Bone marrow injection for the treatment of bone cysts before skeletal maturity
Ahmed Sh. Rizk, Mohamed O. Hegazy, Osama A. Wahab Elmansy

Background
Bone cysts are benign, osteolytic, fluid-filled bone lesions mostly seen before skeletal maturity. Various treatment modalities with variable outcomes have been described in the literature, but there is no consensus as regards the best procedure. Traditional bone grafting techniques have given way to newer cellular therapies that are potentially less invasive and have a lower complication rate and faster recovery time. The percutaneous method can be used with different materials such as bone marrow (BM) or bone substitutes to optimize results. BM contains the osteoprogenitor cells, various bone morphogenetic proteins, growth factors, and other signaling molecules that provide the appropriate environment for bone formation and remodeling.

Aim
The aim of this study was to evaluate the role of autologous BM injection in the treatment of different types of bone cysts in children below the age of skeletal maturity as regards the healing time, the occurrence of pathological fractures, and recurrence after healing.

Patients and methods
Totally, 20 patients with accidentally discovered, uncomplicated bone cysts of different types were included in this prospective case series study. All patients were below the age of skeletal maturity. Patients were evaluated clinically and radiologically before surgery. All cases were treated with three repeated injections (at 3 weeks’ intervals) of BM aspirated from their iliac crests and injected in the cystic lesions under image intensifier. Patients were followed up for a mean time of 26 months postoperatively.

Results
The results were successful in 18 patients (90% of the studied patients), with a mean healing time of 15.4 weeks. Totally, 15 cases (75% of the studied patients) had completely healed and were graded as Neer I, whereas three cases (15% of the studied patients) healed with small defects and were graded as Neer II, with good functional and radiological results. Only two cases (10% of the studied patients) had recurrence and were considered as failure (Neer IV).

Conclusion
The satisfactory clinical and radiographic results of this study support the use of percutaneous autologous BM injection as one of the treatment options in the management of cases with bone cysts of different types in patients below the age of skeletal maturity as an easy, safe, simple, and effective treatment method. Repeated injections improve healing rate and shorten the healing time.

Keywords:
bone cyst, percutaneous bone marrow injection, satisfactory results

Introduction
True bone cysts are common cause for pathological fractures during the first two decades of life. The two most important differential diagnoses of cystic lesions in children include unicameral bone cyst and aneurysmal bone cyst (ABC).

Unicameral bone cysts are benign lesions that usually spontaneously regress with skeletal maturity; however, the high risk for pathologic fractures often justifies treatment that could reinforce a weakened bone cortex. Various treatments have been proposed, but there is no consensus as regards the best procedure [1].

ABCs are benign expansile tumor-like bone lesions of uncertain etiology. ABCs are primarily seen in children and adolescents, with 80% occurring in patients under 20 years of age [2]. ABCs consist of blood-filled spaces...
of variable size that are separated by connective tissue containing trabeculae of bone or osteoid tissue and osteoclast giant cells. They are not lined by endothelium. Fine needle aspiration cytology is usually nondiagnostic and is dominated by fresh blood [3].

Bone marrow (BM) is a substance between the sinusoids of spongy bone, which is organized in trabeculae. Trabeculae form crypts (intertrabecular spaces). Arterioles and venules are only observed in a small proportion of intertrabecular spaces [4]. BM is found in the center of large flat bones and can be transplanted.

Cellular therapies to replenish bone loss due to acquired conditions such as trauma, infection, tumor, peri-prosthetic osteolysis, and other etiologies have become widespread. Traditional, open, surgical bone grafting techniques have given way to newer cellular therapies that are potentially less invasive and have a lower complication rate and faster recovery time [5]. BM contains abundant adult stem cells. Cells are the most critical component of a successful bone graft [6].

Cells are the answer; without osteoblasts or precursor cells, bone will not form [7]. The ‘gold standard’ for bone grafts suggests that harvested autogenous bone will provide osteoblasts. A recent article by Soltan et al. [8] presents the rationale and method of obtaining adult stem cells from BM aspirate that differentiates to osteoblasts.

BM contains abundant adult stem cells. Recent studies have shown that adult stem cells are more plastic than previously thought [9]. The term plasticity refers to the ability of adult stem cells to cross lineage barriers and adopt the expression and function of other cell types [10,11]. It might be that adult stem cells hold the same clinical potential of embryonic stem cells, thus allowing researchers to bypass the ethical and practical issues related to the preparation and use of embryonic stem cells [12].

BM-derived stem cells include hematopoietic stem cells [13,14], marrow stromal cells (mesenchymal stem cells) [15,16], and multipotent adult progenitor cells [17,18]. BM represents the main source of mesenchymal stem cells [19]. The hematopoietic cells are irreversibly committed toward a blood lineage, but other stromal cells can differentiate to form adipocytes, chondrocytes, osteoblasts, and other connective tissue cells [20,21]. Therefore, transplantation of marrow cells contributes to hematopoietic and osteogenic cells, which are accountable for direct bone formation without the presence of additional stimuli.

Patients and methods
This prospective case series study was carried out in the Orthopedics Department of Benha University Hospital from December 2011 to October 2014 and included 20 patients with accidentally discovered bone cysts of different types. Patients were evaluated clinically and radiologically using plain radiographs and MRI before surgery (Fig. 1).

Diagnosis depended only on clinical and radiological data (patient age and the site, size, and appearance of the lesion in plain radiographs and MRI). Pathological diagnosis using closed biopsy techniques such as computed tomography-guided core biopsy or fine needle aspiration cytology was not made in any case.

All patients were planned to receive three injections (at 3 weeks’ intervals) of BM aspirated from their iliac crests and injected into the lesion under image intensifier. Patients were followed up for a mean time of 26 months postoperatively. Clinical and radiological outcomes were studied according to modified Neer’s classification system [22].

Inclusion and exclusion criteria
Any case with isolated, uncomplicated cystic lesion below the age of skeletal maturity with no previous diagnostic or therapeutic intervention was included in this study. Cases complicated with pathological fractures at the time of presentation or suspected as having a secondary cystic changes in addition to other

Figure 1

Preoperative radiographs of three cases with true bone cysts presented in this study. (a) Aneurysmal bone cysts; (b) simple bone cyst; and (c) aneurysmal bone cysts.
primary pathologies or presented after skeletal maturity were excluded from this study.

Operative procedure
Under general anesthesia and complete aseptic conditions, patients were made to lie in the supine position and were operated on standard radiolucent table to allow access to the image intensifier in cases with lower limb cysts or in a semisitting position in cases with upper limb cysts, with the affected limb outside the table. The trocar and cannula or the metal sheath of two sets of epidural anesthesia was prepared. The first step was to insert the trocar and cannula in the proximal end of the lesion and confirm the position on C-arm (Fig. 2). The second trocar and cannula were inserted in the iliac crest of the patient by screwing with the hand until we pass the resistance of the iliac crest. It is important to insert the trocar and cannula in the proper position with the direction of application parallel to the imagined plane of the iliac bone, usually in a 45° tilt from the vertical and passed for about 4–6 cm in the core of the iliac bone. With both metal sheaths in place, the aspiration/injection begins.

The cyst was aspirated to evacuate the lesion and thus remove the abnormal pathological cystic fluid that contains inflammatory mediators and proteolytic enzymes that cause bone destruction and confirm the diagnosis according to the nature of the fluid (either altered serous fluid or blood). Aspiration of 5 cm³ of BM was carried out and the aspirated marrow was immediately injected in the lesion. It is important to rapidly inject the BM as soon as possible after aspiration before clotting of the aspirated marrow.

In large extended cysts (Fig. 1b), another 5 cm³ of BM was injected in the lesion from distal to proximal to properly load the entire cyst with the marrow fluid. It is critical to change the site of BM aspiration or at least redirect the needle to another site if more than 3–5 cm³ of marrow to avoid aspiration of blood rather than marrow cells at greater than 5 cm³ of marrow in cases with multilocular cysts (Fig. 1a). It is important to pierce the soft trabeculations within the cystic lesion to open most of the loculli and lay the marrow within.

At the end of the procedure, sterile dressing was applied to cover the aspiration site in the iliac crest and just a sling for lesions in upper limbs or a protective slap in lower limb cysts. The procedure was then repeated two times at 3 weeks’ intervals to guarantee a biologically stimulated environment.

Plain radiography to assess the result of intervention was obtained after 8 weeks of the first injection. The early signs of progression are gradual thickening of the cortex with early new bone formation within the cyst (Fig. 3). Another clinical clue for improvement is the difference in resistance while penetrating the cortex between the first and third injections, denoting improved bone strength.

Patients were followed up clinically and radiologically every 6 weeks in the first 6 months and then every 3 months. Radiological results were assessed using modified Neer’s classification system [22].

The final outcome was considered a failure if pathological fracture occurred during or after treatment or there was persistence, enlargement, or recurrence of the cyst until the last follow-up. It was considered successful if the cyst was radiologically...
healed or healed with a defect and requiring no subsequent treatment (Table 1).

**Results**

This study included 16 boys and four girls. The mean age at the outset of treatment was 7.3 years (range: between 5 and 13 years). Totally, 15 patients had simple bone cysts (SBCs), whereas the other five cases had ABCs. The humerus was affected in 15 patients, the tibia was affected in four patients, and the femur was affected in one patient. The mean follow-up was 26 months (range: 14–32 months).

Clinically, all patients had painless full range of motion of the adjacent joint and were pain-free with sports or activities of daily living until the last follow-up. Radiologically, initially all cases were healed with new bone formation obliterating the cyst. The results were successful in 18 patients (90% of the studied patients). Totally, 15 cases (75% of the studied patients) had completely healed and were graded as Neer I, whereas three cases (15% of the studied patients) healed with small defects and were graded as Neer II with good functional and radiological results (Fig. 4a and b). Only two cases (10% of the studied patients) had recurrence (Neer IV) and were considered as failure (Fig. 4c and d). Recurrence occurred after 14 months in one case and after 18 months in the second case, both patients were still active with nearly pain-free range of motion. No intraoperative or perioperative complications occurred. No pathological fractures occurred postoperatively until the last follow-up. No injection was required and there was no donor site morbidity.

Generally, the younger the patient, the shorter the healing time. Lower limb cysts healed faster than

<table>
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<tr>
<th>Table 1 Modified Neer’s classification of radiological results of bone cysts</th>
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<td>I Healed</td>
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<td>II Healing with defects</td>
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<td>III Persistent cyst</td>
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<td>IV Recurrent cyst</td>
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**Figure 4**

Radiography at the last follow-up with new bone formation in the site of bone marrow injection. (a) Neer’s I completely healed cyst filled by new bone formation. (b) Neer’s II healed with defect with radiolucent area more than 1 cm with enough cortical thickness. (c–d) Patient with aneurysmal bone cyst showed early healing with defect with radiolucent area more than 1 cm with enough cortical thickness (Neer’s II). The same patient 18 months after the initial treatment with reappearance of the cystic lesion and cortical thinning in a previously healed cyst (Neer’s IV).
that of the humerus (probably because of the added mechanical stimulation by weight-bearing). The mean time for healing for cases with aneurismal cysts was 18.9 weeks (range: 18–24 weeks), whereas for cases with SBC it was 14.2 weeks (range: 13–17 weeks). The mean healing time for all studied cases (both groups of cases) was 15.4 weeks (range: 11–24 weeks). The two cases that were considered as failure because of recurrence were aneurismal bone cysts, mostly because of their much more aggressive nature and proximity to the growth plate.

The radiological results were better in the group of cases with SBC, with 86.66% of cases graded as Neer I and 13.34% of cases graded as Neer II. No cases were graded as Neer III or IV. In the second group of cases with aneurismal bone cysts, only 40% of cases were graded as Neer I, 20% of cases were graded as Neer II, and 40% of cases were graded as Neer IV. In both groups, no cases were graded as Neer III, denoting initial healing of all cases as a biological response to the injected BM. Results are better presented in Table 2.

**Discussion**

Although SBC is often asymptomatic and tends to disappear after skeletal maturity, repeated pathological fractures and growth arrest may occur before spontaneous resolution. If the percentage of bone occupied by the cyst is more than 85% in both radiographic planes, the risk for fracture is high, and spontaneous healing usually does not occur [23].

The aim of treating SBC is to prevent all possible complications, avoid prolonged restriction of physical activity, and enhance cyst healing [24]. The success rate following open procedures has ranged from 55 to 65%. The remaining 35–45% of patients have had recurrence of the cyst, requiring additional open surgical procedures. As a result of the high reoperation rate and considerable morbidity associated with such procedures, alternate methods of treatment have been pursued [25].

A number of alternative, less invasive methods have been proposed in recent years. Repeated percutaneous injection of corticosteroids was proposed by Scaglietti et al. [26]. Because of the low morbidity, the simplicity, and the high healing rate reported by Scaglietti et al. [26] (90%), this treatment has been widely used [27]. However, subsequent studies reported a lower healing rate for this procedure, with only 41–63% healing after the first injection [28].

Sung et al. [29] reported a failure rate of 84% after the initial treatment with steroids and 76% after the second procedure. The injection of BM alone [30] or in combination with demineralized bone matrix has also been proposed as an alternative to steroids for treating SBC [31].

The use of a single injection has been recommended by some authors [32], whereas multiple injections were recommended by others [33]. The healing rate after the first injection was documented in many studies, with a success rate of 87.5, 42, 43, 52, 23, and 57% [27,28,30,34–36], whereas only one study documented 100% success with complete healing after only one injection [37]. Chang et al. [36] reported a 63% failure rate after the second BM injection. Ulici et al. [38] also used double or triple injections for their cases. In this study, it was planned to carry out three injections at 3 weeks’ intervals to speed up the healing process to enhance new bone formation by repeated laying down of biological progenitors (pluripotent cells and osteoinductives) and stimuli in different stages of healing process by simply creating a continuous cycle of microinjury/inflammation/repair in the site of the pathology.

In a study by Docquier and Delloye [39], they concluded that minimally invasive method is able to promote the self-healing of a primary ABC. As no curettage is required, the proposed minimally invasive treatment avoids extensive surgery and blood loss and is convenient for the treatment of poorly accessible lesions such as those occurring in the pelvis. They

**Table 2 Results of the studied cases in the study**

<table>
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<tr>
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<th>Cases with simple bone cysts</th>
<th>Cases with aneurismal bone cysts</th>
<th>All cases in the study (both groups of cases)</th>
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<tbody>
<tr>
<td>Number of cases</td>
<td>15</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Mean time for healing (weeks)</td>
<td>14.2</td>
<td>18.9</td>
<td>15.4</td>
</tr>
<tr>
<td>Cases graded as Neer I [n (%)]</td>
<td>13 (86.66)</td>
<td>2 (40)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>Cases graded as Neer II [n (%)]</td>
<td>2 (13.34)</td>
<td>1 (20)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Cases graded as Neer III (persistent cysts) [n (%)]</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cases graded as Neer IV (recurrent cysts) [n (%)]</td>
<td>0 (0)</td>
<td>2 (40)</td>
<td>2 (10)</td>
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used demineralized bone powder mixed with BM aspirate. In this study, only cases with primary ABCs were included and treated with three successive injections using only BM with satisfactory results (Neer I–II) in 60% of cases.

Despite the limited number of the studied cases, analyzing and discussing the results could report clearly that all cases showed an early biological response to the repeated BM injections in the form of new bone formation and progressive healing regardless of the pathology; no cases were rated as Neer III, denoting and documenting a local change in the pathological environment of the cyst in response to the osteogenic and osteoinductive potential of the injected BM. Recurrence or failure in some cases (Neer IV) is a different issue and could be due to the nature or aggressiveness of the pathology rather than failure of the BM–induced biological response.

**Conclusion**

1. BM injection, which is considered a type of cell grafting using BM aspirate as a source of pluripotent, bioactive cells with osteogenic and osteoinductive properties, can change the pathological environment and can directly form the new bone within the cystic lesion regardless of the pathology.

2. The satisfactory clinical and radiographic results and findings of this study support the use of autologous BM injection as one of the treatment options in the management of cases with bone cysts of different types in patients below the age of skeletal maturity as a safe, simple, and effective treatment method with no injection or donor site morbidity and unlimited source of rapidly renewed stimulating or biologically active cells and mediators.

3. Repeated injections can improve healing rate and shorten the healing time with better chances of healing and minimal complications and recurrence.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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