Enhancement of Bone Formation During Distraction Osteogenesis: Pediatric Applications

Abstract

Delayed bone healing during distraction osteogenesis negatively affects clinical outcome. In addition to autologous bone grafting, several mechanical, chemical, biologic, and external treatment modalities may be employed to promote bone growth during distraction osteogenesis in the pediatric patient. Mechanical approaches include compressive loading of the distraction regenerate, increased frequency of small increments of distraction, and compression-distraction. Intramedullary nailing and submuscular plating can reduce the time in external fixation; however, these techniques are associated with technical difficulties and complications. Exogenous application of low-intensity pulsed ultrasound or pulsed electromagnetic fields may shorten the duration of external fixation. Other promising modalities include diphosphonates, physician-directed use (off-label use) of bone morphogenetic proteins, and local injection of bone marrow aspirate and platelet gel at the osteotomy site. Well-designed clinical studies are needed to establish safe and effective guidelines for various modalities to enhance new bone formation during distraction osteogenesis in children.

Distraction osteogenesis (DO) involves mechanical stretching of a low-energy osteotomy to encourage the formation of new bone in the gap created between the gradually distracted skeletal fragments. This method was introduced by Gavril Ilizarov. Clinical applications include limb lengthening, deformity correction, and management of segmental bone defects. New bone is generated and remodeled in the distracted gap through a balanced anabolic and catabolic response to biologic, chemical, and mechanical stimuli. However, host and environmental factors may result in the formation of new bone that lacks sufficient mechanical strength to withstand physiologic loading. Suboptimal new bone formation has several negative effects, including prolonged external fixation as well as bending or fracture of the regenerate following removal of the external fixator (Figure 1). Several mechanical and biologic strategies have been developed to improve the rate, quality, and volume of new bone formation and thereby improve clinical outcome following limb reconstruction with DO.

In addition to autologous bone grafting, several therapeutic modalities have the potential to enhance new bone formation during DO. These modalities include mechanical stimulation of the regenerate (ie, new
bone); innovative surgical techniques; exogenous application of low-intensity pulsed ultrasound (LIPU) or pulsed electromagnetic fields (PEMFs); and local injection of bone morphogenetic protein (BMP), pluripotent stem cells, and platelet-rich plasma (PRP). Anticatabolic agents, such as diphosphonates, may be used as well (Table 1). Additional studies are required to establish the safety and indications of these modalities in pediatric patients.

Biology

Three Phases of Distraction Osteogenesis

DO consists of three sequential phases that can be controlled by the surgeon: latency, distraction, and consolidation. The likelihood of robust new bone formation is increased with low-energy osteotomy or corticotomy, preferably in a metaphyseal location, with minimal injury to the surrounding periosteum. The duration of the latency phase is dependent on patient age as well as the quality of the underlying bone and surrounding soft-tissue envelope. A duration of 3 to 10 days is recommended following osteotomy with apposed bone ends. The local inflammatory response, which consists of migration of pluripotential cells with a rich milieu of cytokines and growth factors, facilitates new bone formation during the distraction phase. In this phase, the osteotomized fragments are gradually pulled apart, typically at a rate of 1 mm per day in two to four evenly spaced time increments. This specific rate and frequency of distraction is crucial for reliable generation of new bone in the distraction gap and for adaptive changes and growth in the surrounding soft tissues, including skin, muscles, nerves, blood vessels, and the lymphatic system. In the consolidation phase, the regenerate in the distraction gap matures into normal-appearing bone that can withstand physiologic loads and remodel over time. In general, the consolidation phase is twice as long as the distraction phase.

The external fixation index denotes the number of days the external fixator is attached to the bone per centimeter of length gained. Using conventional Ilizarov fixation, this index is typically 30 days per centimeter of length gained; however, the rate differs based on variables such as patient age, osteotomy site, and amount of lengthening. The bone healing index is the time to bony union in months divided by the amount of lengthening in centimeters. Attempts to accelerate the distraction phase can negatively affect the quality of bone formation as well as limb function secondary to the effect of acceleration on neurovascular and musculotendinous structures. However, several modalities have been used to shorten the consolidation phase of DO, thereby improving these indices.

Histology

The regenerate that fills the distraction gap is formed via intramembra-
nous ossification. In the distraction phase, the regenerate between the two osteotomized fragments has a distinct histologic appearance, with five recognizable zones. The central fibrous interzone measures 4 to 8 mm in length, with immature collagen bundles and fibroblast-like cells arranged parallel to the distraction force. The fibrous interzone is bordered on either side by the primary mineralization front, in which clusters of osteoblast-like cells produce an osteoid-like matrix that consolidates the collagen into longitudinal microcolumns surrounded by capillary buds.

The zone of microcolumn formation rests between the native bone of the osteotomized fragment and the primary mineralization front. The

### Table 1

**Bone Formation Enhancement Modalities in Pediatric Patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Modality</th>
<th>Etiology</th>
<th>Bone Segment Lengthened</th>
<th>No. of Patients</th>
<th>Outcomes</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon et al[^3]</td>
<td>Lengthening over a rigid IM nail</td>
<td>Congenital</td>
<td>Femur</td>
<td>9</td>
<td>Mean lengthening index, 12.2 days/cm (range, 9.5–16.9 days/cm)</td>
<td>IV</td>
</tr>
<tr>
<td>Popkov et al[^4]</td>
<td>Lengthening over a flexible IM nail</td>
<td>Congenital/ acquired</td>
<td>Femur, tibia</td>
<td>92</td>
<td>Flexible IM nails improved healing index (range, 1.9–19.1 days/cm) in various subgroups</td>
<td>III</td>
</tr>
<tr>
<td>Iobst and Dahl[^5]</td>
<td>Lengthening with submuscular plate</td>
<td>Various</td>
<td>Femur, tibia</td>
<td>6</td>
<td>Mean external fixation index, 0.42 mo/cm</td>
<td>IV</td>
</tr>
<tr>
<td>Gebauer and Correll[^6]</td>
<td>LIPU</td>
<td>Congenital/ bone dysplasia</td>
<td>Femur, tibia</td>
<td>13</td>
<td>13 children (17 bones) had delayed union or nonunion following limb lengthening that healed within 3–12 mo without further surgery</td>
<td>IV</td>
</tr>
<tr>
<td>Eyres et al[^7]</td>
<td>PEMF</td>
<td>Various</td>
<td>Femur, tibia</td>
<td>13</td>
<td>No difference in rate or amount of bone formation at the distraction gap. Less bone loss distal to the distraction site with PEMF.</td>
<td>II</td>
</tr>
<tr>
<td>Luna Gonzalez et al[^8]</td>
<td>PEMF</td>
<td>Bone dysplasia</td>
<td>Femur, humerus, tibia</td>
<td>30</td>
<td>Significantly increased cortical thickness, callus thickness, BMD. Fixator was removed 1 mo earlier in the PEMF group.</td>
<td>III</td>
</tr>
<tr>
<td>Kitohe et al[^9]</td>
<td>BMC/PRP</td>
<td>Various</td>
<td>Femur, tibia</td>
<td>3</td>
<td>Average healing index, 23 days/cm (range, 18.8–26.9 days/cm)</td>
<td>IV</td>
</tr>
<tr>
<td>Kitohe et al[^10]</td>
<td>BMC/PRP</td>
<td>Bone dysplasia</td>
<td>Femur, tibia</td>
<td>20</td>
<td>Average healing index was lower in the BMC-PRP group than the control group (27.1 versus 36 days/cm). The effect was more pronounced in the femur than in the tibia.</td>
<td>III</td>
</tr>
<tr>
<td>Kiely et al[^11]</td>
<td>Diphosphonates</td>
<td>NR</td>
<td>Femur, tibia</td>
<td>7</td>
<td>Increased BMD and BMC measured at onset of treatment and frame removal (62.1% to 85.6% and 47.3% to 83.2%, respectively). Six patients did not require additional intervention. No significant systemic complications were encountered.</td>
<td>IV</td>
</tr>
</tbody>
</table>

*BMC = bone marrow cells, BMD = bone mineral density, IM = intramedullary, LIPU = low-intensity pulsed ultrasound, NR = not reported, PEMF = pulsed electromagnetic field, PRP = platelet-rich plasma*
primary bone units begin to mineralize in this zone, expanding to a maximum diameter of 150 to 200 µm. The primary bone units cross-link with other units that are surrounded by vascular sinusoids and span the cross-section of the distraction gap. During the consolidation phase, the primary mineralization front traverses the fibrous interzone, followed by the zone of microcolumn formation. In this way, the distraction gap is replaced by mature bone that remodels with formation of the medullary canal and distinct cortices, in accordance with Wolff’s law. Endochondral bone formation has been noted in experimental models of DO, in which new bone formation is delayed secondary to poor blood supply or lack of stable external fixation.

**Radiographic Assessment of Bone Formation**

A valid and reliable means of assessing the quality of new bone formation during DO is essential. Imaging techniques such as ultrasonography and quantitative bone scintigraphy have been investigated. However, plain radiography is the mainstay in assessing the quality and quantity of distraction regenerate. Pattern recognition of the radiographic appearance of new bone formation has typically been used to make clinical decisions regarding the rate of distraction, advancement of weight-bearing status, and scheduling the removal of external fixation. Poor healing is suggested by delayed radiographic appearance of bone formation (ie, >30 days post-osteotomy); multiple radiolucencies in the distraction regenerate; axial deviation of the regenerate, which is suggestive of suboptimal mechanical stability; and hourglass configuration of the regenerate. Attempts have been made to classify the shape, consistency, and polarity of bone regeneration during limb lengthening based on plain radiographic appearance.

Surgeon experience with limb lengthening and use of digital image enhancement techniques can improve the reliability and accuracy of radiographic assessment of bone formation during DO. Clinical decision-making is facilitated by directing the radiographic beam orthogonal to the lengthening site, avoiding the placement of nonradioopaque materials directly over the osteotomy site, periodically obtaining oblique radiographic views to adequately visualize the distraction gap, and reviewing sequential radiographs.

**Risk Factors for Poor Bone Formation**

Poor bone formation with prolonged external fixation and bone healing indices can take a physical, emotional, and financial toll on patients and caretakers alike. A frail regenerate may not withstand physiologic loads and is prone to deformation and fracture following removal of the external fixator (Figure 1). Several factors can negatively affect the volume and quality of bone formation during DO, including advanced age and a diaphyseal lengthening site. Adequate blood supply and mechanical stability are crucial to the formation of a healthy regenerate. Two clinical studies indicated fracture rates of 8.1% to 9.4% in adult and pediatric patients who underwent limb lengthening with external fixation for a variety of diagnoses. Predisposition to poor bone formation can be attributed to host-related factors as well as local and iatrogenic causes. Host-related factors in pediatric patients include use of nonsteroidal anti-inflammatory drugs, congenital etiology, and systemic illness (eg, diabetes, osteogenesis imperfecta). Local predisposing factors include a scarred soft-tissue envelope (Figure 1, A), overlying infection, and prior radiation therapy as well as deformities such as congenital pseudarthrosis of the tibia. Iatrogenic causes include compromised soft-tissue coverage at the osteotomy site, resulting from poor location selection; suboptimal osteotomy technique (eg, thermal necrosis resulting from use of an oscillating saw); a persistent gap >1 cm at the osteotomy site during the latency phase; application of a mechanically unstable frame configuration; a short latency phase (<5 days); and rapid distraction (>2 mm/day). A recent study of patients undergoing tibial lengthening noted the biologic superiority of Gigli saw osteotomy, especially in the presence of osteopenia. Preoperative recognition of host, local, and iatrogenic factors that are predisposing to poor bone formation fosters improved patient selection and allows modification of the postoperative protocol (eg, prolonging the latency period, decreasing the distraction rate to allow formation of a healthy regenerate).

**Modalities for Enhancing Bone Formation**

New bone formation during DO depends on a complex interplay of anabolic and catabolic pathways. In patients with the potential for formation of a healthy regenerate, therapeutic modalities often can be combined to maximize their effect. Typically, it is more efficacious to anticipate problems with bone formation than to manage an atrophic regenerate or nonunion.
Mechanical Modulation

Controlled, repetitive axial loading of healing fractures can stimulate callus formation and accelerate restoration of bone strength. Animal data exist to support the use of various means of modulating loading of the distraction regenerate (eg, early weight bearing, temporary distraction, compression following osteotomy, dynamicization following callus distraction).1 However, there are limited data regarding the effects of alteration of mechanical load on bone healing in humans.22 Increasing the frequency of distraction while decreasing the amount of lengthening at each interval, whether manually1,22 or with a motorized distractor, may improve bone formation and shorten the external fixation index. In a study of elderly patients with medial compartment osteoarthritis and hemicallotasis of the proximal tibia, Mizuta et al22 reported increased bone mineral density and a shorter period of external fixation in patients who underwent distraction at a rate of 0.125 mm eight times per day (total, 1 mm/day), compared with those who underwent distraction at the standard frequency of 0.25 mm four times per day.

Innovative Surgical Techniques

Technical variations on the conventional Ilizarov method have been developed with the goal of reducing the duration of external fixation or eliminating its use. New techniques include lengthening over an intramedullary (IM) nail,4,23-26,29 lengthening followed by nailing,29 lengthening combined with plating,3,30 and use of internal lengthening devices.31-33 These techniques are not without risk,23,24,27 and they may not be appropriate in patients with a history of local infection. Although these methods decrease the external fixation index, protect against refracture, and promote faster rehabilitation, they have not been shown to consistently improve the bone healing index.23,24,26-30 Other disadvantages include the possibility of IM infection, the potential for customized instrumentation, increased surgical time, excessive blood loss, additional surgery for removal of deep hardware, limited applicability in skeletally immature persons, added cost, and a steep learning curve.

To perform lengthening over an IM nail, an undersized reamed IM nail is inserted and locked at one end, and an external fixator is attached to the bone. Direct contact between the fixator pins and the nail must be avoided. Once the required length is achieved via gradual distraction at the osteotomy site, the IM nail is statically locked, and the external fixator is removed (Figure 2). Compared with classic Ilizarov lengthening, some authors have noted a substantial reduction in the duration of external fixation with decreased time to full consolidation of the regenerate.23 In the pediatric patient, a humeral nail is inserted via a trochanteric entry site for femoral lengthening. In a study of nine preadolescent patients, a mean healing index of 12.2 days per centimeter (range, 9.5 to 16.9 days/cm) was reported.3 Complications occurred in four patients, including osteomyelitis, failure of the distal interlocking site, and femoral fracture at the distal end of the nail. However, no patient experienced osteonecrosis of the femoral head. In another pediatric study, smaller-diameter flexible nails were inserted during application of the external fixator for limb lengthening (1.5 to 2 mm).4 These children experienced an average decrease in the duration of external fixation of 27 days compared with children who were treated with the conventional Ilizarov method.

We used a flexible IM nail in a 4-year-old girl with type 1 neurofibromatosis, congenital pseudarthrosis of the tibia, and limb shortening measuring 3.5 cm (Figure 3). The patient had undergone four previous unsuccessful surgeries to repair the pseudarthrosis. BMP-2 was applied in a physician-directed (off-label) capacity. Autogenous iliac crest bone graft was used, and proximal tibial osteotomy with lengthening was performed. The tibia was stabilized with a flexible IM nail to protect the lengthened section and the distal pseudarthrosis site against mechanical failure. An external fixator was applied to aid in tibial lengthening and to achieve compression across the distal pseudarthrosis site. External application of pulsed electromagnetic field (PEMF) via a transducer was used postoperatively.

In a case series, six children underwent lengthening over a percutaneously inserted submuscular plate.5 The mean external fixation index was approximately 13 days per centimeter for all patients. Several complications were reported, including premature consolidation requiring repeat osteotomy, residual procurvatum deformities of >10°, and one fracture proximal to the plate.

A predisposition for fracture or bending of the regenerate exists following removal of external fixation after classic lengthening in patients with certain metabolic diseases (eg, osteogenesis imperfecta) (Figure 1, C) and specific conditions (eg, congenital shortening of the femur).20 Secondary IM nailing with external fixation after DO has been used to prevent mechanical failure of the distraction regenerate.14 Limb casting may be used to protect the regenerate. To minimize the risk of secondary infection following insertion of an IM nail, prophylactic oral antibiotics should be used until all pin sites are clean and dry.
Physical Forces

Strain-generated potentials may be critical in the regulation of new bone formation. Two distinct forms of physical forces have been used to enhance DO: LIPU and PEMFs.

Low-intensity Pulsed Ultrasound

LIPU delivers high-frequency, low-intensity acoustic pressure waves to the maturing distraction regenerate. An ultrasound transducer placed on the skin enhances endochondral ossification and callus formation, especially in acute fractures of the distal radius and tibial shaft managed with a cast. Most authors recommend LIPU over the healing fracture site for 20 minutes per day. The role of LIPU in DO, especially in pediatric patients, is less well defined and is considered a physician-directed (off-label) application.

In a study of 108 children who underwent external fixation using the Ilizarov method, Gebauer and Correll reported that 13 patients with deficient bone formation achieved complete union 3 to 12 months following initiation of LIPU treatment. No other intervention was used. In a study of 20 young adults with segmental tibial defects who underwent DO using external fixation, 10 underwent LIPU applied to the distraction site during the consolidation phase. The mean healing index was 30 days per centimeter in the ultrasound group compared with 48 days per centimeter in patients treated with rigid fixation (range, 27 to 36 days/cm and 42 to 75 days/cm, respectively).

Tsumaki et al studied 21 patients aged 53 to 78 years with bilateral genu varum and medial compartment osteoarthritis who underwent single-stage bilateral opening-wedge high tibial osteotomy using hemicalotasis. Limbs managed with LIPU following distraction had a slight increase in bone mineral density com-
pared with untreated contralateral limbs. Mean time in external fixation was 7 days shorter with LIPU than without.

Although evidence exists in support of LIPU during the consolidation phase during DO of the tibia, the efficacy of ultrasound on other long bones, especially those associated with a large overlying soft-tissue envelope (eg, femur) and with internal fixation (eg, lengthening over nails), remains speculative. The effect of LIPU on adjacent growth plates in skeletally immature patients is unknown.

Figure 3

Preoperative AP (A) and lateral (B) radiographs demonstrating persistent pseudarthrosis with a short, angulated distal fragment and generalized osteopenia in a 4-year-old girl with type 1 neurofibromatosis and 3.5 cm tibial shortening. The pseudarthrosis was repaired with autogenous iliac crest bone graft, physician-directed (off-label) application of bone morphogenetic protein-2, and proximal tibial osteotomy with flexible intramedullary nails, as well as postoperative external application of pulsed electromagnetic field. Proximal tibial osteotomy was performed at the same time to address the associated limb shortening, using distraction osteogenesis for gradual lengthening. AP tibial radiographs during the late distraction (C) and consolidation (D) phases demonstrating progressive healing of the lengthening regenerate. External fixation was used to achieve proximal tibial lengthening and compression across the distal pseudarthrosis site. AP (E) and lateral (F) tibial radiographs following removal of the external fixator, demonstrating adequate healing at the proximal lengthening site and tenuous union across the distal pseudarthrosis site.
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Pulsed Electromagnetic Field
Electromagnetic stimulation is a non-invasive modality that has long been used to enhance fracture healing; however, a recent meta-analysis of randomized controlled trials revealed inconsistent outcomes.39

Use of PEMF in children is considered a physician-directed (off-label) application. Clinical evidence pertaining to the use of PEMF for enhancing bone formation during DO is limited (Figure 3). A small double-blind study of adolescent patients who underwent limb lengthening did not demonstrate a difference in the rate or amount of new bone formation in patients treated with an active PEMF coil versus the control who underwent limb lengthening with an inactive coil.7 However, when dual-energy x-ray absorptiometry was used to measure bone density, patients treated with PEMF were found to have less bone loss adjacent to the distraction gap. In a study of adolescent patients of short stature who underwent bilateral humeral lengthening, the extremity managed with PEMF exhibited faster callus formation and had greater bone density than did the contralateral control side.4 In addition, external fixation was removed an average of 1 month earlier from the extremity that was treated with PEMF. Unlike the study by Eyres et al,7 PEMF was maintained during both the distraction and the consolidation phases.8 Because of limited data and multiple variables, including duration of PEMF treatment and its use in upper versus lower extremities, the role of PEMF during DO remains unclear.

Growth Factors and Stem Cells
A variety of BMPs play an active role in osteogenesis, including recruitment of stem cells, cellular proliferation and differentiation, and bone formation. Recombinant BMP-2 and BMP-7 have been used primarily in adults as an autograft substitute for single-level spine fusions and certain open tibial shaft fractures and non-unions. Although these products have not been approved by the US FDA for pediatric applications or for DO, physician-directed (off-label) applications in recalcitrant cases involving limb lengthening and reconstruction have been reported40 (Figure 3). Currently, limited information exists on the clinical use of BMPs for DO in humans.

In 2008, Burkhart and Rommens40 reported on a case study of a 19-year-old woman with insufficient bone regeneration following tibial transport over an IM nail. The patient was successfully treated with exchange reamed nailing and IM application of recombinant BMP-7 mixed with reamed debris at the site of the atrophic regenerate. However, several simultaneous interventions were used in this case; thus, the role of BMPs in DO remains unclear and warrants further study.

PRP contains a variety of osteoinductive growth factors that may play a role in the proliferation and differentiation of osteoprogenitor cells and thereby enhances new bone formation during DO.21 In a case series, three adolescent patients who underwent lower limb lengthening received an injection of culture-expanded bone marrow cells and PRP at the site of lengthening during the distraction and consolidation phases.9 The healing index was 23 days per centimeter, with no untoward effects. The same group of investigators applied a similar protocol in the treatment of a group of teenagers of short stature secondary to achondroplasia and hypochondroplasia who underwent lower limb lengthening.10 Eleven patients (24 bones) were treated with transplantation of culture-expanded bone marrow cells and PRP during DO. These patients had a significantly lower average healing index compared with the nine patients (32 bones) in the control group (27.1 ± 6.89 days/cm versus 36.2 ± 10.4 days/cm, respectively; P = 0.0005). The osteogenic effect was more pronounced with femoral lengthening than with tibial lengthening.

Although the initial results of injection of culture-expanded bone marrow cells and PRP at the lengthening site seem encouraging, this treatment option requires additional visits to the operating room and special equipment, as well as additional training to harvest the stem cells. This technique must be studied in other patient populations, especially those with typically prolonged healing times, to evaluate whether these results can be duplicated.

Anticatabolic and Other Agents
Diphosphonates are a family of anticatabolic agents that prevent bone resorption. They may be administered orally or systemically. These agents have been used in a physician-directed (off-label) capacity in children with osteopenia to reduce the rate of bone turnover, thereby improving bone mineralization and density. In 2007, Kielty et al11 reported that six of seven children treated with parenteral diphosphonates for poor quality of regenerate following DO eventually healed without further intervention. No side effects related to diphosphonate therapy were reported.

Given the prolonged half-life of diphosphonates and their influence on bone growth and remodeling, as well as other systemic effects, use of these agents requires further study. Other anticatabolic agents (eg, calcitonin) may have a role to play in en-
hancing bone formation during DO. However, animal studies have not been promising.42

Several other agents, such as parathyroid hormone,43 vitamin D analogs,44 and hyperbaric oxygen,45,46 have been studied in animal models of DO with encouraging results. However, no human study of such therapies is available. Anecdotally, reaming of the atrophic regenerate with or without local bone grafting to enhance osteogenesis during DO has been described. However, clinical studies with control subjects are lacking.

### Healing of the Docking Site Following Bone Transport

The docking site is prone to delayed healing in DO following gradual transport of a bony fragment in patients with a skeletal defect. Satisfactory outcomes without the need for supplemental management of segmental defects of the tibia following sequestrectomy and bone transport have been reported in children with chronic hematogenous osteomyelitis.47 However, the potential exists for impaired bony union. Several options are available to minimize external fixation and enhance union at the docking site, including autologous bone graft (Figure 4), shingling or reshaping of the bony edges,48 bifocal transport,49 transport over an IM nail,50 secondary IM nailing,28 and application of LIPU to the docking site.51 Acute shortening following segmental resection with lengthening using DO at a distant site in the same bone is an effective alternative to the classic bone transport technique in some patients with moderate-sized skeletal defects.52 Formation of fibrous caps at the bone ends may be avoided with this technique. Use of other modalities to enhance healing of the docking site, such as BMPs and anticitabolics, has not been reported.

**A** Preoperative AP radiograph demonstrating nonunion, shortening, and deformity in the distal radius of an 11-year-old boy who sustained an open fracture of the distal radius 2 years earlier and developed a draining sinus with chronic osteomyelitis and nonunion. He was treated with surgical débridement and a 6-week course of intravenous and oral antibiotics, in addition to gradual soft-tissue correction of the distal forearm deformity followed by proximal-to-distal bone transport of the radius. **B** Postoperative lateral radiograph demonstrating a healthy regenerate proximally (arrow) following proximal-to-distal bone transport of the radius. Autologous bone graft harvested from the iliac crest was applied to the distal docking site (arrowhead) to facilitate union. AP (C) and lateral (D) radiographs 6 months following fixator removal demonstrating healing of the proximal lengthening site and distal docking site of the radius. Residual deformity of the distal radioulnar joint is noted.
Summary

DO is a clinically applicable method of new bone formation based on sound biologic and mechanical principles. Appropriate patient selection, surgical technique, and rate and frequency of distraction are important prerequisites for the timely formation of a robust distraction regenerate. Several methods can improve the rate and quality of bone formation while decreasing the external fixation index during DO. These modalities include mechanical stimulation, innovative surgical techniques that require a variety of IM nails and plates, exogenous application of LIPU or electromagnetic fields, and anticatabolic agents (eg, diphosphonates, local injection of certain BMPs, pluripotent stem cells mixed with PRP). Few clinical studies exist supporting the use of such options.

The role of various therapeutic modalities in enhancing osteogenesis during fracture healing and spinal arthrodesis has been studied extensively; however, the distinctive features of bone formation during DO make it difficult to assume similar efficacy in patients undergoing limb lengthening. No well-designed, prospective randomized study with a sufficient number of patients exists that has critically evaluated any of the available methods of improving bone formation during DO of long bones in children. Most of the existing reports (Table 1) consist of a small, heterogeneous group of patients who may have had a statistically, although not always clinically, significant difference compared with patients in the control group. Moreover, the safety profile, including long-term effects, cost-effectiveness, ideal dosage, and duration and timing of these modalities, has not been well studied in children. A higher level of evidence is needed to establish the safety profile and define the exact role of each modality during DO in the pediatric population.

References

Evidence-based Medicine: Levels of evidence are described in the table of contents. In this article, there are no level I studies. References 7 and 39 are level II studies. References 4, 8, 10, 21, 22, 25, 29, 37, and 38 are level III studies. References 3, 5, 6, 11, 12, 15, 17-20, 23, 24, 26-28, 31-34, 41, 47, 48, 50, and 51 are level IV studies. References 30, 40, and 49 are level V expert opinion.

Citation numbers printed in bold type indicate references published within the past 5 years.


