Review

# Management of acute bone loss following high grade open tibia fractures. Review of evidence on distraction osteogenesis and induced membrane techniques

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**Summary.** *Introduction:* Optimal treatment for acute post-traumatic bone loss in the tibia remains unclear. Distraction osteogenesis (DO) and induced membrane technique (IM) have been established as the mainstays of treatment. Aim of this article is to review the current evidence regarding the use of these two methods. *Methods:* A review of the MEDLINE database was performed with strict inclusion and exclusion criteria focusing on treatment of the acute bone loss after open tibia fractures with DO and IM. Bone union rate was taken as the primary outcome and infection rate as secondary outcome. *Results:* Four studies out of 78 on the use of the DO and three studies out of 18 on the use of the IM technique matched the inclusion criteria. Union rate in the DO group ranged between 92% and 100%, with infection rates between 0 and 4%. In the IM group, union was reached in 42% to 100% of cases, with septic complications occurring in 12% to 43%. Differences in union rate and infection rate reached statistical significance. *Discussion:* We found a considerable evidence gap regarding treatment of bone loss in high grade open tibia fractures. The limitations of our study prevented us from drawing clear causative conclusions on the results. Although our study points to higher union rates and lower infection rate with the use of the DO technique, the results remain preliminary and further high-level evidence is needed to establish the roles of DO and IM in treatment of acute bone loss in open tibia fractures. (www.actabiomedica.it)

**Key words:** tibia, bone loss, infection, union, distraction osteogenesis, induced membrane

## Introduction

Open fractures with associated bone loss are rare injuries. They represent approximately 0,4 % of all fractures and 11,4 % of all open fractures (1). Most of them are high degree Gustilo-Anderson (GA) fractures affecting primarily the tibia, which represents the site of 25% of all open fractures (2, 3). Mechanisms of these injuries usually involve high energy transfers (1). Apart from bone loss, these injuries are further complicated by soft tissue loss, contamination, neurovascular injuries, compartment syndrome and injuries to other organ systems.

Prevention of infection with systematic debridement and early soft tissue coverage in a mechanically stable environment, supported by systemic antibiotic therapy, is the most important treatment in the early phase. Guidelines established by the British Orthopedic Association / British Association of Plastic Surgeons (BOA/BAPRAS) address these crucial first steps of treatment (4,5).

The optimal treatment regime for acute post-traumatic bone defects in the tibia remains unclear.

A critical-size bone defect is qualitatively defined as the smallest osseous defect that will not heal spontaneously during the lifetime (6). A quantitative definition is still lacking since many factors beyond the extent of the bone defect affect its ability to heal. Factors regarding bone status, soft tissue envelope and host need to be considered (7,8). The broad spectrum of injury patterns and complexities have so far precluded the establishment of clear guidelines for treatment. Recognition of the problem led to the development of the "diamond concept" of bone healing (9,10). This conceptual framework, however, gives no clear guidelines on which surgical technique is to be used for optimal healing of the bone defect.

In the absence of clear suggestions many techniques have been proposed. Historically, autologous bone grafting has been the gold standard of bone defect treatment (11). Its use has been challenged in the management of larger bone defects, where increased rates of graft resorption have been observed[8]. With the development of microsurgical techniques, the free vascularized fibular graft has been popularized. Due to the technical complexity, donor site morbidity and high rate of refractures in weight-bearing bones, it has been mostly limited to treatment of bone defects in the upper extremity (1,12).

Following its conception in the 1950s, Ilizarov's distraction osteogenesis (DO) has revolutionized the treatment of bone defects. The concept of new bone formation under controlled tension stress with the use of a circular external fixator has led to the development of a versatile system, which enables simultaneous or sequential limb shortening, lengthening and deformity correction (13,14). High rates of bone union (60 to 100%) are to a certain extent off-balanced by a long duration of treatment and a broad spectrum of frequent complications (15,16). To overcome certain drawbacks of the Ilizarov technique, a two-stage procedure has been introduced by Masquelet in 2000 (17). Following debridement, the bone defect is filled with a cement (PMMA) spacer. The latter induces formation of a well-vascularized pseudo membrane. After restoration of the soft tissues, the cement spacer is removed and fresh autologous bone graft implanted into the envelope created by the induced membrane (IM) (18). Previously reported high union rates around 90%, have recently been challenged in the use of post-traumatic defects in the lower limb (19-21).

Aim of the present paper is to review and critically evaluate the current evidence regarding the treatment of acute post-traumatic bone loss in the tibia. Focus will be given to the two most established techniques: distraction osteogenesis and induced membrane technique.

## Methods

A review of the MEDLINE database in agreement with the Preferred Reported Items for Systematic Reviews and Meta-Analyses Statement for Individual Patient Data (PRISMA-IPD) was performed.

### *Search strategy*

A search strategy was developed, involving keywords for the three key concepts (bone defect, open fracture, tibia) and two interventions of interest (DO, IM). Keywords bone defect*" OR "bone loss" AND "Fractures, Open"[Mesh] OR "open fracture*" OR "compound fracture*" AND "Tibia"[Mesh] OR "tibia*"were combined with the Boolean operator AND either with "Osteogenesis, Distraction"[Mesh] OR "Ilizarov Technique"[Mesh] OR "Bone Transplantation"[Mesh] OR "Bone Lengthening"[Mesh] OR "bone transport" OR "segmental bone transport" OR "Ilizarov bone transport" for distraction ostegenesis or with "induced membrane" OR "induced membrane technique" OR "pseudo-membrane" OR "pseudo-membrane technique" OR "Masquelet technique" OR "Masquelet method" OR "Masquelet" for the induced membrane technique.

### *Inclusion and exclusion criteria*

Studies were included when focused on the treatment of acute bone loss in the setting of an open tibia fracture. Articles reporting on bone defects in different body regions were included only if outcomes of interest were given separately for the tibia. Our evaluation focused on adult patients (>18 years old) and on studies presenting results of at least 5 cases. A mean follow-up of at least one year was a prerequisite for inclusion. Treatment modalities included were distraction osteogenesis or the induced membrane technique, combined either with external or internal fixation methods. Studies published between 1990 and 2020 in English or German language were eligible. We filtered our search to studies on humans and those containing a full text. Primary outcome was bone union, while deep infection rate represented the secondary outcome. Studies were included if reporting at least one outcome of interest (Table 1).

Studies were excluded if the etiology of the bone defect was infection, bone tumor or nonunion. Bone periprosthetic and peri-implant fractures were also excluded, as were case reports and small case studies regarding less than 5 patients or having an inadequate follow up (Table 1).

## Analysis

Narrative synthesis was used to describe the main results of each study and summarize the findings. Comparisons between the two approaches (DO and IM) were done using independent samples' t-test or Fisher's exact count test. Meta-analysis was not performed due to high heterogeneity of studies, lack of control groups, or incomplete data reported in the original studies.

## Results

For DO treatment modality, the search resulted in 73 articles. Based on the title and abstract, 23 articles were chosen for detailed reading. Additional 5 relevant articles were identified from the reference lists. Of the 28 articles, 4 studies met our inclusion criteria (Fig. 1).

For the IM technique, the search resulted in 18 articles. Based on the title and abstract, 9 were elected for further reading. Additional 2 relevant studies were identified from the reference lists. Of the total of 11 studies, 3 met our inclusion criteria (Fig. 2).

We found 4 articles reporting the results of DO treatment of bone defects in open tibia fractures which met our inclusion criteria. Number of patients per study ranged from 5 to 24. Mean patients age ranged between 31 and 34 years. All fractures were grade III open tibia fractures according to the Gustilo-Anderson classification. Mean length of bone defects ranged from 5 to 11 cm. Bony union was achieved in 92 to 100% of cases, with deep infection rates between 0 and 4% (Table 2).

In the IM group 3 articles were found in the MEDLINE database that met the inclusion and exclusion criteria. Number of cases per study ranged from 8 to 12. Mean patient age was between 25 and 37 years. All fractures were grade III open tibia fractures according to the Gustilo-Anderson classification. Mean bone defect size ranged from 6 to 10 cm. Union

**Table 1.** Inclusion and exclusion criteria for the study.

| **Inclusion Criteria:** | **Exclusion Criteria:** |
|---|---|
| acute posttraumatic bone defects | Defects following infection |
| open tibia fracture (GA III) | Defects following bone tumor |
| age > 18 years | Defects following nonunion |
| more than 5 cases | Defects following peri-implant fractures |
| follow-up > 1 year | |
| distraction osteogenesis or/and induced membrane technique | |
| publication 1990 – 2020 | |
| language: English or German | |
| Studies on human | |
| Outcomes of interest:<br>- primary outcome: union rate<br>- secondary outcome: infection rate | |

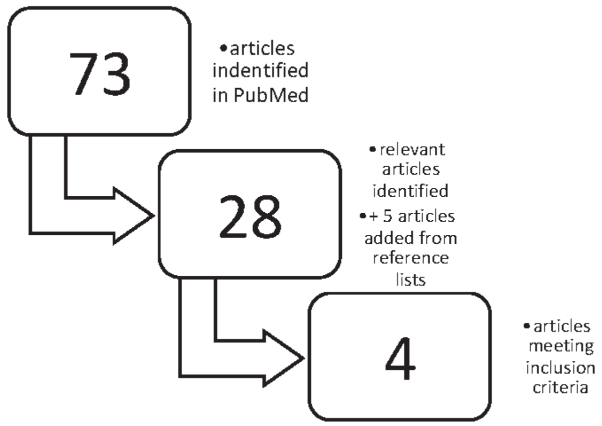


**Figure 1.** Distraction osteogenesis literature search results.

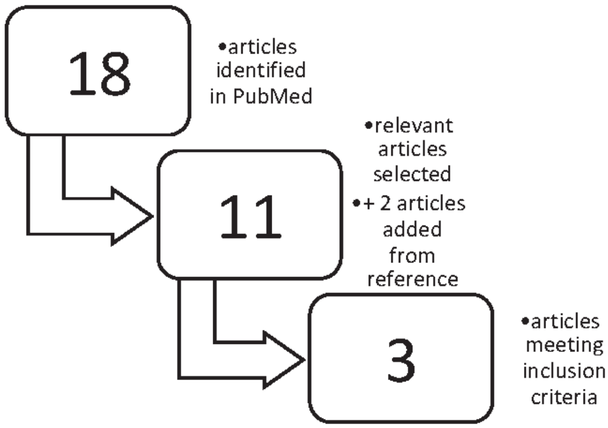


**Figure 2.** Induced membrane technique literature search results.

**Table 2.** Included studies on distraction osteogenesis.

| Study | Nr. of patients | Mean age (years) | Gustillo-Anderson | Mean bone defect (cm) | Union (%) | Amputation (%) | Infection (%) |
|---|---|---|---|---|---|---|---|
| Sen (22) | 24 | 31 | III | 5 | 100 | 0 | 4 |
| Koettstorfer (23) | 5 | 34 | III | 11 | 100 | 0 | 0 |
| Niekerk( 24) | 12 | 32 | III | 8 | 92 | 8 | 0 |
| Hutson (25) | 19 | 32 | III | 9 | 100 | 0 | 0 |

**Table 3.** Included studies on induced membrane technique.

| Study | Nr. of patients | Mean age (years) | Gustillo-Anderson | Mean bone defect (cm) | Union (%) | Amputation (%) | Infection (%) |
|---|---|---|---|---|---|---|---|
| Christian (26) | 8 | 25 | III | 10 | 100 | 0 | 12 |
| Giotikas (21) | 7 | 37 | III | 6 | 57 | 0 | 43 |
| Morris (27) | 12 | 36 | III | 6 | 42 | 16 | 42 |

was achieved in 42 to 100% of cases, with deep infection rates between 12 and 43% (Table 3).

Our analysis shows that the groups did not differ in mean age (p=0,45), nor in bone defect size (p=0,32). There were significant differences in the primary outcome between DO and IM (union rate 98,3 % vs. 62,9 %) (p<0,001) and also in the secondary outcome, with lower incidence of deep infection in DO group (1,7 % vs. 66,7 %) (p<0,001) (Table 4).

## Discussion

Looking at the literature, we found a considerable evidence gap on the treatment of acute bone loss in grade III open tibia fractures. The current evidence is mostly based on case reports and small case studies. With our strict inclusion and exclusion criteria we were able to find only seven studies in the last 30 years dealing with the topic. We were able to compare

**Table 4.** Number and proportion of individuals in each method that achieved full bone union or experienced infection

| | DO (N=60) | IM (N=27) | Test statistic[a] |
|---|---|---|---|
| **Union rate** | | | **p<0.001** |
| Yes | 59 (98,3 %) | 17 (62,9 %) | |
| No | 1 (1,7 %) | 10 (37,1 %) | |
| **Infection rate** | | | **p<0.001** |
| Yes | 1 (1,7 %) | 9 (33,3 %) | |
| No | 59 (98,3 %) | 18 (66,7 %) | |

Note: [a]Fisher's Exact test; DO = distraction osteogenesis; IM = induced membrane technique.

60 patients in the DO group with 27 patients in the IM group. We assume that might be due to a combination of low incidence with a lack of adherence to clear protocols, which would promote early referral to specialized centers. Open fractures are, in many hospitals, still treated as surgical emergencies. However, the view of urgent treatment (within 6 hours) of high-grade open fractures is outdated (28). Time from injury to the initial debridement procedure is not a significant predictor for complications such as infection, while early referral to a high volume trauma center is (29). A 10 year review on the adherence to British national guidelines (BOA/BAPRAS) has shown high revision rates for soft tissue and bone related complication in 56% of patients referred to tertiary units (30). Late communication and referral, inadequate initial treatment due to lack of experience with this rare pathology and logistic issues were primary reasons for such results. Absence or non-adherence to protocols with late presentations to specialized centers is thus associated with high rates of complications such as nonunion and/or infection. This situation is also mirrored in the literature. Most studies focus on the treatment of bone defects following septic or aseptic nonunion in the lower limb. All the above mentioned factors have so far precluded larger studies and thus high-level evidence on the treatment of acute bone loss in grade III open tibia fractures. Ilizarov distraction osteogenesis technique has stood the test of time and is regarded as established method for the treatment of bone defects following nonunion and bone infection (31). Focusing on the use of this method in the treatment of acute bone defects after high grade open tibia fractures, we found unanimous results. Cumulative results of four studies involving 60 patients declared only one nonunion and one infection. Sen et al (22) used acute limb shortening and sequential limb lengthening at a remote osteotomy site. Union was achieved in all patients, with deep infections occurring in one patient. Acute shortening of the limb enables the surgeon to close the soft tissue defect without complex reconstructive procedures and eliminates problems with union at the docking site. Compared to bone transport techniques, shorter treatment times and decreased rates of complications and secondary procedures can be achieved. However, this method is limited by the amount of acute shortening of the tibia that can be achieved without neurovascular compromise. Acute shortening of up to 6 cm have been described in the literature with low complication rates (32). The other three studies in DO group treated acute bone defects in the tibia using staged bone transport (23-25). Union rates were reported in 100% of cases, except for one case in the study from Niekerk et al (24) where secondary amputation was required after failure of an unsatisfactory reconstruction attempt of a mangled extremity. Sequential reconstruction enables separation of the early phases of flap healing from bone transport. This method is especially useful for larger bone defects (>5 cm), which preclude the use of the acute compression-distraction technique. However, long treatment times and frequent complications, such as pin tract infections (from 5 % to 100%) and joint contractures (rates of knee and ankle joint stiffness ranging from 4% to 100%) remain major drawbacks (15). To address those, conversion to internal fixation (intramedullary nail or plate) has been proposed at the end of the distraction phase. In the study of Koettstorfer et al (23), the authors were able to shorten the time

in the external fixator frame, preserve limb alignment and enable early functional rehabilitation by conversion to internal fixation. However, the incidence of infectious complications using this modification of the original Ilizarov technique remains a major concern.

In 2000, Masquelet introduced a novel, two stage technique for the treatment of bone defects. The initial studies reported high union rates between 90 % and 100% (17,33,34). However, these studies mixed bone defects in the upper and lower extremity following different etiology and clinical scenarios. Regarding the specific biologic environment of the tibia, we were able to find limited evidence on the use of the IM technique in acute post-traumatic bone defects in the tibia. The largest clinical study by Karger et al (35) reports on 84 post-traumatic bone defects, 61 of them in the tibia. Treatment of bone defects was delayed for an average of 8 months, with high percentage of infected cases. Successful bone union was reported in 90% of cases, being more rapid in the upper limb. All 8 described failures occurred in the tibia, 6 of them requiring amputation of the limb. Apard et al (36) reported on 12 post-traumatic bone defects in the tibia treated with the IM technique, 4 following trauma, 1 case of aseptic nonunion and 7 cases of septic nonunion. Bone union was reported in 92% of cases. However, deep infection was seen in 42% of patients. Delayed presentation with established septic or aseptic nonunion and infection in these studies make it difficult to draw conclusions on the use of the induced membrane technique in acute bone defects following high grade open tibia fractures. Our study was designed, through strict inclusion criteria, to focus only on acute cases of traumatic bone loss. In three relevant studies we were able to analyze 27 patients. In 10 patients fractures did not heal and in 9 patients infection occurred. Morris et al (27) used the IM technique in 12 patients with bone defects after an open tibia fracture, finding contradictory results with respect to the original studies. The major complication was deep infection, occurring in 5 patients (42%), two of which proceeded to amputation.

Besides the specific healing environment of the tibia, initial surgery in a smaller unit also showed an increased rate of complications and a greater need for revision surgery. Giotikas et al (21) observed high rates of union failure and frequent septic complications (43%). However, Christian et al (26) treated eight patients with acute bone loss in open tibia fractures with good results. They were able to achieve bony union in all cases and had one case of infection. Comparing results from our selected studies with the original articles on the Masquelet method we see a trend toward worse union and complication rates in the tibial defects. Further research and high-level evidence are needed to determine the indications for IM technique in high grade open tibia fractures.

Following analysis of the data, both outcomes of interest were significantly in favor of DO. Low infection rates as well as high union rate are associated with early soft tissue coverage. The BOA/BAPRAS guidelines (4) recommend covering of soft tissue defects within 5 days following injury, ideally sooner (<72 hours). These recommendations are based on the pioneering work of Godina (37) who observed lower rates of flap failure, infections and other complications in the group with early flap cover (within 72 hours), as compared to groups with delayed (3 days to 3 months) and late (<3 months) soft tissue cover. Although our study was focusing on management of bone loss, we also appreciated importance of soft tissue coverage in these patients. In the study of Sen et al (22), they were able to close all soft tissue defects with (delayed) primary closure by using compression-distraction techniques. Niekerk et al (24) covered soft tissue defects early (within 72 hours post-injury), while Hutson et al (25) reported on an average of 4 debridement procedures before proceeding to soft tissue cover, which was delayed to an average 34 days after injury. The last study in the DO group did not report on the method of soft tissue cover (23). In the IM group, Christian et al (26) postponed soft tissue covering for at least 4 days after injury. In acute cases it was performed with an average 2 weeks delayed, while transferred patients received a flap with an average of 9 weeks delay. Giotikas et al (21) report on soft tissue reconstructive procedures being performed at the time when the bone defect was filled with a cement (PMMA) spacer, which was done on average 5 days (1 to 18 days) after injury. Morris et al (20) did not report on the method of soft tissue cover. These results only underline the methodological heterogenicity of the published studies, thus making it difficult to extract clear clinical recommendations on the treatment of acute bone loss in open tibia fractures.

The limitations of our study prevented us from drawing clear causative conclusions on the results. However, we hypothesize the difference might be due to technical aspects of both methods. While the DO technique is a well-established and refined method of bone defect treatment, many aspects of the Masquelet technique have not yet been defined. Limits in bone defect size, optimal spacer material, role of the adjunctive local antibiotics, optimal second stage timing and fixation method still need to be determined, especially for its use in the lower limb. Another limiting factor of the IM might be the tenuous blood supply of the tibia (38). The latter, combined with devastating high energy mechanisms limits the biologic reserve of the tissue, thus precluding formation of a quality pseudo-membrane and graft incorporation. Failure to revascularize the bone graft thus predisposes the site to infection. On the other hand, distraction histogenesis presents a powerful mechanical stimulus for neo-angiogenesis and might account for the low incidence of septic complications with this method. The IM technique has also been modified with conversion to internal fixation in the second stage. Presence of a metal implant significantly lowers the inoculum of bacteria needed to establish biofilm formation and thus sustain infection. Compared with the DO, where mostly circular external fixators are used, that might again predispose the IM technique to higher infection rates. Many factors influence outcome in both techniques, with the quality of the initial debridement being cited as the most important one (4,29). Patients with this rare devastating injury do benefit from established national protocols with early referral to specialized centers and treatment through a staged ortho-plastic approach

*Limitations*

Limitations of our study come from the small number of relevant articles found in the literature. We were able to compare 60 patients in DO group with 27 patients in IM group. These articles are heterogenic in number of patients, protocols of treatment and timing as well as methods of soft tissue coverage. Another drawback is the fact that in the reviewed articles the authors performed and analyzed just one treatment mode and they did not compare the results of both treatment modalities as they were performing just one or another. Our comparison showed significant differences in both investigated outcomes. The results are, however, preliminary and highlight the need for further research on the treatment of bone loss in the specific healing environment of a high-grade open tibia fracture. Extrapolation of results from mixed upper and lower limb bone defect treatment studies or comparison with bone defects originating from other etiologies might lead to unexpected negative outcomes in face of these devastating injuries.

*Clinical implications*

It was not the wish of the authors to promote one or discard another method of bone defect treatment. We believe that every described technique represents a powerful tool in the surgeon's armamentarium for the treatment of the broad spectrum of patterns and complexities in which bone loss following open tibia fractures presents itself. Treatment methods should be thus regarded as complementary. In practice, IM technique has a place in the treatment of smaller (<6 cm) defects, especially in the metaphyseal area. Larger metaphyseal defects and shaft defects, however, call mostly upon treatment with DO technique following the Ilizarov method. For smaller shaft defects (<6 cm) the acute compression-distraction technique enables an easier closure of the soft tissue defect. Larger (>6 cm) defects, which cannot be safely shortened, can be effectively treated with segmental bone transport. Because of complexity of pathology combining soft tissue and bone related problems interdisciplinary approach (ortho-plastic) is the prerequisite for satisfactory result.

We would like to emphasize the preliminary nature of our results and the urgent need for future multicentric, prospective, randomized clinical trials to investigate and guide the treatment of bone defects in high grade tibia fractures.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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