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Automated Continuous Distraction Osteogenesis May Allow Faster Distraction Rates: A Preliminary Study

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Abstract

Purpose—To determine if automated continuous distraction osteogenesis at rates > 1mm/day would result in clinical and radiographic bone formation in a minipig model.

Materials and Methods—An automated, continuous, curvilinear distraction device was placed across a mandibular osteotomy in 10 minipigs. After 12 mm of distraction and 24 days fixation, animals were sacrificed and bone healing evaluated. The continuous distraction rates were 1.5 (n=5) and 3 mm/day (n=5). A semiquantitative scale was used to assess ex-vivo clinical appearance of the distraction gap (3= osteotomy not visible; 2= <50%; 1= >50%; 0= 100% visible); stability (3 = no mobility; 2 and 1 = mobility in 2 or 1 plane respectively; 0= mobility in 3 planes); radiographic density (4 = 100% gap opaque, 3= >75%, 2 = 50% – 75%, 1= <50%, or 0 = radiolucent). Groups of 4 minipigs distracted discontinuously at 1, 2, and 4 mm/day served as controls.

Results—The continuous DO 1.5 mm/day group had significantly higher scores for appearance and radiographic density compared to the discontinuous 4 mm/day group. The continuous DO 3mm/day group had significantly higher scores for appearance and radiographic density compared to the discontinuous 4 mm/day group, and higher stability compared to the discontinuous 2 and 4 mm/day groups.

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Conclusions—Results of this preliminary study indicate that continuous DO at rates of 1.5 and 3.0 mm/day produces better bone formation when compared to discontinuous DO at rates faster than 1mm/day.

Keywords

continuous distraction osteogenesis; craniofacial surgery; micrognathia; mandible

Introduction

The first clinical application of distraction osteogenesis for correction of craniofacial deformities was published in 1992 by McCarthy et al.[1] Since that report, distraction osteogenesis (DO) has become a commonly used technique for expansion of the craniomaxillofacial skeleton. An osteotomy is created, a rigid distraction device fixed across the gap and the bone gradually lengthened by activation of the device. DO utilizes the body's natural healing process to form new bone within a slowly expanding osteotomy gap.[2–5] It eliminates the need for bone and soft tissue grafts and complications associated with donor site operations.[6, 7]

As a result of extensive studies in a canine long bone model and evaluation of a large number of clinical cases, Ilizarov established the ideal rate of distraction at 1 mm/day with faster rates resulting in inadequate bone formation and non-union.[3–5] A rate of 1 mm/day has also been shown to be the most predictable rate of distraction in the craniofacial skeleton, based on experimental and clinical data.[8, 9] After a variable latency period, 1 mm/day lengthening is achieved by manually turning an activation screw 1 to 4 times/day.[8, 10] This is followed by a consolidation period typically twice the amount (millimeters) of distraction in days.[3, 4] As DO is generally employed for large movements, the overall treatment is long and fraught with complications.[11]

Currently, cumbersome distraction devices require considerable patient and caregiver cooperation and skill to manage the activation process. This leads to difficulties with treatment acceptance and compliance. Frequent office visits and radiographs are required to monitor compliance, gap size and distraction vector. An automated distraction device would eliminate the reliance on patient compliance. Continuous distraction has been reported to improve bone fill and may allow distraction at rates up to 2 mm/day.[4, 12–16] An automated, continuous device for distraction osteogenesis (United States Patent #8177789) has been developed through a collaboration between the Department of Oral and Maxillofacial Surgery at Massachusetts General Hospital and Physical Sciences Incorporated (Andover, MA USA) funded by NIH SBIR grant #5R44DE014803-03. A preliminary feasibility study served to test the design and safety of the device.[17] The purpose of the current study was to assess whether automated continuous DO at rates greater than 1 mm per day would result in bone formation and clinical union in a standardized minipig model. Our hypothesis was that automated, continuous distraction at rates greater than the standard 1 mm/day would allow equivalent bone fill.

The specific aims of this study were: 1) To further validate the safety and efficacy of a device developed for automated continuous DO in minipigs, 2) To assess bone healing of the distraction gap using clinical and radiographic criteria at continuous distraction rates of 1.5 and 3 mm/day.

Materials and Methods

An automated, continuous, semiburied distraction device for mandibular DO was tested in Yucatan minipigs. The predictor variables were the rates (mm/day) and type (continuous or incremental) of DO. Group 1 was programmed to distract continuously at 1.5 mm day while Group 2 was programmed at 3 mm/day. Control groups consisted of minipigs that underwent mandibular DO discontinuously at 1, 2, and 4 mm/day. The assessment of the DO wound included the evaluation of clinical appearance, stability, and radiographic density of the distraction wound, on a semiquantitative scale, at end-fixation.

The Automated Device

A semiburied, automated, continuous distraction device powered by a battery was used in these experiments (NIH SBIR grant #5R44DE014803-03, and U.S. Patent #8177789). (Figure 1) The distraction device is hydraulically driven by a digital controller with position feedback. A spring-powered, hydraulic reservoir supplies 2.0 Megapascals (MPa) at full spring extension to 3.4 MPa (full spring compression) of pressurized water to the distractor through a microdispensing solenoid valve. The hydraulic system can provide 25N–40N of force to expand the distraction site. Based on feedback from an inductive position sensor in the distractor, a digital controller opens the valve for a period of 100 µs-10 ms at 15 minute intervals. This results in continuous movement along the curvilinear slider-rail to the desired position.

Current position, motion time history, battery level and other parameters can be monitored through a computer program using Bluetooth® connection with the control box. The controller produces alarms in the form of blinking LEDs on the external box in response to a range of device or tracking errors, including deviations from the desired distraction distance or low batteries. Through this same software, the parameters of distraction are set and can be adjusted during the course of treatment.

Animals

Female Yucatan minipigs (n=10) in the mixed-dentition stage (4–6 months old; weighing 25–35 kg) were used in this study. This standardized model has been the focus of a series of mandibular distraction experiments since 1997.[8, 9, 18–26] The Yucatan minipig model was selected because it has mandibular size, morphology and chewing patterns similar to humans.[27, 28] It also has ginglymo-arthrodial function of the temporomandibular joint, as well as similar bone turnover rates as compared to humans.[28–30]

The animals were acclimated to living quarters, a cloth jacket containing the control unit and a pureed diet for 9–10 days prior to distractor placement. After implantation, the device's control-unit was housed within the jacket and was directly connected to the hydraulic and sensor lines. The pigs were assessed twice daily for signs of infection, weight, activity level and general appearance. The care and use of the minipigs met the requirements of the Accreditation of Laboratory Animal Care standards and was approved by the Massachusetts General Hospital Subcommittee on Research Animal Care (SRAC 2009N0000073). The authors have read and are in full compliance with the Declaration of Helsinki.

Surgical Procedure

The animals were sedated with 4.4 mg/kg telazol and 2.2 mg/kg xylazine and administered 0.04 mg/kg atropine intramuscularly. After oral intubation, anesthesia was maintained with isofluorane. Pre- and postoperative photographs, overjet measurments and lateral cephalograms were obtained on a standardized porcine cephalostat.[8] Through a submandibular incision and standard dissection, the mandible was exposed and an osteotomy along a line extending from a point 1 cm anterior to the mandibular angle to the retromolar region in front of the anterior ramus was marked on the bone. The corticotomy was carried out with a reciprocating saw and the distraction device placed along the lateral aspect of the mandible centered over the corticotomy. The distractor was then secured with Synthes® (West Chester, PA, USA) 2.0 mm diameter titanium screws 8 and 10 mm in length. Two screws were placed 10–12 mm apart at the inferior border of the mandible for measurement of the amount of distraction. The osteotomies were then completed. The hydraulic and sensor lines of the device were tunneled subcutaneously (20 cm) to exit from the dorsal skin in an area not accessible to the animal. The device was activated to confirm function, reversed to baseline and the distance between marker screws measured. (Figure 2) The wounds were closed in layers.

Distraction Protocol

The devices in Groups 1 and 2 were programmed to distract to 12 mm with distraction rates of 1.5 and 3 mm/day, respectively. No latency period was used and the fixation period was twice the distraction length in days (24 days).

Distractor position was updated every 15 minutes and recorded remotely using a Bluetooth® connection to the control box. (Figure 3)

Clinical Evaluation

At mid-DO, end-DO, and end-fixation, the animals were again sedated with 4.4 mg/kg telazol and 2.2 mg/kg xylazine and administered 0.04 mg/kg atropine intramuscularly. The wounds were assessed and cleaned. Overjet was measured (Figure 4) and lateral cephalograms were obtained. (Figure 5A, B) At end-fixation, the pigs were sacrificed and the right hemi-mandible was removed. The ex-vivo appearance of the DO gap was graded using a semiquantitative scale: 3 - osteotomy not visible; 2 - osteotomy < 50% visible; 1 - osteotomy > 50% visible; 0 - osteotomy clearly visible. (Figure 6) Bimanual examination of the ex-vivo mandible was graded as: 3 - no mobility; 2 - mobility in 1 plane; 1 - mobility in 2 planes; 0 - mobility in 3 dimensions (unstable). Ex-vivo lateral radiographs, using a previously designed porcine cephalostat,[8] were obtained to assess the density of bone fill within the osteotomy gap. Bone density was graded on a 5 point scale: 4 = entire gap opaque, 3= >75% and < 100% opacity, 2 = 50%–75% opacity, 1= <50% opacity, or 0 = completely radiolucent. (Figure 7)

Statistical Evaluation

Statistical evaluation was calculated using statistical software (IBM® Statistical Package of Social Sciences, version 20.0; SPSS Chicago, IL USA). Independent 2-sample *t* tests (2-tailed) were performed for each group with unequal variance assumed. *P* values were considered significant if less than 0.05.

Results

All mini-pigs survived the operation, distraction, and fixation periods. (Table 1) Group 1 (n=5) averaged 1.4 mm/day of distraction and 25 days of fixation. Mean scores for appearance, stability, and radiographic densities were 2.6, 2.4 and 2.6, respectively. Group 2 (n=5) averaged 2.4 mm/day of distraction and 28 days of fixation. Mean scores for appearance, stability, and radiographic densities were 2.6, 3, and 2.6, respectively. (Table 2) The historical control groups using discontinuous distraction rates of 1, 2 and 4mm/day had mean scores for appearance of 3, 2, and 1.75, stability: 3, 1.75 and 1.5, and radiographic density: 2.5, 2, and 1.33. Group 1 had significantly higher scores for appearance and radiographic density when compared to the incremental distraction groups at 4 mm/day (p =

0.046, p=0.004). Appearance and radiographic density were significantly higher in group 2 when compared to discontinuous DO at 4 mm/day (p = 0.046, p = 0.004). The scores for stability of the mandible in group 2 were significantly higher than both the groups of discontinuous DO at 2 and 4 mm/day groups (p = 0.015, p = 0.014). (Table 3–4, Figure 8)

Discussion

The purpose of this study was to validate an automated continuous distraction device in a minipig model and to assess whether continuous distraction would allow for bony healing of the distraction gap at rates faster than typically used in clinical settings. We hypothesized that the device would function safely and effectively, and that continuous distraction would produce bone fill and osseous union at faster rates of bony expansion than with incremental distraction. Specifically, a continuous and curvilinear distraction device was used to assess distraction rates up to 3 mm/day for clinical and radiographic bone fill of the distraction gap.

Results of this study validate a novel automated device for DO and demonstrate that continuous distraction allows bone fill at faster distraction rates than discontinuous DO. The distraction gap appeared to have near complete bone fill (average scores of 2.6 on the semiquantitative scale) in animals continuously distracted at 1.5 and 3 mm/day. This compared to scores of 2 and 1.75 in the previous study of incremental distraction at 2 and 4 mm/day, respectively.[8] Clinical stability across the distraction gap was 2.4 for the 1.5 mm/day group and completely stable in all 5 animals distracted at 3 mm/day (scores of 3) compared to 1.75 and 1.5 for incremental distraction at 2 and 4 mm/day, respectively. Radiographic density of the distraction wound was 2.6 for both continuous distraction groups compared to 2 and 1.33 for discontinuous distraction at 2 and 4 mm/day.

The curvilinear technique of DO lengthens the mandible at different rates from the superior border to the inferior border. The distraction device was placed at the center of the mandible, midway between the superior and inferior borders. Using the height of the mandible and the 5 cm radius of curvature, the theoretical rates at the superior and inferior borders can be calculated. At the superior border DO occurs at 0.75 mm/day and 1.5 mm/day in Groups 1 and 2, respectively. The inferior border is distracted at 2.25 mm/day and 4.5 mm/day respectively. (Figure 8) Continuous distraction allowed for clinical and radiographic bone fill in Group 2 to the inferior border, which theoretically opened at 4.5 mm/day in 3 of the 5 animals. This rate of distraction has not been shown to produce bone healing in previous studies of incremental or continuous distraction of the craniofacial skeleton.

Currently, DO for craniofacial reconstruction is limited by lengthy duration of treatment, the requirement for frequent activation of external or semi-buried devices, and reliance on the ability of the patient and/or family to activate the devices properly. Distraction protocols for the maxillofacial region have been adapted from studies in long bones.[3, 4, 31] Ilizarov, showed the ideal rate of bone lengthening to be 1 mm/day in canine long bone experiments and in humans and demonstrated that faster rates (e.g. 2 mm/day) result in fibrous tissue or nonunion.[4] Daily lengthening of limbs at 0.5 mm/day with a frequency of 0.125 mm every six hours led to premature consolidation. Lengthening at a rate of 2mm/day with a frequency of 0.5 mm every 6 hours gave rise to non-union and a reduced bone formation. DO at a rate of 1mm/day with frequencies up to 60 times/day produced the most active osteogenesis with little fibrous tissue.

As in long bones, distraction rates faster than 1 mm/day in the craniofacial skeleton have led to fibrous or nonunion.[8] Treatment plans for correction of craniofacial deformities require lengthening of up to 30 mm requiring 30 days for distraction and at least 60 days for consolidation. The continuous distraction technique shown in this study and others may allow for bone fill at rates impossible in incremental distraction.[12, 14, 32–37] It avoids the daily microtrauma and disruption of the healing process when activating an incremental device.[14, 38] Continuous motion and strain on the mandibular wound result in improved bone regeneration and could allow for significantly decreased treatment times for craniofacial deformities.[39]

Several devices that use motors, springs, and hydraulic pressure for mandibular lengthening have been described.[32–34, 40–42] Kessler et al describe a continuous device using hydraulic motion and showed that less force is required to open continuously at 1.5 mm/day and resulted in intra-membranous regeneration without chondroid ossification.[14] The device used in this study has several advantages over previously developed continuous distraction devices. It is the first automated device that is small enough to allow widespread clinical use. Using a spring-loaded reservoir permits a small (4mm) piston diameter which allows the device to sit only 8 mm off the bone surface for curvilinear motion and 6mm if configured for linear motion. The device in the current study is the first to assess curvilinear continuous motion and to be tested at rates faster than 1.5 mm. This device can control and adjust position during the entire distraction process remotely. This could allow assessment and adjustment of the distraction without a clinical visit or radiograph. Also, it could allow for “pumping the regenerate” (i.e. advancing and reversing the device) in compromised wounds.[43]

The current study has several limitations. The sample size is limited with only 5 minipigs in each group limiting statistical comparisons. The device had been tested in 10 previous animals for optimization of safety and effectiveness prior to assessing the faster rates (unpublished data) and not all animals actually distracted at the set rate (i.e. 2 pigs in Group 2 had acute closure of the device requiring more time to stabilize at 12 mm despite opening 3mm/day). Despite the similarities in the minipig and human mandibles, it has not been demonstrated that continuous DO at faster rates would allow for osseous union in humans. Ilizarov also postulated that continuous distraction at rates faster than 1mm/day might result in successful bone formation. However, clinical trials will be necessary prior to widespread use of continuous distraction in humans. In addition, the use of zero latency in these and other experiments is not meant to recommend the same protocol in clinical protocols of discontinuous distraction.

The comparison to incremental DO rates was to historic controls using a different distraction device. The previous animals were distracted incrementally using single-vector distraction devices leading to a parallel DO wound as opposed to the trapezoidal wound with curvilinear DO. The exit port of the activating arm was closer to the exit port than for the automated distractor which potentially could lead to more infections at the site of distraction. Distraction was limited to 12 mm (10% of the minipig mandible) allowing comparison to previous studies using incremental distraction. DO would not usually be employed for only 12 mm of mandibular lengthening in humans. In the next phase of this project, the device will be tested with 20–30 mm of distraction.

The current automated device described in this paper has not yet met our goal of being completely buried. Two hydraulic lines run from the dorsal aspect of the pig to a control box mounted on a jacket. A completely buried device may reduce infection rates seen at the exit port and would be less prone to damage in an active child. The control box, in its current iteration, is analogous to Baja hearing aids or insulin pumps for patients with Treacher Collins syndrome or Type 1 diabetes mellitus, respectively, and likely would be similarly tolerated. Further refinement of the device will be geared toward making the control box smaller or integrated within a buried device.

Conclusion

Automated continuous distraction osteogenesis allows for faster rates of distraction in the minipig model when compared to discontinuous distraction. Continuous distraction rates up to 4.5 mm/day at the inferior border of the mandible produced clinical and radiographic bone fill and good clinical stability across the regenerate. This device and technique has the potential to shorten treatment time in the management of craniofacial deformities.

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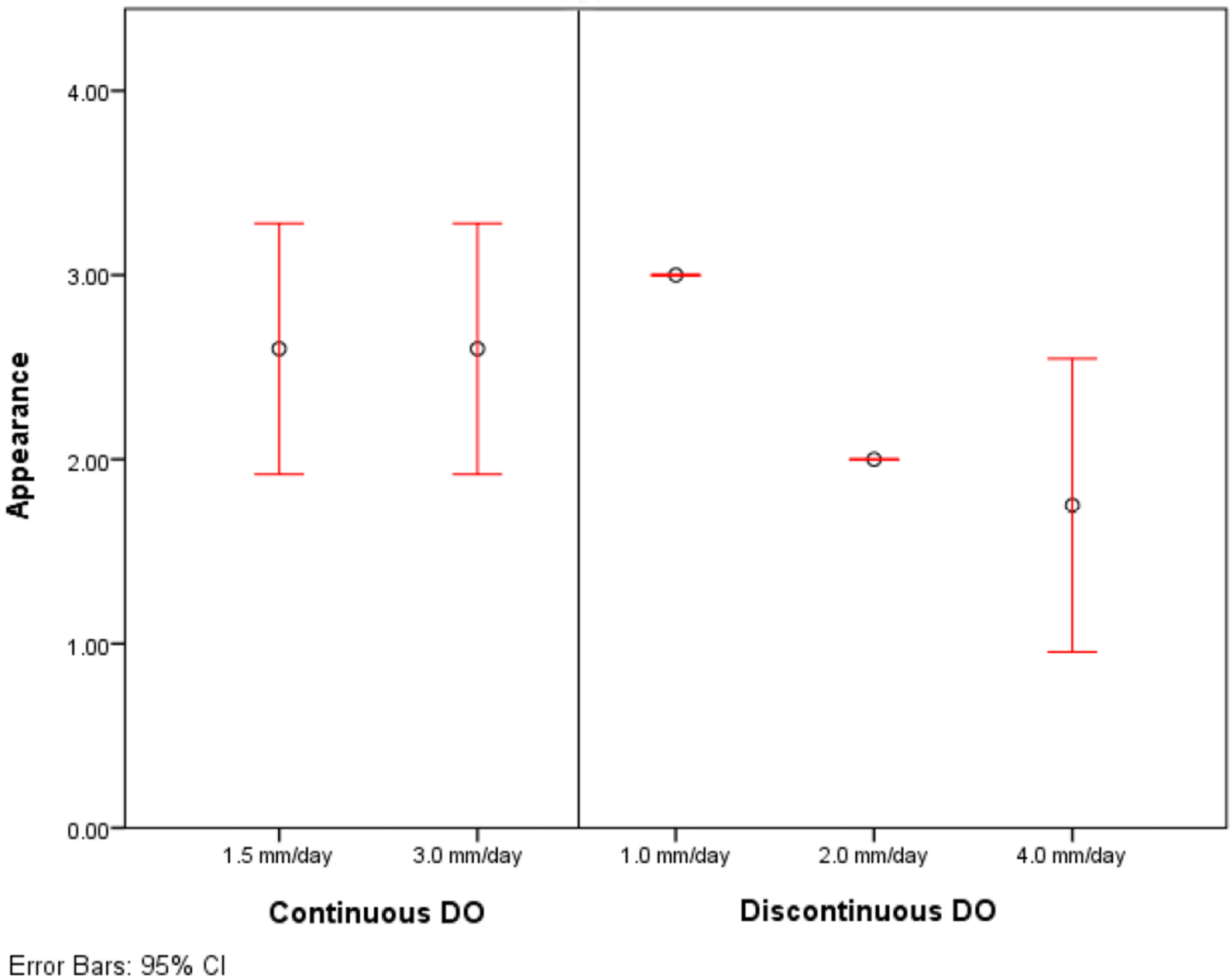
4.00
3.00
2.00
1.00
0.00
Appearance
1.5 mm/day
3.0 mm/day
1.0 mm/day
2.0 mm/day
4.0 mm/day
Continuous DO
Discontinuous DO
Error Bars: 95% CI

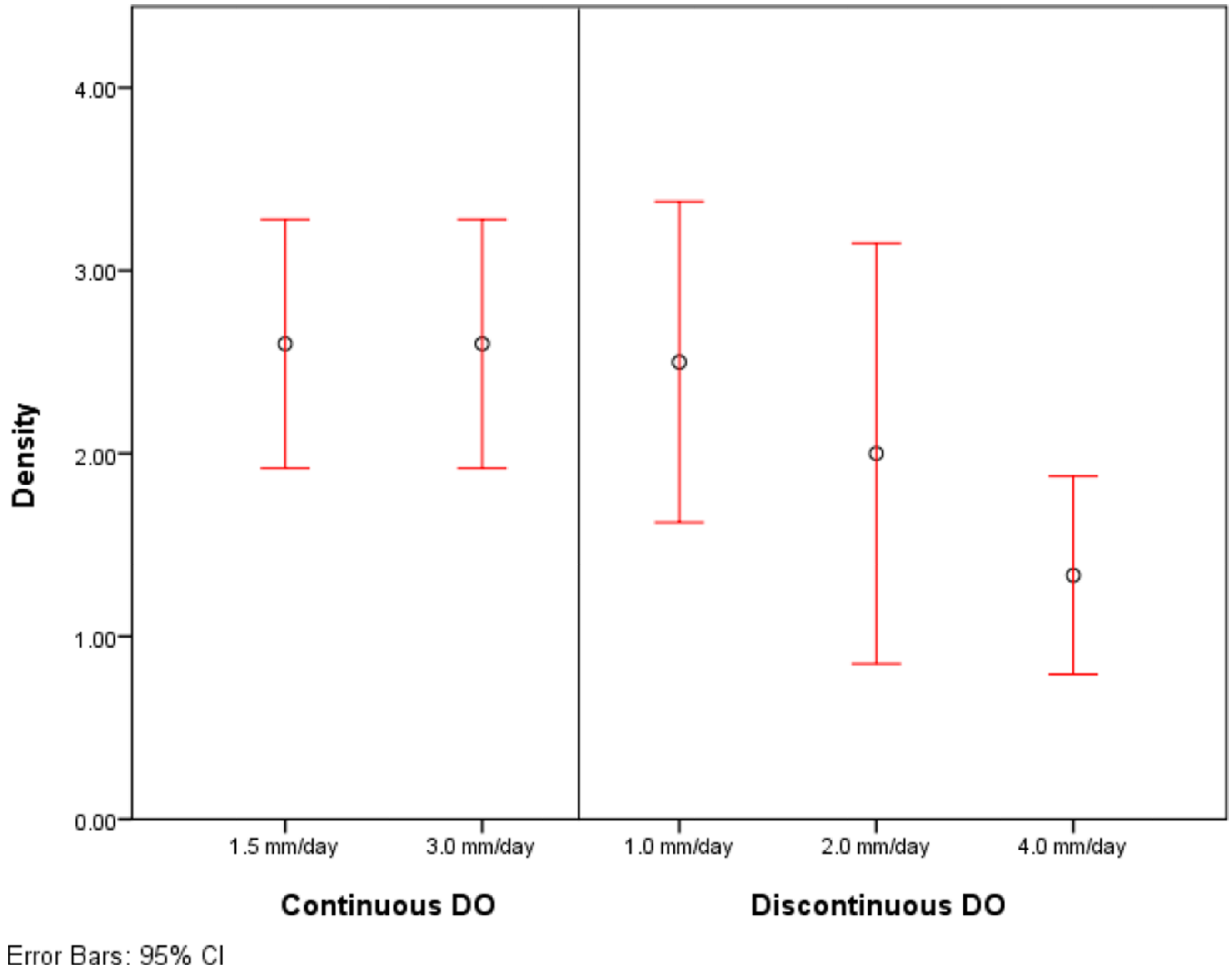

Figure 1.
Automated continuous distraction device attached to opened control box with circuitry and spring driven hydraulic reservoir.

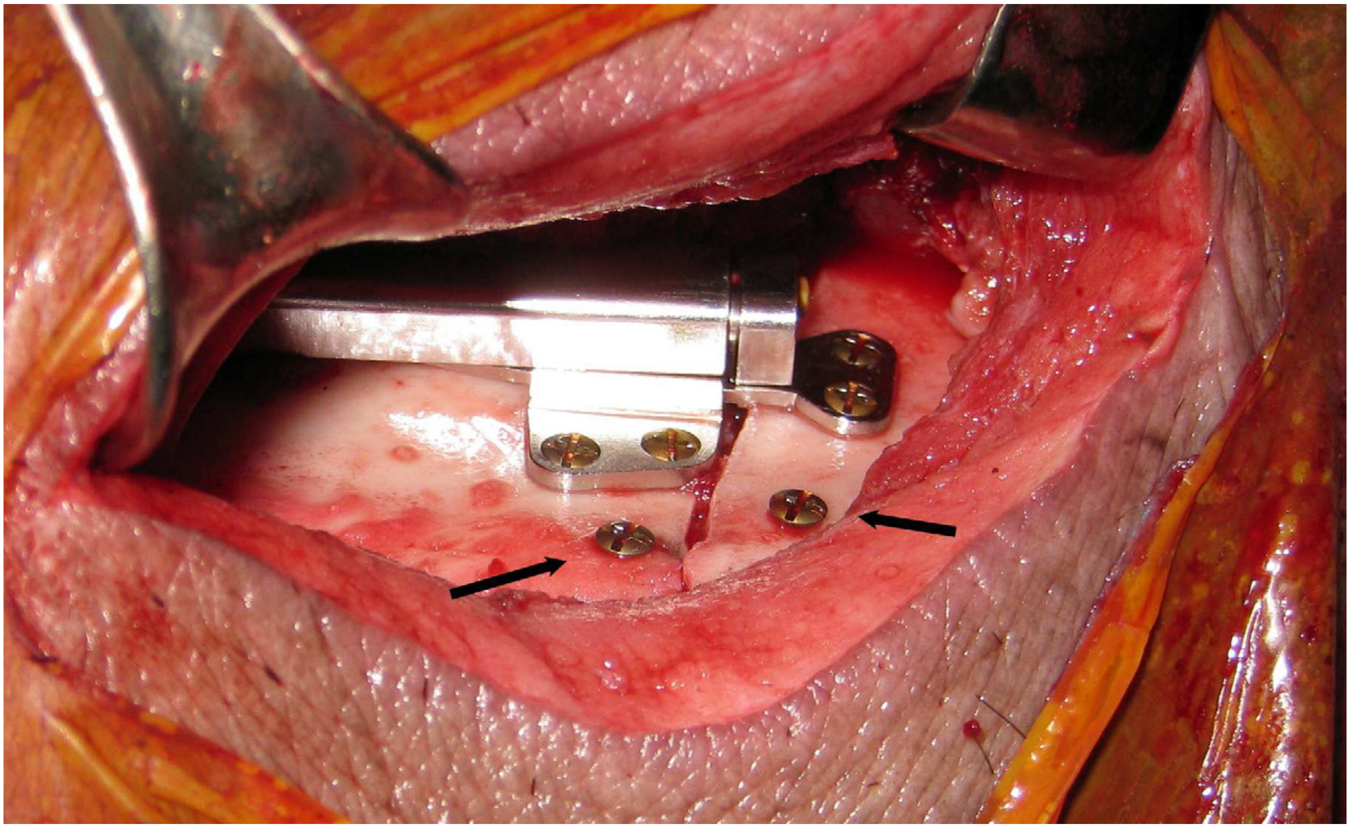

Figure 2.
Automated distraction device secured to the lateral aspect of the mandible across an osteotomy. Marker screws placed at the inferior border (arrows).

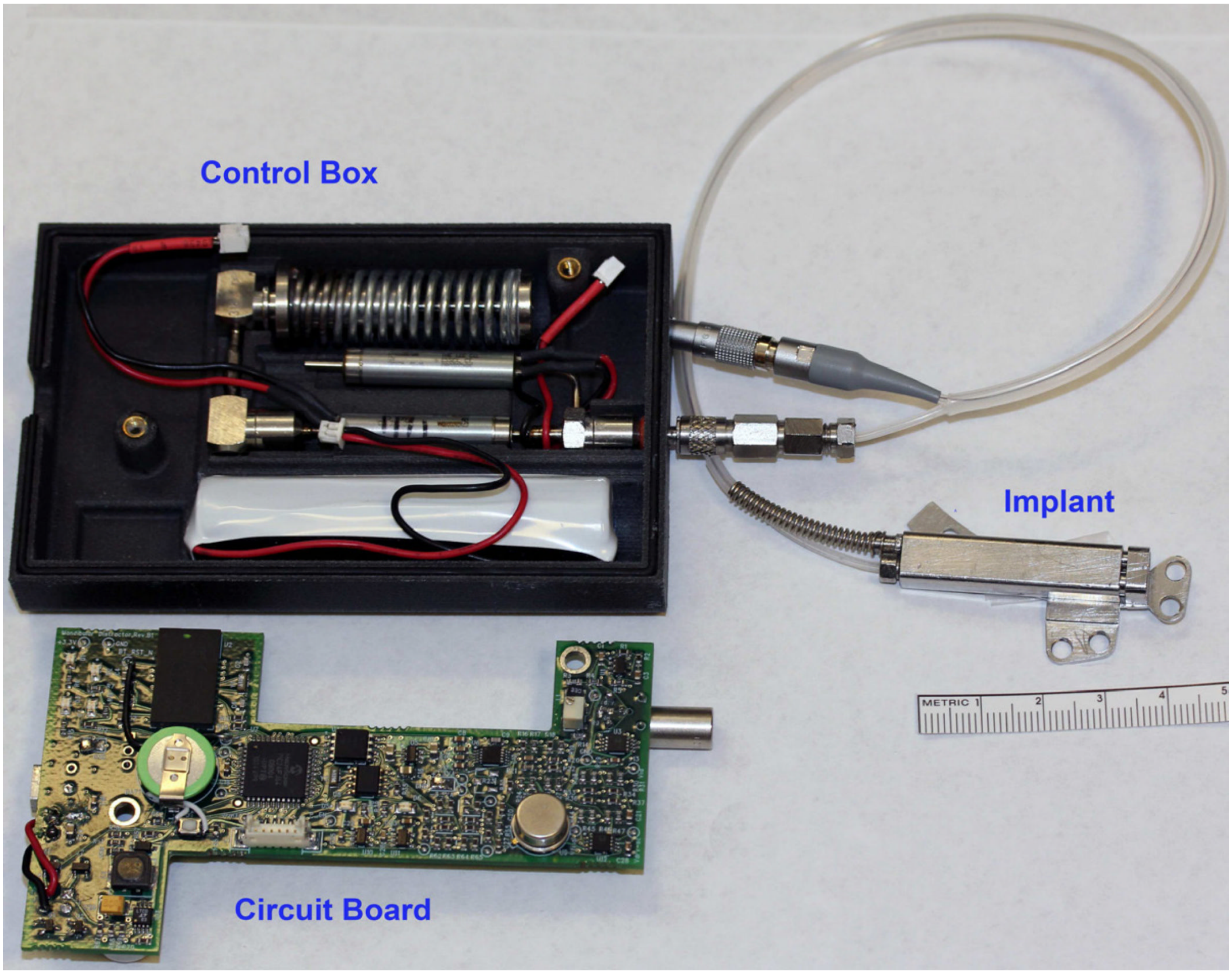

Figure 3.
Graph of projected (black line) and measured distraction (red). The device opened at 1.5 mm/day. The downward projection likely is from the force of the pig biting something solid causing the device to close slightly. The device then returns to programmed position.

Figure 4.
At end-DO, the reverse overjet increases and shifts the mandibular midline (black line) away from the side of distraction and maxillary midline (black line).

Figure 5.

A. End-DO lateral cephalograms showing the trapezoidal distraction gap measured with marker screws (white arrows). There is increased radiodensity at B. End-Fixation.

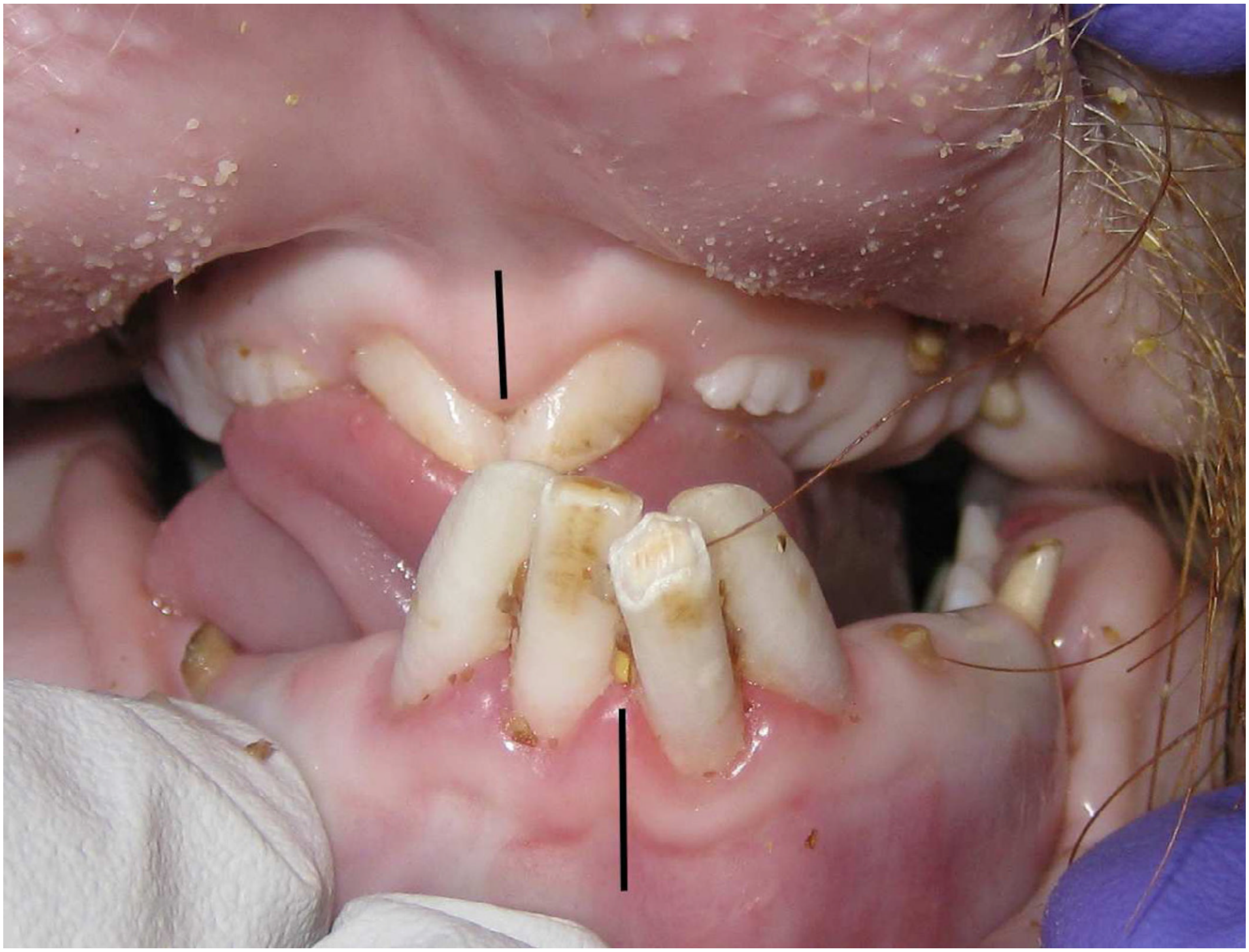

Figure 6.
Clinical photograph of ex-vivo mandible with complete fill of distraction gap of an animal distracted continuously at 3 mm/day. The regenerate is between the marker screws (arrows)

Figure 7.
Ex-vivo mandibular radiograph after sacrifice at end-fixation after continuous DO at 3 mm/ day. The radiographic density of the distraction wound is higher at the superior border where the rate of distraction is less than at the inferior border.

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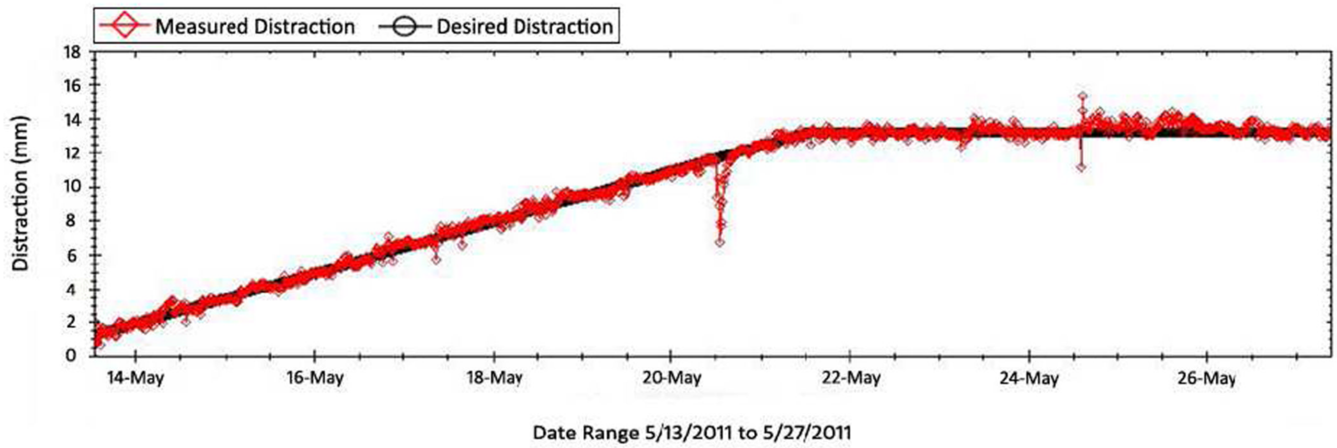

Figure 8.
Mean and 95% confidence intervals for (A) appearance, (B) stability and (C) radiographic density of the experimental and control groups.

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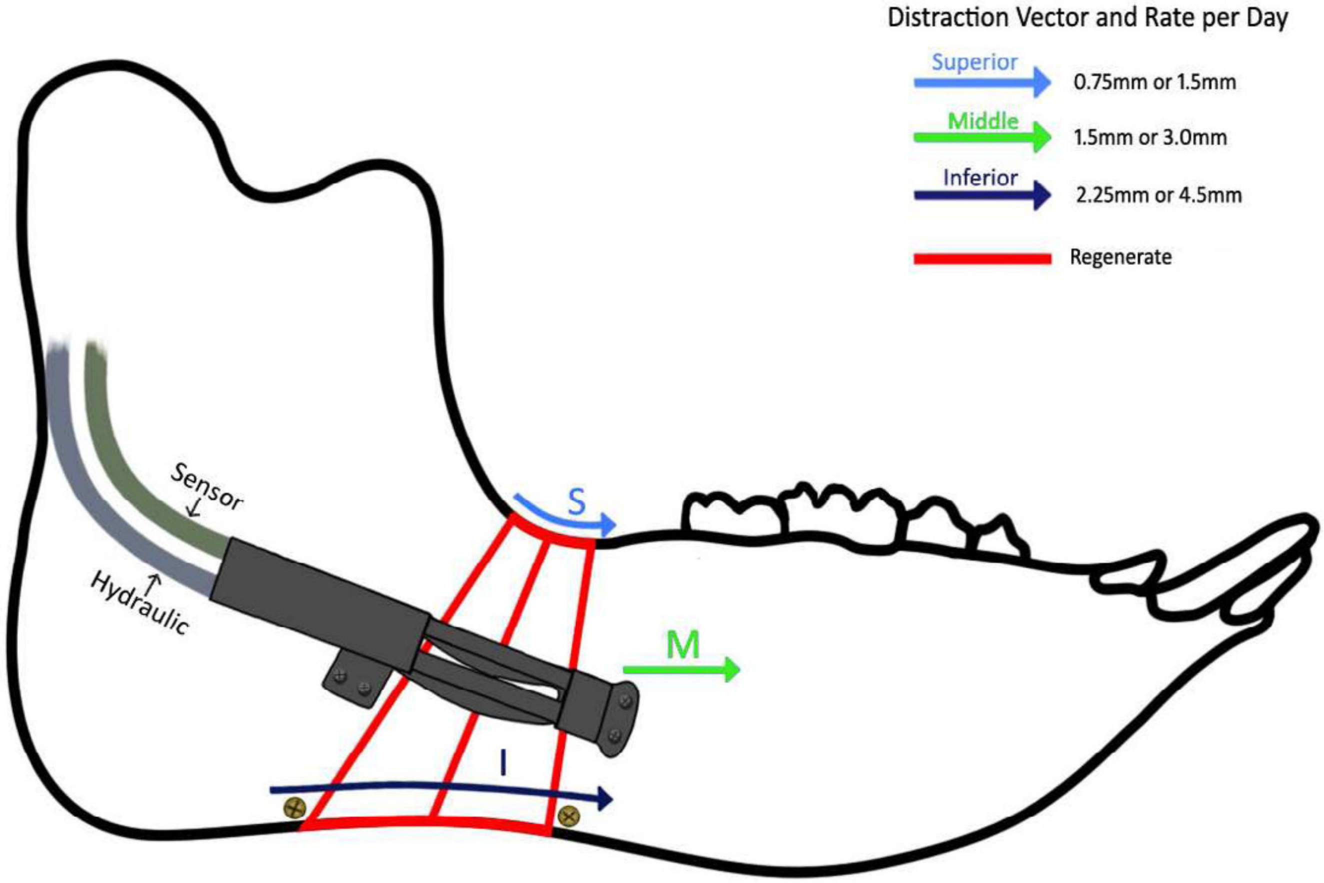

Figure 9.
Schematic of curvilinear automated continuous DO of the minipig mandible. Due to the curvilinear motion, distraction proceeds at faster rates at the inferior border compared to the superior border.

Table 1

Device assessment – distraction period, rate of distraction for each group

Protocol	Subject Number	Distraction Period	Average Rate	Total Distraction	Complications
Group 1					
1.5 mm/d	2–294	8 Days	1.4 mm/d	11.5 mm	Exit port infection
1.5 mm/d	3–079	8 Days	1.0 mm/d	8.0 mm	Wound and exit port infection
1.5 mm/d	4–088	8 Days	1.5 mm/d	12.0 mm	None
1.5 mm/d	4–067	8 Days	1.5 mm/d	7.0 mm	Torn hydraulic line
1.5 mm/d	5–040	8 Days	1.4 mm/d	11.5 mm	None
Group 2					
3.0 mm/d	5–117	4 Days	3.0 mm/d	12.0 mm	None
3.0 mm/d	6–037	5 Days	2.4 mm/d	12.0 mm	Exit port infection
3.0 mm/d	7–105	9 Days	1.4 mm/d	13.0 mm	None
3.0 mm/d	8–056	6 Days	2.1 mm/d	12.5 mm	None
3.0 mm/d	8–028	4 Days	3.0 mm/d	12.0 mm	Minor wound infection

Table 2

Automated Continuous Distraction Osteogenesis: Appearance, stability and radiographic assessment

Protocol	Subject Number	Appearance	Stability	Radiographic Density
Group 1				
1.5 mm/d	2–294	3	3	3
1.5 mm/d	3–079	2	2	2
1.5 mm/d	4–088	3	3	3
1.5 mm/d	4–067	2	1	2
1.5 mm/d	5–040	3	3	3
Average	~	2.6	2.4	2.6
Group 2				
3.0 mm/d	5–117	3	3	3
3.0 mm/d	6–037	3	3	3
3.0 mm/d	7–105	3	3	3
3.0 mm/d	8–056	2	3	2
3.0 mm/d	8–028	2	3	2
Average	~	2.6	3	2.6

Table 3

Control Group: Incremental Distraction Osteogenesis. Appearance, stability and radiographic assessment

Protocol	Appearance	Sample Size	Stability	Sample Size	Radiographic Density	Sample Size
1.0 mm/d						
0-day Latency	3	n = 2	3	n = 2	2.25	n = 4
4-day Latency	3	n = 2	3	n = 2	3	n = 2
Combined	3	n = 4	3	n = 4	2.5	n = 6
2.0 mm/d						
0-day Latency	2	n = 2	1.5	n = 2	1.75	n = 4
4-day Latency	2	n = 2	2	n = 2	2.5	n = 2
Combined	2	n = 4	1.75	n = 4	2	n = 6
4.0 mm/d						
0-day Latency	1.5	n = 2	1.5	n = 2	1.5	n = 4
4-day Latency	2	n = 2	1.5	n = 2	1	n = 2
Combined	1.75	n = 4	1.5	n = 4	1.33	n = 6

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Table 4

Statistical Group Comparison

	Appearance					Stability					Radiographic Density				
Protocol	$P_{1.5}$	$P_{3.0}$	$P_{1.0}$	$P_{2.0}$	$P_{4.0}$	$P_{1.5}$	$P_{3.0}$	$P_{1.0}$	$P_{2.0}$	$P_{4.0}$	$P_{1.5}$	$P_{3.0}$	$P_{1.0}$	$P_{2.0}$	$P_{4.0}$
1.5 mm/d	~	1.000	0.178	0.070	**0.046**	~	0.208	0.208	0.214	0.112	~	1.000	0.818	0.275	**0.004**
3.0 mm/d	1.000	~	0.178	0.070	**0.046**	0.208	~	1.000	**0.015**	**0.014**	1.000	~	0.818	0.275	**0.004**