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Innovation in multifunctional bioabsorbable osteoconductive drug-releasing hard tissue fixation devices

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Abstract We review in this paper the work performed by our group to develop multifunctional bioabsorbable ciprofloxacin releasing bone implants. Poly lactide-co-glycolide (PLGA 80/20 and polylactide (P(L/DL)LA 70/30) were used. Ciprofloxacin (CF) and bioactive glass (BaG) 13-93 were added. The mixture was then extruded and self-reinforced. CF release, mechanical strength, and the effect on *S. epidermidis* attachment and biofilm formation were evaluated. In rabbits, tissue reactions were assessed. Pull out strength was evaluated in cadaver bones. CF was released over 44 weeks (P(L/DL)LA) and 23–26 weeks (PLGA). Initial shear strength of the CF screws was 152 MPa (P(L/DL)LA) and 172 MPa (PLGA). Strength was retained for 12 weeks (P(L/DL)LA) and 9 weeks (PLGA). Histologically, CF releasing implants did not show much difference from control plain PLGA screws except for increased giant cells. CF miniscrews had lower pullout strength than the controls, but CF tacks had better values than controls. BaG led to a drop in pullout strength properties. Bacterial growth, attachment and biofilm formation on CF implants was significantly reduced when compared to controls. Accordingly, bioabsorbable multifunctional implants with appropriate CF release, mechanical, and biocompatibility properties are possible to develop and are considered appropriate to apply clinically.

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Introduction

Various surgical devices are increasingly implanted in the human body for management of various conditions in the form of sutures, stents, prostheses, bone fixation devices, etc. The presence of such foreign materials does, however, involve the risk of increasing bacterial colonization and infection, because bacteria prefer colonization of nonviable materials and tissues. Once the surface of such implants is colonized, attached bacteria proceed by forming biofilm which protects them from attack by body immunological mechanisms, including phagocytic cells, and antibodies. Bacteria residing in such protective biofilms are difficult to eradicate using conventionally-delivered antibiotics, e.g. using systemic routes. Very large doses are needed to kill such bacteria. Even with the use of larger doses of antibiotics, it is often difficult to treat without the ultimate removal of the implant. Such implant removal procedures are more challenging than primary surgical operations, and they are associated with more complications and costs. Thus, strategies to reduce implant related infections are worth developing. One of such strategies is to try to interfere with bacterial colonization of the implants to prevent subsequent development of infection. One good type of implant would be one that can release antibiotics that may kill such bacteria right from the start, and can interfere with biofilm formation by bacteria. As a therapeutic means, the concept of local antibiotic therapy was introduced by in 1970 [1] when antibiotic-impregnated

bone cement was used for the treatment of infected prostheses. Later, prophylactic use of antibiotic-impregnated bone cement has also been applied to prevent infection. A good example is the use of Gentamicin-releasing beads which are currently in clinical use. However, non-absorbable materials are left behind as nonviable material. Having the antibiotic released, the non-absorbable carrier material may get itself colonized and infected by bacteria.

Bioabsorbable devices are being increasingly used in bone surgery, e.g. in the craniomaxillofacial (CMF) surgery, trauma, orthopaedics and hand surgery [2–4]. Among the most commonly used bioresorbable polymers for manufacturing of such implants are polylactide-co-glycolide (PLGA) and poly-L/DL-lactide (P(L/DL)A). The use of such bioabsorbable polymeric materials as drug releasing systems has also been explored. So far, polyglycolide (PGA) beads loaded with gentamicin were found to be effective when studied in an experimental canine model [5]. In the form of rods, PGA was used to release ciprofloxacin and studied in rabbits' femora demonstrating good penetration to bone tissue [6]. Vancomycin carried by polylactide (PLA) or polylactide-co-glycolide (PLGA) was also studied in experimental rabbit osteomyelitis model [7].

Although various antibiotics can be used to prevent or treat bone infections, one has to consider many factors when embarking on antibiotic to be used in multifunctional drug releasing implants. First, it should cover the causative or potential infecting agent. Secondly, it should have appropriate bone penetration and capability of achieving high concentration in the bone tissue where bacteria reside. Thirdly, it should be amenable to processing into the implant without unwanted interactions with the polymer. Fourthly, it should be releasable from the implant. Fifthly, it should be approved for clinical use and preferably low of cost. Ciprofloxacin does cover common bone infection causing bacteria such as *S. aureus, S. epidermis* and *P. aeruginosa* and good penetration to the bone. It has a minimum inhibitory concentration (MIC) of 2.0 μg/ml [8–10]. It was found to have good penetration of bone tissue including compact cortical bone and to achieve acceptable levels in the immediate vicinity of the implant (5, 10 and 15 mm) [6]. It has a high melting temperature, and thus it can be processed under conditions involved in melt extrusion manufacturing techniques that were used for developing the multifunctional implant of the present work. However, other methods can theoretically be used, such as injection moulding. It is, however, the challenge of having mechanically reliable devices remains unmet. Non-self-reinforced, e.g. injection molded P(L/DL)LA 70:30 fixation pins have initial bending strength of 126 MPa [11].

The effect of using an additive in the implant matrix has usually unfavorable effect on the mechanical properties of the final product. The other challenging issue has been the appropriate control of drug release from the implant in a way that avoids falls below therapeutic levels (may lead to selection of resistant bacterial strains [12]) or above toxic levels (systemic organ toxicity). In our work we have explored the use of a new manufacturing technique of self-reinforcement, to circumvent these challenges and to develop reliable antibiotic-releasing implants that can be used in the form of screws or tacks for bone fixation. Drug release and strength retention were studied *in vitro*. Biocompatibility was studied *in vitro* to define tissue reactions. Biomechanical characteristics were also defined.

Material and methods

Manufacture of bone fixation devices

Two types of polymers have been used in this work. The first was a commercially-available Resomer® LR708 (Boehringer Ingelheim, Germany) was used. It is copolymer of L-lactide and DL-lactide with monomer ratio 70L, 30DL and inherent viscosity of 6.3 dl/g. The second was a commercially-available PuraSorb®PLG (Purac Biochem bv., Gorinchem, Netherlands). It is a copolymer of L-lactide and glycolide with monomer ratio 80L, 20G, with an inherent viscosity of 6.4 dl/g. Ciprofloxacin (purchased from Jinxing Kangle Pharmaceutical Factory, Zhejiang, China) was used as antibiotic in manufactured devices. Antibiotic and matrix polymer were mixed together and extruded into billets. The billets were then die-drawn into self-reinforced (SR) rods [13]. Prototype drug-releasing hard tissue fixation devices, rods, screws with the same geometry as BioSorb™PDX 1.5 screws (SR-PLGA) or BioSorb™FX 2.0 screws (SR-P(L/DL)LA) and tacks with the same geometry as BioSorb™FX 2.0 tacks (SR-PLGA) (Linvatec Biomaterials Ltd., Tampere, Finland), were machined from SR-rods. In one type of screws bioactive glass granules (Bioactive glass 13-93, Vivoxid Ltd., Turku, Finland) were also added to the mixture of P(L/DL)LA, and ciprofloxacin in order to develop osteoconductive screws. Prototype devices (cylinders "chops of rods", screws, and tacks) were sterilized with γ-irradiation (25 kGy, Willy Rüsch AG, Kernen-Rommelshausen, Germany). Ciprofloxacin was bacteriologically tested and proved to be bioactive (unpublished data).

Mechanical properties

(1) Mechanical properties in vitro

In the lab of Institute of Biomaterials, an Instron 4411 universal testing machine (Instron Ltd., High Wycombe, England) was used for mechanical testing. Implant samples ($n = 5$–6) were tested to evaluate bending, shear and torsion strength as well as modulus. For evaluation of changes

in strength properties in time, implant specimens were immersed in a phosphate buffer solution (PBS) KH_2PO_4 (0.05 M) and NaOH (0.04 M) at a pH of 7.4 in closed brown flasks at 37°C for a period extending up to 52 weeks. The immersion solution was changed every 1–2 weeks and the pH of the solution was measured. Plain SR-P(L/DL)LA and SR-PLGA based implants (that do not contain ciprofloxacin or bioactive glass) were also tested to serve as controls according to the same protocol.

(2) Pullout strength

Various types of miniscrews and tacks were tested in human cadaver bones (skull and fibula) [14–18]. Pullout strength was determined using Lloyd LR30K materials testing machine (Lloyd Instruments Ltd., Hampshire, UK). There was 50 pieces of each type that underwent evaluation for pull-out strength. Evaluated implants included: (1) Ciprofloxacin-releasing P(L/DL)LA miniscrews, (2) Ciprofloxacin-releasing bioactive glass-containing P(L/DL)LA miniscrews, (3) Plain (Control) P(L/DL)LA miniscrews, (4) Ciprofloxacin-releasing PLGA miniscrews, (5) Ciprofloxacin-releasing bioactive glass-containing PLGA miniscrews, (6) Plain (Control) PLGA miniscrews, (7) Ciprofloxacin-releasing PLGA tacks, and (8) Plain (Control) PLGA miniscrews. The results were statistically evaluated.

Drug release

Screws (500 mg, 50 ml either P(L/DL)LA or PLGA) or tacks (20 mg, 10 ml) were placed into phosphate buffer solution (PBS) KH_2PO_4 (0.05 M) and NaOH (0.04 M) at a pH of 7.4. Five samples of each type in each experiment were kept in brown drug bottles in an incubator shaker at 37°C. Samples were retrieved and the concentration of released ciprofloxacin was determined using a UV-spectrometer (UV-2501PC, Shimadzu, Japan and UNICAM UV 540, Thermo Spectronic, Cambridge, UK). Absorbance values at UV spectra maximum of ciprofloxacin in PBS at $\lambda = 270.5$ nm were determined. Concentrations of released ciprofloxacin were then calculated according to the Beer-Lambert law and drug release profiles of each type of prototype were determined.

Activity against bacteria

Inhibition of bacterial growth was assessed by incubating ciprofloxacin-releasing PLGA or ciprofloxacin-releasing SR-PLGA cylinders in blood agar plates containing *S. epidermidis* ATCC 35989 suspension (at a concentration of *ca*. 10^7 cfu/ml) in Trypticase soy broth (TSB) medium overnight at 35°C and the diameters of bacterial growth inhibition areas around implants were measured. As control implants, plain PLGA (not containing ciprofloxacin) and titanium were also studied. Five parallel samples of each material were examined.

For evaluation of implant effect on bacterial attachment and biofilm formation, the specimens were incubated with *S. epidermidis* (ATCC 35989) suspension (*ca*. 10^5 cfu/ml) at 35°C (with intermittent shaking) for 1, 3, 7, 14 and 21 days and examined using scanning electron microscopy [19]. Standard examination fields were determined by SEM as follows: analysis of the circular surface of cylindrical specimens was started from the central point, proceeding 1/2 mm at a time to the edge of the circular area along x and y axes in both directions. Analysis was performed at a magnification of ×3000. The number of bacterial cells was counted and the extracellular polymer material was classified by semiquantitative scale: − (no biofilm), + (weak or moderate biofilm formation) and ++ (strong biofilm). Evaluated implants included: (1) Ciprofloxacin-releasing PLGA, (2) Ciprofloxacin-releasing bioactive glass-containing PLGA, (3) Plain (Control) PLGA, (4) Bioactive glass-containing PLGA and (5) Titanium.

For counting mean values of bacterial cell counts for SEM study, only the non-zero values were taken into account. The frequency of zeros (no bacterial cells) was also registered. Due to the high number of zero-values the statistical analysis of bacterial cell counts was carried out in two parts: (1). The proportion of zeros was analyzed by the chi-square test or Fisher's exact test. (2) Non-zero values were analyzed by analysis of variance (ANOVA) or the non-parametric Kruskal-Wallis test. Analysis of biofilm formation was done by Fisher's exact test. The Mann-Whitney U-test was utilized for the comparison of growth inhibition diameter. Two tailed p values were reported. All analyses were done using SPSS for Windows (version 11.5).

Behaviour *in vivo*

Ciprofloxacin-releasing SR-PLGA 80/20 miniscrews were implanted in rabbits' bones, one screw on either side of the sagittal suture ($n = 28$ rabbits) [20]. Plain PLGA and titanium screws were also implanted in rabbits' crania to serve as controls [21]. Animals were sacrificed after 2, 4, 8, 16, 24, 54 and 74 weeks, four animals per group. Histological examination was performed to assess tissue reactions (effect on osteoblasts, bone formation, inflammatory cell infiltrate and fibrous tissue formation) and implant biodegradation profiles.

Results

It was feasible to produce functional bone fixation devices made of ciprofloxacin-releasing SR-PLGA, ciprofloxacin-releasing SR-P(L/DL)LA and ciprofloxacin-releasing

Fig. 1 Examples of developed and studied multifunctional bioabsorbable drug-releasing hard tissue fixation devices including from left to right screws, miniscrew and tack

bioactive glass containing SR-P(L/DL)LA (Fig. 1). Initial shear strength of the studied ciprofloxacin-releasing implants were 172 ± 20 MPa (SR-PLGA screws), 152 ± 15 MPa (SR-P(L/DL)LA screws), and 118 ± 9 MPa (SRPLGA tacks) (Table 1). Studied implants retained their mechanical properties *in vitro* for at least 6–12 weeks [22].

In general, ciprofloxacin-releasing miniscrews had a lower pullout strength than corresponding plain screws, with ciprofloxacin-releasing SR-P(L/DL)LA had 142.9 ± 25.9 N [17] and ciprofloxacin-releasing SR-PLGA had 66.8 ± 4.9 N [14] as compared to corresponding plain SR-P(L/DL)LA (162.7 ± 37.8 N) and the SR-PLGA (96.3 ± 9.3 N) miniscrews. The difference in pullout strength between ciprofloxacin-containing and plain SR-PLGA and between the PLDLA groups was also statistically significant ($p < 0.001$). However, ciprofloxacin-releasing SR-PLGA tacks had 146.9 ± 10 N. Plain (control) SR-PLGA tacks had 141.4 ± 12 N [18]. Among PLDLA miniscrews, bioactive glass containing P(L/DL)LA miniscrews had the lowest pullout strength values, followed by ciprofloxacin bioactive glass and containing P(L/DL)LA miniscrews [17]. The most common cause of failure was thread breakage for the ciprofloxacin-releasing SR-P(L/DL)LA miniscrews, shaft breakage for the ciprofloxacin-releasing SR-PLGA miniscrews, and barb breakage for ciprofloxacin-releasing SR-PLGA tacks (Table 2).

Table 1 Initial mechanical properties of studied γ-sterilised plain (*P*) and ciprofloxacin-releasing (*C*) self-reinforced poly-L/DL-lactide [SR-P(L/DL)LA] 70:30 screws, polylactide-co-glycolide (SR-PLGA) 80:20 screws and process-modified PLGA 80:20 (SR-mPLGA) tacks

Sample	Shear strength (MPa)	Bending strength (MPa)	Torsion strength (MPa)
P SR-P(L/DL)LA screw	185 ± 10	171 ± 5	58 ± 5
C SR-P(L/DL)LA screw	152 ± 15	151 ± 10	46 ± 2
P SR-PLGA screw	184 ± 20	–	65 ± 10
C SR-PLGA screw	172 ± 20	186 ± 20	65 ± 10
P SR-mPLGA tack	125 ± 9	–	–
C SR-mPLGA tack	118 ± 9	–	–

Table 2 Results of pullout strength testing in cadaver bones of plain, ciprofloxacin (C) and bioactive glass (B) containing miniscrews and tacks

Tested implant	Pullout strength (N)	Tested bone	Source
PLDLA miniscrew	162.7 ± 34	Fibula	Leinonen et al. [17]
PLDLA + C miniscrew	142.9 ± 26	Fibula	Leinonen et al. [17]
PLDLA + C + B miniscrew	114.9 ± 34	Fibula	Leinonen et al. [17]
PLDLA + B miniscrew	99.1 ± 16	Fibula	Leinonen et al. [17]
PLGA miniscrew	96.3 ± 9	Skull	Tiainen et al. [14]
PLGA + C miniscrew	66.8 ± 5	Skull	Tiainen et al. [14]
PLDLA tack	135.0 ± 26	Skull	Leinonen et al. [16]
PLGA tack	141.4 ± 12	Skull	Tiainen et al. [18]
PLGA + C tack	146.9 ± 10	Skull	Tiainen et al. [18]

All of the contained ciprofloxacin was released from the screws by 44 weeks (SR-P(L/DL)LA) and by 23–26 weeks (SR-PLGA) *in vitro*. Release burst was detected immediately at the start of the release, after which achieved ciprofloxacin concentrations were 0.06–8.7 μg/ml/day for SR-P(L/DL)LA, 0.6–11.6 μg/ml/day for SR-PLGA, and 0.05–3.9 μg/ml/day for SR-PLGA tacks. The maximum reached values were recorded by the 15th week for P(L/DL)LA screws [23], by the 8th week for PLGA screws [24], and by the 3rd week for PLGA tacks [25] (Fig. 2).

Ciprofloxacin-releasing PLGA materials had significantly ($p < 0.025$) lower number of attached bacteria to their surface as compared to titanium or plain PLGA cylinders [25]. No biofilm was observed in 74–93% of situations for titanium, 57–78% for PLGA and 98–100% for ciprofloxacin-releasing PLGA. Ciprofloxacin-releasing PLGA also inhibited bacterial growth on blood agar plates showing an average radius of growth inhibition area (measured from the outer surface of the biomaterial to the edge of the growth inhibition area) of 27 mm, while no inhibition was seen with plain PLGA and titanium specimens (Fig. 3). Ciprofloxacin-releasing self-reinforced implants had still a better effect

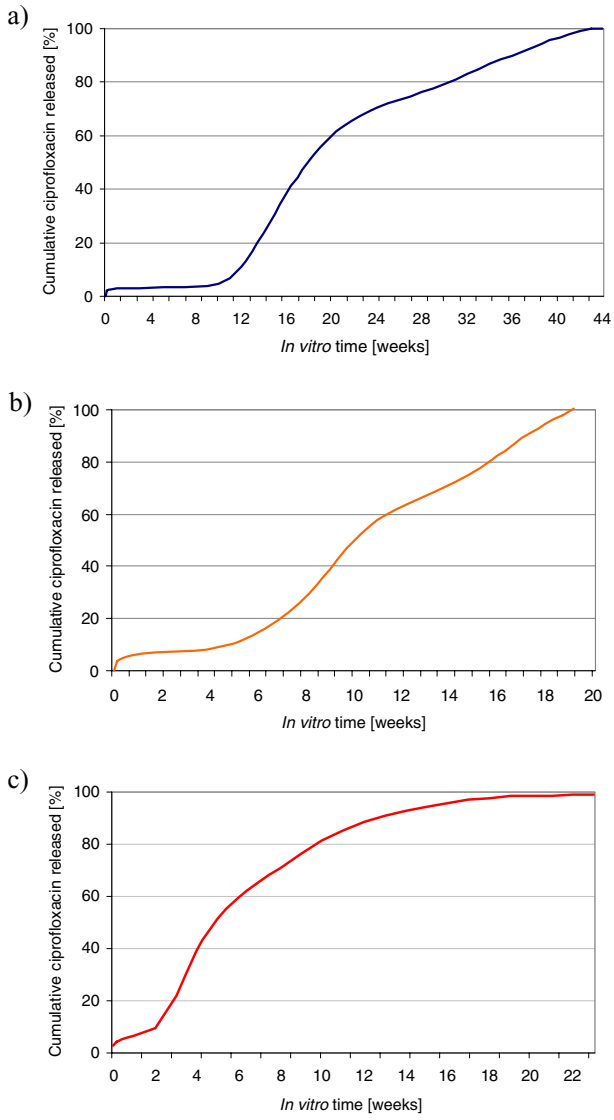

Fig. 2 Cumulative percentage of released ciprofloxacin from studied bioabsorbable γ-sterilized ciprofloxacin-releasing SR-P(L/DL)LA screws (a), SR-PLGA (b) screws and SR-PLGA tack (c)

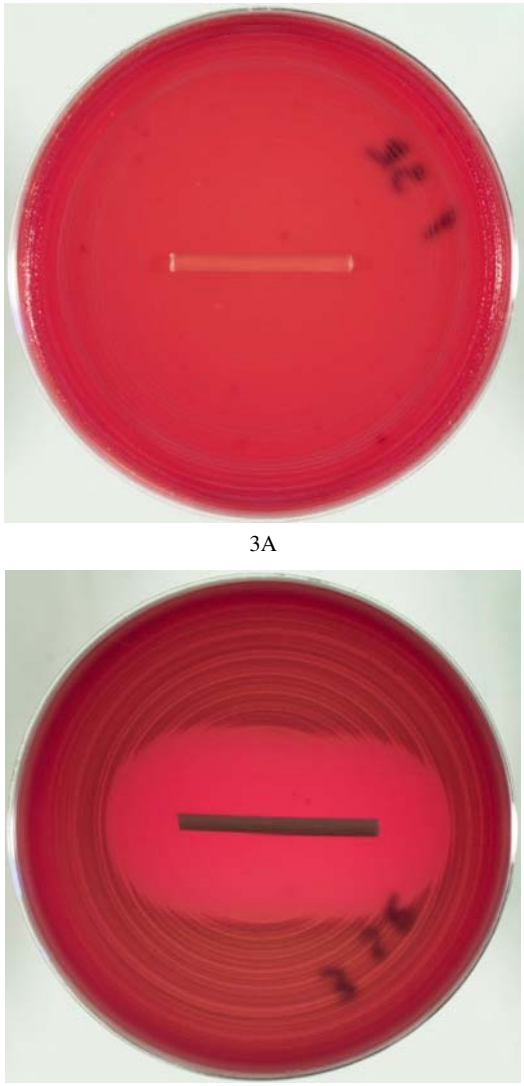

Fig. 3 Inhibition of bacterial growth and biofilm formation. Growth inhibition of *S. epidermidis* ATCC 35989 on agar plates: There was no inhibition of bacterial growth around plain self-reinforced polylactide-co-glycolide (SR-PLGA) 80/20 rods (A) but clear bacterial growth inhibition areas around ciprofloxacin-releasing SR-PLGA 80/20 (SR-PLGA-C) rods (B). Scanning electron micrographs (C) of various biomaterials incubated with *S. epidermidis* ATCC 35989 for 1 day. Tested materials were PLGA 80/20 (A), PLGA 80/20 containing ciprofloxacin (AC), PLGA 80/20 containing bioactive glass (AB), PLGA 80/20 containing bioactive glass and ciprofloxacin (ABC) and titanium (T)

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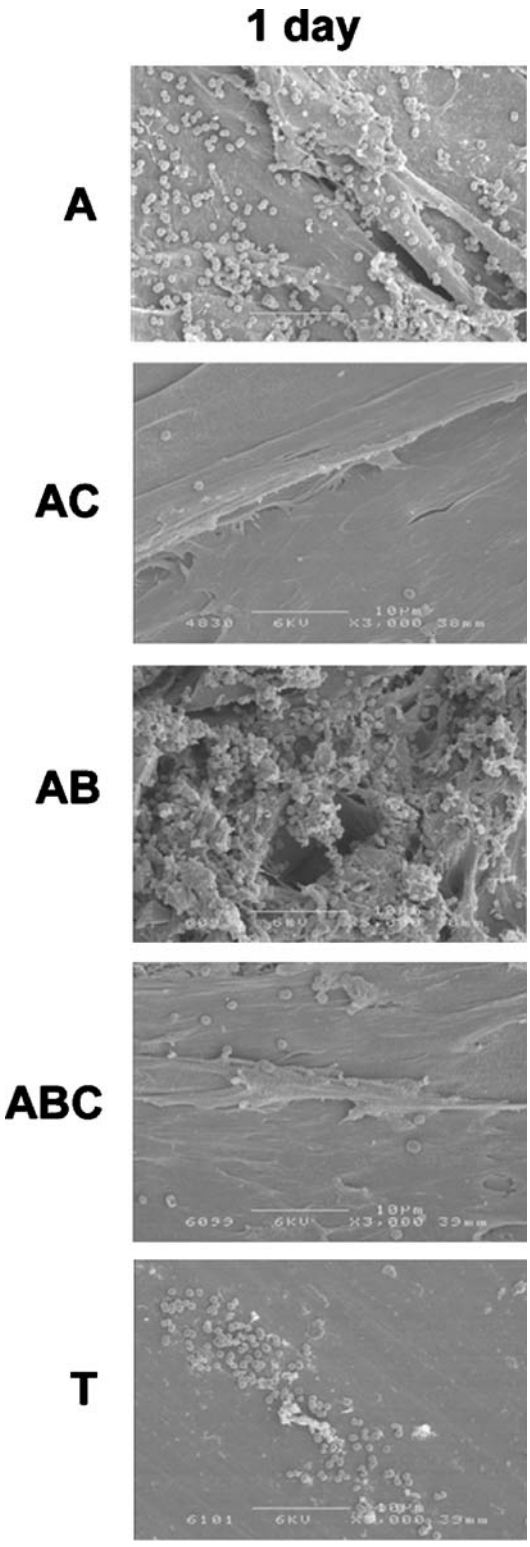

3C

Fig. 3 (*Continued*)

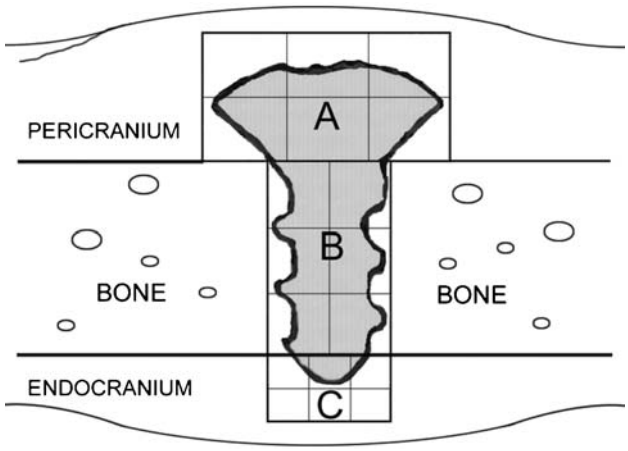

Fig. 4 Examination areas (A, B and C) of histological samples. Original figure was published in: Tiainen J, Soini Y, Suokas E, Veiranto M, Törmälä P, Waris T and Ashammakhi N, Tissue reactions to multifunctional bioabsorbable ciprofloxacin-releasing polylactide-polyglycolide 80/20 screws in rabbits' cranial bone, Fig. 1, J Mater Sci Mater Med 2006 (In press). Reproduced with with kind permission of Springer Science and Business Media

showing an average radius of growth inhibition area of 34 mm. No attached bacteria were observed in 68–89% and no biofilm formation in 97–99% of the examined areas of the ciprofloxacin-releasing SR-PLGA specimens.

The highest number of giant cells infiltration was seen near the heads of the screws at two weeks postoperatively. The number of giant cells had decreased by at 4 and 8 weeks postoperatively, but that of macrophages started to decrease from 16 weeks and on. Fibrous tissue formation had occurred around screws. Such fibrous tissue capsule had progressively increased in thickness over time. In the bone, active osteoblasts (cuboidal in shape) were seen in bone areas around the shafts of the screws, with the highest number of active osteoblasts was seen at 4 weeks postoperatively. At 16 weeks postoperatively, compact fragmentation of the screw heads was seen, and macrophages could be seen inside screw matrices. By 24 weeks postoperatively, no polarizing biomaterial was seen. By one year postoperatively, only traces of the screws could be found in the extracellular space. By $1\frac{1}{2}$ year postoperatively, no material traces could be found extracellularily, but all material that could be detected was intracellular in macrophages [20]. No major differences from controls (PLGA) could be demonstrated except for some increased giant cells around the head of the screw two weeks after implantation and a slightly thinner fibrous tissue layer 16 weeks after implantation.

Discussion

To our knowledge, there is no published work by other groups on antibiotic releasing bioabsorbable screws or tacks,

to compare the results with. In the present work, initial mechanical properties of the developed screws were comparable to those obtained with commercially-available SR bioabsorbable fixation screws. In regards to shear strength, multifunctional ciprofloxacin devices had relatively lower values than corresponding plain absorbable devices (172 MPa for PLGA and 152 MPa for P(L/DL)LA). An important requirement for bioresorbable bone fracture fixation devices is also the retention of their strength until bone healing is achieved, which requires 4–8 weeks to occur [26]. In our groups' work, ciprofloxacin-releasing implants were found to retain their mechanical properties at a level that is considered appropriate for achieving bone fixation for at least 12 weeks (ciprofloxacin releasing SR-P(L/DL)LA screws) and nine weeks (ciprofloxacin releasing SR-PLGA rods, Ø 3.0 mm) *in vitro*. Pullout strength of ciprofloxacin miniscrews, however, was lower than that of plain screws and it was recognized that more work to improve them is needed. They do have appreciable holding power to the cadaver human cranial bone [for P(L/DL)LA miniscrews 143 N and for PLGA miniscrews 67 N] but this can be improved further. Tacks, however, have better pull-out strength properties probably because of the geometry of their teeth that can hold to the bone when pulling forces are exerted.

Ciprofloxacin release properties were satisfactory (above therapeutic level and below toxic level with good high burst peak). Hence, it was thought that these devices can be used either for prophylaxis (high early shot) or for treatment (prolonged maintained release) of bone infections. Fluoroquinolones have a concentration-dependent killing capacity for microbes [27]. Niemelä et al. [19] showed that in the first few days locally released ciprofloxacin concentrations exceed by more than 30 times the observed MIC for the *S. epidermidis* strain used in their experiment. Released ciprofloxacin was demonstrated to inhibit bacterial growth in the vicinity of the implant. Should bacteria get access to the implant its proliferation and also biofilm formation seems to be inhibited. Systemic antibiotics can not always achieve appropriate local concentrations in the bone, given the fact that local circulation can be compromised when there is fracture or osteotomy. In addition, systemically administered high antibiotic drug levels have their own dangers in leading to organ toxicity and failure, mostly of kidney failure.

Tiainen et al. [20] have demonstrated that ciprofloxacin releasing miniscrews have close profiles of tissue reactions to plain miniscrews [21] when implanted in the cranial bone of rabbits, except for the earlier appearance of giant cells in the vicinity of the implant. This reaction did not seem to interfere with osteoblast activity in the bone.

Ciprofloxacin releasing implants were found to inhibit bacterial proliferation in an average are of 30 mm, which can be expected to be adequate for killing bacteria in the area surrounding the implant when it is applied in tissue. It was also found that ciprofloxacin-releasing PLGA was superior to titanium in preventing *S. epidermidis* attachment and biofilm formation *in vitro*, whereas pure PLGA was poorer than titanium in this respect [19]. This would warrant future precautions, when using plain polymeric implants, for possible vulnerability to colonization. Although, so far, there are no clinical reports on increased incidence of infection with polymeric bioabsorbable implants as compared to metals, the study raises questions in this regards. In Niemelä et al. study [19], no bacterial growth was found in 57.5% of the examined areas on ciprofloxacin releasing PLGA implants on the first day, whereas less than a fifth of the findings in the other plain PLGA and titanium groups were negative. During the whole study period, the mean bacterial count was lowest with ciprofloxacin PLGA specimens. Biofilm was not seen in any of the incubation periods in 93–100% of the ciprofloxacin PLGA specimens or it surrounded some cells only slightly.

Because of these encouraging results, the first prospective clinical trial on the use of these screws in the treatment of ankle fractures (that are associated with appreciable risk of infection) is due to start soon. Clinical applications in other areas of surgery are expected to follow also in future [28].

Conclusions

Novel ciprofloxacin-releasing SR-PLGA and SR-PLDLA screws that have sufficient strength retention and effective drug release properties can be produced. Such materials can significantly reduce attachment and biofilm formation by *S. epidermidis in vitro*. These devices are promising for clinical indications for prevention or treatment of bone infections.

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