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CORR Insights®: Percutaneous CO_2 Treatment Accelerates Bone Generation During Distraction Osteogenesis in Rabbits

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Where Are We Now?

Distraction osteogenesis is an important treatment for growth deformities, malunions, and traumatic bone loss. After the first description of the clinical use of distraction osteogenesis with a circular external skeletal fixation system [4], a range of external systems have been developed, including unilateral frames and Taylor spatial frames. However, the basic technique of distraction osteogenesis has hardly changed; it relies on an osteotomy to avoid soft-tissue disruption, a latency period allowing vasculature to recuperate, a distraction period with a standard lengthening of 1 mm per day, and a consolidation period that allows the regenerated bone to regain physiologic strength. Although the latency period and distraction phases are fairly predictable in duration, the consolidation phase can often vary widely, sometimes resulting in protracted treatment durations in these patients. In addition, lengthy periods of external skeletal fixation are uncomfortable for patients and are associated with frequent complications. To shorten the consolidation phase, strategies have been developed including adaption of distraction with internalized fixators, use of a combination of external frames for distraction and internal stabilization during the consolidation phase, and stimulation of osteogenesis during the distraction and consolidation phases.

Dynamic intramedullary implants are ideally suited to overcome the disadvantages of external lengthening systems. Initially, intramedullary devices relied on ratchet mechanisms with rotation of bone fragments to achieve distraction [9]. The most modern system uses magnets in an intramedullary nail combined with external magnets for rotation, allowing for accurate distraction [1]. In a study of femoral lengthening that compared an intramedullary lengthening nail system with an external fixator monorail system, patients who had the intramedullary nail system had a better healing index (31 days per cm versus 47 days per cm), could bear weight earlier, and experienced fewer complications [6]. Treatment with intramedullary lengthening systems will not be effective in all patients, and dynamic external skeletal fixators will remain important in treating many deformities. Nevertheless, patient discomfort and the frequency of complications can be improved by using external skeletal fixation for dynamic lengthening combined with internal fixation, including plate osteosynthesis, during the consolidation phase [3].

Stimulation of osteogenesis during distraction and consolidation has attracted research interest. Most studies have been conducted using animal models [2, 8, 10, 11]. Nevertheless, some clinical data on this strategy are available. In patients with tibial lengthening with an intramedullary nail, low-intensity pulsed ultrasound has been shown to enhance bone formation during the distraction and consolidation phases, but results are still conflicting [7].

This CORR Insights® *is a commentary on the article* "Percutaneous CO_2 Treatment Accelerates Bone Generation During Distraction Osteogenesis in Rabbits" *by Kumabe and colleagues available at: DOI: 10.1097/CORR.0000000000001288.*

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Numerous experimental studies have reported on the stimulation of bone healing using either fracture or distraction osteogenesis in animal models [2, 8, 10, 11]. Many of these studies were in craniofacial surgery, although some have been in orthopaedic surgery. Most studies focused on the use of growth factors, stem cells, mechanical stimulation, laser therapy, and hyperbaric oxygen [2, 8, 10, 11]. Although most of these studies found that these treatments improved bone healing, questions on the most favorable amount, timing, and delivery methods that allow for bone regeneration and clinical application are still unanswered.

Kumabe et al. [5] reported on the use of percutaneous CO_2 to accelerate bone regeneration and consolidation. This concept is completely new and opens unexplored possibilities as an adjuvant therapy during distraction osteogenesis and bone healing. The authors believe that enhanced osteogenesis is induced by increased angiogenesis and blood flow, but this supposition clearly needs further clarification. However, the present study using CO_2 therapy 5 days per week for 20 minutes during distraction and consolidation in a rabbit tibia model had remarkable results. Clinically, the enhanced biomechanical properties of the regenerated bone after CO_2 therapy are relevant. If these results could be translated to patients, the treatment period could be shortened and patients could return to function earlier.

Where Do We Need To Go?

However, the study raises new questions. Although the study [5] was designed to locally stimulate osteogenesis in the distraction gap, the complete caudal half of the rabbit was exposed to 100% CO_2. Penetration of the skin relies on passive diffusion of CO_2, and using a CO_2 absorption-enhancing hydrogel could result in a higher CO_2 gradient in the distraction gap. At present, it is unclear whether true local application of CO_2 incorporating only the external skeletal fixation and distraction zone would be as effective in this model. Penetration of CO_2 into the distraction gap would ideally have the most effect. In rabbits, the soft-tissue envelope of the tibial diaphysis is very small and facilitates diffusion. It would be interesting to see whether similarly increased angiogenesis, blood flow, and osteogenesis in the tibia are likewise observed in larger animals such as sheep. Distraction osteogenesis of the femur and humerus is equally important, but it typically differs from distraction osteogenesis of the tibia regarding the amount of soft tissue and muscle mass surrounding the distraction zone. CO_2 penetration and its effects on bone consolidation might be more problematic in these locations. Even if the effect is limited to the surrounding soft tissues, osteogenesis and bone consolidation might be improved. For clinical application in healthy people and patients with underlying angiogenic and osteogenic problems, a fuller understanding of the intrinsic mechanisms of CO_2 adjuvant therapy is critical. A multimodal approach to enhance angiogenesis, osteogenesis, and consolidation would be effective and opens up enormous research potential.

How Do We Get There?

Questions on the mechanisms and best amount, timing, and delivery of adjuvant CO_2 therapy should be addressed first; an important endpoint would be the enhancement of angiogenesis, osteogenesis, and consolidation. Small-animal models such as the described tibial distraction model in rabbits are ideal to tackle these basic questions. Before possible clinical application, larger animal models, including sheep and goats, which have a bone architecture and loading profile much closer to that of humans, should be used. Because adjuvant monotherapy with any single agent (such as CO_2 and bone morphogenetic protein) might not be the most effective treatment in enhancing the highly complex processes of osteogenesis, consolidation, and remodelling, combinations of therapies (such as bone morphogenetic protein, vascular endothelial growth factor, CO_2, and stem cells) and their correct timing should be pursued. The dangers of manipulating local angiogenesis, chondrogenesis, and osteogenesis and their possible systemic effects should be thoroughly scrutinized. Because the treatment of bone disorders with distraction osteogenesis heavily relies on fixation systems, improvements in this field should be closely monitored and ideally synchronized with adjuvant therapies. In orthopaedic surgery, three-dimensional printing techniques with custom-designed internal distractors might revolutionize treatment options. Our multimodal approach should delicately balance availability, short-term patient benefits, long-term function, and costs.

References

1. Calder PR, Laubscher M, Goodier WD. The role of the intramedullary implant in limb lengthening. *Injury*. 2017;48: S52-S58.
2. Floerkemeier T, Thorey F, Wellmann M, Hurschler C, Budde S, Windhagen H. rhBMP-2 in an injectable Gelfoam carrier enhances consolidation of the distracted callus in a sheep model. *Technol Health Care*. 2017;25:1163-1172.
3. Grunwald L, Dobele S, Hontzsch D, Slongo T, Stockle U, Freude T, Schroter S. Callus massage after distraction osteogenesis using the concept of lengthening then dynamic plating.

Strategies Trauma Limb Reconstr. 2015; 10:129-135.
4. Ilizarov GA. Clinical application of the tension-stress effect for limb lengthening. *Clin Orthop Relat Res*. 1990;250:8-26.
5. Kumabe Y, Fukui T, Takahara S, Kuroiwa Y, Arakura M, Oe K, Oda T, Sawauchi K, Matsushita T, Matsumoto T, Hayashi S, Kuroda R, Niikura T. Percutaneous CO2 Treatment accelerates bone generation during distraction osteogenesis in rabbits. *Clin Orthop Relat Res*. [Published online ahead of print]. DOI: 10.1097/CORR.0000000000001288.
6. Laubscher M, Mitchell C, Timms A, Goodier D, Calder P. Outcomes following femoral lengthening: An initial comparison of the Precice intramedullary lengthening nail and the LRS external fixator monorail system. *Bone Joint J*. 2016;98:1382-1388.
7. Song MH, Kim TJ, Kang SH, Song HR. Low-intensity pulsed ultrasound enhances callus consolidation in distraction osteogenesis of the tibia by the technique of lengthening over the nail procedure. *BMC Musculoskelet Disord*. 2019;20: 108.
8. Suer BT, Ortakoglu K, Gunaydin Y, Sencimen M, Mutlu I, Dogan N, Kaya A. Effects of the hyperbaric oxygen on de novo bone formation during periosteal distraction. *J Craniofac Surg*. 2014;25: 1740-1745.
9. Wang K, Edwards E. Intramedullary skeletal kinetic distractor in the treatment of leg length discrepancy: a review of 16 cases and analysis of complications. *J Orthop Trauma*. 2010;26: e138-e144.
10. Yang Y, Lin S, Wang B, Gu W, Li G. Stem cell therapy for enhancement of bone consolidation in distraction osteogenesis: A contemporary review of experimental studies. *Bone Joint Res*. 2017; 6:385-390.
11. Zhao ZY, Shao L, Zhao HM, Zhong ZH, Liu JY, Hao CG. Osteogenic growth peptide accelerates bone healing during distraction osteogenesis in rabbit tibia. *J Int Med Res*. 2011;39:456-463.