Size Matters: Defining Critical in Bone Defect Size!

Emil H. Schemitsch, MD, FRCS(C)

Summary: Bone defects are common and are associated with a significant burden of disease. The treatment of these injuries remains controversial, particularly those defects which are critical sized. Despite the need for decision making to be evidence based, a lack of consensus around definitions of critical-sized defects still exists, particularly around those defects in the 1–3 cm range. There is a need to define "critical" in bone defect size because noncritical defects may heal without planned reconstruction and secondary surgery. This article reviews the current evidence around the definition of a critical-sized bone defect and concludes that defects in the order of 2.5 cm or greater seem to have a poor natural history.

Key Words: critical sized, bone defect, union, fracture healing

(*J Orthop Trauma* 2017;31:S20–S22)

Bone defects are common and occur in many clinical situations including high grade open fractures with bone loss, high energy trauma, blast injuries, infection requiring debridement of bone, and resection of bone tumors.[1] There continues to be a significant burden of disease associated with the management of bone defects, particularly if the bone defect is critical sized.[1] Despite the profound clinical and economic impacts, the treatment of these injuries remains controversial.[1] The controversy in part is related to the size of the defect and how to determine whether the defect is critical sized. Moreover, long-term outcomes are limited by high rates of complications and reoperations and poor functional outcomes. Despite the need for decision making to be evidence based, there is a lack of consensus around definitions and subsequently best practices for surgical management of critical-sized defects.[1]

The planned reconstruction of bony defects is complicated by the consequences of secondary surgery and a gold standard, autogenous bone grafting, which is complicated by numerous drawbacks including donor site morbidity, limited graft volume, anesthesia time, need for additional surgical resources, and poor results in a significant number of patients.[2] This makes it critical to be able to diagnose the presence of a critical-sized defect because inability to do so may expose patients to unnecessary delays in management or risks of surgery which may not be absolutely necessary.

There is no one standard definition of a critical-sized defect. Defects may be evaluated both in relative and absolute terms and vary whether considering animal models or humans. In general, a "critically-sized" defect is regarded as one that would not heal spontaneously despite surgical stabilization and requires further surgical intervention.[2] In a survey of the Orthopaedic Trauma Association membership to determine various aspects of definitive treatment and materials used for grafting in "critical-sized" segmental bone defects, the precise size or volume of bone that comprises a critical-sized bone defect was not defined.[3] This absence of standard definitions is consistently seen throughout the literature and has resulted in conflicting opinions in how to manage patients. General guidelines that have been suggested in the literature include defect size length greater than 1–2 cm and greater than 50% loss of the circumference of the bone.[1,2,4] However, this is impacted on by the anatomic location of the defect and the state of the soft tissue envelope surrounding it.[1] Controversy also exists for bone defects in animal models used in preclinical studies. Some have suggested that a critical-sized defect in an animal model is the smallest size intraosseous wound in a particular bone and species of animal that will not heal during the lifetime of the animal or a defect that shows less than 10% regeneration during the animal's lifetime.[5,6]

It is also necessary to realize that a nonunion is not the same as a critical-sized defect. In a nonunion, there is an impaired cellular and molecular signaling and biomechanical instability, often without a bone gap versus a critical-sized defect, where often there is an adequate biology but an inability to replace substantial bone loss that may be complicated by the soft-tissue environment and patient demographics.[7] Critical bone defects can develop into atrophic nonunions because of the nature of the fracture, with impaired vascularity and soft tissue injury, whereas an atrophic nonunion may occur without any bone loss initially.[7] A critical-sized bone defect will always require management of the defect, whereas a nonunion may or may not require management with a bone graft.

There are numerous factors which affect bone defects and their "critical size" is dependent on the absolute versus relative size, whether there is circumferential loss of bone, anatomical location (diaphyseal/metaphyseal/articular), the soft tissue environment including injury to the periosteum and surrounding muscles, age, and presence of chronic diseases and other comorbidities.[1] These associated factors are apparent when one tries to translate or extrapolate findings from animal models, where double osteotomies and minimal

Accepted for publication July 14, 2017.
From the Department of Surgery, Western University, London Health Sciences Centre, University Hospital, London, ON, Canada.
The author reports no conflict of interest.
Reprints: Emil H. Schemitsch, MD, FRCS(C), Department of Surgery, Western University, London Health Sciences Centre, University Hospital, 339 Windermere Rd, Room C9-116, London, ON N6A 5A5, Canada (e-mail: emil.schemitsch@lhsc.on.ca).

DOI: 10.1097/BOT.0000000000000978

soft tissue damage are commonly used to human scenarios which are complicated by the mechanism of injury, soft tissue environment, infections, and patient demographics.[8,9] In the latter case, a much smaller defect may be critical by virtue of the numerous other factors which may be associated with the injury.

Critical-sized defects require planned reconstruction and the gold standard biologic treatment has been iliac crest bone graft.[1,2] There are numerous drawbacks of autogenous bone grafting, making it vitally important to determine which defects will heal without additional treatment. The influence of anatomic location is seen when one considers the outcome of segmental defects of the femur versus the tibia. Segmental defects of the femur often have a good soft-tissue environment and spontaneous healing of segmental defects 6–15-cm long has been reported.[10] By contrast, poor outcomes with the lack of spontaneous healing have been reported with much smaller defects in the tibia, when the defect size is greater than 1–2 cm and greater than 50% of the cortical circumference.[11–13] The problem is that most segmental defects occur in the tibia (>60%) and occur in the diaphysis (>60%).[2] The diaphysis of the tibia is an area with poor soft tissue coverage and limited blood supply.

In the SPRINT trial, 37 of 1225 patients (3%) with tibial fractures treated with intramedullary nailing had a critical-sized defect defined as greater than 1 cm in length and >50% of the cortical diameter and 47% achieved union with no additional treatment.[4] In this study, patients with a critical-sized defect were more likely to have a high energy mechanism of injury, AO-OTA fracture type 42 B or C, and location involving the middle third of the tibia and were more likely to have worse patient-based outcomes. The authors concluded that because tibial diaphyseal defects of >1 cm and >50% cortical circumference healed without additional surgery in 47% of cases, this definition of a critical-sized defect was not "critical." They also concluded that further investigation was required to determine which factors predict union to avoid unnecessary secondary surgery.[4]

In a study of exchange intramedullary nailing by Court-Brown for aseptic tibial nonunion, it was noted that bone loss was important in the development of nonunion after tibial intramedullary nailing.[12] In Gustilo III B fractures with insignificant bone loss (<50% of the tibial circumference and <2 cm defect), there was a 61.5% union rate.[12] With significant bone loss (>50% of the tibial circumference and >2 cm defect), there was a 0% union rate.[12] Robinson and colleagues also found that minor bone loss involving 25%–50% of the cortical circumference of any length or 50%–99% of the circumference up to 25 mm could be managed without surgery.[14]

In a retrospective cohort study of open diaphyseal tibial shaft, fractures with a bone gap of 10–50 mm > or = to 50% of the circumference treated with an intramedullary nail by Haines et al,[15] defect size, and infection were the main determinants of outcome. The radiographic apparent bone gap (RABG) was determined by measuring the bone gap on each cortex and averaging over 4 cortices. Fractures achieving union had a RABG of 12 ± 1 mm versus 20 ± 2 mm in those going on to be a nonunion. A RABG of 25 mm was the optimal threshold for discriminating between the outcomes of union and nonunion.[15] Fractures with a RABG of <25 mm achieved union much more frequently than those with gaps > or = to 25 mm (54% vs. 0%), respectively, and the highest RABG in a patient achieving union was 24 mm.[15] In this study, factors such as age, sex, time to surgery, open fracture classification, number of procedures, additional adjuncts, diabetes, presence of comorbidities, immunosuppression, and polytrauma did not influence outcome.

The lack of consistency in the literature is also seen because it relates to the management of bone defects. Minor defects (loss of 50% cortical circumference and <2 cm defect), intermediate defects (loss of >50% cortical circumference and 2–6 cm segmental defect), and large defects (>6 cm segmental defect) often have very different suggested treatments that are dependent on these arbitrary groupings by defect size.[3] Yet the threshold for a critical-sized defect may be more in line with 2.5 cm.[14,15]

Animal models also are not very helpful in translation to humans, particularly because they are often used to evaluate bone substitutes, biologics, and implants. Using definitions whereby it is expected that no spontaneous healing should occur during the experiment, there is little standardization in species, defect size, presence of open wound, periosteal stripping, fixation method, animal age and weight, weight-bearing, and follow-up.[8,9] This makes it very difficult to draw conclusions when considering trials concerning bone defects in humans that need to follow those performed in animals.

In summary, there is little evidence and little consensus around diagnosis of critical-sized bone defects. They are not well defined in most long bones, the etiology is multifactorial, and the natural history of smaller defects is better than expected. Defects in bones other than the tibia, for example in the femur, often do surprisingly well. Many tibial defects in the 1–2.5 cm range are not critical sized and are not created equal because close to half may heal. Autogenous bone graft is still the gold standard for management, and it is still very unclear when biologic therapies should be considered. Tibial defects in the order of 2.5 cm or greater seem to have a poor natural history but there is no clear preferred management strategy, and there is a significant evidence gap. More robust animal models are also required to further elucidate the role of various bone substitutes, osteobiologics, and new implants.

REFERENCES

1. Nauth A, McKee MD, Einhorn TA, et al. Managing bone defects. *J Orthop Trauma*. 2011;25:462–466.
2. Keating JF, Simpson AH, Robinson CM. The management of fractures with bone loss. *J Bone Joint Surg Br.* 2005;87:142–150.
3. Obremskey W, Molina C, Collinge C, et al. Current practice in the management of open fractures among orthopaedic trauma surgeons. Part B: management of segmental long bone defects. A survey of orthopaedic trauma association members. *J Orthop Trauma.* 2014;28:e203–e207.
4. Sanders DW, Bhandari M, Guyatt G, et al. Critical-sized defect in the tibia: is it critical? Results from the SPRINT trial. *J Orthop Trauma.* 2014;28:632–635.
5. Gugala Z, Gogolewski S. Regeneration of segmental diaphyseal defects in sheep tibiae using resorbable polymeric membranes: a preliminary study. *J Orthop Trauma.* 1999;13:187–195.

6. Hollinger JO, Kleinschmidt JC. The critical size defect as an experimental model to test bone repair materials. *J Craniofac Surg.* 1990;1:60–68.
7. Gomez-Barrena E, Rosset P, Lozano D, et al. Bone fracture healing: cell therapy in delayed unions and nonunions. *Bone.* 2015;70:93–101.
8. Reichert JC, Epari DR, Wullschleger ME, et al. Establishment of a preclinical ovine model for tibial segmental bone defect repair by applying bone tissue engineering strategies. *Tissue Eng Part B Rev.* 2010;16:93–104.
9. Reichert JC, Saifzadeh S, Wullschleger ME, et al. The challenge of establishing preclinical models for segmental bone defect research. *Biomaterials.* 2009;30:2149–2163.
10. Hinsche AF, Giannoudis PV, Matthews SE, et al. Spontaneous healing of large femoral cortical bone defects: does genetic predisposition play a role? *Acta Orthop Belg.* 2003;69:441–446.
11. Blick SS, Brumback RJ, Lakatos R, et al. Early prophylactic bone grafting of high-energy tibial fractures. *Clin Orthop Relat Res.* 1989:21–41.
12. Court-Brown CM, Keating JF, Christie J, et al. Exchange intramedullary nailing. Its use in aseptic tibial nonunion. *J Bone Joint Surg Br.* 1995;77:407–411.
13. Court-Brown CM, McQueen MM, Quaba AA, et al. Locked intramedullary nailing of open tibial fractures. *J Bone Joint Surg Br.* 1991;73:959–964.
14. Robinson CM, McLauchlan G, Christie J, et al. Tibial fractures with bone loss treated by primary reamed intramedullary nailing. *J Bone Joint Surg Br.* 1995;77:906–913.
15. Haines NM, Lack WD, Seymour RB, et al. Defining the lower limit of a "critical bone defect" in open diaphyseal tibial fractures. *J Orthop Trauma.* 2016;30:e158–e163.