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Effect of low-intensity pulsed ultrasound after intraoral vertical ramus osteotomy

Satomi Arimoto, DDS‡[1], Takumi Hasegawa, DDS, PhD†*[1], Daisuke Takeda, DDS, PhD‡[1], Chizu Tateishi, DDS‡[1], Masaya Akashi, DDS, PhD†[1], Shungo Furudoi, DDS, PhD§[1], Takahide Komori, DDS, PhD¶[1]

‡Clinical Fellow, †Assistant Professor, §Associate Professor, ¶Professor and Chairman

[1] Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine (Chief: Prof. KOMORI Takahide)

*Corresponding author: Takumi Hasegawa, DDS, PhD, Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. Tel: +81-78-382-6213 / Fax: +81-78-351-6229

E-mail: hasetaku@med.kobe-u.ac.jp

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Abstract

Objective. The present study investigated the effect of Low-Intensity Pulsed Ultrasound (LIPUS) on long-term osseous healing of the cleavage space between bone fragments after intraoral vertical ramus osteotomy (IVRO).

Study Design. Patients undergoing IVRO were randomly selected to be in the LIPUS group (n=12) or control group (n=9) after surgery. LIPUS treatments were applied daily to the cleavage space between bone fragments for 3 weeks. We observed three-dimensional quantitative color mapping of the whole mandible created by computed tomography (CT) data at one month, six months, and one year postoperatively. Based on CT values, the color grades were classified as D1 to D5 using Misch criteria. We then calculated mean CT values and rated each color grade in different selection ranges.

Results. The mean CT values of the LIPUS group were significantly higher than that of the control group at one month, six months and one year postoperatively ($p<0.01$). The color grades of the cleavage between bone fragments increased from D5 to D1 over time.

Conclusion. Our results indicated that LIPUS promoted osseous healing after IVRO, improving bone density and offering clinical benefits.

Introduction

Many surgical techniques are performed for the treatment of mandibular prognathism. Sagittal split ramus osteotomy (SSRO) and intraoral vertical ramus osteotomy (IVRO) are the most frequently used methods of mandibular ramus osteotomy. Both surgical techniques have risks and benefits. The advantage of IVRO over SSRO is technical simplicity; there is a lower incidence of injury or damage to the inferior alveolar nerve, shorter operation time, and the ability to reposition the condyle.[1] However, IVRO has a prolonged duration of postoperative intermaxillary fixation (IMF) required due to the absence of rigid bone fixation, causing a relatively long time between the operation and osseous healing. IMF prevents an early return to usual dietary life, causes a prolonged functional impairment to patients and most severely, can compromise the airway when vomiting. Several reports showed mandibular prognathism by IVRO can be with supported by intraoral fixation with a plate or screw instead of IMF.[2] However, it is important to promote osseous healing regardless of the use of IMF.

Low-Intensity Pulsed Ultrasound (LIPUS) is known to promote bone healing. In orthopedic surgery, it is a clinically established treatment method used to accelerate long bone fracture healing and is a medical service covered by health insurance in Japan. There has been great interest due to its portability, ease of handling, and noninvasive nature.[3] On the other hand, Schandelmaier S et al.[4] demonstrated that LIPUS does not improve outcomes important to patients and probably has no effect on radiographic bone healing in patients with fresh fractures. However, they described that the applicability to other types of fracture or osteotomy is open to debate. We previously demonstrated that cells within mandibular fracture haematomas contribute to mandibular fracture healing and that the osteogenic activity of human mandibular fracture haematoma-derived cells (MHCs) is enhanced by LIPUS stimulation.[5,6] We provided significant evidence for the potential utility of the clinical application of LIPUS to accelerate mandibular fracture healing. Some recent studies have shown significant effect of LIPUS on mandibular defects and fractures.[7-9] However, the therapeutic effect of LIPUS on the healing process after IVRO still remains unclear.

Recently, we demonstrated osseous healing in the cleavage between bone fragments after IVRO using Computed Tomography (CT) values in the axial CT images.[10] The CT values between bone fragments significantly increased at one month, six months, one year and two years after surgery. However, radiographic assessment is limited by 2D interpretations of a 3D structure, and no report so far has investigated detailed osseous healing of the whole mandible in three dimensions. The purpose of this study was to determine the effect of LIPUS on the healing of osteotomy sites after IVRO and observe the long-term osseous healing of the cleavage space between bone fragments after IVRO surgery using quantitative 3D analyses of clinical CT data. We hypothesized that LIPUS can accelerate mandibular osseous healing similar to HMCs studied previously.

Materials and Methods

Ethics

The present study was a prospective cohort study. This study has been conducted in full accordance with the World Medical Association Declaration of Helsinki. All procedures used in this research were approved by the Ethical Committee of Kobe University Hospital (approval number: No.789) and informed consent was obtained from each patient.

Participants

The inclusion criteria were (i) patients who had mandibular prognathism and received mandibular set-back surgery with bilateral IVRO, (ii) no previous orthognathic surgery and no maxillary surgery, (iii) no history of facial fracture or jaw trauma, and (iv) patients available for all evaluation time points. The exclusion criteria were (i) patients who do not agree to participate, (ii) patients lost to follow-up at specific time interval, (iii) patients receiving steroids, anticoagulants, prescription non-steroidal anti-inflammatory medication, calcium-channel blockers, or diphosphonate therapy, (iv) patients with a history of thrombophlebitis, vascular insufficiency, or a recent history of alcoholism or nutritional deficiency.[11]

A total of 21 patients (six males and fifteen females) were randomly selected from mandibular prognathism who underwent bilateral IVRO (42 rami) at the authors' institution between August 2007 and March 2014. The operations were performed by 2 surgeons with a minimum of 20 years of surgical experience in oral and maxillofacial surgery. Patients were then randomly allocated to be treated with LIPUS (12 osteotomies, LIPUS group) or without LIPUS (9 osteotomies, control group) after surgery (Table. 1). At the beginning of the study, the first patient to be accepted was assigned to the active treatment group. Other patients were assigned to the placebo group or treatment group in an alternating order. The patients' ages ranged from 16 to 54 years, with a mean age of 24.0±1.9 years. The mean setback was 6.8±0.4 mm. There was no potential impact of age, sex and the mandibular set back on the present study. All patients underwent IMF with stainless steel wires (0.3 mm) and brackets placed in the maxillary and mandibular arches for 14 days according to the established clinical pathway.

The LIPUS Treatment

Ultrasound was provided by Sonic Accelerated Fracture Healing System 2000 (SAFHS; provided by Teijin Pharma, Tokyo, Japan). Starting 2 days postoperatively, patients in the LIPUS group received one 20-minute LIPUS treatment per day for 3 weeks (intensity: 30 mW/cm^2, burst width: 200 μs, frequency: 1.5 MHz). The transducer was located on the angle of the mandibular ramus at the level of the osteotomy and was firmly fixed with a facial bandage (Fig. 1). Coupling gel was used to ensure effective transfer of the acoustic wave to the tissue. After being properly trained on the correct positioning of the device, the LIPUS treatment was self-administered by patients. The use of the LIPUS machine was checked every day while patients were in hospital for 3 weeks.

CT Measurement Procedure

CT examinations were performed for all patients at one month, six months, and one year postoperatively using Aquilion64® (Toshiba Medical Systems, Tokyo, Japan) at the Wakaba Imaging Support Center (tube current: 100 mA; scanning time: 3 s; slice thickness: 2 mm; slice width: 2 mm; field of view: 25 cm). The slice plane was parallel to the occlusal plane and the scanned area extended from the floor of the orbit to the inferior border of the mandible. To reduce the data variation, a single author (S.A.) measured CT images of this study. This person was blinded with regard to the treatment received and assessed all CT images obtained from each patient. The raw data was transferred to a dedicated workstation

(Ziostation2 ver.2.1.5.0; Ziosoft, Tokyo, Japan) with technical consultation. Based on the Ueki visualization method,[12] the frontozygomatic line (FZ line) was defined as the line connecting the most lateral points of the bilateral frontozygomatic sutures in the coronal CT images (Fig. 2A, C). The right and left side line (RL line) was defined as the line connecting the most anterior points of the bilateral auricles in the axial CT images (Fig. 2B). Kim et al.[13] reported that the color maps created from CT images reconstructed with a section width of 2 mm had better image quality and retained more anatomy details than those reconstructed with a section width of 3 mm. Therefore, three-dimensional volumes were reconstructed with slice imaging by multi-planar reconstruction using a section width of 2 mm as described in Fig 2 A-C. All slices were quantified and bone fragment healing methods were clarified. In the axial CT images, we drew a line tangent to the bilateral foramen-mandibular posterior region to separate the posterior areas (Fig. 2D). In the coronal CT images, we extracted only the part of the mandibular bone that contained the cleavage (Fig. 2E). Based on the Hagino visualization method,[14] we determined reference points of Porion (Po), Crest of Articular Eminence (CAE) in the sagittal CT images. We drew a line perpendicular to the Po-CAE line, starting from the top of the coronoid process in the sagittal images to separate CT values of the mandible bone from wisdom teeth (Fig. 2F). Each analysis volume was divided into two sections of CT slices. In the axial CT images, the upper half of CT slices were defined as the Upper Side of the CT slices and the Lower Side was defined as the lower half of CT slices. Similarly for the other directions of the 3D volume, in the sagittal CT images, half of the CT slices were defined as the Interior Side and the other half were defined as the Lateral Side and in the coronal CT images. The Anterior Side and Posterior Side were defined respectively by half of the CT slices taken.

CT can be used to obtain the desired information about the morphological changes and the linear attenuation coefficient of bone density is measured in Hounsfield units (HU). The CT values are correlated to the bone quality.[15] Misch defined bone quality categories from D1 to D5 based off of HU values.[16] Rokn AR et al. reported that the Misch criteria can characterize the histologic properties of the bone.[17] In the present study, the long-term osseous healing of the cleavage space between bone fragment imaging was shown by color maps coded with CT values in HU. The color grades were classified into five categories using the CT values as follows: >1250 HU, red (D1); 850–1250 HU, yellow (D2); 350–849 HU, green (D3); 150–349 HU, blue (D4) and <150 HU, black (D5) (Fig. 3A). D1 bone is primarily dense cortical bone. D2 bone has dense and thick porous cortical bone on the crest and coarse trabecular bone underneath. D3 bone has thinner porous cortical crest and fine trabecular bone within, and D4 has almost no crestal cortical bone and fine trabecular bone composes almost all of the total volume of bone. The warm colors represent the cortical bone areas with high CT values while the cold colors represent the trabecular bone and the soft tissue areas with low CT values. We measured the mean CT values and rated each color grade in the selection range.

Statistical Analysis

The data collection and statistical analyses were performed using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA). Data was presented as mean ± standard deviation (SD). The Mann–Whitney U-test was used to assess the differences in the means between the control and

LIPUS groups at each time point. A value of $p<0.05$ was considered statistically significant.

Results

During the present study, there were no adverse events in either group of patients. We successfully demonstrated the visualization of the cleavage between bone fragments healing. The color grades of the cleavage between bone fragments increased from D5 to D1 over time (Fig. 3B).

There were no significant differences between the control and LIPUS groups in age, sex, or mandibular set back. In the sagittal CT images, the mean CT values of the control group were 1,054±18 HU preoperatively, 915±20 HU at one month, 916±20 HU at six months, 952±21 HU at one year. The LIPUS group's values were 1,012±13 HU preoperatively, 994±8 HU at one month, 1,011±7 HU at six months, 1049±12 HU at one year. In the sagittal CT images, the LIPUS group's CT values were significantly higher than those of the control group at one month ($p<0.05$), six months, and one year ($p<0.01$) postoperatively (Fig. 4A). In the axial CT images, the mean CT values of the control group were 1,006±17 HU preoperatively, 856±18 HU at one month, 880±22 HU at six months, 909±25 HU at one year. The LIPUS group's CT values were 985±15 HU preoperatively, 923±8 HU at one month, 955±10 HU at six months, and 1002±12 HU at one year. In the axial CT images, the LIPUS group had significantly higher CT values than the control group at one month, six months, and one year ($p<0.01$) postoperatively (Fig. 4B). In the coronal CT images, the mean CT values of the control group were 1,002±20 HU preoperatively, 862±19 HU at one month, 862±22 HU at six months, and 878±21 HU at one year. The LIPUS group had values of 1,003±16 HU preoperatively, 924±10 HU at one month, 930±13 HU at six months, and 963±18 HU at one year (Fig. 4C). In the axial CT images and coronal CT images, the mean CT value of the LIPUS group was significantly higher than that of the control group at one month, six months and one year ($p<0.01$) postoperatively. There were no significant differences between all images at the preoperative time point.

The posterior side of the coronal color mapping CT images showed a significantly higher amount of D1 grade area in the LIPUS group compared to the control group at six months ($p<0.05$) and one year ($p<0.01$) postoperatively (Fig. 5A). As well, the amount of D4 grade area of the control group was significantly higher than that of the LIPUS group at one year ($p<0.05$) postoperatively. The anterior side of images showed a higher amount of D1 grade area in the LIPUS group compared to the control group at one year ($p<0.05$) postoperatively (Fig. 5B). In the lower side of the axial color mapped CT images, the amount of D1 and D2 grade area of the LIPUS group was significantly higher than that of the control group at one month ($p<0.01$ for D1 grade), six months ($p<0.05$ for D1 and D2 grade areas), and one year ($p<0.01$ for D1 grade, $p<0.05$ for D2 grade) postoperatively (Fig. 5C). In the upper side of images, the amount of D1 grade area of the LIPUS group was significantly higher than that of the control group at six months ($p<0.05$) postoperatively (Fig. 5D). In the lateral side of the sagittal color mapping CT images, the amount of D1 grade area of the LIPUS group was significantly higher than that of the control group at one month, six months, and one year ($p<0.01$) postoperatively (Fig. 5E). The amount of D4 grade area of the control group was significantly higher than that of the LIPUS group at one month, six months, and one year ($p<0.01$) postoperatively. In the interior side, the amount of D1 grade area of the LIPUS group was significantly higher than that of the control group at six months ($p<0.01$) and one year ($p<0.05$) postoperatively (Fig. 5F). There were no significant differences at one month.

Discussion

We successfully demonstrated osseous healing in the cleavage between bone fragments after IVRO using quantitative 3D analysis of clinical CT data. The results suggested that LIPUS can increase bone density, offering clinical benefits.

Quantitative color mapping of CT extends a wide range of applications in the medical and dental fields. Recently, it has been used to for the evaluation of the arterial enhancement fraction of the liver,[18,19] diagnosis of coronary artery disease,[20] prediction of intra-ascending aorta[21] and the analysis of bone properties in hip osteoarthritis.[22] Meyer et al.[23] provided evidence that assessing the degree and location of osseointegration of dental implants are valid using quantitative color mapping of the CT.

Buchtala[24] was the first to report the possibility to stimulate osteogenesis with ultrasound in 1950. Since then, LIPUS has demonstrated enhanced fracture healing in animal studies and bone repair in humans. It showed a positive effect on accelerating bone healing of fresh fractures with highly significant evidence in experimental and double-blind, randomized, placebo-controlled studies.[11, 25] Advantages of the use of this technology are its efficacy, safety, and ease of use. In the United States, the Food and Drug Administration approved the use of low-intensity ultrasound for the accelerated healing of fresh fractures in October, 1994 and for the treatment of established nonunions in February, 2000. Erdogan et al.[7] suggested that LIPUS improved the bone healing of mandibular fractures in rabbits. LIPUS administration was conducted for 20 minutes daily for 20 days in which ultrasound signal consisted of 1.5 MHz pressure wave administered in pulses of 200 μs with an average temporal and spatial intensity of 30 mW/cm^2. We utilized this waveform in our previous study[5,6] and demonstrated that human MHCs play an important role in mandibular fracture healing and that LIPUS accelerates this effect by stimulating various osteogenic cytokines. The gene expression levels of alkaline phosphatase (ALP), osteocalcin (OC), Bone Morphogenetic Protein-2, 4, 7 (BMP-2, 4, 7), runt-related gene 2 (Runx2), osterix (OSX), osteopontin (OPN), parathyroid hormone receptor 1 (PTHR1), and mineralization were increased in the LIPUS (+) group compared to the LIPUS (-)group (control). Histologic studies proved that LIPUS influences osteoblasts, osteoclasts, chondrocytes and mesenchymal stem cells in bone healing. This evidence was used to select the waveform properties in the present study. Patel et al.[8] revealed a significant improvement in the healing rate of mandibular fractures by radiographic density findings and a significant, rapid reduction in pain perception in the LIPUS group compared with the control group. Uchida et al.[26] showed that LIPUS stimulated vascular endothelium growth factor (VEGF) expression in the experiment using the femoral fracture model of mice. Young et al.[27] displayed increased angiogenesis in the form of increased blood vessel formation after the application of LIPUS. Rawool et al.[28] found that LIPUS increased blood flow around the fracture and surrounding tissue using Power Doppler imaging for the first 2 weeks after surgery. In the present study, patients in the LIPUS group received daily LIPUS treatments for at least 3 weeks postoperatively. The mean CT values of the LIPUS group were significantly higher than that of the control group at one month ($p<0.05$), six months, and one year ($p<0.01$) postoperatively. Considering the results, it could be hypothesized that the increase in blood flow produced an increase in cellular calcium uptake, resulting in increased protein synthesis, thereby accelerating osseous healing.

In many other studies, the LIPUS transducer is usually placed transcutaneously during clinical treatments, hence fractures of superficial bone and deeper bone fractures at different depths are exposed to the ultrasound beam at different axial distances. There has been much research observing near field LIPUS on fractures or cells cultures; Reher et al.[29] found that near field LIPUS at an axial distance of 5 mm could stimulate bone formation. Fung et al.[30] applied LIPUS at three different axial distance fields to femoral fractured rats and observed that LIPUS augmented callus bone volume and mineralization in far field (130 mm), and near field (0 mm) and mid-near (60 mm) field enhanced woven bone formation. Similarly, we found that the increase of D1 grade area in the posterior side was faster than the anterior side in the coronal images. Furthermore, the lower side was faster than the upper side in the axial images. In addition, the lateral side was faster than the interior side in the sagittal images. These results may be due to differences in distance from the LIPUS transducer areas further away from the LIPUS application site yielding slower healing. Our study shows that LIPUS can accelerate osseous healing in three-dimensions in both near field and far field areas.

In fracture healing, periosteum is the main source of repairing cells, and mainly contributes to callus formation. Ozaki et al.[31] reported that the periosteum is important for mediating in the fracture healing. Tam et al.[32] demonstrated that the positive stimulatory effect of LIPUS on human periosteal cell culture in functional activation of bone formation and cellular differentiation. Previously, we observed the long-term osseous healing of the cleavage space between bone fragments after IVRO surgery on the interior and lateral sides.[10] In that study, LIPUS was not applied, hence the recovery of the CT values on the lateral side was less than that observed on the interior side at two years postoperatively. At our institution, the periosteum of the lateral side of the mandible was elevated and not removed, while the interior side was not elevated or removed. We reported that the blood supply from the interior side periosteum may affect the speed of osseous healing. The present study observed that in the lateral side, the amount of D1 grade area in the LIPUS group was significantly higher than that of the control group at one month, six months and one year postoperatively ($p<0.01$). Considering these results, it could be hypothesized that LIPUS stimulated the periosteal bone formation of the lateral side of the mandible. Leung et al.[33] found that the stimulatory effect lasted much longer after LIPUS treatment. The reason is that the level of plasma bone-specific ALP activity remained persistently higher at weeks 12, 18 and 27. They reported that the number of bone-forming cells increased in the early phase and that the activity lasted much longer in the treatment group. Similar results were obtained in the present study.

Our study has limitations. First, our sample size was small and further studies may be required to confirm the results of this study. Second, there is a large range in patients' age. Although patients did not have a history of osteopenia or osteoporosis we did not measure bone mineral density preoperatively. It is possible that there may be potential risk. Third, LIPUS can improve bone density, however the period of the postoperative IMF remains uncertain and should be further studied. Finally, we did not use a sham device in the control group. We could have applied such a device to patients for a stronger placebo group. Further consideration will be needed to draw additional implications. We plan to continue to quantitatively evaluate the process of osseous healing. In conclusion, the results observed in this study suggest that LIPUS can improve bone density, offering clinical benefits. We identified no side effects related to LIPUS treatment. In addition, patients felt no discomfort during therapy. The purpose of this study was to observe the long-term osseous healing using quantitative 3D analysis of clinical CT data which successfully demonstrated detailed osseous healing of the mandible bone in three dimensions. We believe that our findings will contribute to the successful surgical treatment of patients using IVRO in the fields of dentistry and oral surgery.

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Figure Legend

Figure 1. Position of the Low-Intensity Pulsed Ultrasound (LIPUS) transducer

The LIPUS transducer was located on the angle of the mandibular ramus at the level of the osteotomy and was firmly fixed with a facial bandage. Coupling gel was used to ensure effective transfer of the acoustic wave to the tissue.

Figure 2. Method of measuring three-dimensional quantitative color mapping created by using computed tomography (CT) data

A, C: The FZ line was defined as the line between the most lateral points of the bilateral frontozygomatic sutures.

B: The RL line was defined as the line between the most anterior points of the bilateral auricles.

A-C: Based on the reference point, three-dimensional data were reconstructed with 2 mm width slice imaging by multi-planar reconstruction.

D: We drew a line tangent to the bilateral foramen-mandibular posterior region and measured the posterior areas.

E: We extracted only the part of the mandibular bone that contained the cleavage.

F: We determined reference points of Porion (Po), Crest of Articular Eminence (CAE). We drew the vertical line of Po-CAE line which passed through the top of the coronoid process and measured the posterior areas.

Figure 3. Classification of five color grades

A: Based on the Misch criteria, the color grades were classified into five steps using the CT values.

B: The color grades of the cleavage between bone fragments increased from D5 to D1 over time.

Figure 4. Mean CT values ±standard deviation in the sagittal images (A), the axial images (B) and coronal images (C).

Figure 5. Rating of each color grade in the divided two sections of all slices

Percent of area covered by each bone grade in the divided two sections of all slices.

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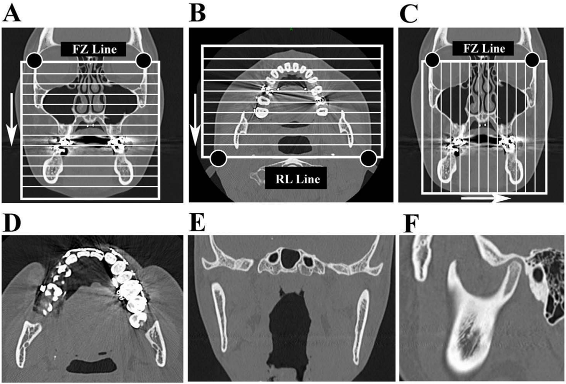
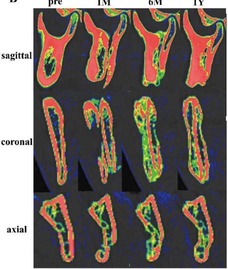
LIPUS Transducer

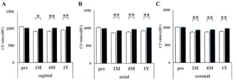

A
FZ Line
B
RL Line
C
FZ Line
D
E
F

A Misch criteria

grade	color	CT values(HU)
D1		>1250
D2		850-1250
D3		350-849
D4		150-349
D5		150>

B



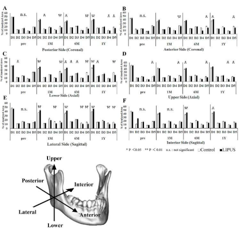


	pre	1M	6M	1Y
□Control	1054±18	915±20	916±20	952±21
■LIPUS	1012±13	994±8	1011±7	1049±12

	pre	1M	6M	1Y
□Control	1006±17	856±18	880±22	909±25
■LIPUS	985±15	923±8	955±10	1002±12

	pre	1M	6M	1Y
□Control	1002±20	862±19	862±22	878±21
■LIPUS	1003±16	924±10	930±13	963±18

* P ＜0.05 ** P ＜ 0.01


A
Posterior Side (Coronal)
B
Anterior Side (Coronal)
C
Lower Side (Axial)
D
Upper Side (Axial)
E
Lateral Side (Sagittal)
F
Interior Side (Sagittal)
% of Analyzed Area
D1 D2 D3 D4 D5
pre
1M
6M
1Y
n.s.
* P <0.05 ** P < 0.01 n.s. : not significant
Control
LIPUS
Upper
Posterior
Interior
Lateral
Anterior
Lower