Did local teicoplanin delivery systems inhibit or aggravate implant-related infection?

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Dear Editor,

We read with great interest the article by Şener et al. [1] and would like to bring four issues to your attention.

First, the authors analysed the difference in the bacterial density between four groups with repetitive Mann-Whitney U test. Unavoidably, type I error (α) would be magnified [2]. It would be appropriate to calibrate the P value as: $\alpha' = 2\alpha/(n^2 - n) = 2 \times 0.05/(4^2 - 4) = 0.0083$ [2]. Thus, we made a second statistical analysis (Table 1). The data showed, however, no difference was found between group 2 and group 3 nor between group 3 and group 4. Combined with the inferior performance of group 3 in both radiological findings and macroscopic findings, antibiotic-loaded bone cement did not show superiority over other treatment modalities.

Second, the results showed that teicoplanin-loaded bone graft could not help, and could even interfere, with the infection control. Apart from the mechanisms discussed by the authors, other interpretations may be considered (Fig. 1). For example, local subacute inflammation was assumed two weeks after the bacterial inoculation. Less encapsulation of granulation tissue and bone callus, more osteolysis and exudation, and greater hyperemia were anticipated compared with chronic osteomyelitis [3]. Also, teicoplanin releasing systems were placed at the fracture site, a more open space than the medullary cavity. As a result, the adopted model of implant-related infection might present greater dilution, absorption, distribution, and elimination of teicoplanin than that of chronic osteomyelitis [4].

Some hidden or distant bacteria might be spared from the locally compromised teicoplanin level and account for recurrence of infection. Moreover, it was reported that the length of time during which the local antibiotic level exceeded minimal inhibition concentration ($T_{>MIC}$) highly predicted antimicrobial potency of glycopeptide releasing systems [4]. Applying morselised cancellous bone, lengthening the duration of immersion in antibiotic solution, and the technique of iontophoresis would facilitate the teicoplanin impregnation into bone and prolong the $T_{>MIC}$ [5]. The authors simply immersed the corticocancellous grafts in teicoplanin solution for only one hour. The adsorption was possibly far below the saturation threshold, which may underestimate the antimicrobial efficacy of teicoplanin-loaded bone grafts. To our disappointment, no in vivo investigation was attempted on the kinetics of antibiotic release from bone. Also, implant removal is a prerequisite for thorough debridement; however, the authors retained the infected implant, where bacteria colonised and biofilm probably developed (Fig. 1). It was difficult to reach effective antibiofilm concentrations of teicoplanin around the implant.

Third, substantial details concerning the fabrication of teicoplanin-loaded bone grafts and acrylic beads [5], such as the concentration and pH of teicoplanin solution, the surface area, the bulk volume and the weight of bone grafts and acrylic beads, were not mentioned, which made comparison on antimicrobial efficacy impossible.

Fourth and finally, the authors indicated that use of antibiotic-loaded beads was superior to debridement and systematic antibiotic treatment while antibiotic-loaded autogenous bone was not. This did not seem reasonable. In fact, debridement and systematic teicoplanin treatment were also offered in groups 3 and 4. What differed from group 2 was additional teicoplanin-loaded beads and

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Table 1 Statistical results of subgroup comparison in microbiological evaluation

Groups compared	Sum of ranks	Mann-Whitney U	Wilcoxon signed-rank	P value
G1 vs G2	98.5 vs 37.5	1.5	37.5	0.001
G1 vs G3	100.0 vs 36.0	0.0	36.0	0.001
G1 vs G4	99.0 vs 37.0	1.0	37.0	0.001
G2 vs G3	81.5 vs 54.5	18.5	54.5	0.143
G2 vs G4	68.5 vs 67.5	31.5	67.5	0.957
G3 vs G4	51.0 vs 85.0	15.0	51.0	0.066

Fig. 1 Schematic diagram of osteomyelitis models of subacute infection (a) and chronic infection (b). In comparison with the model of chronic osteomyelitis (b), the subacute animal model (a) had less encapsulation of granulation tissue and bone callus, more osteolysis and exudation, and greater hyperemia in local lesion. Besides, teicoplanin-loaded releasing systems were placed at the fracture site (a) instead of in the medullary cavity (b), and the infected implant was retained (a). Therefore, greater dilution, absorption, distribution, and elimination of teicoplanin were anticipated in the subacute model compared with the model of chronic osteomyelitis. The teicoplanin concentration in the local lesion would be compromised, which made the clearance of residual bacteria and adhering biofilm impossible. (This figure is not to scale)

teicoplanin-loaded autogenous bone in groups 3 and 4, respectively. It seems more appropriate to conclude that the inhibition by both antibiotic delivery systems was inferior to their aggravation of infection.

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