Title

Efficacy of low-intensity pulsed ultrasound treatment for surgically managed fresh diaphyseal fractures of the lower extremity: multi-center retrospective cohort study

Running title

LIPUS for surgically managed fracture

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Abstract

Background

The effects of low-intensity pulsed ultrasound (LIPUS) has no evidence on surgically-managed fresh fractures. We performed a multicenter retrospective cohort study to investigate the effects of LIPUS on surgically-managed, fresh fractures.

Methods

This study includes patients with surgical treatment for diaphyseal fractures of the femur or tibia between August 2009 and July 2010 collected from 14 institutions. Outcome was the union period. We performed an analysis overall and on fracture site, fracture type, soft tissue condition, and fixation on 78 cases in our LIPUS group and 63 cases in our control group.

Results

There was no significant difference in distribution of cases, with the overall comparison showing no significant difference between the two groups with regard to union period. Analyses comparing subgroups, however, showed a significant difference between the two groups, particularly in type C fractures, regardless of all case analysis or closed case analysis ; there was an approximately 30% reduction in union period on LIPUS group. There were also cases requiring reoperation due to lack stability, even among the type C fractures.

Conclusions

LIPUS is effective for surgically-managed, fresh, type C, comminuted, diaphyseal fractures of the lower limbs when there is appropriate stability at the fracture site.

Text

Introduction

The conditions on the use of ultrasound for promoting bone union in an animal fracture model was published by Duarte in 1983 [1]. Subsequently, the effects of low-intensity pulsed ultrasound (LIPUS) on bone union in fracture repair were confirmed through a range of basic research studies. The clinical effects of LIPUS have been confirmed on both fresh fractures with conservative treatment and on surgically-managed fractures with delayed union or nonunion.

In 1998, Japanese insurance began to cover LIPUS as a treatment for delayed union and nonunion. In 2008, it was also made available for fresh, postoperative, open or comminuted fractures. However, there is still insufficient, substantiated evidence for the effects of LIPUS on surgically-managed fresh fractures. Accordingly, we investigated the effects of LIPUS on this type of fracture through a multicenter, retrospective cohort study at Okayama University, with collaboration from Okayama University's associated hospitals.

Materials and methods

We performed our study with 14 hospitals associated with the author's University and divided them into those actively using LIPUS (active hospitals) and those not using LIPUS (non-active hospitals). We prospectively gathered information on cases involving the use of LIPUS from active hospitals under the criteria and protocol given below. In addition, we based our control group on cases which did not involve the use of LIPUS, which we gathered retrospectively during the same period and under the same criteria, from both the active and non-active hospitals. Subjects were patients who received surgery for diaphyseal fractures of the femur or tibia between August 2009 and July 2010. Patients in the LIPUS group received therapy with the SAFHS2000J (Teijin, Tokyo, Japan). We used the same follow-up protocol for both the control and LIPUS cases. Approval was obtained from the institutional review board, and informed consent was obtained from all subjects. Differences between groups were analyzed using Mann–Whitney U-test and Pearson's chi-square test where appropriate. Results were considered statistically significant when p-value<0.05.

Criteria and protocol

Including criteria in the study are, patients needed to be ≥16 years of age, speak Japanese, consent to participate in the follow-up, and have a fresh femoral or tibial diaphyseal fracture, either open (Gustilo type I, II, or IIIa) [2, 3] or closed, for which LIPUS was available within three weeks of injury. We excluded patients that were <16 years of age, had fractures in bones other than the femur or tibia, had a metaphyseal or pathological fracture or a refracture, had a Gustilo type IIIb or IIIc open fracture or periprosthetic fracture, or if they did not consent to participate in the follow-up .

Outcome was the time until union, or the union period. Two orthopaedic experimental surgeons, the attending surgeons and the surgeons of the other hospitals associated with our University, determined the point of bone union, defined as the point when cortical bony continuity was found in at least three sites using bidirectional X-rays, while also taking into consideration the clinical findings and course. We considered bony continuity as the point when the callus had matured. Follow-up consisted of monthly radiography until union was confirmed and then follow-up surveys until rehabilitation was confirmed. We performed LIPUS for at least three months until union was achieved. Although treatment during recovery was subject to the protocol of each hospital, partial weight bearing began from an average of one month postoperatively with subsequent progression to full weight bearing dependent on the level of callus formation.

Results

Ninety cases were registered in the LIPUS group, but 12 were excluded because of the lack of adequate follow-up data. There were 88 cases from the same period in the control group with 25 excluded because of lack of proper follow-up. We had 78 cases in the LIPUS group with 51 males and 27 females (mean age 48.7 years) and 63 cases in the control group with 38 males and 25 females (mean age 46.9 years). In the LIPUS group, the therapy was started within 3 weeks after the injury. We found no significant differences in distribution of cases by fracture site, fracture type (AO classification A/B/C) [4] (Figure 1), soft tissue condition or fixation. With regard to final outcome, there were four cases requiring revision surgery in the LIPUS group and one in the control group (Table 1).

We performed an overall statistical analysis and subgroup analyses by fracture site, fracture type, soft tissue condition, and fixation for both the LIPUS and control groups, and also analyzed union period. Comparison between the groups showed no significant differences, with an overall mean union period of 4.2 and 4.8 months in the LIPUS and control groups, respectively. Subgroup analyses showed significant differences by site for “tibia” and by fracture type for “type C” fractures (Table 2, Figs 2–6). We performed additional subgroup analyses for the combinations of “fracture site/fracture type” and “soft tissue condition/fracture type” because of the markedly significant differences evident in “type C” fractures. These analyses showed significant differences in “femur/type C,” “tibia/type C,” and “closed/type C” fractures with the union period being approximately 30% shorter in the LIPUS group (Table 3, Figs 7–10).

Although the reoperation rate was high in the LIPUS group, there was no statistically significant difference between the two groups. We analyzed five cases which required revision surgery. One case originally had a large (5cm) bony defect, but union was achieved outside of the defect area. In the other four cases, the smaller nails used in the first operation were insufficient resulting in a nonunion due to lack of stability. Bone union was achieved with a bone graft in the first case and l exchange nailing [5, 6] in the other four cases (Table 4).

We performed subgroup analyses by open fracture group and closed fracture group separately. The open fracture group (LIPUS 21 cases, Control 22 cases) was not acceptable for statistical analysis, because the number of item was too small and had large defference. The closed fracture group (LIPUS 53 cases, Control 42 cases) was analyzed as same method as overall analysis (Table5・6). The number of item of “Tibia/typeA” was too small, it was not acceptable for statistical analylsis. The closed fracture group analysis showed significant differences in “type C” , “tibia” and “tibia/type C” fractures, and showed a tendency (P=0.067) of shortening the union period in the LIPUS group on ”femur/type C” fractures (Figure 10・11).

Discussion

Basic research, including in vitro [7] and animal studies [8-10], has shown that LIPUS accelerates the repair reaction of bone union at the cellular level. Busse [11] published a systematic review of clinical studies on previous LIPUS therapy in 2009. In fresh fractures which were treated conservatively, an analysis of 67 cases of diaphyseal fracture of the tibia [12], 61 cases of distal radius fracture [13], and 30 cases of scaphoid fracture [14] found LIPUS therapy to be effective. The LIPUS group had a 30%–40% shorter union period compared with acontrol group. Multicenter analysis [15, 16] also showed LIPUS to be effective in cases of delayed union and nonunion. In fresh, surgically-treated fractures, however, the effects are not as clear. One study demonstrated no LIPUS effect in 32 cases of diaphyseal fracture of the tibia with intramedullary nailing [17]. Another study showed that LIPUS shortened the period of cortical bridging with callus formation in 11 cases of diaphyseal fracture of the tibia with intramedullary nailing and 19 cases with external fixation [18]. We found no further studies demonstrating the effects of LIPUS on surgically-managed, fresh fractures.

Althought there was no significant difference overall in the union period between the LIPUS and control groups in this study, we found significant differences in subgroup analyses, mainly in groups that included type C fractures. The fracture site is not easily irradiated with precision in the femur where the irradiation site is not easily determined [19]. But the irradiation target of type C fractures, with its wide fracture area, is larger than the targets of types A and B, therefore, targeting is easy on type C fractures even in the femur. In addition, early weight bearing is possible in types A and B if the main segments are stabilized by bony contact after fixation. In these fracture types, stimulation through early and appropriate weight bearing [20] may already evoke the maximum potential for union at the fracture site, in which case, LIPUS would have no additional stimulating effect on the fracture. On the other hand, the fact that a significant difference between the two groups was found with type C fractures, in which contact cannot be achieved between the main fragments, suggests that the LIPUS stimulant effect is equivalent to an appropriate weight bearing stimulus. LIPUS may be particularly useful for this fracture type, because type C fractures cannot tolerate early weight bearing stimulus between the segments, even with surgery.

In the subgroup analysis of open or closed fracture , the factor has been considered to influence the union period. However we did not find significant difference excluded with the “closed/type C” fractures [Figure5, 9, 10]. Because Gustilo type IIIb and IIIc fracture were excluded in this study, there is a possibility that vascular condition around the fracture site in open fractures was almost as similar as it in closed fractures. Therefore, all cases analysis and the closed fracture group analysis might show almost same outcome .

The bias would be bigger on therapy between surgeons in Multi-center study. Therefore this study focused on diaphyseal fractures of the femur and tibia, because the operative method was standardized and determination of bone union is easier than othersites. Furthermore we tried to be the bias smaller on following condition. The surgeons were the members of trauma group of our university, over 10 years of acquirement doctor license, the chief director of orthopaedic trauma service on each hospital, and completed the AO trauma advance course. Secondary the assignment of cases could not randomized on this study design. Because LIPUS treatment for fresh postoperative fractures has been coverd by Japanese health insurance, it would have been ethically problematic to establish a control group, and thus, we were compelled to make a plan of a retrospective cohort study. However, we consider that this study has the significance of case series investigated the effect of LIPUS therapy for fresh fractures .

LIPUS does not compensate for lack of stability. Thus, even in type C fractures in which it was found to be effective in this study, revision surgery was still necessary when the fracture was not stable. For any fracture that may have lack of stability, and in which union has still not occurred three months postoperatively, reoperation (changing the fixation or adding a bone graft) should be considered instead of continuing LIPUS, which is ineffective in this situations.

Conclusion

We investigated the effect of LIPUS on surgically-managed, fresh fracture cases involving the shaft of the femur or tibia through a multi-center retrospective cohort study. We analyzed the union period outcomes of 78 cases in our LIPUS group and 63 cases in our control group. Although there was no overall significant difference found between the two groups, LIPUS appeared to be highly effective, showing significant differences, in a subgroup analysis of type C fractures in particular, and an approximately 30% shortening of union period. But there were cases requiring a revision surgery due to lack of stability, even among type C fractures. Therefore, LIPUS is effective on type C fractures having appropriate stability at the fracture site.

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Tables

Figure Captions

Figure 1. AO/ASIF comprehensive classification of fractures.

Figure 2. All cases, No significant difference was found overall between the two groups for the union period.

Figure 3. Fracture site, No significant difference in union period by fracture site was found for the femur, whereas, a significant difference was found for the tibia.

Figure 4. Fracture type, No significant difference in union period by fracture type was found for types A or B, whereas, a significant difference was found for type C fractures.

Figure 5. Soft tissue condition, No significant difference was found in union period by soft tissue condition for either open or closed fractures.

Figure 6. Fixation, No significant difference was found in union period between nailing or plating fixation.

Figure 7. Femur/Fracture type, No significant difference was found in union period by femur/fracture type for types A or B, whereas, a significant difference was found for type C fractures.

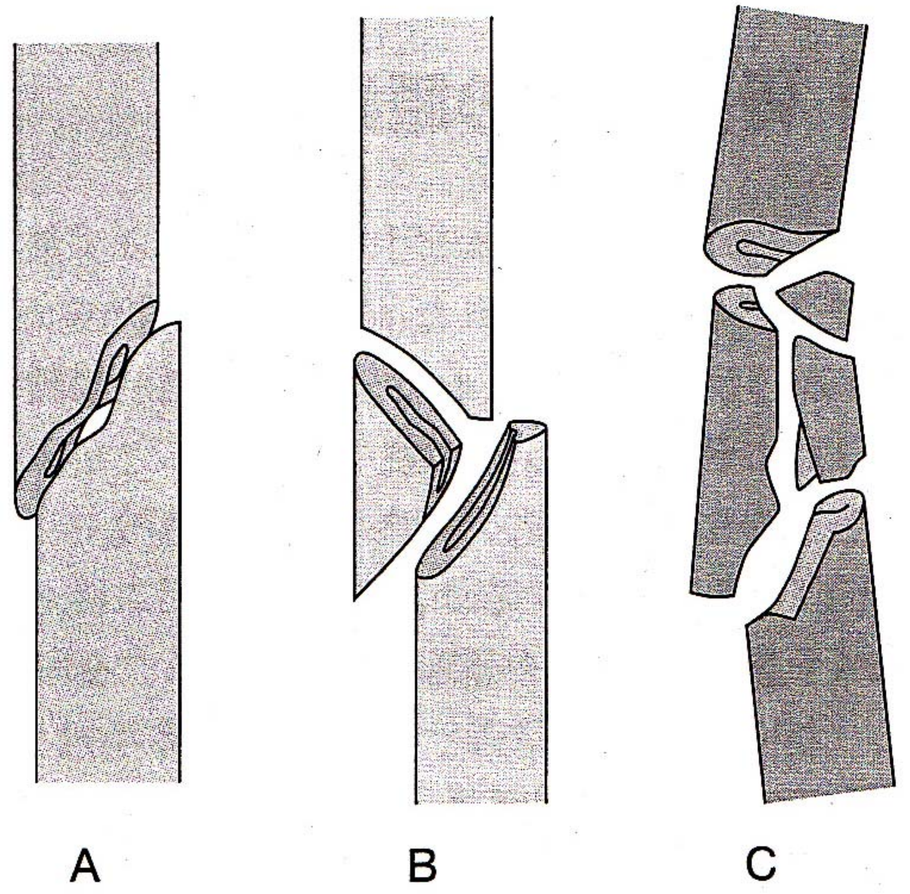
Figure 8. Tibia//Fracture type, No significant difference was found in union period by tibia/fracture type for types A or B, whereas, a significant difference was found for type C fractures.

Figure 9. Open/Fracture type, No significant difference was found in union period by open/fracture type for types A, B, or C

Figure10. Closed/Fracture type, No significant difference was found in union period by closed/fracture type for types A or B, whereas, a significant difference was found for type C fractures.

Figure11. closed fracture group, a significant difference was found for" tibia" and" tibia/C type "fractures. a tendency of shortening the union period was found in the LIPUS group on "femur/type C" fracture.

Figure1 AO/ASIF comprehensive classification of fractures



simple fracture wedge fracture comminuted fracture

Figure 2

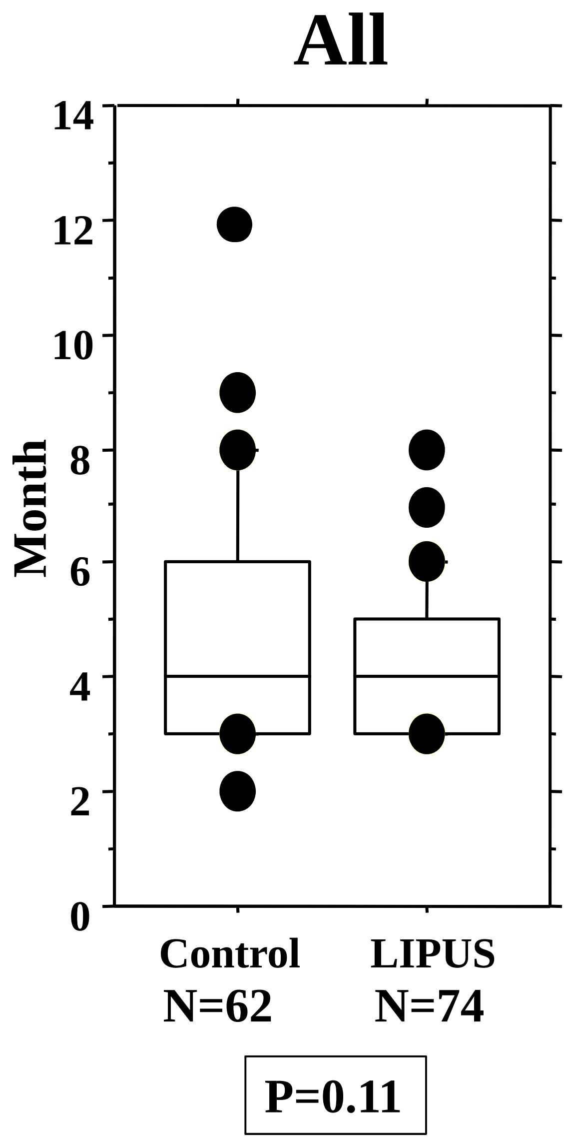


Figure 3

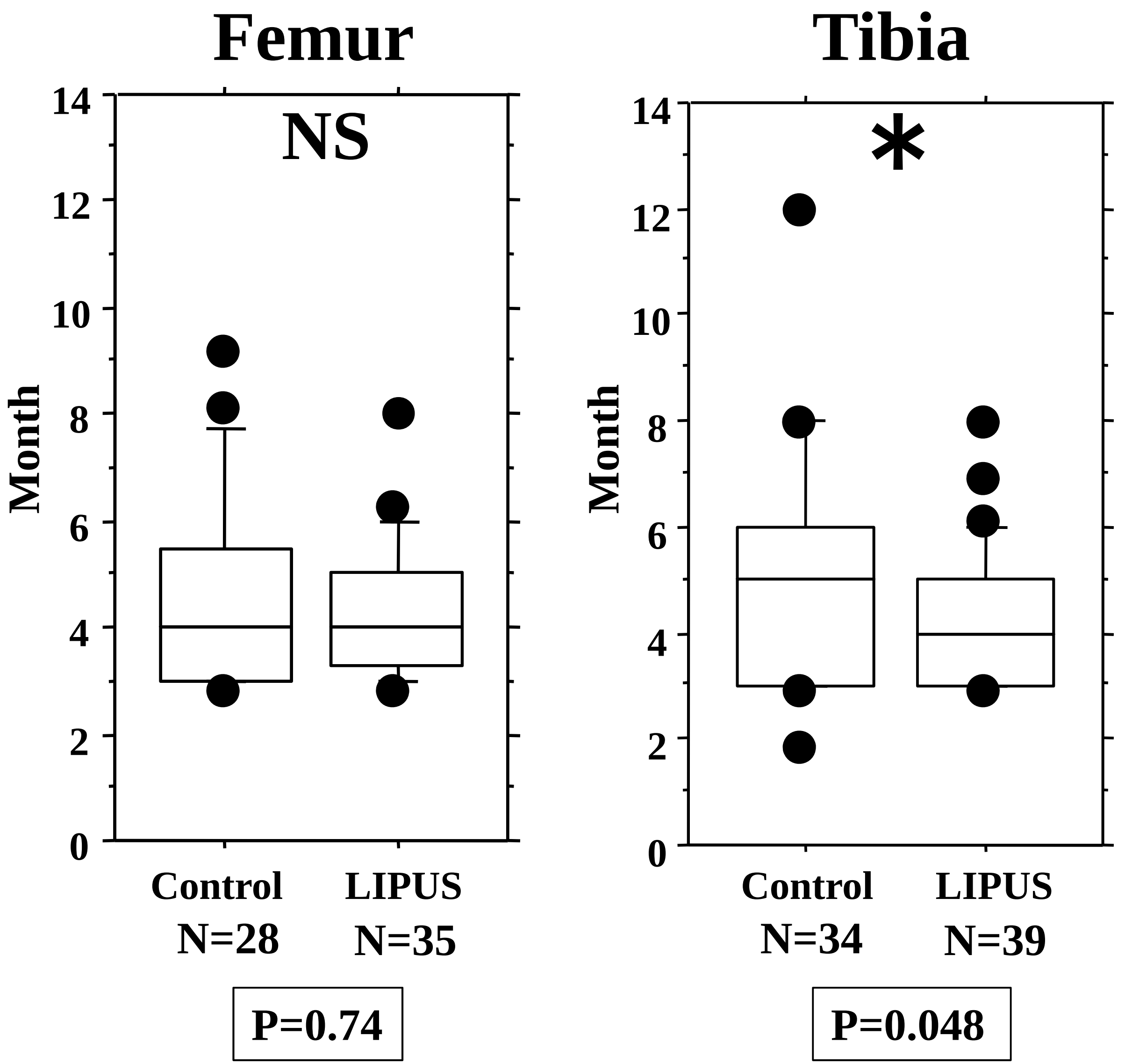
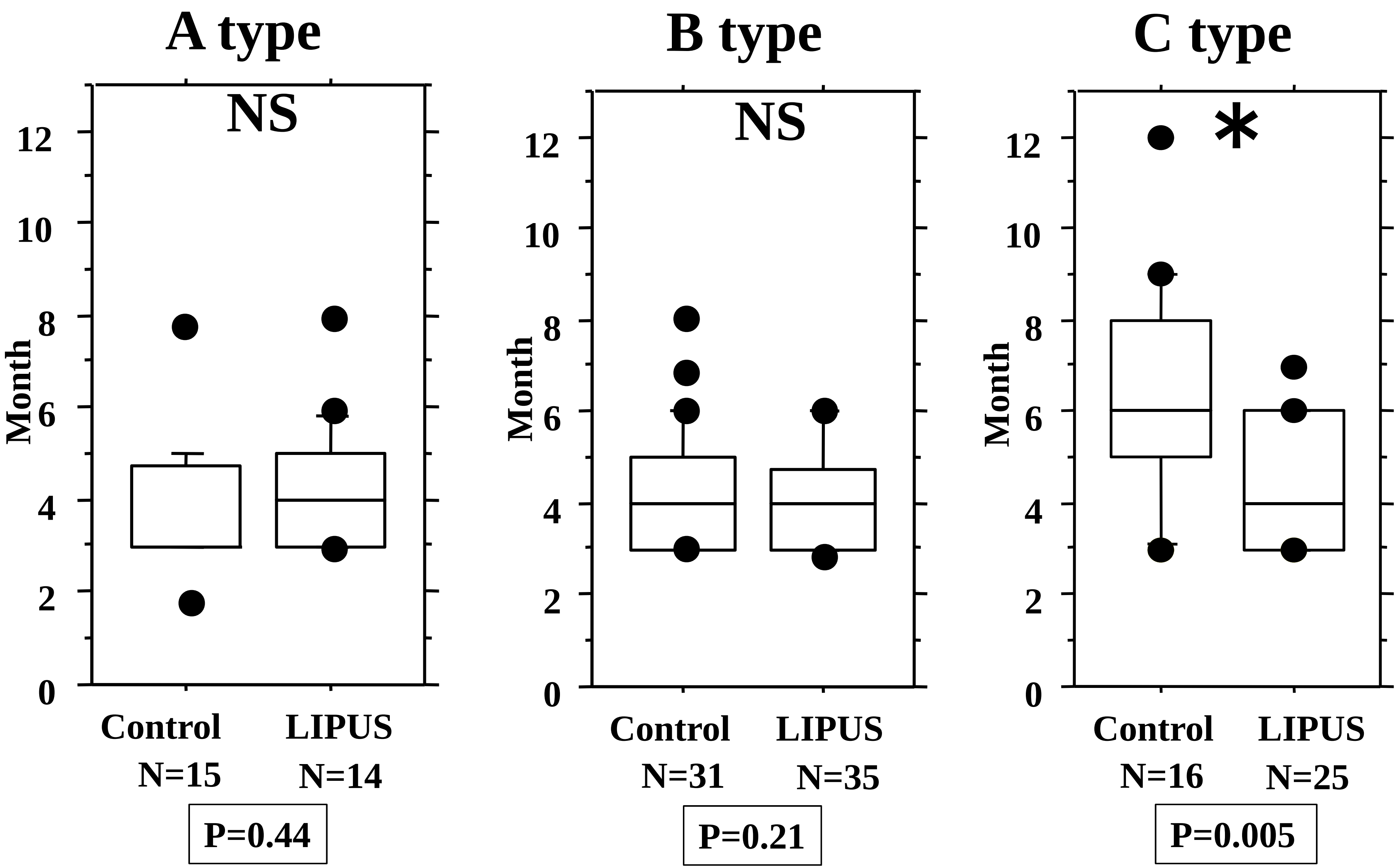

Femur
Tibia
NS
*
Month
14
12
10
8
6
4
2
0
Control
LIPUS
N=28
N=35
N=34
N=39
P=0.74
P=0.048

Figure 4



A type
NS
Month
12
10
8
6
4
2
0
Control
N=15
LIPUS
N=14
P=0.44
B type
NS
Month
Control
N=31
LIPUS
N=35
P=0.21
C type
*
Month
Control
N=16
LIPUS
N=25
P=0.005

Figure 5

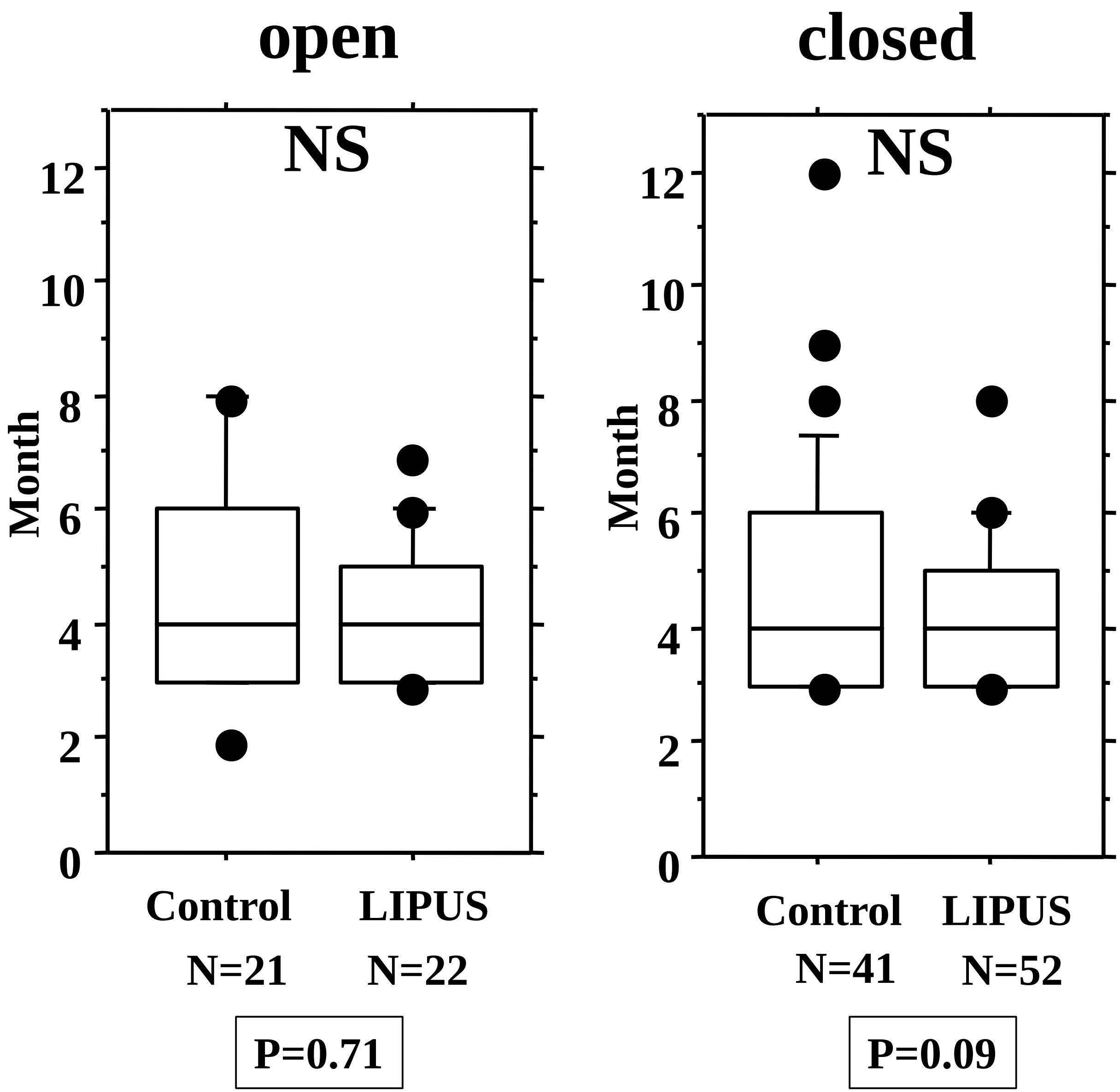
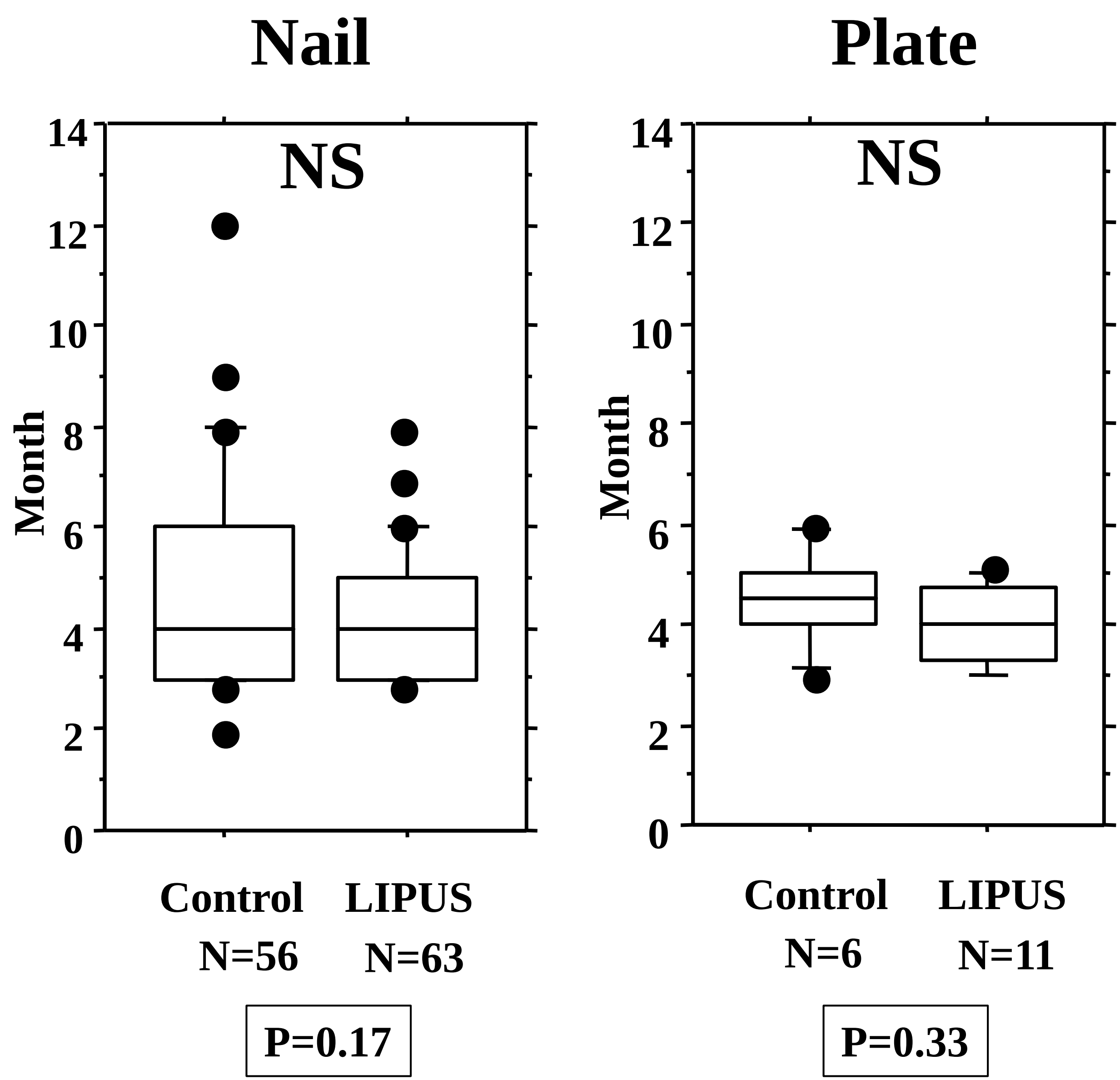

open
closed
NS
NS
Month
Month
0
2
4
6
8
10
12
Control
LIPUS
N=21
N=22
N=41
N=52
P=0.71
P=0.09

Figure 6


Nail
Plate
NS
NS
Month
Month
14
12
10
8
6
4
2
0
Control
LIPUS
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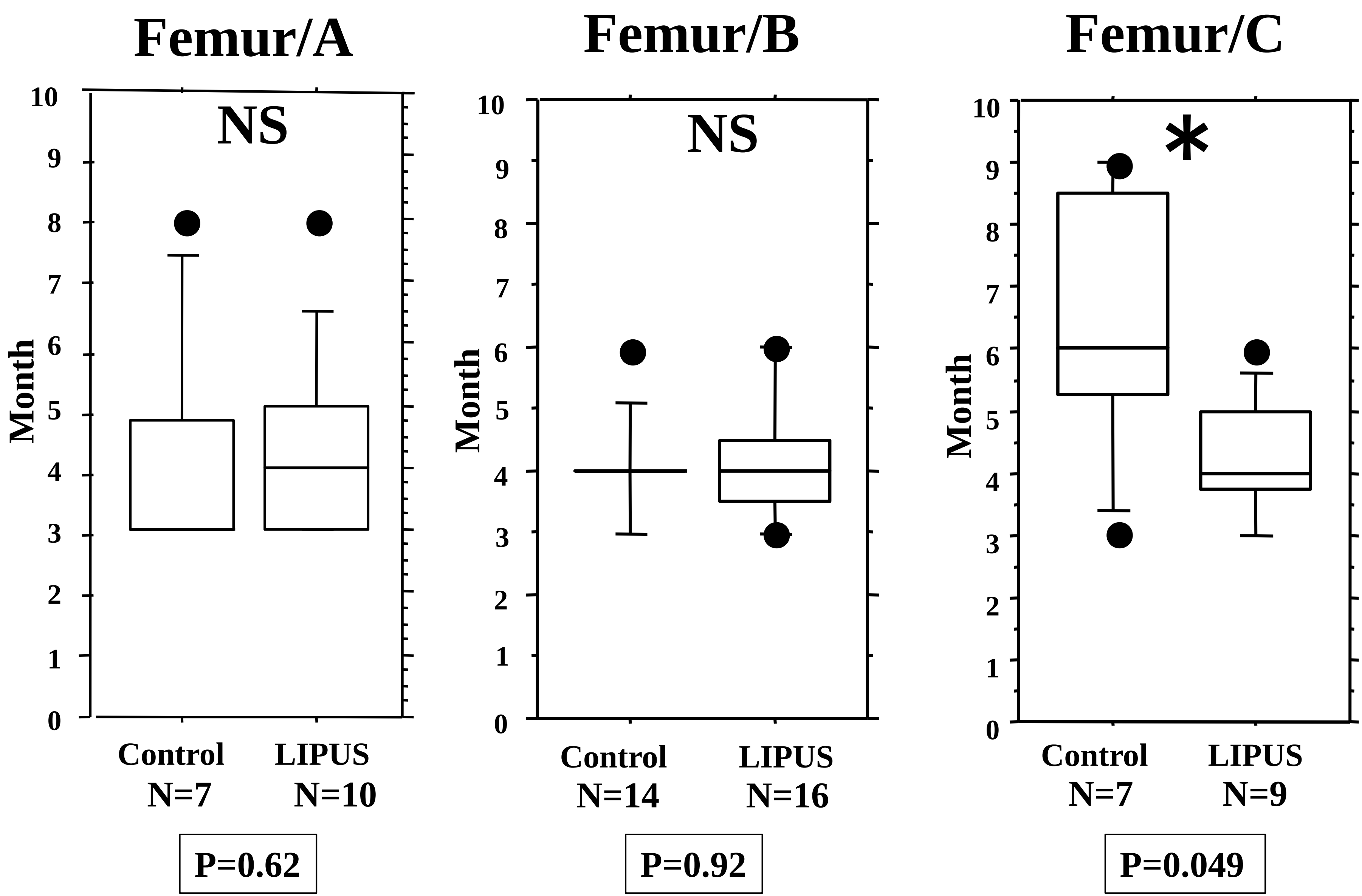
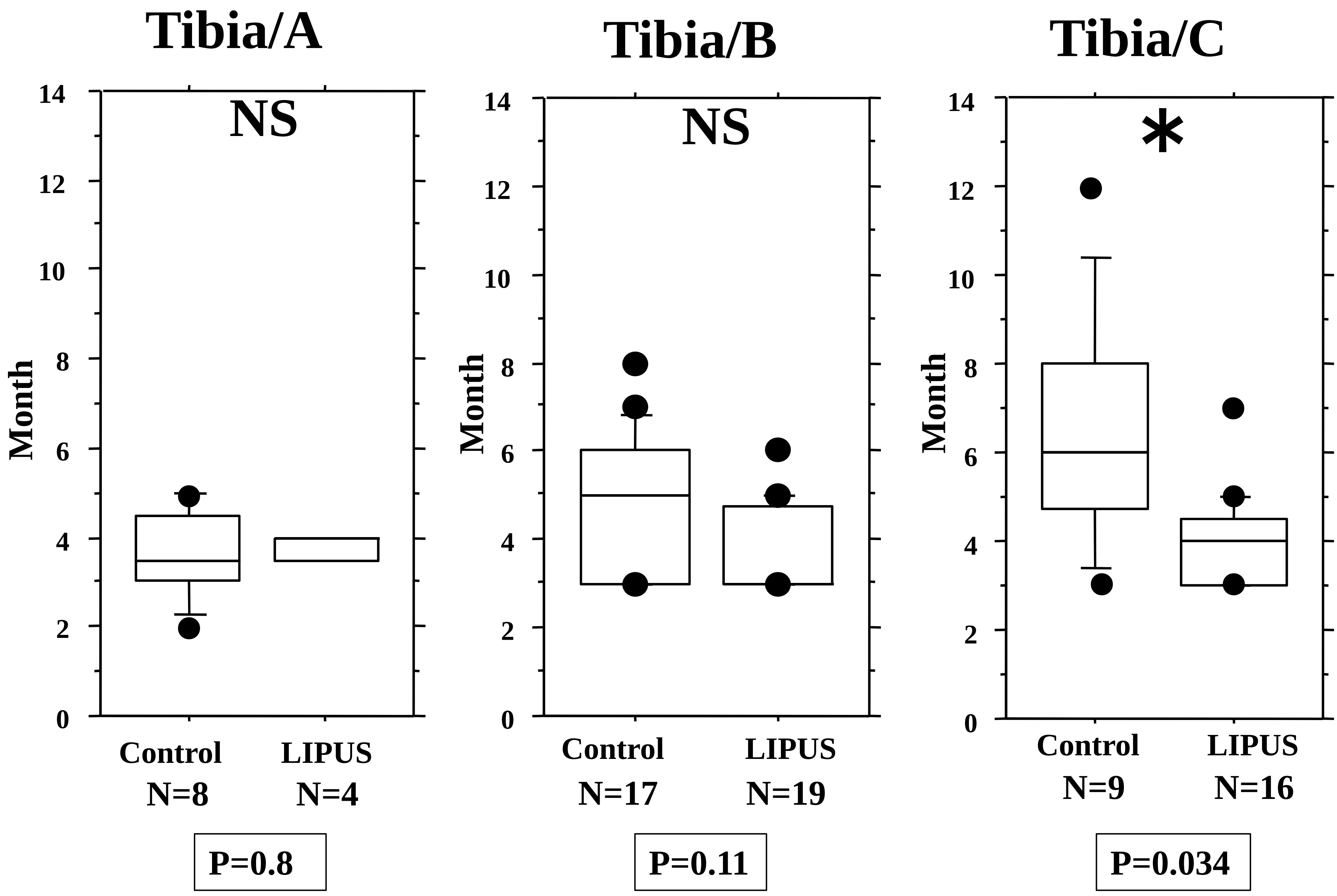
N=63
N=6
N=11
P=0.17
P=0.33

Figure 7



Femur/A
NS
10
9
8
7
6
5
4
3
2
1
0
Month
Control
N=7
LIPUS
N=10
P=0.62
Femur/B
NS
10
9
8
7
6
5
4
3
2
1
0
Month
Control
N=14
LIPUS
N=16
P=0.92
Femur/C
*
10
9
8
7
6
5
4
3
2
1
0
Month
Control
N=7
LIPUS
N=9
P=0.049

Figure 8



Tibia/A
NS
Month
14
12
10
8
6
4
2
0
Control
N=8
LIPUS
N=4
P=0.8
Tibia/B
NS
Month
14
12
10
8
6
4
2
0
Control
N=17
LIPUS
N=19
P=0.11
Tibia/C
*
Month
14
12
10
8
6
4
2
0
Control
N=9
LIPUS
N=16
P=0.034

Figure 9

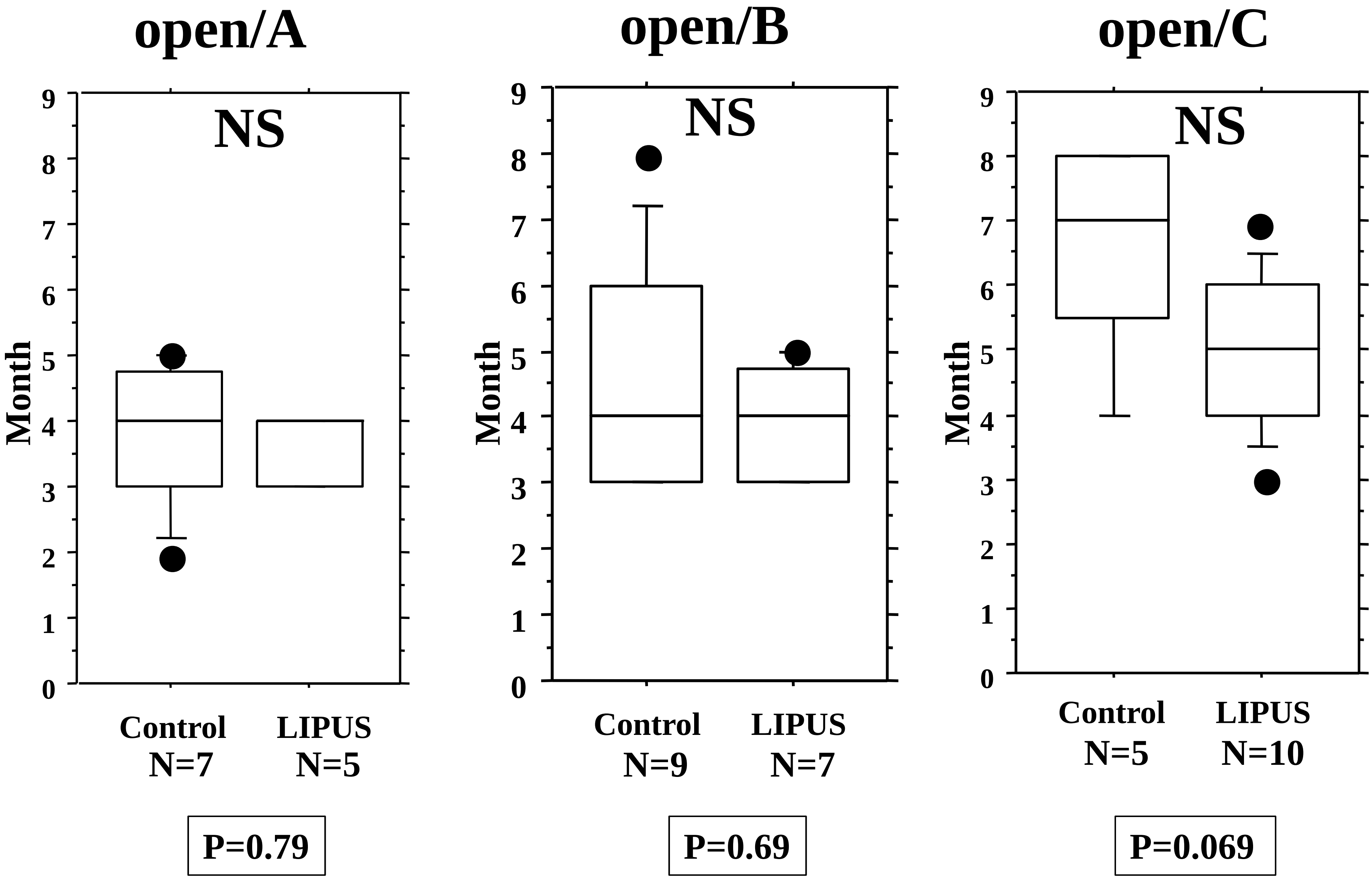
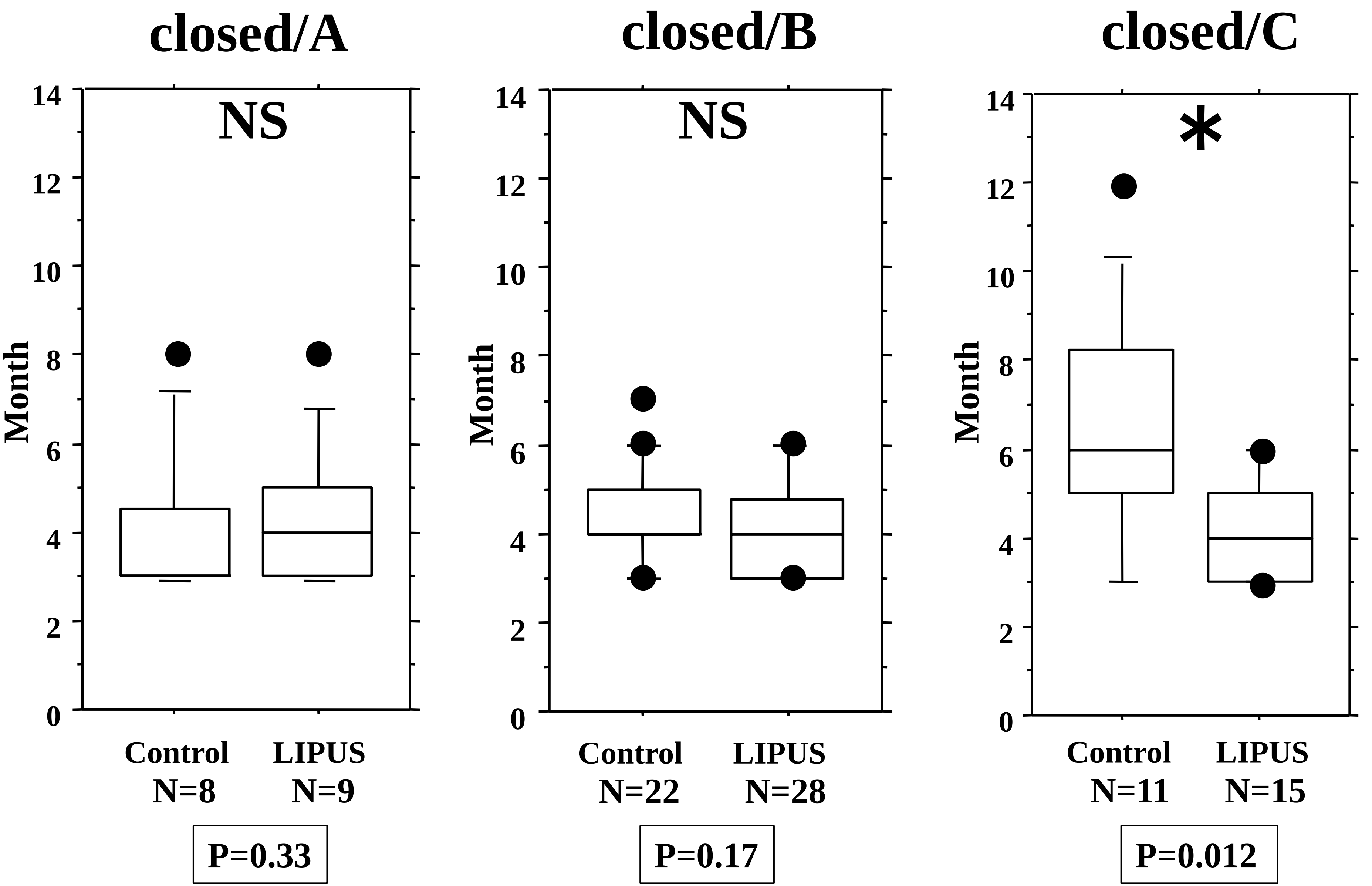
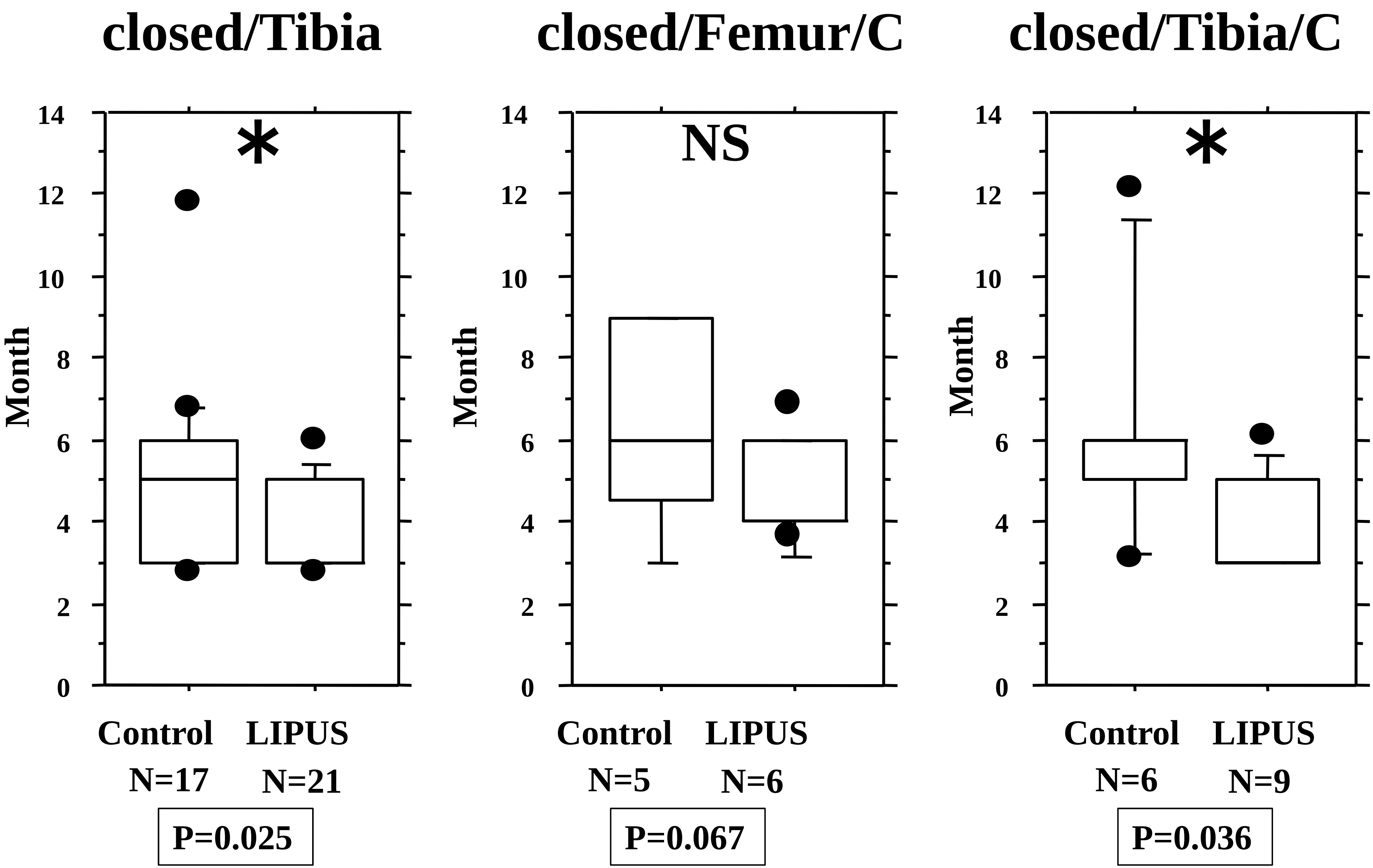

open/A
NS
Month
9
8
7
6
5
4
3
2
1
0
Control
N=7
LIPUS
N=5
P=0.79
open/B
NS
Month
9
8
7
6
5
4
3
2
1
0
Control
N=9
LIPUS
N=7
P=0.69
open/C
NS
Month
9
8
7
6
5
4
3
2
1
0
Control
N=5
LIPUS
N=10
P=0.069

Figure 10



closed/A
NS
Month
14
12
10
8
6
4
2
0
Control
N=8
LIPUS
N=9
P=0.33
closed/B
NS
Month
14
12
10
8
6
4
2
0
Control
N=22
LIPUS
N=28
P=0.17
closed/C
*
Month
14
12
10
8
6
4
2
0
Control
N=11
LIPUS
N=15
P=0.012

Figure 11



closed/Tibia
closed/Femur/C
closed/Tibia/C
*
NS
*
Month
14
12
10
8
6
4
2
0
Control
LIPUS
N=17
N=21
P=0.025
N=5
N=6
P=0.067
N=6
N=9
P=0.036

Table 1 base line characterristics

	Control 63	LIPUS 78	Total 141	P-Value
Gender				
Male	**38**	**51(4)**	**89**	**0.8**
Female	**25(1)**	**27**	**52**	
Age	**46.9y.o(16-94)**	**48.7y.o(16-95)**	**141**	**0.64**
Fracture site				
Femur	**29(1)**	**37(2)**	**66**	**0.81**
Tibia	**34**	**41(2)**	**75**	
AO classification				
A	**15**	**15(1)**	**30**	**0.53**
B	**32(1)**	**35**	**67**	
C	**16**	**28(3)**	**44**	
Soft tissue				
Open	**21**	**25(3)**	**46**	**0.64**
Closed	**42(1)**	**53(1)**	**95**	
Surgery				
Nail	**57(1)**	**67(4)**	**124**	**0.42**
Plate	**6**	**11**	**17**	
Result				
union	**62**	**74**	**136**	**0.25**
nonunion(reoperation)	**1**	**4**	**5**	

( )=revision surgery case number

Table 2　outcome measures 1

union period (mean)	Control(Month)	LIPUS(Month)	P value
All	4.8	4.2	0.11
Fracture site			
femur	4.7	4.3	0.74
<u>tibia</u>	<u>4.9</u>	<u>4</u>	<u>0.048</u>
AO classification			
A type	3.9	4.1	0.44
B type	4.9	4	0.21
<u>C type</u>	<u>6.4</u>	<u>4.5</u>	<u>0.005</u>
Soft tissue			
open	4.7	4.3	0.71
closed	4.8	4.1	0.09
Surgery			
nail	4.8	4.2	0.17
plate	4.5	4	0.33

underline= p-value<0.05

Table 3 outcome measures 2

union period (mean)	**Control (Month)**	**LIPUS (Month)**	**P value**
femur/A	**4.1**	**4.4**	**0.62**
femur/B	**4.1**	**4.0**	**0.92**
femur/C	**6.4**	**4.2**	**0.049**
tibia/A	**3.6**	**4.0**	**0.8**
tibia/B	**4.6**	**4.4**	**0.11**
tibia/C	**6.4**	**4.0**	**0.034**
open/A	**3.7**	**3.6**	**0.79**
open/B	**4.4**	**3.8**	**0.69**
open/C	**6.6**	**5.0**	**0.069**
close/A	**4.0**	**4.4**	**0.33**
close/B	**4.4**	**4.0**	**0.17**
close/C	**6.4**	**4.2**	**0.012**

underline= p-value<0.05

Table 4 revision surgery cases

group	age	gender	site	classification	soft tissue	surgery	revision surgery	comments
LIPUS	**18**	**male**	**tibia**	**C**	**open ⅢA**	**nail**	**bone graft**	**large bone defect**
LIPUS	**65**	**male**	**tibia**	**C**	**open Ⅱ**	**nail**	**exchange nail**	**unreamed nail**
LIPUS	**37**	**male**	**femur**	**C**	**open Ⅰ**	**nail**	**exchange nail**	**unreamed nail**
LIPUS	**18**	**male**	**femur**	**A**	**close**	**nail**	**exchange nail**	**distal diaphyseal fracture**
Control	**19**	**female**	**femur**	**B**	**close**	**nail**	**exchange nail**	**gap 5mm**

5 cases had revision surgery .1 case was operated by bone graft because of large bone defect, 4cases was operated by exchange nailing because of non-uinon.all cases got union finally.

Table 5 base line characterristics closed fracture group

	Control 42	LIPUS 53	Total 95	P-Value
Gender				
Male	**22**	**32(1)**	**54**	**0.43**
Female	**20(1)**	**21**	**41**	
Age	**47.7y.o(16-94)**	**50.0y.o(17-95)**	**95**	**0.65**
Fracture site				
Femur	**25(1)**	**32(1)**	**57**	**0.93**
Tibia	**17**	**21**	**38**	
AO classification				
A	**8**	**10(1)**	**18**	**0.99**
B	**23(1)**	**28**	**51**	
C	**11**	**15**	**36**	
Surgery				
Nail	**37(1)**	**45(1)**	**82**	**0.65**
Plate	**5**	**8**	**13**	
Result				
union	**41**	**52**	**136**	**0.87**
nonunion(reoperation)	**1**	**1**	**5**	

( )=revision surgery case number

Table 6 outcome measures closed fracture group

union period (mean)	Control(Month)	LIPUS(Month)	P value
Fracture site			
femur	4.6	4.3	0.84
<u>tibia</u>	<u>5.1</u>	<u>3.8</u>	<u>0.025</u>
AO classification			
A type	4.0	4.4	0.33
B type	4.4	4	0.2
<u>C type</u>	<u>6.4</u>	<u>4.1</u>	<u>0.018</u>
Surgery			
nail	4.9	4.2	0.2
plate	4.6	3.8	0.14
femur/A	4.1	4.4	0.46
femur/B	4.2	4.2	0.86
femur/C	6.4	4.5	0.067
tibia/A	-	-	-
tibia/B	4.6	3.8	0.12
<u>tibia/C</u>	<u>6.3</u>	<u>3.9</u>	<u>0.036</u>

underline= p-value<0.05