Original article
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Impact of transphyseal intramedullary nailing on tibial distraction regenerate and subsequent tibial growth in sheep: an experimental study

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Abstract

Introduction In lengthening of limbs in children, the combination of elastic intramedullary reinforcement and external fixation has advantages over standard techniques, but requires the removal of elastic nails and does not provide the possibility of their locking, that could significantly reduce the period of external fixation.

The **purpose** of the work was to study the features of tibial distraction regenerate formation and residual growth of the lengthened segment in lambs under the conditions of external fixation combined with a transphyseal rigid titanium rod.

Materials and methods *In vivo* experiments were performed on lambs (n = 7) during their growth period. In the control group, the right tibia was lengthened using transosseous distraction osteosynthesis for 28 days. In the study group, the segment was additionally reinforced with an intramedullary rigid rod. The following were measured in radiographs: the height of the distraction gap between the fragments, the transverse dimensions of the distraction regenerate, the height of the bone sections of the regenerate and the growth zone, the length of the tibia; the anatomical angles of the proximal articular end of the tibia. To determine the intrinsic growth dynamics of the segment under lengthening, the size of the distraction regenerate was subtracted from the length of the tibia.

Results In the main group, the transverse dimensions of the distraction regenerate were larger, and the height of the growth zone was smaller than in the control group. Consolidation of the regenerate in the main group occurred after 30 days, and in the control group 60 days after the cessation of lengthening. No slowdown in the longitudinal growth of the elongated segment was noted compared to the contralateral one, the orientation angles of the inclination of the proximal articular surfaces did not change.

Discussion Transphyseal implants should be located centrally to reduce the risk of epiphysiodesis, their area should not exceed 7 % of the growth zone. These conditions were met in the study. The reduction in the time of distraction regenerate corticalization and early termination of external fixation was associated with pronounced periosteal osteogenesis and increased bone fragments stability. The location of the rod in the growth plate does not lead to epiphysiodesis and does not interfere with normal growth of the segment.

Conclusion Pronounced periosteal osteogenesis and additional stabilization of the bone fragments with a transphyseal rigid titanium rod contribute to the faster bone regenerate formation and maturation. There are no signs of inhibition of spontaneous growth of the segment under lengthening and radiographic signs of epiphysiodesis at the transphyseal level. The central location of the transphyseal rod relative to the growth zone plane and its cross-sectional area of less than 5 % of the physis area can be considered conditions under which epiphysiodesis does not develop.

Keywords: intramedullary nail, limb lengthening, discrepancy, physis

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INRODUCTION

It is recommended to perform limb lengthening in children in early childhood if magnitude of shortening is significant and there are associated deformities as well as when parents insist [1, 2]. Lengthening with classical techniques requires external fixation for a prolonged period, that is associated with both an increased risk of complications and a psychological burden on the patient and his/her family [3, 4]. The use of fully implantable lengthening intramedullary nails in children is impossible due to the small diameter of the bone and open growth zones [5]. The use of elastic intramedullary reinforcement has shown its advantages: reduced time of wearing the external fixation device (EFD), decreased incidence of complications, the possibility of using the technique in small diameters of the bone marrow canal [6, 7]. However, this method implies an additional operation to remove the elastic rods [8]. Moreover, elastic titanium rods are not capable to perform locked osteosynthesis, which theoretically would speed up the removal of the EFD. Our recent experimental studies have shown that a transphyseal titanium rigid rod with its threaded parts in the epiphyses and a smooth part at the level of the growth zones in the metaphyses and in the diaphyseal parts of the tibia under experimental conditions does not lead to a slowdown in the growth of the lengthened segment [9].

The **purpose** of the work was to study the features of tibial distraction regenerate formation and residual growth of the lengthened segment in lambs under the conditions of external fixation combined with a transphyseal rigid titanium rod.

MATERIALS AND METHODS

Study design

A prospective, randomized, controlled, monocentric in vivo experimental study was performed in two groups of lambs during their growth period: a control one (n = 3) and a study one (n = 5). All animals underwent lengthening of the right tibia with the method of transosseous distraction osteosynthesis at a distraction rate of 1.0 mm/day in 4 steps for 28 days. In the study group, the segment was additionally reinforced with an intramedullary rigid rod. The pre-distraction period was 7 days.

Inclusion criteria

The experiment involved clinically healthy sheep of both sexes, who had a tibial medullary canal diameter of at least 5 mm and a biological age ranging from 4.5 to 5 months (inclusion criteria). The exclusion criteria were: death of animals or pathological conditions not related to the experimental conditions.

Experiment time-points

Before the start of the experiment, the following study time-points for control were determined: immediately before the surgical intervention; end of the lengthening period; 30 days of fixation after the end of the lengthening period; end of fixation with the EFD; 30 days after the end of EFD fixation.

Description of surgical intervention

Surgical interventions were performed in the operating room by one surgical team. The Ilizarov apparatus, consisting of four supports forming two subsystems, proximal and distal (Fig. 1 a), was mounted on the right shin of the animals in the control group. The subsystems were connected to each other with threaded rods with the possibility of subsequent longitudinal distraction along them. Transverse osteotomy of the tibial diaphysis was performed through a longitudinal incision of the soft tissues using a Gigli saw. Sutures were applied to the soft tissues upon completion of osteotomy.

In the animals of the study group, two supports were mounted, proximal and distal. Before performing the osteotomy, the tibia was reinforced with an intramedullary rigid titanium rod (Ti6AI4V alloy) (Fig. 1 b).

The rod diameter (4.5 mm or 5.0 mm) depended on the diameter of the medullary canal. The rod was selected so that the diameter of the canal in the narrowest part exceeded the rod diameter by 2–3 mm. The medullary canal was not drilled. The length of the rod was determined for each animal individually. The rod was installed through the parapatellar approach. In the intercondylar space of the tibia, a cannulated drill was used along a guide pin at slow speed to drill a canal in the proximal epiphysis, passing to the medullary canal. A rigid rod was inserted through this canal, its threaded part was screwed under X-ray control. The height of the threaded part did not exceed the height of the epiphysis and did not enter the growth cartilage zone. The diameter of the threaded part of the rod was 11 mm. Through a longitudinal incision of soft tissues, a transverse osteotomy of the diaphysis of the tibia was performed using a Gigli saw, followed by layer-by-layer suturing of the wound.

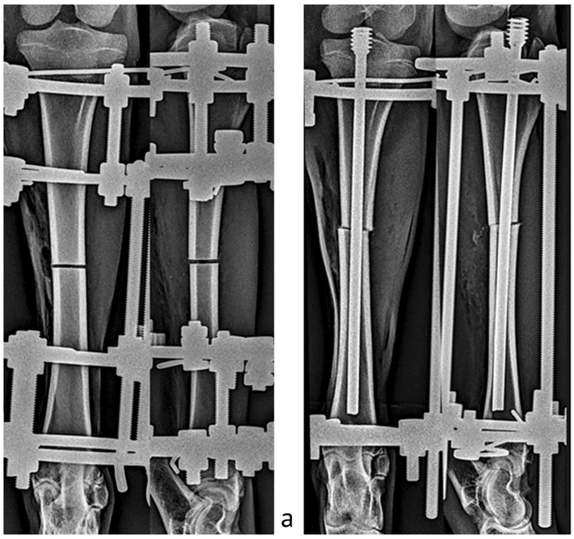

Fig. 1 Radiographs taken on the day of intervention: *a* control case; *b* study group case

All animals were administered ketoprofen intramuscular injections (50 mg/ml) of 0.5 ml per day for 5 days after surgery. The skin around the wires and sutures were treated with a 3 % hydrogen peroxide solution.

All animals underwent radiography of the experimental and contralateral segment using a Premium VET X-ray system (TOSHIBA (Rotanode) Model E7239. N: 10G749, Japan) and a digital radiography system supplied with a CANON CXDI-401C COMPACT flat-panel detector (Canon Inc. Medical Equipment Group, Japan).

The animals were kept in vivarium conditions in accordance with the requirements of GOST R 33044-2014 "Principles of Good Laboratory Practice", GOST 33215-2014 "Guidelines for the Care and Maintenance of Laboratory Animals. Rules for the Equipment of Premises and Organization of Procedures", GOST 34088-2017 "Guidelines for the Care and Maintenance of Laboratory Animals. Rules for the Maintenance and Maintenance of Farm Animals". The requirements of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes and Directive 2010/63/EU of the European Parliament and of the Council of the European Union of 22.09.2010 on the protection of animals used for scientific purposes were observed.

Main outcome measures

To determine the characteristics of the distraction bone regenerate, the structure of its shadows, its shape, zones, the presence and expressiveness of the middle zone of enlightenment (growth zone) were studied in radiographs.

For quantitative assessment, the height of the gap between bone fragments (cm), the transverse dimensions of the distraction bone regenerate, the height of its bone sections and the height of its growth zone (cm) were measured in digital X-ray images.

Additionally, the features of segment growth under the created conditions and the formation of the proximal articular end were studied. For this purpose, the length of the tibiae in the lateral projection (cm), the mechanical medial proximal tibial angle (mMPTA), and the mechanical posteroir proximal tibial angle (mPPTA) were measured. The intrinsic growth dynamics of the segment under lengthening were calculated by subtracting the value of the distraction regenerate from the length of the tibia.

Statistical analysis was performed using the AtteStat version 13.1 for Excel spreadsheets (2016, 16.0.5278.1000). Descriptive statistics methods were used: mean values (M) and standard deviation (SD). Comparative studies were performed using the Mann – Whitney test. Differences were considered statistically significant at $p \leqslant 0.05$.

RESULTS

The entire periods of distraction, fixation and the period after removal of the EFA were fully completed in seven animals. In one case of the main study group, premature bone consolidation occurred in the second week of distraction, which forced us to exclude this case from the study analysis.

The results of osteometry of all lambs' tibiae before the experiment did not reveal a reliable difference ($p = 0.7$) between the length of the experimental and intact segments. In the control group, these indicators were (20.07 ± 0.3) cm and (20.03 ± 0.31) cm, and in the main study group (19.81 ± 1.05) cm and (19.83 ± 1.05) cm, respectively.

The evaluation of the radiographic features of the distraction regenerate determined that by the end of the lengthening period, the contours of the fragment ends in the animals of the control group were smooth and clear. The gap between the bone fragments averaged (3.1 ± 0.1) cm, (12.3 ± 1.8) %. Shadows of the distraction bone regenerate with a longitudinally striated structure and zonal formation were determined in its cavity. Regularly, the height of the proximal bone section of the regenerate ((1.74 ± 0.29) cm) was greater than the height of the distal bone section ((0.9 ± 0.21) cm) by more than 90 %. The length of the middle zone of enlightenment varied from 0.41 cm to 1.68 cm, and averaged (0.85 ± 0.35) cm. Its values were 27.42 % of the gap height. The regenerate growth zone was bridged by the shadows of bone trabeculae in some areas. The transverse dimensions of the regenerate exceeded the diameter of the ends of the fragments by more than 35 %. Their values were in the range from 1.61 cm to 2.36 cm and averaged (1.87 ± 0.27) cm (the diameter of the bone was (1.36 ± 0.1) cm).

By the 30th day of fixation, the contours of the fragment ends in the animals of the main study group became less clear in comparison with the previous period of examination. The shadows of the bone regenerate acquired a homogeneous structure. Its bone sections (proximal and distal) merged with each other in some areas. The diameter of the regenerate in the projection of the growth zone was (1.99 ± 0.4) cm. The growth zone was represented by separate areas of enlightenment or was in the form of a zigzag line. Its height sharply decreased in relation to the previous time-point and averaged (0.25 ± 0.14) cm.

Under the conditions created in the main study group, the formation of a weight-bearing bone regenerate occurred by the 60th day of fixation after the termination of the lengthening period. At this time-point, the contours of the ends of the fragments became even less clear. The zonal structure of the newly formed bone distraction regenerate completely disappeared. It was represented by continuous homogeneous shadows. The growth zone was most often revealed in the projection of the peripheral part of the regenerate in the form of single areas of enlightenment on one or both sides. A thin cortical plate continued development.

In that period during the clinical test, neither pathological mobility nor pain in the lengthening area was detected, which allowed removal of the Ilizarov apparatus.

Thirty days after the Ilizarov apparatus removal, the contours of the fragment ends were blurred. The newly formed section of the diaphysis had uniform shadows. Its height did not change in comparison with that at the end of lengthening, and the transverse dimensions averaged (1.83 ± 0.16) cm. Signs of the formation of the medullary canal were present.

The radiographic dynamics of the distraction bone regenerate formation in the animals of the control group is presented in Fig. 2.

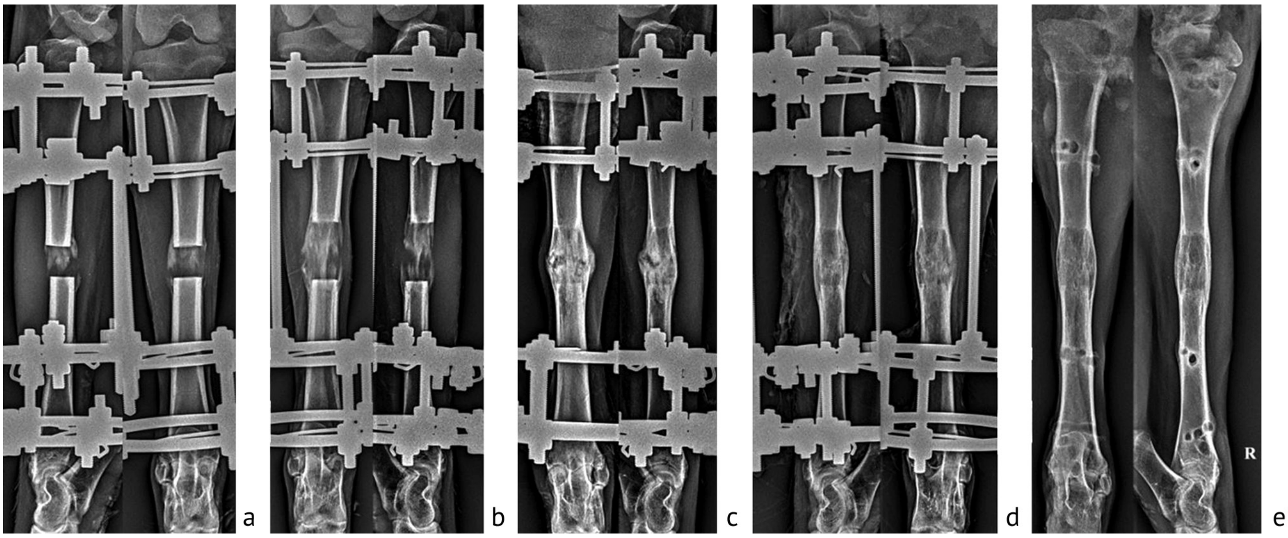

Fig. 2 Radiographs of the tibia during lengthening with the classical technique, control group: *a* 14 days of distraction; *b* 28 days of distraction (end of lengthening); *c* 30 days of fixation period; *d* 60 days of fixation period, bone union, day of EFD removal; *e* 30 days after dismantling the external fixation device

The evaluation of the radiographic characteristics of the distraction regenerate in the animals of the main study group showed that the gap between the bone fragments at the end of distraction averaged (2.75 ± 0.14) cm, (12.1 ± 1.5) %. In the gap cavity, shadows of the bone distraction regenerate of zonal structure were determined. The transverse dimensions of the regenerate averaged (2.32 ± 0.38) cm and exceeded the diameter of the maternal bone by 51.6 %. The height of the proximal bone section of the regenerate varied from 0.75 to 2.75 cm and averaged (1.56 ± 0.69) cm. The length of the distal section, as in the control group, was smaller. Its values corresponded to (0.94 ± 0.97) cm (from 0.44 cm to 1.26 cm). The growth zone, (0.54 ± 0.22) cm high, was most often determined in the periphery. It was usually bridged by shadows of bone trabeculae of a longitudinally striated structure, more pronounced than in the control group.

After 30 days of fixation following the end of the lengthening procedure, the contours of the fragment ends were poorly defined on radiographs. The distraction bone regenerate lost its zonal structure. Its transverse dimensions averaged (2.38 ± 0.42) cm. The shadows of the bone sections of the regenerate were of a uniform longitudinally striated structure and merged with each other. The growth zone had small isolated areas of enlightenment, and averaged (0.43 ± 0.2) cm. A thin cortical plate started formation along the periphery.

In the animals of the main study group, fixation with the Ilizarov apparatus was stopped at that time-point based on the results of the clinical test and radiographic findings.

Following 30 days after dismantling the EFD, the axis of the elongated segment on the radiographs was correct. The contours of the ends of the fragments were not defined. The shadows of the newly formed distraction bone regenerate were partially compacted in comparison with the previous time-point of the experiment. Its transverse dimensions slightly decreased and were (2.14 ± 0.14) cm. A continuous cortical plate was formed on all sides. A single continuous bone marrow canal was formed along the rod.

The radiographic dynamics of the distraction bone regenerate formation in the animals of the main study group is presented in Fig. 3.

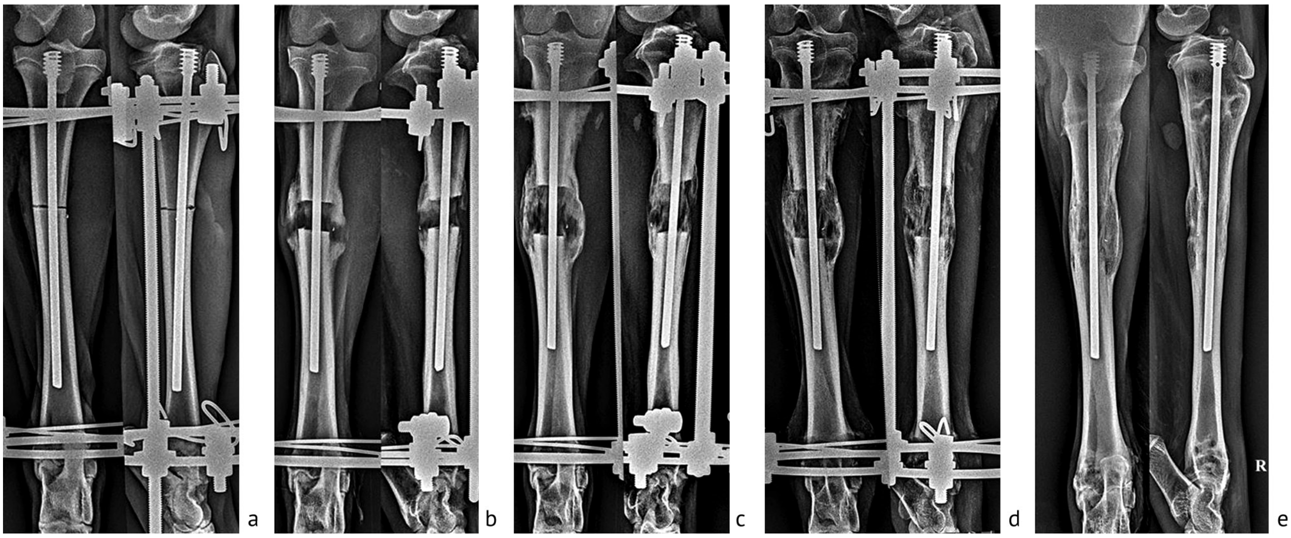

Fig. 2 Radiographs of the tibia during lengthening over the titanium rod, main study group: *a* day of surgery; *b* 14 days of distraction; *c* 28 days of distraction (end of lengthening); *d* 30 days of fixation period, bone union, day of EFD removal; *e* 30 days after dismantling the external fixation device

The measurements showed that the area of damage to the growth plate averaged (4.08 ± 0.32) %. The length of the tibiae due to spontaneous growth (subtracting the height of the distraction regenerate) following 60 days after the end of the fixation period is presented in Table 1.

Table 1

Length of the operated and intact tibiae 60 days after the end of the fixation period

Groups	Intact tibia; cm	Operated tibia; cm	Significance
Classical lengthening (control)	20.9 ± 0.32	21.54 ± 0.19	$P = 0.045$
Lengthening over the titanium rod (study)	21.14 ± 0.41	21.31 ± 0.23	$P = 0.274$

Thus, no disorders in the longitudinal growth of the lengthened tibiae were detected in comparison with the intact contralateral ones.

There was no difference in the values of the radiographic angles of inclination of the proximal articular surfaces of the MPTA ($p = 0.51$) and PPTA ($p = 0.03$) either immediately before surgery or subsequently at different time-points in both groups in comparison with the contralateral (intact) limb (Table 2).

Table 2

Radiographic anatomical angles of the proximal articular end of the tibia

Parameter	Intact tibia		Experimental tibia	
	Before surgery	30 days after EFD removal	Before surgery	30 days after EFD removal
Control group				
mMPTA; °	91.65 ± 0.50	95.02 ± 2.25	91.15 ± 1.78	94.01 ± 2.08
mPPTA; °	62.47 ± 3.02	65.07 ± 1.97	64.55 ± 5.83	71.1 ± 1.08
Study group				
mMPTA; °	92.4 ± 1.35	92.4 ± 1.39	92.35 ± 3.02	92.5 ± 1.22
mPPTA; °	65.7 ± 1.36	69.6 ± 3.1	66.92 ± 4.17	70.3 ± 0.92

It should also be noted that none of the animals that underwent lengthening over the rod experienced its blockage in the medullary canal during distraction, nor did the threaded portion lose fixation in the proximal epiphysis of the tibia.

DISCUSSION

In pediatric orthopaedics and traumatology, the issue of the long-term presence of transphyseal implants has been most actively discussed in three areas: surgical treatment of fractures of long bones involving damage to growth zones, reconstruction of the anterior cruciate ligament of the knee joint before closure of the growth zones, as well as reconstruction and/or preventive transphyseal reinforcement in bone tissue pathology accompanied by decreased bone strength [10–16].

In experimental surgery, various models are used to determine the effect of injuries and implants on the function and structure of the growth plate and articular cartilage of the knee joint. In most cases, studies are conducted on lambs, rabbits, and piglets [17–20]. It is recognized that the model of operations on the knee joint and the growth plate area of lambs is more suitable for translating the experimental results into clinical practice [21]. Trials of testing pathological features and effectiveness of the principles of new surgical methods on an experimental model have remained mandatory in evidence-based medicine [22].

The incidence of physeal injuries was nealy 20 % in paediatric limb fractures [23]. One third of such injuries results in epiphysiodesis zones [24]. In traumatological practice, the opinions of authors on the effect of transphyseal pins during fixation of small fragments in osteoepiphysiolysis on the function of physis and the formation of limited epiphysiodesis are contradictory. Thus, Horn et al. described partial epiphysiodesis and the development of angular deformity in the treatment of fractures in children [25]. In turn, Yung et al. and Langenhan et al. did not find any effect of transphyseal straight Kirschner wires on the subsequent growth of the operated limb [11, 12]. Garrett et al. [26] did not reveal statistical correlations between diafixation of distal epiphysiolysis and osteoepiphysiolysis of the femur and the incidence of epiphysiodesis either, while the severity of injury and the type of fracture according to the Salter-Harris classification had a reliable effect. In the context of eliminating the consequences of injuries in growth zones by resection of epiphysiodesis areas, experimental studies played a role, showing the absence of physeal bone bridge formation between the epiphysis and metaphysis in the case of filling the resection zone with autologous cartilage tissue [20]. Bone bridging was observed in all cases at the site of the removed growth cartilage after filling the zones with fatty tissue or leaving them empty. The importance of slowing down the resorption of transphyseal material and its inert properties for preventing formation of epiphysiodesis zones was demonstrated in the work of South Korean researchers: microarc oxidation of thin implants made of Mg-Ca-Zn alloys slowed down resorption in the physis zone and excluded the formation of bone bridging between the epiphysis and metaphysis [27].

There is an opinion that for reconstruction of the anterior cruciate ligament of the knee joint in children, anatomical reconstruction is possible only with transphyseal formation of canals and location of autoimplants [28, 29]. However, this method of performing the operation increases the risk of shortening and valgus deformity due to traumatization of the growth zones [14, 15]. Experimental studies of the methods of anterior cruciate ligament reconstruction revealed factors that reduce the risks of epiphysiodesis: the central location of the canals in the growth zones, their small diameter (5 mm) and the location of biologically inert material (autologous tendon grafts). In a larger diameter of the canals (8 mm), their posterolateral localization and lack of filling with tendons led to the formation of epiphysiodesis in lambs [30]. The importance of the tendon grafts introduced in the drilled transphyseal canal to prevent epiphysiodesis was also confirmed experimentally [31].

The question of the impacts of transphyseal implants on limb growth during reconstructive surgeries on limb bones used in clinical practice for treating children with genetic diseases has not yet been answered due to both the lack of methods for predicting spontaneous growth in such pathologies and the low relevance of this problem until recently [32–34].

It is in the field of reconstructive orthopaedics that experimental studies are the vanguard of scientific research, rather than following in the wake of expanding indications for established clinical technologies. Thus, studying the extent of damage and the duration of diafixation with any material, Mäkelä et al. [35] were able to show that the transphyseal location of straight steel pins with a diameter of 2 mm for less than 12 weeks did not cause the development of growth dysfunction, but after 12 to 24 weeks, epiphysiodesis and shortening of the segment were observed. The pins of 3.2–3.5 mm diameter pins that occupied 7 % of the growth zone area inevitably led to epiphysiodesis and shortening. This critical damage area (7–9 %) of the growth zone was confirmed by another study, but the location in the canal of autologous tendon graft enabled to avoid the formation of bony fusion [31]. In our own study, the 6 % damage of the physis area with transphyseal steel pins and long-term placement of implants *in situ* (for 25 weeks), led to a loss of 5.4 % of residual growth, and in a combination of reinforcement and osteotomy, to a loss of 9.5 % of residual growth of the reinforced tibia [36]. It is important to note that the telescopic transphyseal implants (sliding one inside the other), made of titanium alloys and introduced into the tibia centrally relative to the geometry of the growth zones and without additional bone osteotomies, did not lead to inhibition of the physis function [9]. Of importance in this discussion are the results of an experimental study of retrograde insertion of a massive titanium rod into the femur of piglets for 8 weeks (without additional osteotomy) that did not lead to inhibition of longitudinal growth [37]. That work was aimed at substantiating the possibility of using fully implantable electromagnetic rods in children for limb lengthening, but the authors acknowledge that experimental studies should be continued to study the effect of transphyseal implants on growth function in the context of surgical segment lengthening.

Thus, to reduce the risks of epiphysiodesis, transphyseal implants that can be potentially used in reconstructive orthopaedics should have inert properties with respect to surrounding tissues, be non-resorbable (or with a long resorption period), be located centrally, and not exceed an area of 7 % of the growth zone.

In our experimental series, titanium transphyseal rods were used, the method of application of which met the above criteria, with the exception that they were a component of a combined limb lengthening technique.

The results of the experimental series showed not only the possibility of such lengthening but also a faster maturation and consolidation of the distraction regenerate in the conditions of a thin rigid rod compared to the standard technique. We see two explanations for this phenomenon: a pronounced periosteal reaction and increased stability of bone fragments [38–42]. Our study confirmed the advantage of lengthening with intramedullary implants, in this case with a rigid intramedullary rod with possibility blocking. In all the cases of the experimental lengthening using the combined technique, bone consolidation with full corticalization of the distraction regenerate was achieved within 30 days of fixation.

As for the effect of a permanent transphyseal rod on growth, a promising result is the absence of growth inhibition of the elongated segment and, especially, the absence of epiphysiodesis. No statistically significant difference in the length of the intact and elongated (subtracting the height of diastasis) segment was found.

The limitation of this study for the clinical interpretation of the results is its experimental nature, as well as the magnitude of relative elongation within 13 %. Another limitation is the small number of animals used in the experiment. In subsequent research, it is planned to increase the number of cases in each of the groups.

Nevertheless, it is obvious that compliance with proven requirements for transphyseal implants and under elongation conditions provides avoiding a negative impact on the function of the involved growth zone.

CONCLUSION

Experimental lengthening of the tibia under the conditions of external fixation combined with transphyseal rigid titanium rod has been achieved. Pronounced periosteal osteogenesis and additional stabilization of bone fragments contribute to faster formation and maturation of bone regenerate compared to the classical lengthening technique. There are no signs of inhibition of spontaneous growth of the lengthened segment and no radiographic signs of epiphysiodesis at the level of the transphyseal part of implant The central location of the transphyseal rod relative to the plane of the growth zone and its cross-sectional area of less than 5 % of the physis area can be considered conditions under which epiphysiodesis does not develop during experimental limb lengthening.

Conflict of interests *The authors declare no obvious or potential conflicts of interest related to the research conducted and the publication of this study.*

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