804-11.

6. Killian JT, Wilkinson L, White S, Brassard M. Treatment of unicameral bone cyst with demineralized bone matrix. J Pediatr Orthop. 1998;18:621-4.

7. Campanacci M, Capanna R, Picci P. Unicameral and aneurysmal bone cysts. Clin Orthop Relat Res. 1986;204:25-36.

8. Scaglietti O, Marchetti PG, Bartolozzi P. The effects of methylprednisolone acetate in the treatment of bone cysts. Results of three years follow-up. J Bone Joint Surg Br. 1979;61:200-4.

9. Lokiec F, Ezra E, Khermosh O, Weintroub S. Simple bone cysts treated by percutaneous autologous marrow grafting. J Bone Joint Surg Br. 1996;78:934-7.

10. Yandow SM, Lundeen G, Scott SM, Coffin C. Autogenic bone marrow injections as a treatment for simple bone cyst. J Pediatr Orthop. 1998;18:616-20.

11. Delloye C, Docquier PL, Cornu O, Poilvache P, Peters M, Woitrin B, Rombouts JJ, De Nayer P. Simple bone cysts treated with aspiration and a single bone marrow injection. Int Op. 1998;22:134-8.

12. Young NL, Wright JG. Measuring pediatric physical function. J Pediatr Orthop. 1995;15:244-53.

13. Young NL, Yoshida KK, Williams JI, Bombardier C, Wright JG. The role of children in reporting their physical disability. Arch Phys Med Rehabil. 1995; 76:913-8.

14. Young NL, Yoshida KK, Williams JI, Bombardier C, Wright JG. The context of measuring disability: does it matter whether capability or performance is measured? J Clin Epidemiol. 1996;49:1097-101.

15. Young NL, Williams JI, Yoshida KK, Wright JG. Measurement properties of the activities scale for kids. J Clin Epidemiol. 2000;53:125-37.

16. Beyer JE, Denyes MJ, Villarruel AM. The creation, validation, and continuing development of the Oucher: a measure of pain intensity in children. J Pediatr Nurs. 1992;7:335-46.

17. Hester NK. The preoperational child's reaction to immunizations. Nurs Res. 1979;28:250-4.

18. Hester N, Foster R, Kristensen K. Measurement of pain in children: generalizability and validity of the pain ladder and the Poker Chip Tool. In: Tyler D, Krane E, editors. Pediatric Pain. New York: Raven; 1990. p 79-84.

19. Huskisson E. Visual analogue scales. In: Melzack R, editor. Pain measurement and assessment. New York: Raven; 1983. p 33-7.

20. Melamed BG, Siegel LJ. Reduction of anxiety in children facing hospitalization and surgery by use of filmed modeling. J Consult Clin Psychol. 1975;43:511-21.

21. Beyer J, Aradine C. The convergent and discriminant validity of a self-report measure of pain intensity for children. Child Health Care. 1988;16:274-82.

22. Chigira M, Maehara S, Arita S, Udagawa E. The aetiology and treatment of simple bone cysts. J Bone Joint Surg Br. 1983;65:633-7.

23. Capanna R, Dal Monte A, Gitelis S, Campanacci M. The natural history of unicameral bone cyst after steroid injection. Clin Orthop Relat Res. 1982; 166:204-11.

24. Scaglietti O, Marchetti PG, Bartolozzi P. Final results obtained in the treatment of bone cysts with methylprednisolone acetate (depo-medrol) and a discussion of results achieved in other bone lesions. Clin Orthop Relat Res. 1982;165:33-42.

25. Healey JH, Zimmerman PA, McDonnell JM, Lane JH. Percutaneous bone marrow grafting of delayed union and nonunion in cancer patients. Clin Orthop Relat Res. 1990;256:280-5.

26. Connolly J, Guse R, Lippiello L, Dehne R. Development of an osteogenic bone-marrow preparation. J Bone Joint Surg Am. 1989;71:684-91.

27. Stinchfield FE, Sankaran B, Samilson R. The effect of anticoagulant therapy on bone repair. J Bone Joint Surg Am. 1956;38:270-82.

28. Batinic D, Marusic D, Pavletic Z, Bogdanic V, Uzarevic B, Nemet D, Labar B. Relationship between differing volumes of bone marrow aspirates and their cellular composition. Bone Marrow Transplant. 1990;6:103-7.

29. Muschler GF, Boehm C, Easley K. Aspiration to obtain osteoblast progenitor cells from human bone marrow: the influence of aspiration volume. J Bone Joint Surg Am. 1997;79:1699-709. Erratum in: J Bone Joint Surg Am. 1998;80:302.

30. Köse N, Gökturk E, Turgut Akin, Günal I, Seber S. Percutaneous autologous bone marrow grafting for simple bone cysts. Bull Hosp Jt Dis. 1999;58: 105-10.

31. Csizy M, Buckley RE, Fennell C. Benign calcaneal bone cyst and pathologic fracture—surgical treatment with injectable calcium-phosphate bone cement (Norian): a case report. Foot Anke Int. 2001;22:507-10.

32. Tsuchiya H, Abdel-Wanis ME, Uehara K, Tomita K, Takagi Y, Yasutake H. Cannulation of simple bone cysts. J Bone Joint Surg Br. 2002;84:245-8.

33. Roposch A, Saraph V, Linhart WE. Flexible intramedullary nailing for the treatment of unicameral bone cysts in long bones. J Bone Joint Surg Am. 2000;82:1447-53.

34. Chang CH, Stanton RP, Glutting J. Unicameral bone cysts treated by injection of bone marrow or methylprednisolone. J Bone Joint Surg Br. 2002;84:407-12.

35. Docquier PL, Delloye C. Autologous bone marrow injection in the management of simple bone cysts in children. Acta Ortho Belg. 2004;70:204-13.

36. Schulz KF, Altman DG, Moher D. Allocation concealment in clinical trials. JAMA. 2002;288:2406-9.

37. Snyder BD, Hauser-Kara DA, Hipp JA, Zurakowski D, Hecht AC, Gebhardt MC. Predicting fracture through benign skeletal lesions with quantitative computed tomography. J Bone Joint Surg Am. 2006;88:55-70.

38. Hernigou P, Poignard A, Beaujean F, Rouard H. Percutaneous autologous bone-marrow grafting for nonunions. Influence of the number and concentration of progenitor cells. J Bone Joint Surg Am. 2005;87:1430-7.