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PROPRANOLOL ADMINISTRATION HAS A NON-STATISTICALLY SIGNIFICANT POSITIVE EFFECT ON THE OSSEOINTEGRATION PROCEDURE OF STAINLESS-STEEL IMPLANTS

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ABSTRACT

This experimental animal study aimed to assess the potentially positive effect of the administration of beta-blocker propranolol on the osseointegration procedure of stainless-steel bone implants. It was performed in two groups (study, control), consisting of 15 adult (12-weeks old) male Wistar albino rats each. In the proximal metaphysis of each tibia of all animals, a custom designed stainless-steel screw was implanted under sedation on day 0. Starting on the first postoperative day, study group animals received 2.5mg/kgr (1mg/ml) of propranolol daily intraperitoneally. Control group received the same volume of saline. On day 29, all animals were euthanized, both tibias from each animal were harvested and the implants' pullout-strength and removal torque were assessed. All animals completed the study and all harvested tibias were suitable for evaluation. Both parameters were different between the two groups, favoring the study group, albeit in a non-statistically significant manner. The pullout-strength and its Standard Deviation was 104.2±21.3 Newtons (study group) versus 90.8±18.2 Newtons ($p=0.103$), removal torque was 5.4±0.8 Newtons/cm (study group) versus 4.9±0.7 Newtons/cm ($p=0.09$). No statistically significant correlation was found between the animal weight and the pullout strength ($p=0.159$, r_s=-0.279), the animal weight and the removal torque ($p=0.628$, r_s=-0.101) and between the pullout strength and the removal torque ($p=0.193$, r=0.258). Propranolol administration seems to act positively on the osseointegration procedure of stainless-steel bone implants, albeit in a non-statistically significant manner. Further studies will be needed to reach secure conclusions regarding the potential beneficial effect of beta-blocker propranolol on bone implants' osseointegration.

Key words: Propranolol–osseointegration–prosthetic implants–prosthesis–beta adrenergic blocker agents

1 INTRODUCTION

Bone implants are widely used in both elective maxillofacial and orthopaedic surgery and trauma. One of the main issues when dealing with operations involving the use of bone implants, is the primary fixation of the implant to the bone, which probably secures long-lasting survivorship of the implant itself [1, 2] . This fixation procedure partly depends on the growth of bone at the implant-bone interface and may be the end result of a biological process, which is similar in many ways to the fracture healing response [3, 4] . This procedure is elicited by implantation [5, 6] .

Beta-adrenergic receptor antagonists (beta-blockers) are important pharmacological agents in the treatment of angina pectoris, hypertension and arrhythmias [7]. They also have a significant effect on bone metabolism, and therefore may play a potentially important role in reducing fracture occurrence and promoting fracture healing [7, 8]. Fracture healing and implants' osseointegration procedures share common pathways (such as osteoinduction and osteoconduction) [1] , hence beta-blocker administration may enhance the latter as well.

This experimental animal study in rats aimed to assess the potentially enhancing action of beta-blocker propranolol on the osseointegration procedure of a stainless-steel bone implant following its implantation.

2 METHODS

This blinded, in vivo animal study, was approved by the Department of Animal Health and Welfare, Veterinarian Drugs and Applications (Ref. 5741/2014; December 15^{th}, 2014) in accordance with the Presidential Decree 56/2013 and the European Union's Directive 63/2010. It was performed in propranolol treated and control groups, each consisting of 15 young adult 12-week-old male Wistar albino rats. The number of animals that were included in each group was predetermined based on the available related literature [3, 4, 9] . This study was performed on male rats only, in order to avoid unnecessary discrepancies between the two groups. Animals were group-housed (two per cage) in a temperature (22°C)- and humidity (50%) -controlled vivarium, they were maintained on a 12-hour light-dark cycle (lights off at 8 AM) and had ad libitum access to commercial food and fresh water. They all followed the same pharmaceutical perioperative protocol [9] . On day 0, a custom-designed stainless steel 316 L screw (Sanmac®, Sandviken-Sweden) was implanted in the proximal metaphysis of the tibias Figure 1 , with the rats under a standard general anesthesia protocol Figure 2 and following the pre-operative administration of antibiotic prophylaxis [9] .

Starting on day 1, animals were randomly assigned to two groups; either receive 2.5mg/kgr of propranolol daily intraperitoneally (Dociton Injektionslösung® 1mg/ml, MIBE GmbH Arzneimittel, Brehna-Germany) forming the study group, or the same volume of saline, forming the control group. The injections (propranolol and saline) were prepared and administered daily at 09.00 A.M, in a blinded manner by a non-author caretaker. All animals were also labeled in a blinded manner, to ensure that the authors were not aware of which animal belonged to which group. Each animal was weighted at the end of each week during the experiment and the dosage of propranolol or saline were adjusted accordingly. On day 29, all animals were euthanized by exsanguination (cardiac puncture) under general anesthesia, induced by the same procedure as preoperatively [9] .

Following euthanasia, both tibiae were harvested and stripped clear from surrounding soft-tissues. They were then placed in sterile canisters, where they were covered with ambient temperature salineFigure 3 .

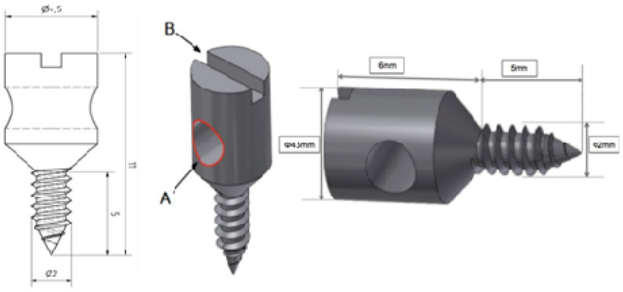

Figure 1. The characteristics of the custom-designed stainless steel 316 L screw (Sanmac®, Sandviken-Sweden). Hole "A" facilitated the measurement of the pullout-strength and the removal-torque. Indentation "B"served as a guide for the screwdriver.

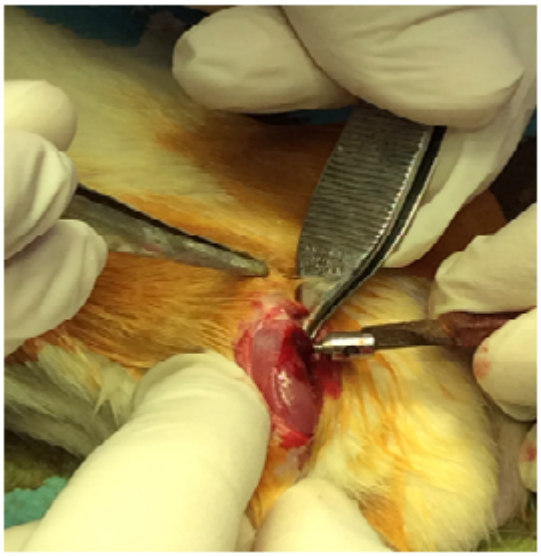

Figure 2. The implantation procedure of the custom-designedstainless-steel screw in the proximal metaphysis of the tibia of a rat undergeneral anesthesia.

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Figure 3. Following euthanasia, both tibiae of each animal were-harvested, stripped clear from soft-tissues and placed in a sterile canister.

The implants' pullout strength and torque were assessed strictly within the first 2 hours following the sacrifice of the animals, with the use of a specially designed and manufactured experimental device consisting of two basic mechanisms. The first mechanism holds stable the position of the bone. The second mechanism consists of a cylindrical shaped piston that uses air pressure in order to pull the screw out of the specimen. The device also runs torque tests after proper modificationFigure 4 .

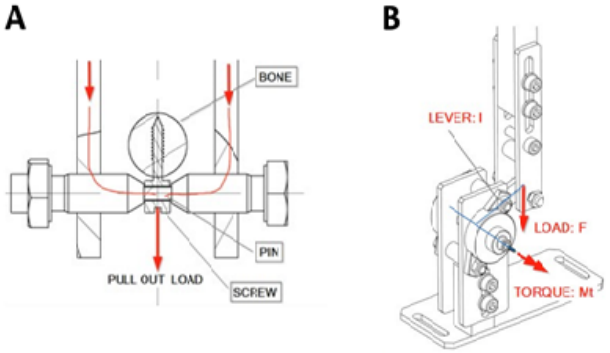

Figure 4. The pullout-strength (A) and the removal-torque (B)were measured with the use of a specially designed and manufacture dexperimental device [9].

The pullout strength was measured in right tibiae and the removal torque in the left [9] . Only after the completion of the study, the results of each animal were unblinded and statistically evaluated. This study was performed in compliance with the ARRIVE guidelines.

Statistical analysis.

For the statistical analysis, both parametric and non-parametric statistical tests were utilized. The assumptions of normality and homogeneity of variances were tested using the Shapiro-Wilk and Levene's test, respectively. The statistical evaluation of the removal strength and the torque was made with the use of the student's t-test. For the statistical evaluation of animal weight in the control group for two different time points, the paired samples t test was applied, whereas the animal weight in the propranolol group was analyzed using the Wilcoxon signed rank test. Data referring to the comparison of the final animal weight between the two groups, were processed with the Mann-Whitney test. Correlations between animal weight and torque, as well as between animal weight and removal strength were tested with Spearman's rho. The evaluation of a possible statistical correlation between torque and pullout-strength was made with the Pearson's correlation coefficient. Statistical significance level was set at $p<0.05$. All experimental data were analyzed with the SPSS version 20.0 (IBM Corp., Armonk, New York-USA) and are presented as mean ± SD.

3 RESULTS

All animals completed the experimental period successfully and uneventfully. There were no cases of tissue healing problems and/or fractures at the operative sites and all harvested tibiae were suitable for evaluation.

The animal weight of both groups increased in a statistically significant manner (study group: $p=0.002$, control group: $p<0.001$). Additionally, the differences in the final animal weight between the two groups was statistically non-significant ($p=0.299$, Mann-Whitney test), hence propranolol administration had no influence whatsoever on the weight of the animals.

The mean value of the pullout-strength for the propranolol group and its Standard Deviation (SD) was 104.2±21.3 Newtons versus 90.8±18.2 Newtons ($p=0.103$). The torque mean value and its SD was 5.4±0.8 N/cm versus 4.9± 0.7 N/cm ($p=0.09$). This suggested better osseointegration of the implants in animals in the study group that postoperatively received beta-blocker propranolol, albeit in a non-statistically significant manner. No statistically significant correlation was found between the animal weight and the pullout strength ($p=0.159$, r_s=-0.279), the animal weight and the torque ($p=0.628$, r_s=-0.101) and between the pullout strength and the torque ($p=0.193$, r=0.258).

4 DISCUSSION

Bone implants are widely used in both elective maxillofacial and orthopaedic surgery and trauma. The osseointegration procedure (initiation, progress and completion) of an implant to the host-bone, is one of the main issues when dealing with operations involving the use of bone implants [1, 2] . An implant is considered to be fully osseointegrated, when no progressive relative movement exists between the implant and the bone with which it has direct contact [10] . The evaluation of osseointegration is not an easy task [11, 12] . Depending on whether the study is performed on animals or is a clinical one, several invasive and non-invasive methods have been proposed and

tested [10, 13]. The evaluation of the osseointegration procedure in the clinical setting, necessitates mid- to long-term, large-scale, multicenter trials, which are very difficult to organize and perform. On the other hand, invasive methods, such as Histomorphometric analysis, tensional test, push-out/pull-out test and removal torque test, involve the removal of the implant following a certain waiting period to determine the extent of osseointegration, hence are limited to animal studies. The main -if not only- disadvantage of animal studies, is the fact that their results cannot be easily extrapolated into humans, since both bone biology and clinical settings differ substantially [3, 4, 13] . However, despite all these difficulties, it is still crucial to determine whether the primary fixation of an implant to the bone is secure.

The foremost part of the osseointegration procedure of a bone implant is the primary fixation [14–16] . This complex procedure is elicited by the implantation. Primary fixation facilitates the early postoperative mobilization of the patient (in orthopaedic surgery) and eventually secures long-lasting survivorship of the implant itself [14]. Primary fixation depends to some extent on the growth of bone at the implant's-bone interface and may be the end result of biological processes, which are similar in many ways to the fracture healing response, at least in terms of initial host response [10, 17–19] . This cascade of biological events is regulated by growth and differentiation factors released by the activated blood cells at the bone-implant interface [20] , recapitulating bone development and can be considered a form of tissue regeneration [6, 21].

Indirect (secondary) fracture healing is the most common form of fracture healing and consists of both endochondral and intramembranous bone healing [6, 22] . Many factors affecting the fracture healing procedure have been identified through extensive research [21, 23–28]. Beta-adrenergic receptor antagonists have a significant effect on bone metabolism and may play a potential role in reducing fracture occurrence and promoting fracture healing [7] . The administration of β-blockers was found to promote fracture healing in several studies [7, 28–34] . Propranolol in particular, was shown to be even able to rescue the deleterious effect of fluoxetine on fracture healing [35, 36] .

The effect exerted by several pharmacological agents on the osseointegration procedure has been studied to some extent as well [10, 36–41] . Since fracture healing and osseointegration procedures share common pathways [10] , it could be assumed that any factor acting positively or negatively on the fracture healing procedure, will affect in the same way and the osseointegration procedure. These actions, need however to be verified for the osseointegration procedure as well.

Our study evaluated the stability achieved during the osseointegration process of a stainless-steel bone implant, by implementing a previously verified biomechanic evaluation model [9] . Our results (pullout-strength and removal torque) were in favor of the propranolol-treated group, albeit in a non-statistically significant manner.

As with all similar studies, this one has certain limitations as well. A limitation of the study is the fact that an animal model was used. However, given the well-established evaluation procedures implemented [9] , the fact that the accurate evaluation of the immediate postoperative osseointegration procedure of implants in clinical studies is extremely difficult and has several limitations [42] , the animal model chosen in this study, seems as a useful alternative. It is true that the rat bone model shares similarities with the human bone, nonetheless, results derived from experimental studies should be interpreted with caution and should not be extrapolated to humans without further evaluation.

Another limitation was the fact that we did not perform an ad-hoc statistical analysis to determine the samples' sizes needed to reach statistically significant results, and this determination was made based on literature research only, which revealed very few similar papers [3, 4, 9] . However, one can only speculate whether with a larger sample, statistical significance could have been reached.

The dosage of administered β-blocker propranolol was another important issue that had to be decided before the beginning of the study. Literature research on studies evaluating the action of propranolol on fracture healing failed to lead to a standard dosage [43, 44] . We decided to avoid extremities and implement the dosage of 2.5 mg/Kg BW. An extrapolation of this dosage to the human, based on body weight only, is certainly not correct. This should be based on allometric scaling, taking also into consideration a correction factor reflecting the relationship between the body weight and the body surface [44] . Based also on literature research, the time period of 4 weeks was also determined to be adequate to evaluate the primary stability of an orthopaedic implant [3, 4, 9] .

To the best of our knowledge, this is the first study examining the ability of β-blocker propranolol to enhance osseointegration of stainless-steel bone implants. Beta-blocker agents are widely used pharmacological agents which are usually prescribed to older patients. Their potential beneficial effect on bone metabolism in general and the osseointegration procedure of a bone implant in particular, may add even more value to their use. By performing a blinded biomechanical study, we tried to eliminate any bias. However, our results should be interpreted with caution and extrapolation of these results to humans should be supported by more research. Further studies with different animal models and/or different implants, and studies evaluating the β-blocker propranolol dose response should be the next logical step to securely reach firm conclusions. Based on their results, large-scale clinical trials, evaluating the effect exerted by propranolol on osseointegration, may come later.

5 CONCLUSIONS

Beta-blocker propranolol administration seems to act positively on the osseointegration procedure of stainless-steel bone implants, albeit in a non-statistically significant manner. Further studies will be necessary in order to accurately determine whether the potential beneficial effect of beta-blocker propranolol on the osseointegration procedure of

bone implants really exists.

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