REVIEW ARTICLE

Evolution and Development of Ilizarov Technique in the Treatment of Infected Long Bone Nonunion with or without Bone Defects

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The treatment of infected bone nonunion and bone defects is a considerable challenge in the orthopedics field. The standard clinical therapy methods include local free bone transplantation, vascularized bone graft, and the Ilizarov technique; the first two are controversial due to the iatrogenic self-injury. The Ilizarov bone transport technique has been widely used to treat infected bone nonunion and bone defects, and good clinical effect has been demonstrated. Yet, it brings many related complications, which exerts additional suffering to the patient. The best treatment is to combine bone defect rehabilitation with infection control, intramedullary nail fixation, appropriate time for bone grafts, beaded type scaffold slippage and new Taylor fixation, reducing the external fixation time and the incidence of complications, thereby reducing the occurrence of patients' physical and psychological problems. This review focuses on the induction, summary and analysis of the Ilizarov bone transport technique in the treatment of infected long bone nonunion with or without bone defects, providing new ideas and methods for orthopedic disease prevention and treatment by the Ilizarov technique, which is following the development direction of digital orthopedics.

Key words: 3D printing technology; Ilizarov technique; Infected long bone nonunion; Infected bone defects

Introduction

With the advancement of industrialization and the development of the transportation industry, traffic accidents with high violence and high kinetic energy are frequent, resulting in an increasing number of cases of severe open fracture, which is the most common cause of infected nonunion with or without bone defects, ranging from 4% to 64%.[1–3] Infected nonunion refers to the failure of the fracture healing process and the persistent bone infection at the fracture site for 6–8 months, which is the most challenging category of existing nonunion classification and seriously threatens the limb and life of the patient.[3–6] As a massive challenge in the field of orthopedics, the commonly used methods for clinical treatment of infected bone nonunion and bone defects include large local segment free bone transplantation, bone transplantation with blood vessels, the Masquelet technique, and the Ilizarov technique, etc., both of which are controversial due to iatric autogenous injury.[7,8]

The Ilizarov technique was proposed and named after a former Soviet doctor in 1951.[9] The core biomechanical theory of this technique is the "law of tension stress"(LTS), that is, continuous and slow traction stimulation can promote the regeneration and active growth of biological tissue similar to that of embryonic tissue.[10,11] Due to the robust regeneration and plasticity, bone tissue can be extended to the nerves, blood vessels, muscles and skin in the surrounding areas under the action of appropriate tensile stress.[12] This rule is referred to as distraction osteogenesis (DO) in orthopedics. The essence of the Ilizarov technology lies in that it can not only completely remove infected lesions by osteotome to achieve the purpose of infection control, but also effectively lengthen bone to treat bone defects, and adequately control

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rotation and lateral displacement in the process of handling by adjusting the external fixator.[13] Masquelet's technique is also commonly used to repair infected bone defects, which consists of two stages: (i) the use of antibiotic bone cement spacer after radical debridement; and (ii) the use of induced biofilm cancellous bone graft 6–8 weeks after spacer removal to facilitate bone defect repair.[14] The primary complications of this technique incorporate graft absorption, pseudojoint formation, wound cracking, and loosening of stabilizers.[15] As a comparison, Ilizarov technology allows for early weight-bearing; the entire process can be adjusted at any time, and requires only a single stage of treatment, while Masquelet's technology requires a mandatory two-stage treatment.[16]

Ilizarov technology has been widely used in the treatment of infected bone nonunion and bone defects, and its efficacy has been well verified.[3] In this paper, the keywords of"Ilizarov,","infected bone nonunion," "infected bone defect," "infected nonunion with bone defect" were searched in PubMed, Google Scholar and Web of Science databases. A total of 793 related pieces of literature were retrieved and analyzed. Admission criteria for literature: (i) research types are journaling papers, conference documents and reviews; (ii) the research content is the application of Ilizarov bone transport technology in the infected bone nonunion and bone defect; and (iii) literature of the full text is available. Exclusion criteria: (i) the type of research is review or lecture; (ii) the full text of the literature cannot be obtained; and (iii) repeated publications in English or periodical reports. Twenty-two pieces of literature were finally screened out (Fig. 1). This paper reviews the research progress of the Ilizarov bone transport technique in the treatment of infected bone nonunion and bone defects (Table 1).

The Origins, Advantages And Disadvantages of Llizarov Technology

In the middle of the last century, inspired by the stability structure of bicycle wheels, Ilizarov invented an annular external fixator with tension wires drilled through bone and fixed under tension.[17] In clinical practice, the patient was accidentally found to have rotated the pressurizer in the opposite direction by mistake, resulting in the X-ray showing new bone changes at the osteotomy site. Inspired by this accident, Ilizarov carried out the drawing experiment after the fractured legs of dogs and the study on the bone formation at the broken end of human fractures.[9] It was found that the stable and continuous slow pulling at the broken back

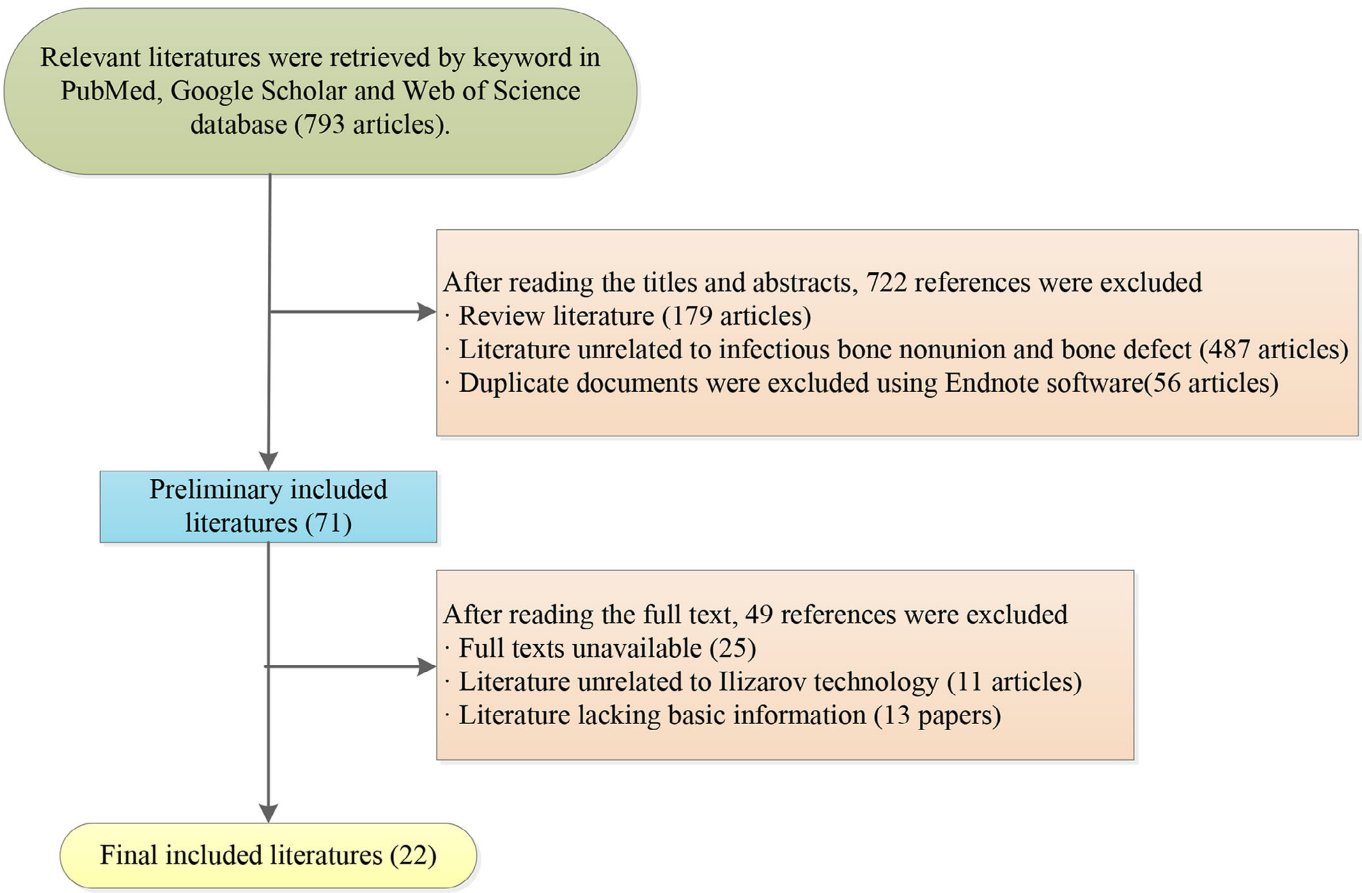

Fig. 1 Literature screening flowchart: 793 articles were selected from January 1998 to October 2021 in the relevant database. According to the inclusion and exclusion criteria, 771 articles were excluded and 22 documents were finally included

TABLE 1 Basic characteristics of the included studies

Lead author	Year	Research type	Cases	Surgical method	Bone transport(cm)	Fracture healing rate(%)	Bone healing (excellent/good/ good/bad)	Limb function (excellent/good/ good/bad)	Mean healing time (month)
Rosteius, T.	2021	RS	42	IEF, BG	7.7 ± 3.4	76.2	19/10/3/0	10/17/2/3	—
Xie, J.	2021	RS	189	CEF, UCEF, AT	6.1 ± 1.5	100	115/31/21/22	76/65/22/26	—
Ren, G.H.	2020	RS	43	IEF, AT	8.84 ± 2.52	100	25/8/3/7	21/13/8/1	—
Li, R.	2020	RS	68	UEF/CEF/UCEF, AT	7.97	100	—	34/18/6/10	—
Tong, K.	2017	RC	39	IEF, UEF, AT, BG	6.76	100	12/19/6/2	11/15/11/2	—
El-Alfy, B. S.	2017	RS	28	IEF, BG	8	100	10/16/2/0	8/17/3/0	13
Abuomira, I. E.	2016	RC	55	IEF, TSF/TF, SF, FR	7.1 ± 3.3	98	28/18/5/4	25/21/5/4	—
Rohilla, R.	2016	RS	35	IEF	6.6	94.3	19/13/0/3	14/19/1/0	11.9
Wani, N. B.	2015	RS	26	IEF, IMN, AT	—	100	13/8/5/0	9/11/5/1	5.1
Yin, P.	2015	RS	110	IEF, AT	1.52	100	68/28/12/2	37/42/21/0	6.15
Gulabi, D.	2014	RS	5	IEF, IMN, AT	9.2	100	5/0/0/0	4/1/0/0	4.6
Khanfour, A. A.	2014	RS	19	IEF, AT	—	94.7	14/3/1/1	10/7/1/1	11.2
Shahid, M.	2013	RS	12	IEF, IMN, AT	—	100	10/2/0/0	6/4/0/2	11.5
Borzunov, D. Y.	2013	RC	83	IEF	5.6 ± 1.8	100	—	—	5.61
Oostenbroek, H. J.	2009	RS	52	IEF, AT	3.8	96.2	—	—	9
Dhar, S. A.	2008	RS	36	IEF	4.76	100	16/14/5/1	13/11/10/2	2.35
Emara, K. M.	2008	PC	33	IEF, IMN, AT, BG	10.2	100	32/1/0/0	25/3/5/0	8.5
Lai, D	2006	RS	27	IEF	10	100	19/5/0/1	15/8/1/1	6.3
Bobroff, GD	2003	RS	12	IEF, AT	9.45	83	6/3/0/3	6/2/2/2	16.7
Sanders, DW	2002	RS	19	IEF, BG	8	84.2	—	9/4/1/5	7.3
Kocaoğlu, M	2001	RS	35	IEF, BG	—	97.1	—	17/7/6/5	5.5
Song, H. R.	1998	RS	27	IEF	8.3	100	14/8/2/3	11/11/2/3	7.1

Abbreviations: AT, Antibiotic treatment; BG, bone graft; CEF, circular external fixator; FR, Full ring retainer; IEF, Ilizarov external fixator; IMN, intramedullary nail; PC, Prospective case–control study; RC, Retrospective case–control study; RS, retrospective case series report; SF, Sheffield ring; TF, TrueLok ring; TSF, Taylor space bracket; UCEF, unilateral-circular external fixator; UEF, unilateral external fixatoror; —, This data was not reported in the study.

and the long metaphyseal end could stimulate the regeneration of bone tissue, and finally formed the LTS. In 1980, Ilizarov technology was introduced to Italy by chance and quickly spread to Europe through academic lectures. After that, orthopedic surgeons in North America began to understand and apply Ilizarov technology, which was widely accepted in a short period and quickly spread around the world. In 1989, Professor Pan Shaochuan introduced Ilizarov technology from the United States and applied it in pediatric orthopedics.[18,19] In the same year, Professor Qin Sihe invited Russian experts of Ilizarov technology to give lectures and teach surgery in China. Since then, Ilizarov technology began to spread in mainland China,with a multitude of scholars emerged from all over the country.[19] After 60 years of development, Ilizarov technology has become a classic orthopedic surgery technology. North American orthopedic community praised Ilizarov technology to be comparable to joint replacement, arthroscopic technology, surgical correction of scoliosis, which were collectively referred to as the four major milestones of orthopedic surgery.

The advantages of Ilizarov technology are as follows: (i) compared with internal fixation, it owns the characteristics of small incision, more minor trauma and damage to local soft tissue and periosteum, which protects soft tissue and blood supply and provides suitable conditions for promoting healing[20]; (ii) while the dead bone can be removed to completely control the infection, bone transport through metaphyseal osteotomy can achieve the purpose of limb extension, which is regarded as the golden standard for the treatment of segmental bone defect and some complex bone nonunion[21]; (iii) in the case of bone and soft tissue infection, external fixation can be used to puncture the needle outside the infected focus, which can promote fracture healing while avoiding infection[9,21]; and (iv) the Ilizarov external fixator can be individually assembled according to the clinical treatment needs of the doctor and the characteristics of the patient's bone, so as to better eliminate the shear force and rotation force, in line with the development direction of digital orthopedics.[22] Despite the advantages of Ilizarov technology, it is undeniable that the technology also has disadvantages, such as complex operations and long treatment times.[23] The external fixation bracket is inconvenient to wear, which limits knee and ankle joint activities; postoperative nursing is troublesome, and the annular external fixator affects the life quality of patients with a nail infections, needle loosening, bone nonunion after broken end contact and pseudarthrosis, ankle joint stiffness, etc.[12,14] However, compared with the traditional methods, the application of Ilizarov technology in the treatment of fracture combined with infection and large bone defect has obvious advantages.[3]

Application in Infected Nonunion

Infected bone nonunion has two major orthopedic problems, "infection" and "bone nonunion." It is often accompanied by bone and soft tissue defects, multiple sinus passages, adjacent joint stiffness, osteomyelitis, limb deformity and multiple drug-resistant bacteria infection and other complications.[24] Management of infected nonunion accompanied with deformity includes gradual correction, complete debridement, reliable fixation of fracture ends, and bone transplantation if necessary.[25] The critical issue of treating infected nonunion with osteonecrosis is the management of infected scar tissue; frequent motion and the resulting local compromise prevent absorption of the surface and healing of fracture segments.[26] Rigid fixation and bypass surgery could relieve soft tissue damage and facilitate healing; if suppurative pseudojoint necrosis is not superficial, sinus passages will often form even if the bone is healed. Ilizarov external fixation offers the most versatile solution to such thorny problems, namely, treating the bone defects and controlling the infection at the same time, and finally achieving the ideal therapeutic effect.

Ilizarov himself believed that the focus of the treatment of infected nonunion should be bone nonunion, and put forward the view that "infection will burn in bone regeneration," that is, by applying pressure on the site of nonunion and distraction osteogenesis, bone infection will be cured naturally in the process of bone regeneration.[27] For example, Dhar *et al.*[28] applied Ilizarov technology in the treatment of 36 patients with tibial nonunion, and the fracture healing rate was 100%, and good functional recovery was achieved. This treatment is effective in clinical practice, but the recurrence rate of infection is very high. Morandi et al.[29] reported in a retrospective study that although all patients with infected nonunion were cured by this method, the recurrence rate of healing infection was as high as 100%. For this reason, this method was improved and formed the Ilizarov technology today. Its theoretical basis is still the tension stress rule proposed by Ilizarov, but the treatment of bone infection is carried out, that is, the infected necrotic bone is completely removed in the first stage, so that the infected bone nonunion becomes an aseptic bone defect. Then the limb was lengthened using Ilizarov technology to repair the bone defect. This method has not only achieved a satisfactory clinical effect in the treatment of infected nonunion, but also significantly reduced the recurrence rate of infection after healing. For example, Khanfour et al.[30] performed debridement and Ilizarov surgery on 35 patients with bone nonunion caused by femoral shaft osteomyelitis. The average length of bone defect was 6.15 cm, the average treatment time was 11.2 months, and the average follow-up time was 3.5 years.

The critical problems of the Ilizarov technique are the duration of external fixation and the discomfort of patients. Emara et al.[31] agree that the Ilizarov technique is an effective method for treating bone nonunion caused by tibial osteomyelitis. Still, the duration of external fixation should be shortened as far as possible. Their study confirmed that early removal of the external fixation followed by replacing the intramedullary nail fixation could achieve the same effect. In recent years, Shahid et al.[32] Gulabi et al.[33] and Wani et al.[34] used Ilizarov combined with intramedullary nail-fixation to treat 20, 5, and 18 cases of tibial infected nonunion, respectively. The results showed that the fracture healing rate of all patients reached 100% and the functional recovery was good. The results showed that combination therapy could significantly shorten the treatment time without causing more complications and dysfunction. After the backbone traction and stretch to the appropriate length, the fixation of intramedullary nails was performed after removing the fixator, which can reduce the occurrence of liver disorders and psychological problems of the patients.

Whether and when bone grafting is required at the junction of bone segment transport remains controversial. Although Ilizarov does not recommend applying bone graft in the treatment of bone nonunion, Kocaoglu et al.[35] believe that early autograft in long bone nonunion can promote bone healing and thus reduce the time of external fixation. He reported 35 cases of humeral shaft nonunion with the Ilizarov technique combined with early bone grafting. The mean healing time was 5.5 months, and the fracture healing rate was 97.1%. Sanders et al.[36] also used the Ilizarov device combined with autologous bone graft to treat 19 cases of tibial nonunion, and tracked the source and incidence of possible complications. The results confirmed that Ilizarov technology combined with bone graft was effective in treating tibial nonunion. Ankle function loss caused by pain is the leading cause of ultimate disability in patients. As early as 1995, Saleh et al.[37] proposed that bone grafting should be performed if the contact area between two bone ends was too small. In the treatment of infected nonunion symptoms, the timing of bone grafting must be selected. To avoid stimulating the infected tissue and aggravating the infection, bone grafting is generally implemented after the infection focus is effectively controlled.

Application in Infected Bone Defects

Infected bone nonunion is often accompanied by massive bone defects after debridement, leading to limb shortening deformity. Even though traditional bone grafting combined plate fixation, intramedullary nail fixation or non-invasive stimulation therapy can cure the bone nonunion while it is challenging to solve the problem of lower limb discrepancy. The Ilizarov technique can reconstruct the limbs at the same time and achieve maximum functional recovery. Ilizarov bone transport technology has been proven effective in promoting the repair of long bone segmental defects. Song et al.[38] used Ilizarov bone transport technology to treat 27 patients with infected bone defects, with an average bone defect of 8.3 cm, of which 25 cases were combined with bone grafting, and all patients achieved bone healing. The bony results were excellent in 14 cases, good in eight cases, fair in two cases and poor in three cases. Some scholars compared bone transport technology with various bone grafting techniques and found that simple bone transport technology is suitable for short segmental bone defects or segmental bone transport. In contrast, more extended bone defects usually require bone grafting.[39] Borzunov et al.[40] used Ilizarov bone transport technology and fibula transplantation to treat 83 patients with segmental bone defects, of which 41 patients were treated with segmental bone transport technology, and the average length of bone defect was (13.1 ± 0.9) cm. Forty-two patients were treated with fibular graft at the same level, and the mean size of the bone defect was (12.5 ± 1.2) cm. Both groups regained the ability to walk with weight, but the bone transport group had better bony healing, less unequal length of the lower extremity, and more related complications in the pedicled vascular fibular graft group. Rohilla et al.[41] treated 35 cases of large tibia defect (defect length >6 cm), with an average age of 36.1 years (20–55 years), an average length of 7.27 cm, and a lower limb length of 3–6 cm. Among them, seven cases were infected, and the average length of pulling was 13.9 months (4.7–22.6 months). Following up for 25.4 months, 32 cases of bone healing and 33 cases of limb function were satisfactory.

In the published literature, there are few cases of treating long segmental bone defects (close to or over 10 cm) with bone transport alone. Bobroff et al.[42] retrospectively analyzed the cases of treating large segmental tibia defects caused by high energy trauma or infected bone disconnection trauma with Ilizarov bone transport technology in the past 10 years. The average length of bone transport was 9.45 cm, and the average time of external fixation was 16.7 months. The bone healing rate after bone transport technology was 83%. Two patients developed persistent bone nonunion, of which one patient healed after internal fixation combined with bone grafting treatment after removal of the fixation, and the other case failed to heal for a long time with poor clinical effect and finally received amputation. Large bone defects and soft tissue defects can be repaired simultaneously by the slip bone segment, and the 27 cm long bone defects have also been reported in the literature.[43] It is an ideal method in theory, but some problems will arise in practical clinical work. Due to the long process of bone segment slip, bone end sclerosis and irregular calluses will appear before the docking of both ends of the bone defect, leading to poor alignment and poor healing ability of the broken end. When the slippage segment is large, it is easy to produce slippage trajectory deviation, and the posture of the slippage segment needs to be adjusted several times, which is easy to cause needle loosening and infection.[44,45] The core of these problems is treatment time and slip distance; shortening the treatment time and reducing the slip distance are of great importance.

The most common complications of segmental bone defect repair include infection, rejection reaction, bone nonunion, bone graft fracture, etc.[46] Therefore, Ilizarov technology combined with vascularized autogenous bone graft is considered to be an effective method to deal with large segmental bone defects. El-Alfy et al.[47] used Ilizarov bone transport technology to treat 28 patients with infected bone defects combined with soft tissue defects, and the average length of bone defects was 8 cm, among which 13 patients had no bone grafting and 15 patients had cancellous bone grafting. The external fixation lasted 9–17 months (average 13 months), and all patients achieved bone healing.

Application in Infected Nonunion With Bone Defects

The large bone defect around the distal joint of long bone caused by trauma and the complete debridement of infected bone nonunion are more complicated. Repeated operations will destroy the blood supply of soft tissue and bone. Periarticular fixation is another major challenge. The presence of infected lesions may limit the use of plates, screws, and intramedullary nails. Most patients have a long treatment period, which inevitably leads to complications such as joint stiffness and limited functional activity. Lai et al.[48] reported five patients with distal femoral bone defect and infected nonunion treated with Ilizarov bone transport combined with pedicled vascular fibular graft. The average length of the distal femoral defect after debridement was 15.8 cm, and the size of bone transport was 8.2 cm. The mean healing time was 10.2 months, and the mean lengthening length was 12.4 cm. The patient could walk again 12 months after surgery, and no limb shortening or infection recurrence was observed during follow-up. The authors suggested that the Ilizarov bone transport technique combined with pedicled vascular transplantation can effectively heal fracture ends, control infection, restore limb length and shorten the treatment period in patients with infected nonunion or bone defects.

Emara et al.[31] applied the Ilizarov bone transport technique to 33 patients with infected tibial shaft defect and nonunion, of which 17 patients were fixed with intramedullary nails after bone transport, and all patients achieved bone healing. The results of the two methods were compared according to the ASAMI score. There was no significant statistical difference in the bone and functional outcomes. It was believed that the removal of the bone transport fixator and the replacement of intramedullary nails after bone transport could achieve the same effect as the traditional Ilizarov external fixator. It has the advantages of early recovery, more comfort, shortening the application time of external fixator, reducing the complications of long-term application of external fixator, and avoiding the physiological and psychological problems caused by long-term application of external fixator. Magadum et al.[23] reported the application of the Ilizarov technique in the treatment of 27 cases of infected tibial fracture nonunion with bone defect, with a follow-up period of 25–39 months. According to the ASAMI standard, 19 cases were excellent, five cases were good, two cases were residual deformity, and one case was nonunion. The authors believe that the Ilizarov bone transport technique is an effective method for treating large segment defects of the tibia, which can avoid the secondary operation at the fracture end and shorten the treatment period. However, the risks of long treatment time and associated complications should also be taken into account.

The Taylor stent simplifies the operation of the Ilizarov external fixator. Based on strictly following the concept of Ilizarov technique traction osteoformation, Taylor stents improved the external ring fixator. Six oblique mirror cylindrical platforms were connected between the two rings. The connection points were universal joints, which could be rotated freely to complete any spatial change.[49] It can synchronously correct the deformities for angulation, deflection and rotation through a visible hinge and computer system. Abuomira *et al.*[50] reported 55 cases of tibial nonunion treated with Ilizarov external fixator combined with Taylor stent. The average bone transport distance was 7.1 ± 3.3 cm. It is suggested that the combined use of Taylor stent is especially suitable for the bone defects caused by multiple trauma long bone fractures.

Prospects of Llizarov Technology

Ilizarov technique is an effective method for treating complex nonunion of limbs with severe infection and bone defects, which has become the internationally recognized gold standard. Although Ilizarov technology can solve the complications existing in the treatment of bone nonunion, it cannot completely replace other technologies in the treatment of some special conditions of bone nonunion, for example, patients compliance are poor or anatomical conditions are not allowed. Ilizarov technology provides an effective alternative method for the clinical treatment of bone nonunion. The clinical treatment of infected bone nonunion and bone defect should follow the principle of individuation and weigh the advantages and disadvantages according to the specific situation of patients to design the most reasonable regimens.

With the introduction of precision medicine, the idea of personalized medicine has attracted more and more attention. With the rapid development of digital technology and its wide application, personalized medicine in orthopedics has undergone qualitative changes. The rapid growth of 3D printing technology, which is the concentrated embodiment of digital technology, provides an effective means to realize precision and personalized medicine. As a cutting-edge manufacturing technology, current applications of 3D printing technology in orthopedics include the application of spinal deformity, the placement of auxiliary pedicle screws, the preparation of bone tumor prosthesis, the individualized treatment of knee replacement, etc. Therefore, how to combine the "classic" Ilizarov technology with the "advanced" digital bone science is an essential topic for better inheritance and development of Ilizarov technology in the future.

The author's assumption of Ilizarov technology combined with digital orthopedics is as follows, for example: (i) combined with existing X-ray, CT, MRI and other imaging data before surgery, the characteristics of bone blocks and the classification of bone defects of patients were analyzed by computer digital assisted technology, and digital Ilizarov external fixator more matching with the patients' bones was printed by 3D printing technology to design individual surgical plan for patients. (ii) Computer-Aided Design (CAD) design and 3D printing and rapid prototyping individualized intraoperative navigation template can be used to determine the direction of the Kirschner pinhole channel and to accurately and individualized control the angle and size of the orthopedicosteotomy, which is beneficial to improve the success rate of surgery. (iii) Satisfactory reduction and appropriate fixation are essential for fracture healing, and postoperative remote computer modeling can better assess the prognosis of patients. By dynamically collecting the bone healing and new bone growth data of patients, the patients can be guided to adjust the Ilizarov external fixator flexibly and determine the reasonable time for the removal of the fixator. (iv) The combination of Ilizarov and 3D printing technology to produce prostheses with antibiotic bone cement to control infection and maintain limb length may have additional therapeutic effects such as reducing the incidence of complications, the recurrence of infection, and the wearing time of external fixation. With the rapid development of digital technology and the gradual maturity of its application in orthopedics, the problem of infected nonunion and bone defects will be better addressed using Ilizarov technology.

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