RESEARCH ARTICLE

Finite Element Analysis of Mechanical Characteristics of Internal Fixation for Treatment of Proximal Femoral Osteolytic Lesions in Children

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Objectives: Clinically, it is very difficult to prevent pathological fracture caused by high recurrence rate of osteolytic disease of proximal femur in children. At present, there is no consensus in clinical studies of which internal fixation method can significantly reduce the probability of recurrence of pathological fracture. The study aims to research the mechanical properties of different internal fixations in the treatment of osteolytic lesions of proximal femur in children by finite element analysis, and to find out the optimal treatment.

Methods: Based on finite element analysis, the osteolytic disease models of the femoral neck and intertrochanter in a child (8-year-old, boy) were established respectively, and different internal fixation models (plate and titanium elastic intramedullary nails, TENs) were assembled. For the osteolytic lesion of the femoral neck: model A1 was assembled with a plate; model A2 with two TENs crossing the physis; model A3 with two TENs without crossing the physis. And for pertrochanteric osteolytic lesion: model B1 was assembled with a plate, model B2 with two TENs crossing the physis and model B3 with two TENs without crossing the physis. The Eccentric bearing load, torsional restraintal restraint of calcar femorale and composite load were analyzed for each models.

Results: When the yield strain of each model is reached, the stress concentration points are located in the proximal and distal femoral calcar. In the model of femoral neck lesions, the failure load of model A1 and model A2 are the same (1250 N), and the failure load of model A3 (980 N) is significantly lower than that of the former two; in the model of intertrochanteric lesions, the failure load of model B2 is the largest (1350 N), and the failure load of model B1 (1220 N) is lower than that of model B3 (1260 N), but both are smaller than that of model B2.

Conclusion: Through finite element analysis, TENs through the epiphyseal plate, is found to be the better internal fixation method for femoral neck lesions and intertrochanteric lesions under two different working conditions. The results of clinical correlation study provide new biomechanical information for orthopedic doctors to consider different treatment options for osteolytic lesions of proximal femur.

Key words: Biomechanics; Femur; Finite Element Analysis; Internal Fixation; Osteolytic Lesions

Introduction

At present, curettage and bone grafting has been widely accepted as a surgical treatment for osteolytic lesions. However, lesions close to the proximal metaphysis of the femur have a high recurrence rate after operation, which finally generates the pathological fracture that greatly increases the difficulty of clinical treatment,[1–3] Mankin *et al.* reported that the recurrence rate of osteolytic lesions in children were higher than that in adults, which may be related to the location of the lesion,[4–7] After the recurrence of the

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lesion, the local bone mass is insufficient, resulting in the pathological fracture caused only by slight external force. Therefore, appropriate internal fixation is particularly important for the prevention of pathological fracture. Due to the special anatomical structure of children, it is difficult to completely remove the lesions and avoid injuring the epiphyseal plate during the operation, leading to the high recurrence rate. Appropriate internal fixation can reduce the risk of pathological fracture after recurrence, but due to the particularity of children's metaphysis, there is no biomechanical basis for internal fixation for osteolytic lesions in children.[8]

Traditional internal fixations used in the treatment of proximal femoral osteolytic lesions in children include intertrochanteric screws, plate fixation, and Kirschner wires fixation[9] (Fig. 1). Wang *et al.*[10] used a dynamic hip screw (DHS) plate to treat Aneurysmal bone cyst (ABC) lesions located in the greater trochanter of the femur, and achieved good surgical results with no pathological fracture after operation. In recent years, elastic stable intramedullary nailing for osteolytic lesions of proximal femur has been proposed by some authors. Either, plate or elastic intramedullary nailing, as proposed by Erol *et al.*[11] can be used for the treatment of greater trochanter lesions. Elastic stable intramedullary nailing or Kirschner wires have been used for the treatment of femoral neck lesions and achieved good surgical results.

However, the type of internal fixation which has better supporting effect and reduces the risk of pathological fracture when local recurrence happens has not yet been confirmed, and has not been reported by a relevant biomechanical study. The purpose of this study is to: (i) compare the failure load of each internal fixation methods under eccentric bearing load plus torsional restraint through finite element analysis; and (ii) find out the best treatment scheme for proximal femoral osteolytic lesion in children.

Materials and Methods

Establishment of Three-Dimensional Femoral Model

In this study, a healthy 8-year-old boy was recruited. This study was approved by the Ethic Committee (2019R025-F01). Written informed consent was obtained before the study. The lower limbs of the patient were scanned by CT, three-dimensional finite element models of the femur were established by Mimics 21.0 (Materialise Company, Belgium), Geomagic Studio 2017 (Geomagic Company, Cary, NC, US), Solidworks 2018 (Dassault Aircraft Company, Paris, France) and ANSYS 19.0 software (ANSYS Company, Canonsburg, PA, US). The CT images were stored as DICOM format files and output to the medical 3D reconstruction software Mimics 21.0. The appropriate gray value was selected to distinguish the bone and tissue, and the region growth, mask editing and other commands was used to establish the original three-dimensional model of femur, and export the model to STL format file and import it into Geomagic studio 2017 software, the original model was fitted and smoothed.

Osteolytic Lesions of Proximal Femur and Establishment of Internal Fixation Model

According to the common osteolytic lesions in the proximal femur, six finite element models (pertrochanteric lesion and neck lesion, combination of three fixation methods)[12] were simulated by SolidWorks 2018 software. Due to osteolytic lesions, We used Mimics software to extract the data of 8-year-old children with femoral osteolytic lesions. The gray

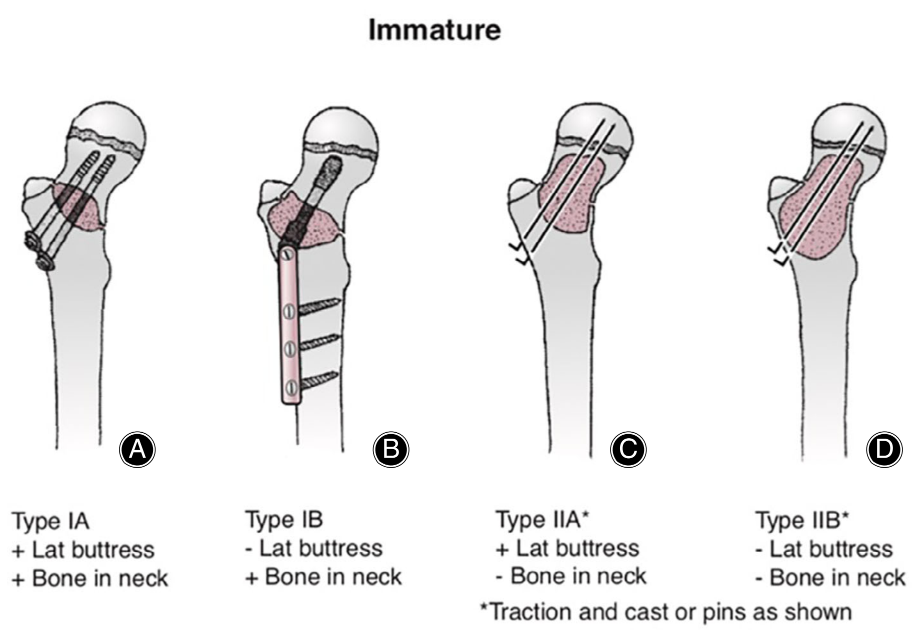

Fig. 1 The femoral intertrochanteric lesions did not invade the lateral cortex by using screw and DHS and the femoral neck lesions near the epiphyseal plate were treated with Kirschner wire whether or not they invaded the lateral cortex.

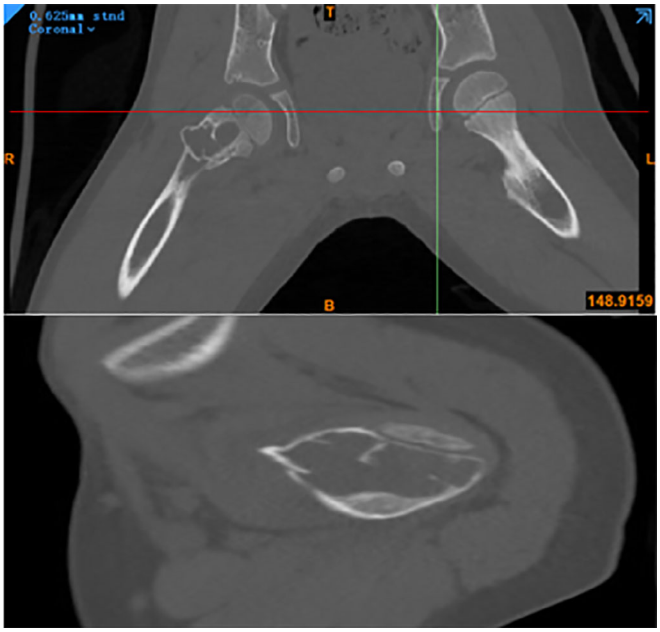

Fig. 2 8-year-old children with femoral osteolytic lesions.

value above 1886 Gv was defined as the lesion area that was simulated to be 1 mm and the elastic modulus of the lesion E = 1 MPa. (Fig. 2) Three different internal fixation configurations were assembled. Internal fixations included a 3.5 mm locking plate and elastic intramedullary nails. Six models were established as follows (Fig. 3).

Osteolytic Lesions Located in the Femoral Neck

In the model A1, conventional plate construct, three screws were inserted into the proximal femur from the posterolateral side of the proximal femur, the upper two screws were inserted into the femoral neck and placed in the capsule (not traversing the growth plate). One screw was fixed to the femoral calcar through the contralateral cortex; (model A2) titanium elastic intramedullary nails (TENs) were inserted in a retrograde fashion from the distal femoral metaphysis and two nail tips were placed in the epiphysis through the epiphyseal plate; (model A3) TENs were inserted in a retrograde fashion from the distal femoral metaphysis and two nail tips were placed in the lesion around the metaphysis.

Osteolytic Lesions Located in the Intertrochanteric Region

In the model B1, conventional method plate construct, three screws were inserted into the proximal femur from the posterolateral side of the proximal femur, two screws were placed in the epiphyseal cancellous bone and one screws penetrated the contralateral talus cortex; (model B2) TENs were inserted in a retrograde fashion from the distal femoral metaphysis and two nail tips were placed in the epiphysis through the epiphyseal plate; (model B3) TENs were inserted in a retrograde fashion from the distal femoral metaphysis and two nail tips were placed in the cancellous bone of the metaphysis.

The distal four screws were placed in the normal bone and penetrated the contralateral cortical bone. The model is imported into ANSYS software for meshing. The three-dimensional model of femur was simulated by 2.0–3.0 mm tetrahedral solid element, and the outer surface of cortical bone was simulated by 0.4 mm triangular shell element(Fig. 4). All screws were locked screws. The model and material properties of titanium plate (Synthes, Monument, CO, US), screw and TENs are as follows, titanium plate: elastic modulus = 110GPa, v = 0.34; 10: elastic modulus = 105GPa, v = 0.34; the geometric characteristics of locking plate (Da Bo Company, Dalian, China), screw and 10 are similar to those hardware approved by FDA. At the age of 8, the proximal femur of children is in the stage of growth and development. There are a lot of cartilage and cancellous bone in the proximal femur. The two methods of assigning material attributes to bones are as follows: modify the XML file through notepad in Mimics in the way of Look-up file, import the XML file into Mimics, import the XML file into Mimics, define the gray value above 1686 Gv as cortical bone, and the elastic modulus is 14.4GPa; The gray value of 1172 ~ 1685 Gv is defined as cancellous bone, and the elastic modulus is 0.75 GPa.

The physis was modeled as three adjacent concave disks with a 44 mm diameter and a 24 cm radius of curvature. The middle disk, modeling the "hypercellular" zone, was 1.2 mm thick. Two 0.3 mm concave plates modeling the perichondral zones sandwiched the hypercellular zone. A 0.1 mm thin wall surrounded the physeal construct to model the ring of Lacroix.[131415]

Material Parameters

The proximal femur of children is in the stage of growth and development when they are 8 years old. There are a lot of cancellous bone and cartilage in the proximal femur. When the stress does not exceed the threshold, the stress–strain relationship of proximal femur is very similar to that of many engineering materials. In order to simplify the model, the proximal femoral cortical bone was regarded as a continuous, anisotropic and inhomogeneous linear elastic material.[16]

Loading Compliance and Constraints

Two different loading conditions of walking of lower limbs as: (1) eccentric bearing load; and (2) eccentric bearing load plus torsional restraint (Fig. 5) were applied to test the fixation constructs,[17,18] It is predicted that there will be a peak value of joint load at an angle of about 20 degrees to the vertical axis of the femur. The composite load is longitudinal eccentric bearing load and external rotation torque 2000 N* mm. According to much of literature, contact method and contact relationship are studied. Friction was used between internal fixation screw and femur, and the friction coefficient was 0.46.[19,20]

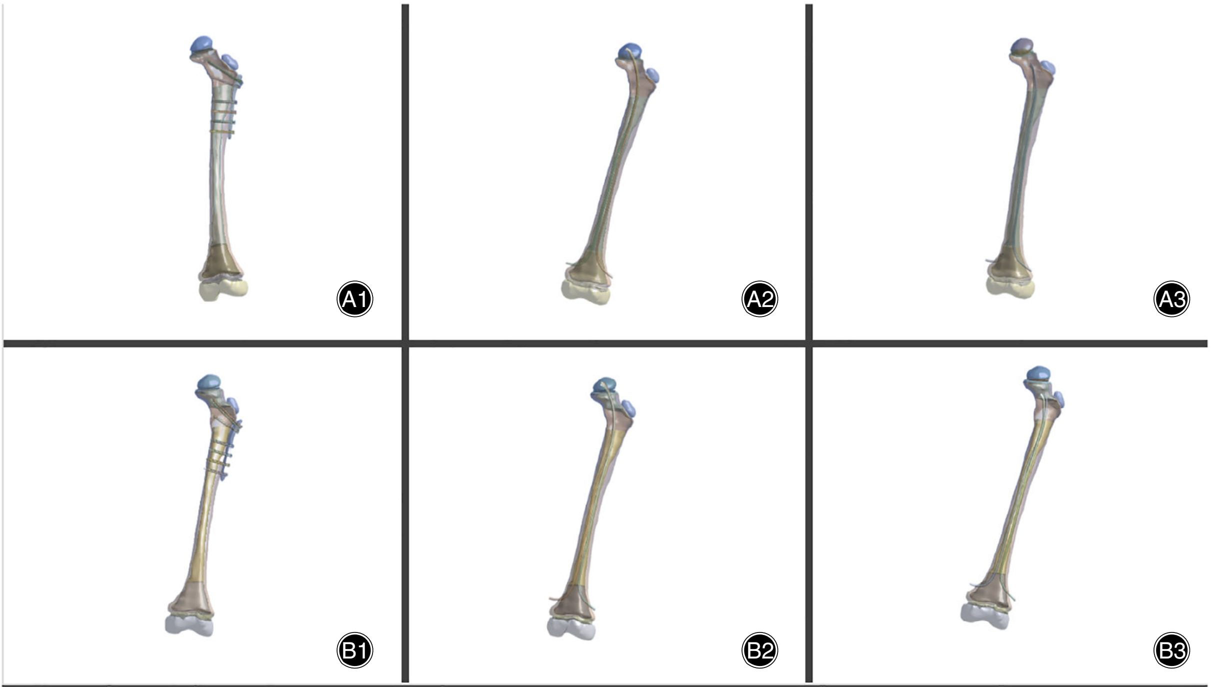

Fig. 3 A1–A3: Osteolytic lesions located in the femoral neck: (model A1) Three proximal femoral screws were inserted from the proximal posterolateral femur, two were placed in the cyst cavity and one penetrated the contralateral femoral talus cortex; (model A2) TENs were penetrated from the distal femoral metaphysis and two nail heads were placed through the epiphyseal plate at the femoral epiphysis; (model A3) TENs were penetrated from the distal femoral metaphysis and two nail heads were placed at the distal femoral metaphysis. Epiphyseal lesions. B1–B3: Osteolytic lesions were located between the trochanters: (model B1) three screws were inserted into the proximal femur from the posterolateral side of the proximal femur, two were placed in the epiphyseal cancellous bone and one penetrated the contralateral femoral talus cortex; (model B2) TENs were penetrated from the distal femoral epiphysis and two nails were placed in the epiphyseal plate.(model B3) TENs were penetrated from the distal metaphysis of femur and two nail heads were placed in the cancellous bone of the metaphysis.

Main Measures in FEA

Failure load was measured as eccentric bearing load of cortical bone at a certain point, when the yield strain of cortical bone reached 1.13 and caused fracture.[21] When the yield strain reaches 1.13, the cortical bone fracture is assumed to occur. At this moment the greater the eccentric bearing load, the better the supporting effect of internal fixation, and the lower the risk of pathological fracture.

In addition, we also verify the effectiveness of the finite element model. Due to ethical reasons, it is impossible to study the living bone through experiments, and the corpse bone cannot completely simulate the real osteolytic lesions. CT-dicom of osteolytic lesions of proximal femur were collected. Three dimensional printing technology was used to simulate the proximal femur, and the photosensitive resin material similar to cortical bone was used to simulate model B1. The model fractured at 2378.5 N. The fracture location is basically consistent with the stress concentration point of the finite element model under the same eccentric bearing load, so we infer that the finite element model is effective. (Figs 6 and 7).

The focus model and constraint state given in method are used to simulate different working conditions. The model is adjusted through simulation calculation to make the convergence of the model more stable. Three to six tests are carried out under different working conditions, and the following results are obtained.

Results

The Lesion Located at the Femoral Neck near the Metaphysis

When there was no internal fixation, the simulated failure load is 980 N under eccentric bearing load and 960 N eccentric bearing load plus torsional restraint. In all three models, the yield lesions of cortical bone were concentrated in the femoral talus, and the destruction point was located near the distal boundary between osteolytic lesions and normal bone tissue, where the yield strain of cortical bone of femoral talus was the largest.

Among the three internal fixation methods, model A1 and model A2 were fixed with titanium plate and elastic intramedullary nail through epiphyseal plate respectively, and the failure load was increased by 20%, but some cortical bones of model A1 had stress shielding effect, which proved

Fig. 4 Mesh model after assembly and internal fixation.

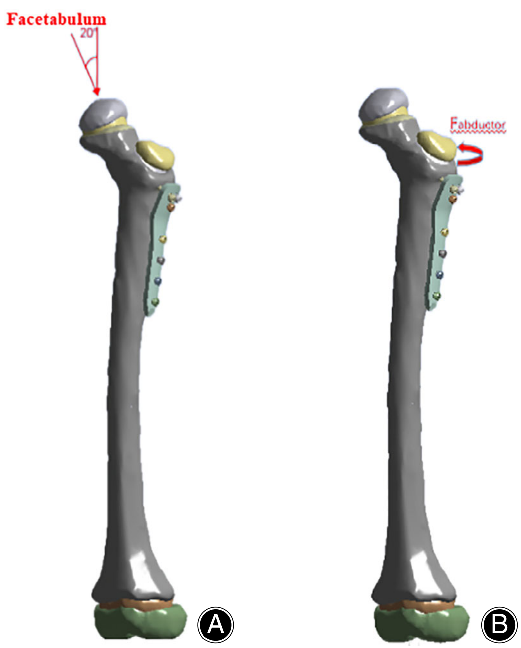

Fig. 5 F acetabulum: Contact force from the acetabulum roughly 20° inclination with respect to the vertical axis of the femur; F abductor: Force from the abductor muscles. External torsional restraint force of 2000 Nmm is applied to the greater trochanter.

both internal fixation methods can effectively reduce the risk of pathological fracture. Under the condition of equivalent failure load, the lateral bone cortex of model A1 has stress shielding, so model A2 is better. Model A3 is elastic intramedullary nail, but not through epiphyseal plate fixation, and the failure load is increased by 0%, which proves that the effect of internal fixation on the improvement of eccentric bearing capacity is not significant (Fig. 8), (Fig. 9), (Table.1).

Fig. 6 The picture shows the pressure test and the cracking part of the model.

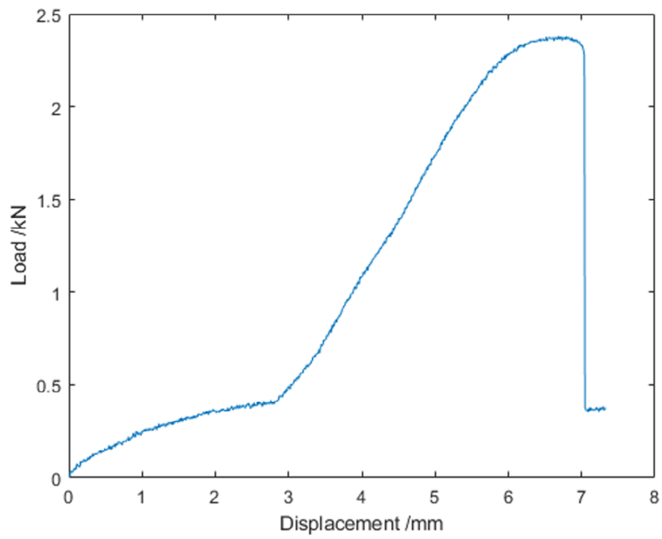

Fig. 7 Test data of pressure test.

The Lesion Located at the Pertrochanteric

When there is no internal fixation, the measured failure load is 990 N under eccentric bearing load and 970 N under eccentric bearing load plus torsional restraint.

In all three models, the yield lesions of cortical bone were concentrated in the femoral talus, and the destruction point is located at the distal boundary of osteolytic lesions

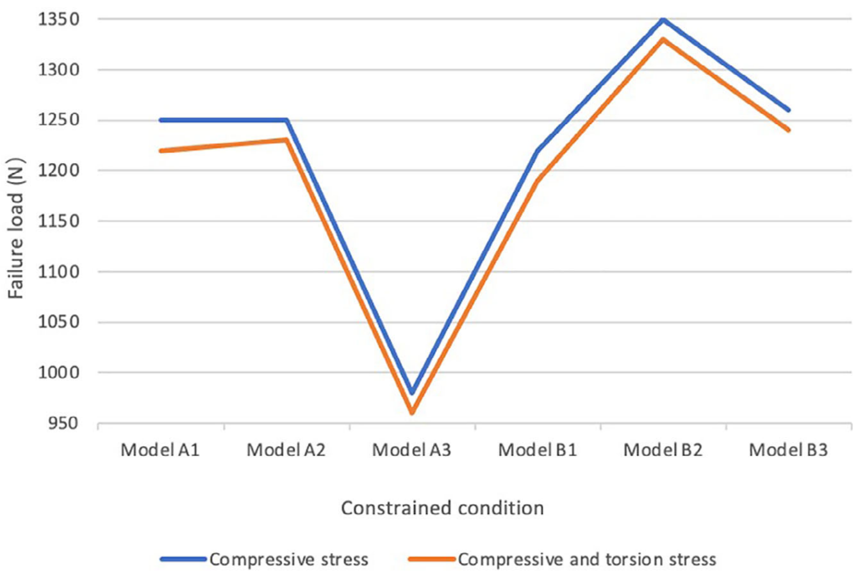

Fig. 8 The combined load was longitudinal eccentric bearing load and external rotation and torsional restraint force of 2000 N*mm. When the yield strain of bone cortex at a certain point reached 1.13, the load of Eccentric bearing load and combined load were measured.

and normal bone tissue, where the yield strain of femoral calcar cortical bone is the largest.

Among the three internal fixation methods, the three internal fixation methods can effectively reduce the risk of pathological fracture. The failure load of model B1 was increased by 18.8%, model B2 was increased by 26.7%, and model B3 was increased by 21.4%. As with model A1, some cortical bones of model B1 had stress shielding effect, which proved all internal fixation methods can effectively reduce the risk of pathological fracture. In comparison, model B2 has the highest failure load, so we think model B2 has a better internal fixation method (Figs 8 and Fig. 9, Table 1).

The higher the failure load, the better the internal fixation effect. According to the results of finite element analysis. With the lesion located at the femoral neck near the metaphysis, the failure load of model A2 was the largest (1250 N). With the lesion located at the pertrochanteric, the failure load of model B2 was the largest (1350 N). With this, we used three internal fixation methods for the two osteolytic disease models of the femoral neck and intertrochanter, and the final simulation mechanics results were that the TENs through the epiphyseal plate were the best under two different working conditions (eccentric bearing load, eccentric bearing load plus torsional restraint).

Discussion

For femoral neck lesions, Among the three internal fixation methods, model A1 and model A2 were fixed with titanium plate and elastic intramedullary nail through epiphyseal plate respectively, and the failure load was increased by 20%, but some cortical bones of model A1 had stress shielding effects, which proved both internal fixation methods can effectively reduce the risk of pathological fracture. Under the condition of equivalent failure load, the lateral bone cortex of model A1 has stress shielding, so model A2 is better. For pertrochanteric lesions of the femur, model B2 showed the best supporting role of internal fixation and largest eccentric bearing load, the failure load is the largest.

Treatment Status of Osteolytic Lesion of Proximal Femur and Case Selection of FEA

Currently, curettage and bone grafting are widely recognized as the surgical treatment for osteolytic lesions of the proximal femur. However, pathological fracture secondary to recurrence is always difficult to treat, which makes it necessary to choose appropriate internal fixation. Usually, the choice of internal fixation is based on the surgeon's experience and judgment. However, even in the case of proper internal fixation, pathological fracture still occurs clinically (Fig. 8). In the last decade, elastic intramedullary nails have been gradually used in the field of pediatric orthopedics. The main choices of internal fixation methods are plate or TENs when treating osteolytic lesions of the proximal femur. However, there is no unanimous conclusion as to which internal fixation reduces local stress. Moreover, whether these internal fixation methods used in pediatric orthopedics conform to biomechanical principles has not been reported.

In this study, we selected an 8-year-old child to establish a finite element model for the following reasons:[1] osteolytic lesions (aneurysmal bone cysts, bone cysts) tend to occur in juvenile and adolescents;[2] for children older than 12 years, the growth potential of the proximal femoral epiphyseal is lower since skeletal maturity is approaching and the screws can usually be fixed through the physis, this is the reason we did not include children older than 12 years in this study. Although the properties of bones do vary for individuals of different ages, we believe that the results of this study are suitable for application in patients of different ages, which will help clinicians treat this disease more properly with biomechanical proof.

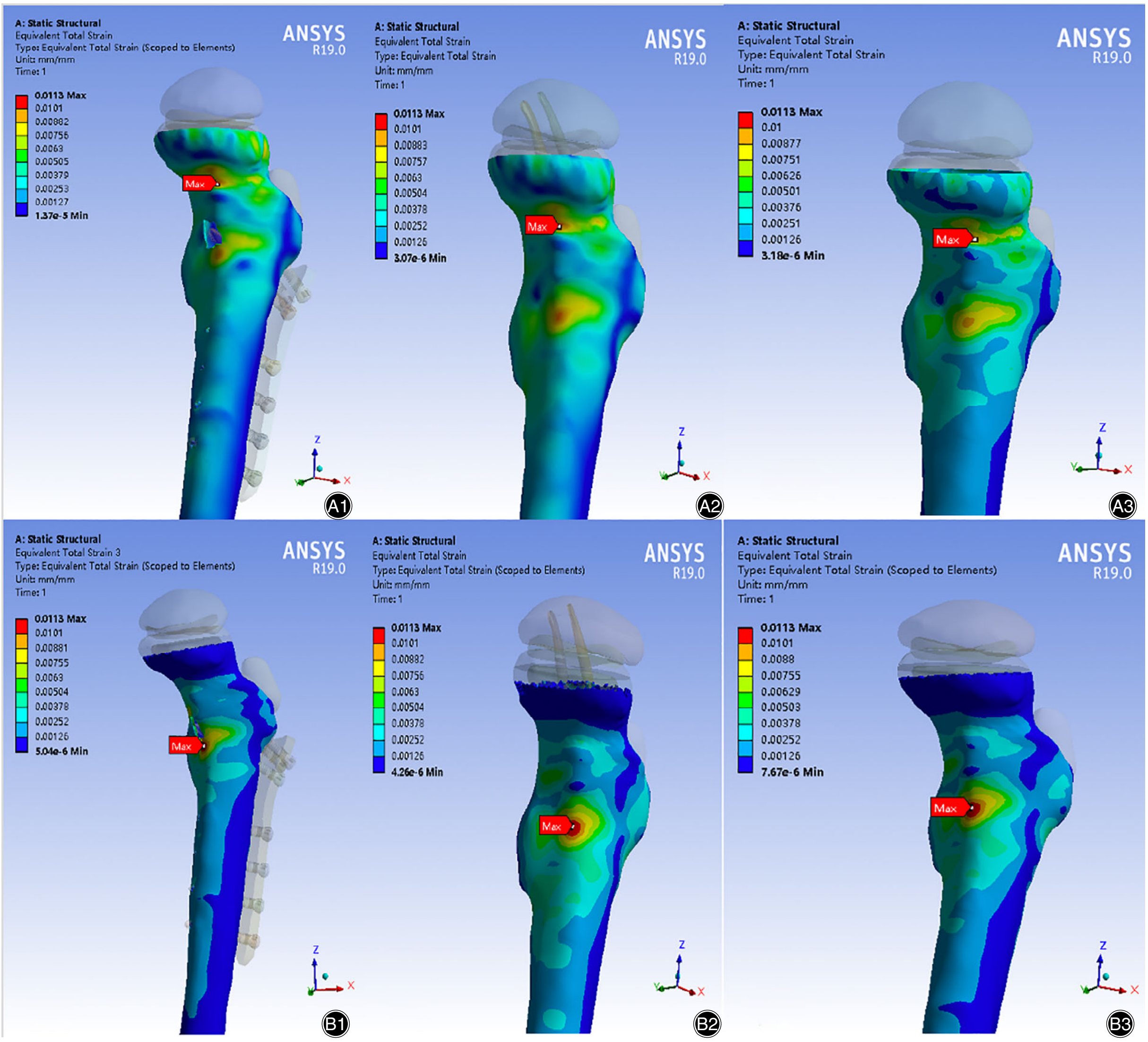

Fig. 9 A1–A3. When the yield strain of bone cortex at a certain point reached 1.13, the load of eccentric bearing load were measured; B1–B3 (model B1–B3): When the yield strain of bone cortex at a certain point reached 1.13, the load of eccentric bearing load were measured.

TABLE 1 Failure load of each model, when the yield strain reaches 1.13

Constrained condition	Failure load(N)					
	mModel A1	Model A2	Model A3	Model B1	Model B2	Model B3
Compressive stress	1250 N	1250 N	980 N	1220 N	1350 N	1260 N
Compressive and torsion stress	1220 N	1230 N	960 N	1190 N	1330 N	1240 N

Note: Yield strain of bone cortex at a certain point reached 1.13.

Selection of Internal Fixation Scheme For Osteolytic Lesions of Proximal Femur

At present, plate and TENs are widely used in the treatment of osteolytic lesions of proximal femur. The traditional treatment of osteolytic lesions of the femoral neck is plate.[9] In model A1 and model B1, a traditional plate was used as the internal fixator. Through finite element analysis, we found that the stress of only one screw in model A1 changed significantly after the bone structure was loaded. In contrast, all three screws have stress distributions in model B1. Nevertheless, the failure load in model A1 is slightly better than that in model B1, which could be explained by that the force arm of model B1 is longer than that in model A1, which may lead to pathological fracture with smaller failure load. Erol *et al.*[11] proposed in 2016 that elastic intramedullary nail fixation could achieve good results in the treatment of greater trochanter lesions. In this study, the same fixations as used in Erol B's study were designed in model A3 and model B3. We further found that in model A3, the internal fixations did not play a significant supporting effect under three kinds of forces, on the other hand, fixation in model B3 also showed a better supporting effect compared with that in model B1, but not as good as in model B2.

Through finite element analysis, we found that in model A3, if the lesion recurred completely near the epiphysis, the internal fixation methods could not play a local supporting role, at the same time, the internal fixation support effect in model A1 and in model A2 were the same. This result changes our traditional choice of internal fixations. If lesion recurs partially and the bone near the physis remains intact, we can refer to model B1 and model B3. In both cases the internal instructs can play a certain supporting role. Comparing model B1 and model B3, The failure load is similar, and the effect of internal fixation is also similar.

In this case, however, we recommend the TENs in model B3. The reasons are as follows: (i) the internal fixation with plate is traumatic and requires extensive peeling of periosteum; and (ii) the plate has biological occlusion on the proximal lateral femur, which affects the local blood supply of the cortex, and hinders and prolongs the healing time of the cortex. Plate, TENs or Kirschner wires are commonly used to treat osteolytic lesions of the femoral neck. However, the Kirschner wire is often not fixed firmly and cannot be retained in the body for a long time. That is why we excluded Kirschner wire in this study. We suggest that model A2 and model B2 in this study can be used to imitate this lesion.

TENs through Various Epiphysis

For the treatment of osteolytic lesions of the proximal femur, we recommend scraping and bone grafting combined with elastic intramedullary nail fixation inserted up to the epiphysis. Flynn *et al.*[21] asserted that the treatment of ulnar fracture with intramedullary nailing passing through the olecranon epiphyseal plate did not affect the growth of epiphysis. Staheli[22] speculates that TENs may traverse the growth plate. For tumors, plan to leave fixation until the lesion is healed. In addition, Flynn and other authors,[23-25] described placing the proximal tip of the nail entering the lateral cortex of the femur distal to the greater trochanteric. Trochanteric apophysis with a smooth pin without any clinical implications with regard to future growth, indicated that TENs should be performed. Placing the nails more proximally can aid the control of rotation and angulation, reduce the forces at the fracture site, and maintain fracture stability. The growth potential of the epiphyseal plate of the femoral neck is rather great, similar to epiphyses of olecranon and trochanteric apophysis. So, we believe that premature epiphyseal closure is very unlikely to occur after TENs crossing the epiphyseal plate of the femoral neck, and clinically we did not observe premature epiphyseal closure with leg length discrepancy in treating these patients with TENs crossing the epiphyseal plate. Traditionally, it was believed that plate could achieve good supporting effect and prevent pathological fracture after operation in treating osteolytic lesions of proximal femur. Through this biomechanical study, we found that TENs are similar, not only superior to plates in local

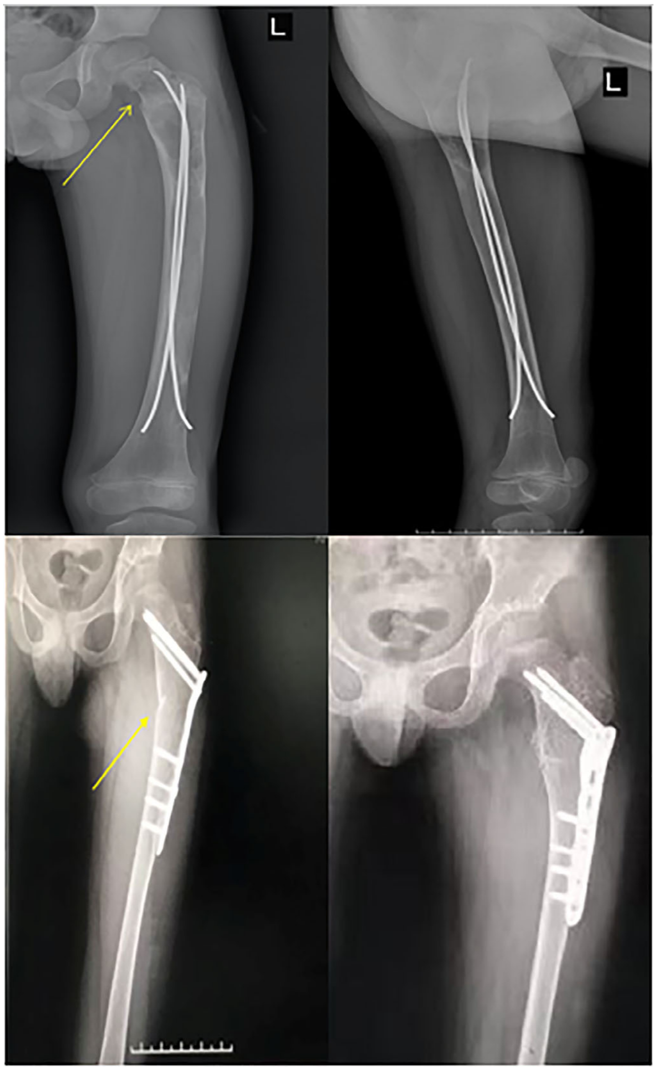

Fig. 10 Two children (Left: 8-year-old, boy, the case was diagnosed as fibrous dysplasia ; Right: 9-year-old, boy, the case was diagnosed as bone cyst) got proper internal fixation, however pathological fracture still occurred clinically.

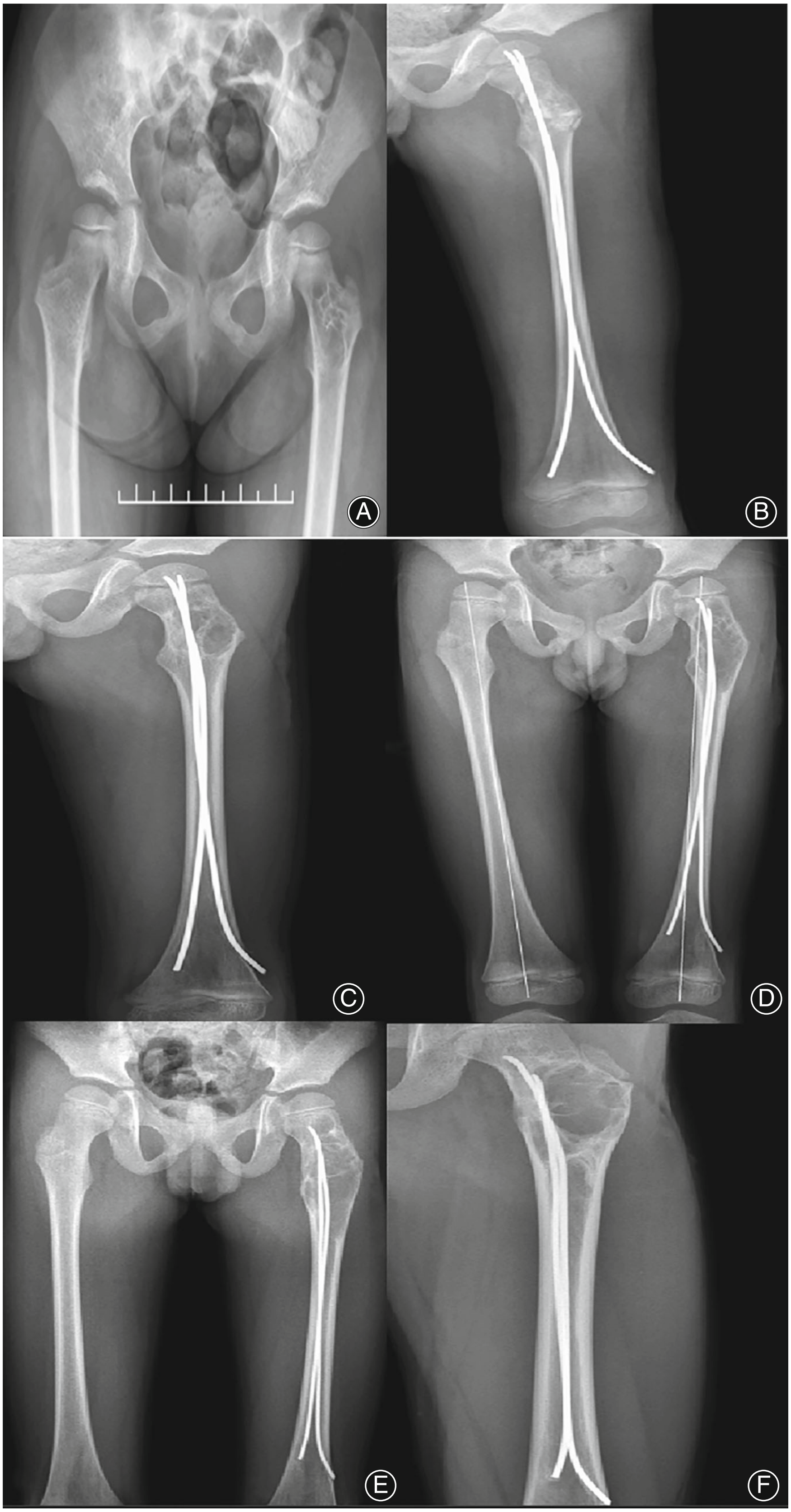

Fig. 11 Proximal femoral osteolytic lesions in 8-year-old children, Pathological diagnosis was Aneurysmal bone cyst, (A) preoperative treatment; (B) 2 months after operation; (C) 5 months after operation; (D) 8 months after operation; (E) 14 months after operation; (F) 25 months after operation. Internal fixation of the children shrank back the lesion for reoperation in 25 months after operation.

supporting effect, and also obviate stress shielding, which makes it harder for the cortex to heal. Meanwhile, compared with TENs, titanium plate is more traumatic.

Clinically, TENs can effectively reduce the risk of pathological fracture in the treatment of greater trochanteric osteolytic lesions. However, as time goes on, TENs gradually moves away from the epiphyseal plate into the lesion. According to model A3 of this study, we can infer that TENs without contacting the cancellous bone have no supporting effect at all. In this case, we need to be alert to the risk of pathological fracture and if timely surgical intervention is indicated. Clinically, we have a similar situation with pathological fracture (Fig. 10) Applying this biomechanical study to clinical practice, we can conclude when the risk of pathological fracture is high, within 2 years of postoperative follow-up, once, the recurrence is active or invasive, and when the internal fixation is still in contact with cancellous bone, we can temporarily postpone the operation until the focus is at rest, which can greatly improve the cure rate. When TENs are in the state of model B3, in clinic, such children can take part in physical exercises. (Fig. 11).

Limitations

The finite element method as a mathematical simulation method of theoretical mechanics is applied in this study to simulate lesion of proximal femur in children. However, we have to admit that this study has certain limitations: (i) three-dimensional finite element models of proximal femur of children were generally established on the basis of CT scanned skeletal data. However, the biomechanics of soft tissues such as muscle and ligament also play important roles in the proximal femur. The mechanical analysis data in this study may not be exactly the same as the actual state and need to be further improved; (ii) during the analysis process, many assumptions and simplifications were used to the geometry and stress state of the model. How to minimize the bias of assumptions and simplifications is a key research direction in the future; (iii) the femoral neck shaft angle and anteversion angle of children vary greatly in different age groups. This study only reflects the situation of an 8 year old, and the design of experimental angle cannot represent all the situations of different age groups; (iv) the effect of screw thread on the model was not considered in this study. This can be a difficult part to simulate in the lesion. We expect to pay attention to screw thread in further study with consideration of sliding coefficient. Even with these limitations, however, the comparisons as presented provide worthwhile and novel information for the orthopedic surgeon considering different treatment options. The stress results from the study, for example, detail the changes in load transfer for the bone and each part of the construct otherwise difficult to measure clinically and experimentally; and (v) the validity of the finite element model lacks strict evidence.

Conclusion

TENs through the epiphyseal plate is the best internal fixation method for the treatment of femoral neck lesions and intertrochanteric lesions. Although this study needs clinical confirmation of its practicability in the treatment of osteolytic lesions in the proximal femur, we have obtained this preliminary conclusion in the finite element analysis, and can also give clinicians a clinical suggestion with a mechanical theoretical basis.

Author Contributions

Bo Xiao and Yi-chen Wang participated in the planning of the study and performed the operations. Dan Yang and Yi-chen Wang collected the data and participated in manuscript writing. Xiang Li and Yu-guo Zhang design finite element model, 3D printing and biomechanical experiment. Li-hua Zhao and Yi Luo coordinated the study and had overall responsibility. Yi-chen Wang, Liang-Chao Dong, Qi-Chao Ma and Yi Luo revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Data Availability Statement

All the data used in the article can be obtained from the medical record information system of Shanghai Children's Hospital, Shanghai Jiao Tong University. Any questions or enquiries regarding the present study can be directed to Yi Luo, MD (luoy@shchildren.com.cn), as the corresponding author.

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