Role of the Ilizarov non-free bone plasty in the management of long bone defects and nonunion: Problems solved and unsolved

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**Abstract**

**BACKGROUND**

Ilizarov non-free bone plasty is a method of distraction osteogenesis using the Ilizarov apparatus for external fixation which originated in Russia and was disseminated across the world. It has been used in long bone defect and nonunion management along with free vascularized grafting and induced membrane technique. However, the shortcomings and problems of these methods still remain the issues which restrict their overall use.

**AIM**

To study the recent available literature on the role of Ilizarov non-free bone plasty in long bone defect and nonunion management, its problems and the solutions to these problems in order to achieve better treatment outcomes.

**METHODS**

Three databases (PubMed, Scopus, and Web of Science) were searched for literature sources on distraction osteogenesis, free vascularized grafting and induced membrane technique used in long bone defect and nonunion treatment within a five-year period (2015-2019). Full-text clinical articles in the English language were selected for analysis only if they contained treatment results, complications and described large patient samples (not less than ten cases for congenital, post-tumor resection cases or rare conditions, and more than 20 cases for the rest). Case reports were excluded.

**RESULTS**

Fifty full-text articles and reviews on distraction osteogenesis were chosen. Thirty-five clinical studies containing large series of patients treated with this method and problems with its outcome were analyzed. It was found that
Distraction osteogenesis techniques provide treatment for segmental bone defects and nonunion of the lower extremity in many clinical situations, especially in complex problems. The Ilizarov techniques treat the triad of problems simultaneously (bone loss, soft-tissue loss and infection). Management of tibial defects mostly utilizes the Ilizarov circular fixator. Monolateral fixators are preferable in the femur. The use of a ring fixator is recommended in patients with an infected tibial bone gap of more than 6 cm. High rates of successful treatment were reported by the authors that ranged from 77% to 100% and depended on the pathology and the type of Ilizarov technique used. Hybrid fixation and autogenous grafting are the most applicable solutions to avoid after-frame regenerate fracture or deformity and docking site nonunion.

CONCLUSION

The role of Ilizarov non-free bone plasty has not lost its significance in the treatment of segmental bone defects despite the shortcomings and treatment problems encountered.

Key words: Bone defect; Ilizarov method; Distraction osteogenesis; Bone transport; Bone nonunion; Free vascularized grafts; Induced membrane technique complication

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INTRODUCTION

Segmental long bone defects resulting from acute trauma, post-traumatic sequelae, resection due to tumor or bone infection, nonunion or congenital deficiencies lead to significant negative consequences or disability if not managed properly with surgical interventions involving the use of bone grafting and fixation systems\(^1\)\(^2\)\(^3\). The universally acknowledged surgical techniques such as autogenous bone grafts for small defects (< 5 cm), free vascularized grafts (FVG), distraction osteogenesis (DO) and induced membrane technique (IMT) for larger defects are contemporary strategies of reconstruction\(^4\)\(^5\)\(^6\). These techniques are based on autogenous grafting, either free or non-free, as long as the autogenous bone possesses osteoinductive, osteoconductive and osteogenic properties to induce bone healing. Moreover, the techniques which preserve the vascularity of the graft with the surrounding tissues or generate new vessels would be most effective in promoting bone remodeling. Therefore, FVG, DO and IMT have become the main methods in bone defect management.

DO was developed by G.A. Ilizarov for a number of orthopedic diseases and injuries and was initially realized with the author’s external apparatus\(^6\)\(^7\)\(^8\). Nowadays, the regeneration philosophy of the Ilizarov method is a cornerstone of contemporary bone lengthening and reconstruction surgery and is implemented with a number of designed devices\(^8\). The author of bone fragment transport for segmental long-bone defect management first reported on the technique in 1969\(^5\)\(^7\). Since the 1990s, it has become a vital method for compensation of bone loss and infected nonunion across the world, and has been named the Ilizarov non-free bone plasty\(^8\). Bone nonunion
and defects still remain the conditions for which the Ilizarov method has gained most popularity.

Vascularized free grafting and the IMT were reported by their authors in 1975 and 2000, respectively. The first had been used for the reconstruction of many types of bone defects until Ilizarov bone transport (IBT) became popular in the 1990s and IMT later demonstrated successful outcomes in long bone defect management. Management of segmental long bone defects is one of the challenges of contemporary orthopedics due to the severity of high-energy trauma, traffic accidents and military activities that are so characteristic of life in the modern world. It is dictated by the defect size, patient comorbidities, soft-tissue condition, local vascularity, nonunion type and possible infection in the defect. Choosing between the three major options for large-scale defects depends on clinical factors, orthopedic surgeon training and preferences, as well as on the availability of the instrumentation needed for successful implementation of the methods.

We aimed to study the recent available literature on the role of Ilizarov non-free bone plasty in the management of bone defects, the problems to solve and future prospective trends which would enable better treatment outcomes.

MATERIALS AND METHODS

Three databases (PubMed, Scopus, and Web of Science) were screened for recent literature on long bone defect and nonunion treatment within a five-year period (2015-2019) using the key words: Bone defect, large bone defect, nonunion, Ilizarov bone transport (BT), Masquelet (induced membrane) technique, FVG, and free vascularized fibular graft (FVFG). The titles and abstracts were reviewed while screening, potentially relevant articles were retrieved and assessed for inclusion. Table 1 presents the findings of search engines in the databases indicated above. In total, 232 articles were assessed for eligibility according to the abstracts. The selected 65 full-text clinical articles and reviews available in English were based on the inclusion and exclusion criteria.

Inclusion criteria for literature sources in the study

Full-text articles in English: (1) Reviews on the management of segmental long bone defects and nonunion; (2) Clinical studies stating that patients with segmental bone defects and nonunion were treated using DO, IMT or FVFG. Clinical articles were chosen if they contained treatment results, complications after treatment and described large patient samples (not less than ten cases for congenital, post-tumor resection cases or rare conditions such as subtotal defects, and more than 20 cases for the remainder). Major adverse events were considered problems if they involved operative procedures to correct the treatment failure or its sequelae; and (3) Original articles that compared DO with the methods of IMT or FVFG used for long bone defect management and contained quantitative data on the evaluation of the methods.

Exclusion criteria for literature sources in the study

Exclusion criteria: (1) Case reports, pilot and preliminary studies; and (2) Duplicate studies.

RESULTS

The search showed that there are numerous studies on long bone defect and nonunion management with DO and IMT published in the period under survey while the use of FVFG is less reported (Table 1). Reports on FVFG and DO were mainly clinical studies, while there were a number of technical descriptions, reviews and experimental research on the impact of IMT due to the fact that the technique is relatively new. IMT was described technically and reviewed in 18 articles while DO and FVFG were described only in seven and five reviews, respectively. IMT was investigated experimentally in 24 studies while DO was investigated in three and FVFG in none. The full texts of a total of 65 articles using these three techniques were reviewed, including 35 clinical reports on the use of DO or its comparison with two other methods, which described large series of patients and were published in the recent five-year period (2015-2019) (Table 1). Merits, shortcoming and problems of the Ilizarov non-free bone plasty, IMT and FVFG are summarized in Table 2. The summary shows that the main severe adverse events in the management of bone defects that impede the success of these treatment methods are common: Failure to achieve union and graft incompleteness.
Table 1  Number of five-year literature sources found and studied

|                          | Total number of sources found / articles on bone defects | Number of selected sources, including congenital conditions | Number of articles per year / number of reviews / basic research articles | Number of full text articles included in this review |
|--------------------------|----------------------------------------------------------|------------------------------------------------------------|-----------------------------------------------------------------------|---------------------------------------------------|
| Distraction osteogenesis techniques |                                                                         |                                                          |                                                                       |                                                   |
| PubMed                   | 155/116                                                  | 108                                                       | 2015: 18/1/1                                                          | 50                                                |
| Scopus                   | 169/136                                                  |                                                           | 2016: 33/2/0                                                          |                                                   |
| Web of Science           | 144/105                                                  |                                                           | 2017: 23 /2/0                                                         |                                                   |
|                          |                                                          |                                                           | 2018: 17/1/2                                                          |                                                   |
|                          |                                                          |                                                           | 2019: 17/1/0                                                          |                                                   |
| Induced membrane technique |                                                                         |                                                          |                                                                       |                                                   |
| PubMed, Scopus, Web of Science | 121/104                                                | 87                                                       | 2015: 8/2/2                                                           | 10                                                |
|                          |                                                          |                                                           | 2016: 16/5/4                                                          |                                                   |
|                          |                                                          |                                                           | 2017: 24 /7/4                                                         |                                                   |
|                          |                                                          |                                                           | 2018: 17/2/10                                                         |                                                   |
|                          |                                                          |                                                           | 2019: 22/2/4                                                          |                                                   |
| Free vascularized fibular graft |                                                                         |                                                          |                                                                       |                                                   |
| PubMed, Scopus, Web of Science | 138/52                                                 | 37                                                       | 2015: 5/0/0                                                           | 5                                                 |
|                          |                                                          |                                                           | 2016: 7/2/0                                                           |                                                   |
|                          |                                                          |                                                           | 2017: 11/2/0                                                          |                                                   |
|                          |                                                          |                                                           | 2018: 8/0/0                                                           |                                                   |
|                          |                                                          |                                                           | 2019: 6/1/0                                                           |                                                   |

Out of the total number of articles on DO found, only nine were devoted to bone defects in the upper extremity while infected and aseptic post-traumatic defects of the lower limbs were reported in more than 70% of the articles (Table 3), infected tibia being the most frequent pathology (Table 4). The clinical studies using DO to treat segmental long bone defects that included the largest series of patients and the problems of their treatment are presented in Table 4. Most patient series were retrospective and used the ASAMI scoring system for assessment of bone and functional results and Paley’s classification of complications. High rates of successful outcomes were reported by the authors that ranged from 77% to 100% and depended on the pathology and the type of Ilizarov method protocols used. It was not possible to demonstrate quantitatively the outcome success rates of all the studies included due to their heterogeneity and ambiguity. Therefore, primary and secondary treatment failures reported in the studies are presented in Table 4. Table 4 also indicates the country the authors belong to in order to show where the DO method was used as the samples of patients are numerous. Several comparative studies of the methods used in bone defect and nonunion management were identified by the search and their conclusions are presented in Table 5.

**DISCUSSION**

The Ilizarov method which involves the use of a circular external fixator is one of the most widely used techniques of bone reconstruction in bone nonunion and defects due to physiological bone growth induced by distraction, tension stress and axial forces enabling adequate new bone tissue distribution providing bone gap bridging and union\[14-45\]. Four Ilizarov protocols are used for bone nonunion and defect management\[20\]. Two physical phenomena can be executed for bone fragments, compression and distraction, for either: (1) Approximation of fragments for union by compression and subsequent distraction through osteotomy if required; or (2) BT of an osteotomized fragment for gap filling with new bone and compression at the docking site to achieve bone union\[20,38\]. The bone tissue thus regenerated for lengthening and bone gap coverage can be charged as almost a perfect type of grafting as a vascularized bone callus is formed inside the surrounding soft tissues which remodels into mature bone tissue over time\[11\]. The Ilizarov techniques for bone nonunion and defects stabilize the limb, lead to bone union and at the same time address malalignment, leg length discrepancy and soft-tissue problems\[15\]. They yield
Table 2  Summary of merits and problems of the methods used for nonunion and bone defect management

| Merits | Shortcomings | Problems or adverse events that are considered failures or may cause it |
|--------|--------------|---------------------------------------------------------------|
| **Ilizarov non-free bone plasty** | | |
| (1) High-quality, biologically normal new bone tissue of massive proportions is generated through distraction osteogenesis; (2) The regenerated bone has good vascularity; (3) The limb is well stabilized with the circular fixator leading to union at the same time; (4) Coexistent bone issues such as deformity correction, equalization of leg length can be addressed simultaneously and effectively; (5) There is no risk of rejection or necrosis of the non-free graft; (6) Soft tissue healing, free tissue transfer after frame placement is possible; (7) The risk of deep infection is low; (8) The method is suitable for both infected and non-infected cases; (9) It is practical in financially constrained cohorts of patients in medical centers; (10) Full weight-bearing is early after the operation; (11) There are no problems of the donor site; and (12) Stimulation with osteoprogenitor cells is possible | (1) Implementation needs trained professionals; (2) The complexity of the Ilizarov apparatus placement necessitates its re-arrangements during treatment; (3) Scarring associated with the wires and half-pins as they progress down occurs; (4) Pin-tract infection is frequent; (5) Wearing time of the circular frame is long; (6) Breakage of wires and pins that may result in frame instability; (7) Patients have physical stress due to pain, inconvenience of sleep and doing hygiene, negative impact on the patients’ mental health; (8) There is some risk of joint contractures and the necessity of doing exercise therapy constantly; (9) It is difficult to mount the apparatus in the areas with a large soft-tissue envelope such as the thigh; (10) The method implies frequent postoperative manipulations (change of dressings, radiographic monitoring of bone formation); (11) Bone grafting at the docking site is mostly required; and (12) The cost of the circular fixator ranges a lot and depends upon the country | (1) Frequent pin-tract infection may lead to wire-tract osteomyelitis; (2) Fractures of the regenerate upon frame removal in massive defects are possible; (3) Deformity of the regenerated bone within 3-4 mo upon frame removal may develop; (4) Osteogenesis failure or incomplete osteogenesis due to technical mistakes or low bone regeneration potential may occur; and (5) Failure of union at the docking site may happen |
| **Induced membrane technique** | | |
| (1) Extensive segmental defects may be bridged; (2) The induced membrane favours osteogenesis as it is vascularized, bioactive and protects the graft from resorption; (3) Suitable for both infected and non-infected cases; (4) Antibiotics may be impregnated locally into the spacer; (5) Stimulation with osteoprogenitor cells during the second stage is possible; and (6) Weight-bearing is possible as bone fragments are stabilized with external or internal fixators | (1) Long period of treatment and several stages of the surgical procedures are necessary; (2) A considerable amount of autogenous graft is needed to fill the bone defect; (3) The average time to bone union is rather long; (4) Intraosseous blood supply is not adequate; (5) Incomplete remodeling of massive grafts is frequent; (6) Leg length discrepancies in large defects cannot be corrected completely due to restricted graft material; (7) Possibility to address gross deformity and leg length discrepancy is limited; and (8) Gross scarring is inevitable | (1) Necrosis and rejection of grafts, especially when allograft is added for graft volume; (2) Pathological fractures in the defect area may happen; (3) An Internal fixator may break or become instable; (4) Re-grafting due to failure of primary graft healing occurs; and (5) Coexistent bone issues such as gross deformity and leg length discrepancy need to be addressed separately following treatment |
| **Free vascularized fibular graft** | | |
| (1) Defect may be covered with one procedure; (2) Bone union is achieved within the regular terms for fracture treatment; (3) Primary postresection defect grafting due to tumors is effective; and (4) Weight-bearing is possible as bone fragments are stabilized with external or internal fixators | (1) Surgical intervention is executed with two operative procedures and is rather time-consuming; (2) It requires special training as microsurgery is used; (3) It is rather expensive as needs special medication and equipment; (4) Material for grafting is limited; (5) There are problems of donor site, such as pain and ankle joint problems; (6) Extensive scars are inevitable; (7) Graft remodeling may be incomplete due to hemocirculation disorders in a large graft; (8) Limb bracing is required until adequate hypertrophy of the graft; (9) Valgus deformity may develop at the donor site after harvesting the fibula; (10) The procedure is problematic after previous surgeries and if soft tissues are damaged by scars; (11) Gross scarring is inevitable; and (12) Possibility to address gross deformity and leg length discrepancy is limited | (1) Gross vascular problems (thrombosis) may develop and may lead to necrosis, graft rejection and infection; (2) Pathological fractures of massive grafts may develop; (3) Internal fixator break or instability may occur; (4) Failure of grafting due to nonunion is possible; and (5) Coexistent bone issues such as gross deformity correction and equalization of leg length need to be addressed separately following treatment |

Satisfactory outcomes using limited resources for both aseptic and infected bone defects and nonunion, but should be implemented in medical centers with trained personnel. Moreover, bone distraction and compression may be produced with a number of external and internal devices that have been developed for this purpose and are currently available on the market. Therefore, the DO procedure has been universally accepted by the orthopedic community throughout the world. However, the shortcomings and problems of the method still remain the issues which restrict its overall use (Table 2). Poor regeneration that may occur due to different causes, infection and poor condition of soft tissues in the defect area may result in various stages to fill in the defect, especially if it is massive, or has previously failed. There is a controversial view on regular bone grafting at the docking site if BT is implemented. Most authors currently recommend routine docking site revisions.
Table 3  Web of Science + Scopus search results for the period 2015-2019 (key words: ilizarov method, bone defects)

| Web of Science + Scopus search | Number of sources found | 100% |
|-------------------------------|-------------------------|------|
| Infected defects              | 73                      | 43.2%|
| Post-traumatic defects        | 59                      | 34.9%|
| Acute trauma                  | 13                      | 7.7% |
| Bone tumors                   | 8                       | 4.7% |
| Congenital diseases           | 7                       | 4.1% |
| Other                         | 6                       | 3.6% |
| Animal model, basic research  | 3                       | 1.8% |

during BT and use supportive bone grafting\(^{[43]}\). The authors of the clinical studies conclude that BT is a safe option for treatment of aseptic and infected nonunion of the tibia and femur despite the complications encountered. The average bone and functional scores significantly improve within two years after the end of treatment\(^{[47]}\). The authors underline that it is essential to explain the complications to the patients and their relatives before the application of external fixators to increase their compliance with a long and highly emotional course of treatment due to severe pain, mental, and physical stress\(^{[47,48]}\).

Table 4 shows that DO is a solution for segmental long bone defects and nonunion in a number of conditions caused by acute injuries, trauma sequelae, bone infection and bone tumor resection in the tibia and femur, but infected tibia is the segment in which DO and the Ilizarov apparatus have been used extensively. According to the studies, the Ilizarov BT and acute shortening and then lengthening techniques remain reliable methods to repair bone defects\(^{[16,18,29]}\). The following are some of the main conclusions and recommendations the authors focus on: (1) DO is a good method that can treat the triad of problems simultaneously (bone loss, soft-tissue loss and infection) without the need for major plastic surgery\(^{[21]}\); (2) The Ilizarov fixator is better suited for infected nonunion of the tibia because it can provide a stable mechanical environment, BT, correction of deformities, and enables weight bearing\(^{[19]}\). The current findings suggest that the Ilizarov methods in the treatment of infected nonunion of the tibia and femur result in satisfactory outcomes. Radical debridement is the key step to control bone infection\(^{[42]}\); (3) The use of a ring fixator is recommended in patients with an infected tibial bone gap of more than 6 cm. Patients with a bone gap up to 6 cm can be managed with either a ring or rail fixator\(^{[24,30]}\); (4) Antibiotic-impregnated spacers were used in open tibial trauma and reduced the external fixation index considerably\(^{[25,28]}\); (5) Patients treated with combined fixation spent less time in the external fixator. The frequency of adverse events and ability to restore limb length was not different to the group treated with the external fixator only\(^{[39]}\); (6) Acute shortening followed by distraction histogenesis is a safe method for acute treatment of open tibial fractures with bone and soft-tissue loss\(^{[51]}\). The technique is limited by the defect size and the condition of the surrounding soft tissues. The technique of acute shortening and re-lengthening was not recommended in post-gunshot defects\(^{[9]}\); and (7) DO is a method an orthopedic surgeon with limited conditions can use, though it has a long treatment period\(^{[26]}\).

Tables 2 and 4 reveal that docking site nonunion and after-frame regenerate fracture or deformity are the major causes of DO failures\(^{[3]}\). Therefore, orthopedic surgeons and researchers search for the ways to improve the DO procedure for segmental bone defect and nonunion management. They report on a number of solutions to overcome the problems and gain better results. The following is a summary of these solutions according to the literature under our investigation.

Solutions to the shortcomings and problems within the DO method or combining it with other methods as offered in the studies reviewed

The following are solutions to the shortcomings and problems within the DO method or combining it with other methods as offered in the studies reviewed: (1) Accurate study of the regenerate with radiographic methods and clinical tests to exclude premature removal of the external fixator and potential treatment failure\(^{[8]}\); (2) The accordion technique combined with minimally invasive percutaneous decortications to stimulate regeneration\(^{[49]}\); (3) Compaction of the problematic regenerate to rescue DO and achieve union\(^{[9]}\); (4) Bifocal or multifocal BT to reduce BT time, time in the frame, and total treatment time in one stage\(^{[8,17,19,23,30,31]}\); (5) Acute shortening and
| Ref.                      | Number of patients | Fixation type / bone union rate | Problems requiring reoperations after frame removal or failures |
|--------------------------|--------------------|---------------------------------|----------------------------------------------------------------|
| **Defects of tibia**     |                    |                                 |                                                                |
| Kinik et al[14], 2019, Turkey | 30                | Ilizarov/96.66%                | 1 nonunion, 1 refracture of the regenerate, 1 late deformity of the regenerate |
| Fahad et al[15], 2019, Pakistan | 51            | Ilizarov/96%                   | 2 nonunions (1 amputation due to sepsis), 2 reinfections eradicated during main treatment |
| Thakeb et al[16], 2019, Egypt | 50                | Ilizarov/100%                  | 4 refractures                                                   |
| Catagni et al[17], 2019, Italy | 86            | Ilizarov/100%                  |                                                                |
| Wu et al[18], 2018, China | 40                | Ilizarov/100%                  |                                                                |
| Yihamhu et al[19], 2017, China | 129            | Ilizarov + Orthofix/100%       |                                                                |
| McNally et al[20], 2017, United Kingdom | 79        | Ilizarov/86.1%                 | 2 refractures, recurrence of infection, 6 after-frame reoperations |
| El-Alfy et al[21], 2017, Egypt | 28            | Ilizarov/100%                  |                                                                |
| Meleppuram et al[22], 2016, India | 42        | Ilizarov/100%                  |                                                                |
| Abuomira et al[23], 2016, Italy | 55            | Ilizarov + Taylor spatial frame/89% |                                                                |
| Rehilla et al[24], 2016, India | 70            | Ilizarov vs rail fixator/77% vs 80% of primary union | The rail fixator was converted to a ring fixator in two patients, 2 after-frame refractures |
| Sadek et al[25], 2016, Egypt | 30            | Ilizarov vs two stage internal osteosynthesis | 1 nonunion in internal group |
| Bernstein et al[26], 2015, United States | 30          | Ilizarov/77%                   | -                                                              |
| Peng et al[27], 2015, China | 58                | Ilizarov/100%                  | 4 equinovarus deformities, 1 infection recurrence at the docking site |
| **Defects due to acute fractures** |                    |                                 |                                                                |
| van Niekerk et al[28], 2017, South Africa | 24       | Ilizarov/91.7%                 | 2 amputations, 1 persistent deep infection in a HIV-positive patient, mangled extremity |
| Salih et al[29], 2018, United Kingdom | 31        | Ilizarov/96%                   | 4 after-frame refractures, 2 regenerate deformities after frame, 1 stiff non-union |
| Fuermitz et al[30], 2016, Germany | 25          | Ilizarov or hybrid/92%         | 2 amputations due to comorbidities |
| Azzam et al[31], 2016, Egypt | 30            | Ilizarov/93.3%                 | 1 post-frame fracture                                           |
| Thakeb et al[32], 2016, Egypt | 161           | Ilizarov                      | 1 failure                                                      |
| Ajmera et al[33], 2015, India | 30            | Monolateral/93%                | 2 nonunions                                                    |
| **Large-scale defects requiring tibilization of the fibula** |                    |                                 |                                                                |
| Meselhy et al[34], 2018, Egypt | 141           | Ilizarov/100%                  | 1 supracondylar femoral fracture while removing frame |
| Zaman et al[35], 2017, Pakistan | 121           | Ilizarov/100%                  |                                                                |
| **Defect of femur**      |                    |                                 |                                                                |
| Bakhsh et al[36], 2019, Pakistan | 50           | Ilizarov/98%                   | 2 nonunions, 1 re fracture                                       |
| Zhang et al[37], 2017, China | 41          | Monolateral/98%                | 1 re fracture, 5 cases of docking site nonunion                 |
| Mudiganty et al[38], 2017, India | 22          | Monolateral/rail/97.5%         | 5 delayed union with autograft                                 |
| Agrawal et al[39], 2016, India | 30          | Monorail/100%                  |                                                                |
| **Defects of femur and tibia** |                    |                                 |                                                                |
| Ariyawatkul et al[40], 2019, Thailand | 171       | Ilizarov/94%                   | 1 nonunion                                                     |
| Lowenberg et al[41], 2015, United States | 127       | Ilizarov/96%                   | 3 amputations due to comorbidities |
| Yin et al[42], 2015, China | 110            | Ilizarov for tibia, monolateral for femur/100% | 2 after-frame refractures                                       |
| **Tumor- resection defects** |                    |                                 |                                                                |
| Eralp et al[43], 2016 (Turkey, United States, Egypt) | 20       | Various types of external fixators/100% | 1 knee arthrodesis                                             |
| Wang et al[44], 2019, China | 101           | Monolateral/90%                | 1 amputation at long-term due to cancer relapse                 |
Smaller groups for rare conditions treated with the Ilizarov method (severely comminuted fractures, pan tibial defects, large periarticular defects). HIV: Human immunodeficiency virus.

The latter allows for artifact-free visualization on magnetic resonance imaging, which is important for monitoring the treatment response. However, besides its high cost, it was found clinically that the nail performs poorly in long-bone surgery. The latter allows for artifact-free visualization on magnetic resonance imaging, which is important for monitoring the treatment response. However, besides its high cost, it is evident that bone marrow derived autologous mesenchymal stem cells as an add-on therapy to the DO procedure improvement[84]; and (13) Teriparatide treatment during the consolidation phase to stimulate bone formation[85].

Current clinical tendencies in segmental bone defects management with the method of DO

It is evident that significant advancements such as internal cable transport, multifocal transport, and combined techniques with internal fixation have helped increase the effectiveness of the ring fixator by minimizing many of its drawbacks. However, the main problems in the management of bone defects and nonunion (failure to achieve docking site union and bone graft incompleteness) impede the DO success irrespective of the fixator used and need to be solved with osteogenesis stimulation and perfection of bone fixators.

Advances in bone fixation techniques

We have come to a conclusion that it is the combination of external and internal technologies that is the main clinical tendency in the use of DO for long bone defects in the tibia and monolateral fixation in the femur[14,24,26,30,43]. It seems to be logical as it solves some of the external-fixator associated shortcomings, mainly the long-term wearing of ring external devices that worsen patients’ quality of life and a long rehabilitation time[86]. Thus, the combined techniques of BT over nail (BT over nail and BT) and then nailing have recently been used for reconstruction of post-traumatic and post-resection defects in the lower limbs, including the infected nonunion and defects once the latter have been debrided thoroughly[87]. Their main merits are: (1) Reduction of external fixation time; (2) Less knee stiffness and opportunity to do more exercise therapy for joints after frame removal; (3) Comfort after frame removal; (4) Alignment of the regenerate on the nail; and (5) Exclusion of regenerate deformities and fractures. However, the regeneration features and complication rates were similar and not statistically different[88]. Closed intramedullary nailing (IMN) was found to be an effective and easy solution for cases without pin-tract infection to manage the nonunion problem of the docking site[89]. Moreover, the risks of pin-tract and deep infection as well as pain due to stretching and nail breaking risks remain[90].

Some more options of a combined technique have been reported, such as a lengthening nail for transport and a locking plate for docking and a carbon-fiber IMN, including an antibiotic-coated carbon fiber IMN nail, specifically designed for femurs[91,25]. The latter allows for artifact-free visualization on magnetic resonance imaging, which is important for monitoring the treatment response. However, besides its high cost, it was found clinically that the nail performs poorly in long-bone surgery and cannot be added to external fixation instead of a titanium nail even for combination. Nevertheless, Ilizarov’s fundamental principles must still be followed even with internal devices. Internal telescopic lengthening nails show similar bone results and significantly improve patients’ quality of life, as well as exclude pin-track infection problems. It is evident that IMN fixation alone would be much more comfortable than the combined techniques[84]. Recently, new IMNs have been investigated to provide a one-stage alternative to external fixators for reliable DO in defect management. Lately, some reports on their designs supplied with clinical cases involving the tibia and femur have been made by German researchers[84]. The system is called a cylindrical
Table 5  Comparative studies of the methods in the period 2015-2019

| Ref.                          | Number of patients | Method, segments, fixator                                      | Complications and problems requiring operations after frame removal or failures                                                                 | Recommendations to solve the problems (conclusions)                                                                 |
|-------------------------------|--------------------|----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Wen et al[3], 2019, China     | 317                | IMT (106), DO (132), FVFG (79), post-traumatic long bones, monolateral, ring fixators, nails, plates                  | Major complications: (1) IMT: Hardware failure (3 cases), joint ankylosis or fusion (6 cases), > 3 cm LLD (5 cases), clubfoot or dropping foot (3 cases), and residual deformity requiring secondary procedures (4 cases); (2) DO: Deep infection (1 case), joint ankylosis or fusion (8 cases), > 3 cm LLD (3 cases), clubfoot or dropping foot (6 cases), and residual deformity requiring secondary procedures (2 cases); (3) FVFG: Hardware failure and/or refracture (7 cases), nonunion (5 cases), joint ankylosis or fusion (6 cases), > 3 cm LLD (3 cases), and residual deformity requiring secondary procedures (3 cases); and (4) Complication rates were 22.6%, 25.8%, and 26.6% (P > 0.05), respectively. | The methods compared resulted in equivalent long-term outcomes. Overall complication rates were analogous among the three methods. A circular external fixator and intramedullary nail provide better stability than a monolateral external fixator and locking plates, which may benefit early partial weight bearing, thus stimulating consolidation. An approach worth exploring is to cross over from external to internal fixation in step 2 in patients treated with IMT. Special attention should be paid to alignment, external fixator stability, and care of all foot and ankle joints. |
| Tong et al[75], 2017, China    | 39                 | IMT (20), IBT (19), posttraumatic osteomyelitis, tibia, femur                                                  | The bone outcomes were similar between groups [excellent (5 vs 7), good (10 vs 9), fair (4 vs 2) and poor (1 vs 1)]. IMT group showed better functional outcomes than IBT group. | Both IBT and IMT lead to satisfactory bone results following posttraumatic osteomyelitis. IMT had better functional results, especially in femoral cases. IBT should be preferred in cases of limb deformity. IMT may be a better choice in cases of perarticular bone defects. |
| Abdelkhalek et al[82], 2016,  | 24                 | IBT (13), FG (free grafting, 11), tibial defects                                                               | 1 refracture at the regenerate site in IBM group after removal of the external fixator, 1 stress fracture in FG group. Rates of poor results: 7.6%, 9.1% respectively. | Segmental tibial defects can be effectively treated with both methods. The FG method provides satisfactory results and early removal of the external fixator, but its limitation is severe infection and LLD. Also, it requires a long duration of limb bracing until adequate hypertrophy of the graft. IBT has the advantages of early weight bearing, treatment of postinfection bone defect and LLD in a one-stage surgery but a long external fixation time. |
| Borzunov et al[78], 2019, Russia| 13                | IMT + DO (6) vs DO (7), congenital pseudarthrosis of the tibia                                                   | 1 nonunion in IMT + DO but no refractures within a year, 29% after-frame refractures in DO group. | The combined use of non-free Ilizarov bone grafting according to Ilizarov and Masquelet technology achieves bone fusion of congenital pseudarthrosis and disease-free course of the condition within a year follow-up. |

LLD: Leg length discrepancy; IMT: Induced membrane technique; DO: Distraction osteogenesis; IBT: Ilizarov bone transport; FVFG: Free vascularized fibular graft; FG: Fibular graft.
It was proposed to combine the two biological effects, those of DO and IMT, for signs of osteogenic differentiation confirmed by expression of osteopontin. Therefore, the layer is structured with low-differentiated connective tissue cells manifesting the spacer was called a “neoperiosteum” in the other basic research study. Growth factor, BMP-2 and transforming growth factor-β1. This membrane on the tissue, which secretes several growth factors, including the vascular endothelial growth factor to promote osteogenesis. It was discovered that the mature induced membrane matured between the 4th and 6th week and secreted that the induced membrane matured between the 4th and 6th week and secreted growth factors to promote osteogenesis. It was revealed recently been thoroughly investigated to explain the phenomena[77,78]. It is apparent that the role of the induced membrane in promoting bone formation has been under investigation but have not been used clinically yet due to unanswered concerns regarding clinical safety of the long-term effect of nanomaterials on human health. Tissue engineering and cell-based therapies have not found their place in long bone defect management yet as was expected by previous reviews[2]. The issue necessitates much advancement in stem cell biology, novel biomaterials, and 3D bioprinting. Therefore, the comprehension of the merits, shortcomings and adverse events of the established methods of DO, IMT and FVFG as well as proper understanding of the recent practice in the reconstruction of large segmental bone defects may guide the clinician towards the right choice (Table 2).

Our search for recent literature confirmed an increasing popularity, larger series of patients treated with IMT and more reports on its results in segmental bone defects[69,70,71,72]. Recently, IMT has been widely used for septic, traumatic, neoplastic or congenital bone defects in adults and children[2,70-73]. The pearls and tricks of the technique were explained by its author and followers in an illustrative way[3]. Although some authors find this type of reconstruction rapid and safe, gross problems are not excluded either (Table 2). Others point out that although it is a simple and straightforward procedure, the total time required for growth and maturation of the graft is similar to DO and FVFG[5,9]. The polymethylmethacrylate spacer used to induce membrane is not degradable and needs to be removed surgically with a rigorous technique during cement sleeving followed by grafting and stabilization of the defect to prevent nonunion with the bone fixation means available. The main complications are stabilization loosening and resorption of the graft which need reoperations that are gross procedures. It was proposed that a circular Ilizarov-like external fixator that is able to apply compressive stresses and prevents shear stresses is more favorable for IMT reconstruction than a monolateral external fixator[69]. Both Ilizarov BT and IMT lead to satisfactory bone results in the treatment of segmental lower extremity bone defects but several authors revealed better functional results with IMT, especially in femoral cases and periarticular bone defects, and conclude that BT should be preferred in cases of limb deformity[69]. In pediatrics, BT and IMT may both be also used for post-tumor reconstructions but there are constraints related to chemotherapy and tumor recurrence[69,70]. Better rates of success are expected in aseptic and septic nonunions with the use of this technique and diamond concept[3].

The reconstruction procedure with IMT first induces a membrane and then promotes osteointegration and remodeling of the graft as well as osteogenesis that was proven on animal models and a human induced membrane study[71]. It is apparent that the role of the induced membrane in promoting bone formation has recently been thoroughly investigated to explain the phenomena[77,78]. It was revealed that the induced membrane matured between the 4th and the 6th week and secreted growth factors to promote osteogenesis. It was discovered that the mature induced membrane and periosteum had similar structures and abilities to promote osteogenesis of mesenchymal stem cells but the induced membrane was found to be thicker than the periosteum and characterized by maturing vascularized fibrous tissue, which secretes several growth factors, including the vascular endothelial growth factor, BMP-2 and transforming growth factor-β1. This membrane on the spacer was called a “neoperiosteum” in the other basic research study[78]. Its inner layer is structured with low-differentiated connective tissue cells manifesting the signs of osteogenic differentiation confirmed by expression of osteopontin. Therefore, it was proposed to combine the two biological effects, those of DO and IMT, for...
treating congenital pseudarthrosis of the tibia, as both methods promote vascularized
new bone formation. Congenital anomalies, including congenital pseudarthrosis of
the tibia, treated using IMT have promising results[70,78].

Vascularized free grafting has been the workhorse for reconstruction of many kinds
of bone defects, including massive post-resection and infected defects[9,79-81]. Being
blood supplied, these grafts have high success rates in bone reconstruction and
accelerate the repair process at the injury site. However, FVFG in the lower limbs and
mainly in the tibia should be well protected with internal or external fixation and
bracing during the first year to undergo remodeling. External fixator frames are
advocated for this purpose nowadays to provide load-sharing and mechanical
alignment to exclude a stress fracture. Best results were achieved in the management
of upper extremity defects where the vascularized grafts unite with the recipient bone
in the period which is close to the average fracture consolidation terms in upper
extremity and where the DO procedure would be very complex[80]. However, the
FVFG procedure is technically difficult, involves microsurgical equipment and skilled
microsurgeons.

The application of the three techniques was thoroughly reviewed in numerous
literature and clinical reports (Table 1). Several authors demonstrated sufficient
literature verification of the merits and shortcomings of the methods in their
reviews[1-3,60,81]. Moreover, there were clinical studies that compared the contemporary
techniques of segmental bone defect management (Table 5)[75,78,82]. However, due to
few systemic reviews and comparative studies between different surgical methods,
the orthopedist should choose the appropriate treatment according to particular
situations, types of bone nonunion or defect, being guided by his/her skills and
economic issues.

Main conclusions of the literature review
DO with circular frames (Ilizarov techniques) remains particularly useful for complex
problems in the tibia while monolateral external fixators are preferably applied in the
femur. Free vascularized fibular grafts have recently been used mainly in the upper
limb and post-tumor cases. The IMT has become an important method for the
treatment of bone nonunion with large bone defects.

We performed this study to identify whether the role of the Ilizarov method has
changed in the recent five-year period due to the emergence of new trends and
methods of long bone defect treatment. The search revealed that its important role has
not diminished. At present, ring fixation continues to provide the most effective
means of treatment for large bone defects in many clinic situations while DO is the
leading technique that is used with a number of available external fixators. The use of
the IMT has expanded in recent years and also offers valid solutions.

In conclusion, DO techniques provide the most widespread means for the
treatment of segmental bone defects and infected nonunion of the lower extremity in
many clinical conditions, especially in complex lower limb problems. Management of
tibial defects mostly utilizes the Ilizarov ring fixator. The role of the Ilizarov non-free
bone plasty has not lost its significance in the treatment of segmental bone defects and
nonunion despite its shortcomings and unsolved problems.

ARTICLE HIGHLIGHTS

Research background
Segmental long bone defects are one of the challenges in contemporary orthopedic practice due
to severity of high-energy trauma, traffic accidents and military activities. Current strategies for
their reconstruction [distraction osteogenesis (DO), free vascularized grafting (FVG), and
induced membrane technique (IMT)] are based on autogenous type of grafting, either free or
non-free, which is their main merit. However, the shortcomings and problems of these methods
still remain the issues which restrict their overall use. The Ilizarov non-free bone plasty is a
method of DO used with the Ilizarov apparatus which originated in Russia and has been used in
other countries since 1990s.

Research motivation
Being experienced in the Ilizarov method of limb reconstruction, we studied the most recent
available literature on these three methods for long bone defect and nonunion management to
determine the present role of the Ilizarov techniques in this orthopedic field and to investigate
the solutions proposed by the authors to the problems they encounter for improving treatment
outcomes.

Research objectives
The main objectives were to find scientific material in the databases of orthopedic medical
journals and to select suitable articles on the management of segmental long bone defects using
current methods that show treatment results, merits, shortcomings, ways to overcome failures
and prospective trends for future research in this field. In addition, we searched for original articles that compared the Ilizarov techniques with the methods of IMT or FVG and contained quantitative data on the evaluation of these methods.

Research methods
Three databases (PubMed, Scopus, and Web of Science) were screened for recent studies in long bone defect and nonunion treatment within a five-year period (2015-2019). Sixty-five full-text clinical articles and reviews in English were selected for data analysis. Clinical studies were included if they described large patient samples (not less than ten cases for congenital, post-tumor resection cases or rare conditions, and more than 20 cases for the remainder) and contained treatment results and complications. Major adverse events involving operative procedures to correct the treatment failure, or its sequelae were of particular interest. Merits, shortcomings and problems of the ilizarov non-free bone plasty, IMT and free vascularized fibular graft were summarized. Out of a total of 50 articles on DO found, only nine were devoted to bone defects in the upper extremity while infected and aseptic post-traumatic defects of the lower limbs were reported in more than 70% of the articles, infected tibia being the most frequent location.

Research results
The search showed that there are numerous studies on long bone defect and nonunion management with DO and IMT. The use of free vascularized fibular graft has been less reported. Full texts of a total of 65 articles using these three techniques including 35 clinical reports on the use of DO or its comparison with two other methods were reviewed for outcome measures. It was found that DO techniques provide solutions to many complex problems as it addresses the triad of problems simultaneously (bone loss, soft-tissue loss and infection). Management of tibial defects mostly utilizes the Ilizarov circular fixator. Monolateral nail fixators are preferable in cases with an infected tibial bone gap of more than 6 cm. High rates of successful treatment were reported by the authors that ranged from 77% to 100% and depended on the pathology and the type of the Ilizarov technique used. Unfortunately, the outcome success rates were heterogeneous and lacked definite statistical findings. Docking site nonunion and after-frame regenerate fracture or deformity were the major causes of failures. One of the solutions to these problems is the application of hybrid external and internal fixation. Most authors currently recommend docking site revisions during bone transport and use supportive bone grafting. Effective technical solutions and add-on therapies to improve quality and control over osteogenesis have been developed.

Research conclusions
The main solutions to the problems of DO that are recommended by the authors focus on the following developments: (1) Mechanical stimulation of regeneration; (2) Multifocal bone transport to reduce total treatment time; (3) Acute shortening followed by distraction histogenesis; (4) Gradual transport of a fibular fragment in subtotal and total tibial defects; (5) Bone transport over an intramedullary nail; (6) Hydroxyapatite coated pins; and (7) Intraosseous injection of bone-marrow derived autologous mesenchymal stem cells. There are few comparative clinical studies that evaluate outcomes of the three methods used for long bone defects and nonunion.

Research perspectives
The combination of the biological effects of DO and IMT for treating congenital pseudarthrosis of the tibia has been proposed, as both methods promote vascularized new bone formation. New comparative studies that evaluate outcomes of the three methods used for long bone defects mostly utilize the Ilizarov circular fixator. Monolateral nail fixators are preferable in cases with an infected tibial bone gap of more than 6 cm. High rates of successful treatment were reported by the authors that ranged from 77% to 100% and depended on the pathology and the type of the Ilizarov technique used. Unfortunately, the outcome success rates were heterogeneous and lacked definite statistical findings. Docking site nonunion and after-frame regenerate fracture or deformity were the major causes of failures. One of the solutions to these problems is the application of hybrid external and internal fixation. Most authors currently recommend docking site revisions during bone transport and use supportive bone grafting. Effective technical solutions and add-on therapies to improve quality and control over osteogenesis have been developed.

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