

Research Article

The Topical Tranexamic Acid Have Potential Hazard of Promoting Biofilm Formation of *Staphylococcus aureus* in Microenvironment of the Prosthetic Joint

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Background. Perioperative topical tranexamic acid as antifibrinolytic agent is often used for total joint replacement to reduce bleeding currently. *Staphylococcus aureus* was the most common isolates from perioperative infection of prosthetic joint. The influence of topical application with tranexamic acid on the incidence of acute prosthetic joint infection of *Staphylococcus aureus* has not been clarified. **Methods.** Mouse model of *Staphylococcus aureus* knee prosthesis infection was constructed. Tranexamic acid was intra-articular injected during the perioperative period. CFU counting from tissue and implant sample was evaluated 3 days and 7 days after inoculating of *Staphylococcus aureus*. Bacterial growth curve, biofilm formation, aggregation, and plasmin inhibition of *Staphylococcus aureus* were tested with tranexamic acid added to the synovial culture medium. **Results.** There were no significant differences of CFU counting from tissue and implant samples in knee prosthesis infection after a single local injection of tranexamic acid at the postoperative 3 or 7 days. The amount of bacterial colonization on the surface of implant increased after 3 days' continuous local injection of tranexamic acid. Tranexamic acid has no effect on bacterial growth at the concentration (10 mg/ml) of clinical application, but it can inhibit bacterial aggregation and mildly inhibit biofilm formation. Plasmin can significantly inhibit biofilm formation which can be revised by adding tranexamic acid. **Conclusion.** Although continuous local injection of tranexamic acid can promote the biofilm formation of *Staphylococcus aureus* on the surface of articular implant, it has clinical safety for using one single local injection of tranexamic acid during the perioperative period.

1. Introduction

Tranexamic acid can competitively inhibit the activation of plasminogen and the binding of plasmin to fibrin as synthetic analogues of the amino acid lysine, thus inhibiting fibrin degradation [1, 2]. A large number of studies have confirmed that tranexamic acid can significantly reduce the amount of blood loss during surgery without increasing the risk of thromboembolism [3–6]. Intravenous administration and local injection of tranexamic acid are usually used in the perioperative period of total joint replacement [7]. A large num-

ber of clinical studies showed that tranexamic acid can significantly reduce the incidence of postoperative adverse events [4, 8].

Prosthetic joint infection is considered to be the most severe complication related to total joint replacement [9, 10]. *Staphylococcus aureus* was predominant pathogen in postoperative and acute prosthetic joint infection [10–12]. Because of the numerous virulence factors and the ability to form biofilm on the surfaces of implant, *Staphylococcus aureus* leads to more severe clinical presentation and worse prognosis [12].

Some studies has found that application of tranexamic acid can exacerbate infections of *Staphylococcus aureus* in mice model [13, 14].

But in clinical practice, the topical application of tranexamic acid has been used more and more widely and has not shown increasing of infection rate [15–19]. The influence of topical tranexamic acid on *Staphylococcus aureus* infection is still controversial.

Therefore, it needs to be clarified whether local injection of tranexamic acid promotes the formation of biofilm and leads to the increased risk of *Staphylococcus aureus* infection.

2. Materials and Methods

2.1. Bacterial Strains, Reagents, and Ethics Statement. The strains used in this study were methicillin-susceptible *Staphylococcus aureus* (MSSA) ST1792 isolated from PJI prosthesis. The fluorescently label *Staphylococcus aureus* ST1792-sfGFP which was preserved in our laboratory were used for confocal microscopic assay. The tranexamic acid (Aladdin, Shanghai, China) was used in in vivo and in vitro study of bacterial growth, aggregation, and biofilm formation. The plasmin (PLM, Sigma Aldrich, St Louis, MO, USA) was used in in vitro study of biofilm formation was purchased from and used at final concentrations of 100 $\mu\text{g}/\text{ml}$. Synovial fluid (SF) was added to the medium and used in in vitro experiment. Collection of human synovial fluid from patients with osteoarthritis was approved by the Institutional Review Board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Because synovial fluid was aspirated as part of the routine procedure before injection of hyaluronic acid and would have been discarded otherwise, and patient information not collected, a waiver for informed written consent was granted by the IRB.

2.2. *Staphylococcus aureus* Prosthetic Joint Infection Mouse Model. All procedures of animal experiment had been reviewed and approved by the Animal Care and Experiment Committee of Shanghai Jiao Tong University affiliated Sixth People's Hospital.

Six-week-old and weighing (20 \pm 5) g male C57BL/6 mice were used to construct *Staphylococcus aureus* prosthetic joint infection model. The mice were anesthetized intraperitoneally with 3% pentobarbital sodium (0.1 ml per 10 g body weight) and then shaving the both knees. A medial parapatellar incision was made at the knee joint of mice after sterilized with 75% alcohol. Proximal tibia was exposed, and the medullary cavity was inserted with sterile stainless steel implant rods. After closing the wounds by sutures, tranexamic acid was injected into the joint cavity of one side at a dose of 10 mg/kg; the other side was injected with an equal volume of saline as control. Two hours later, both knee joints were inoculated with ST1792 solution of $\sim 5 \times 10^6$. And then, the mice were randomly divided into three groups (Table 1). The first group was housed for 3 days, and the second group was housed for 7 days. The third group was continuous local injected with tranexamic acid at a dose of 10 mg/kg every 24 hours and housed for 3 days. Three days and 7 days after surgery, the mice with a single local injection

of tranexamic acid (i.e., first and second groups) were euthanized, and the mice with continuous local injection of tranexamic acid were euthanized in 3 days after surgery. Peri-implant tissues and implant in tibia were harvested for CFU counting.

2.3. Bacteria CFU Counting. The peri-implant tissues were weighed and homogenized in tubes with 1 ml normal of saline (NS) by high-speed homogenizer (Jingxin Industrial Limited Company, Shanghai, China). The implant were washed gently 3 times with NS to remove the planktonic bacteria and placed in tube containing 1 ml of NS, sonicated, and homogenized to detach the adherent bacteria. The homogenates and suspensions were serially diluted in NS and spread on sheep blood agar (SBA). The plates were cultured overnight at 37°C. The colonies were counted and expressed by $\log_{10}\text{CFU}/\text{g}$ of peri-implant tissues and $\log_{10}\text{CFU}/\text{per}$ implanted rods.

2.4. The Effect Test of TXA In Vitro. The ST1792 were cultured overnight at 37°C on SBA plates before each experiment. Single colony of each strain was collected and cultured overnight in TSB at 37°C. The ST1792-sfGFP were cultured on Tryptic Soy Agar (TSA) plates with 10 $\mu\text{g}/\text{ml}$ chloramphenicol and cultured overnight in TSB containing 10 $\mu\text{g}/\text{ml}$ chloramphenicol at 37°C.

The preconditioning method of medium was divided into six groups: the first group containing 10% SF, the second group containing 10%SF and 10 mg/ml TXA, the third group containing 10%SF and 50 mg/ml TXA, the fourth group containing 10%SF and 100 $\mu\text{g}/\text{ml}$ PLM, the fifth group containing 10%SF and 100 $\mu\text{g}/\text{ml}$ PLM and 10 mg/ml TXA, and the sixth group containing 10%SF and 100 $\mu\text{g}/\text{ml}$ PLM and 50 mg/ml TXA.

2.4.1. *Staphylococcus aureus* Growth Curve Assay. Overnight culture of ST1792 was serially diluted 1 : 1000 in groups 1, 2, and 3 with TSB and cultured at 37°C. 100 μl of solution were aspirated at 0-2-4-6-8-12 hours and transferred to the wells of a 96-well tissue culture plate (Corning Co., NY, USA). The absorbance was measured by a microplate reader (BIO-TEK, ELX 800) at a wavelength of 600 nm.

2.4.2. *Staphylococcus aureus* Aggregation Test. Overnight culture of ST1792 was serially diluted to 1 : 1000 in groups 1, 2, and 3 with TSB and three additional control groups without 10%SF and cultured at 37°C. Strain clumped together and sank to the bottom of the tube after 8 h; the turbidity of medium supernatant was significantly decreased. 100 μl of culture medium supernatant were aspirated and transferred to the wells of a 96-well tissue culture plate, measuring the absorbance at a wavelength of 490 nm by a microplate reader.

2.4.3. Biofilm Formation and Biomass. Overnight culture of ST1792 was serially diluted to 1 : 1000 in TSB supplemented with 0.5% glucose (TSBG). Diluted bacteria, with supplementation from group 1 to group 6, were used for assessment of biofilm formation on (1) the bottom of 96-well polystyrene microtiter plate (Corning Co., NY, USA) or (2) Ultra High Molecular Weight Polyethylene (UHMWPE) washers that

TABLE 1: The grouping of mouse.

Group	Left knee	Treatment	Right knee	Time (day)
1	A single local injection of TXA		A single local injection of NS	3
2	A single local injection of TXA		A single local injection of NS	7
3	Continuous local injection of TXA		Continuous local injection of NS	3

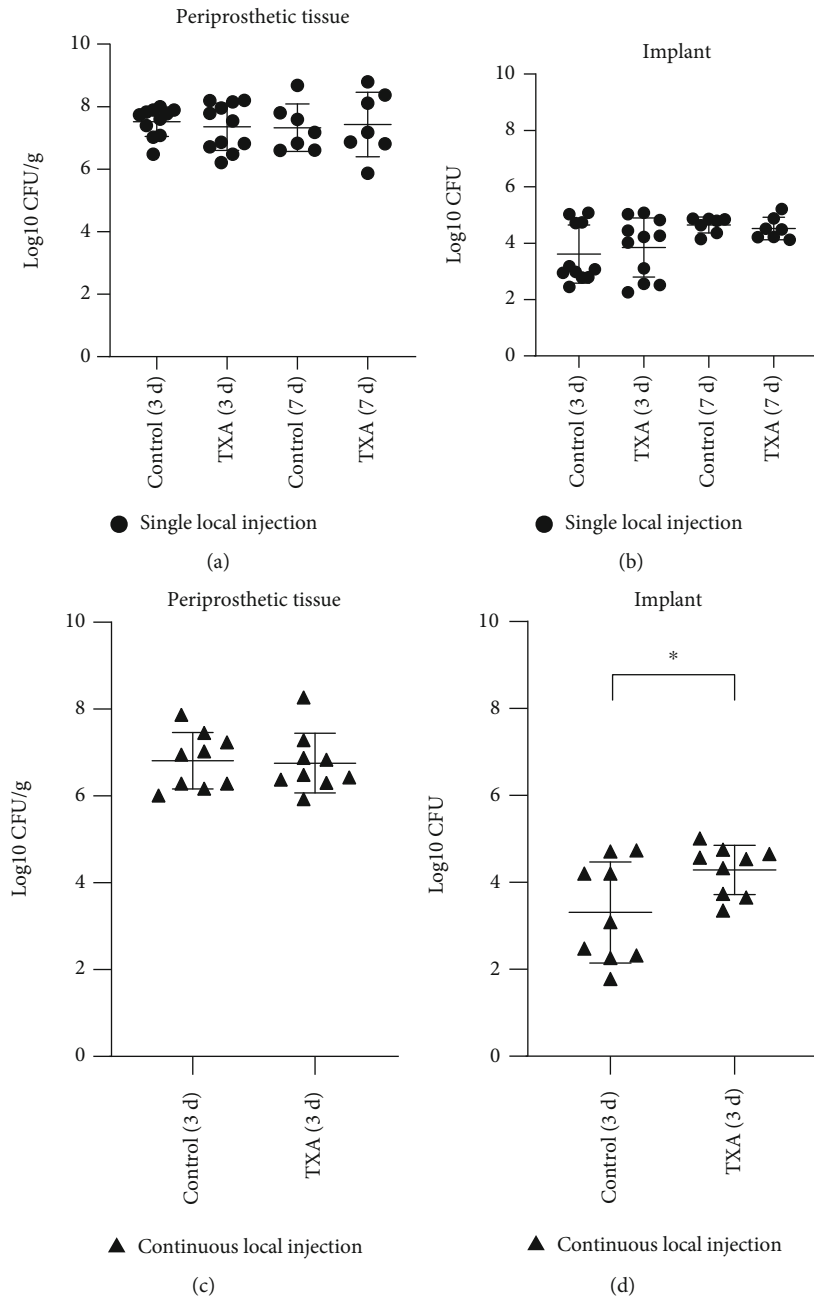


FIGURE 1: CFU counting after local injection of tranexamic acid on *Staphylococcus aureus* PJI mouse model. (a, b) The bacterial CFU of PJI mice with a single local injection of tranexamic acid in periprosthetic tissue (Figure 2(a)) and implants (Figure 2(b)) after 3 and 7 days. (c) The bacterial CFU of periprosthetic tissue after continuous local injection of tranexamic acid for 3 days. (d) The bacterial CFU of implants after continuous local injection of tranexamic acid for 3 days. * $P < 0.05$; error bars represent standard deviations.

were affixed to bottom of 24-well polystyrene plates (Corning Co., NY, USA) with LubriSeal grease (Thomas Scientific) and sterilized by UV irradiation.

96-well plate were incubated overnight at 37°C. Completely aspirating the supernatant from each well and washing gently 3 times with 200 μ l NS to remove the planktonic bacteria. Then, 100 μ l methanol was used to fix the biofilm for 30 min and then dried. After that, biofilm was stained with 100 μ l of 0.1% crystal violet for 15 min. The biofilm biomass on the bottom of the well was dissolved in 200 μ l 33% acetic acid after the unbound crystal violet was rinsed by NS for 3 times. 100 μ l solution of each well were transferred into a new 96-well tissue culture plate. The absorbance was measured by a microplate reader at a wavelength of 590 nm.

UHMWPE washer inoculated with ST1792 in groups 1, 2, 3, 4, 5, and 6 with TSBG was incubated overnight. The UHMWPE washers were washed 3 times with saline to remove nonadherent cells. The washed UHMWPE washers were transferred into a new 24-well polystyrene plate. Adherent biofilms were fixed with methanol and stained with crystal violet and washed 3 times with sterile water. Biomass on the surfaces of UHMWPE washers was determined by solubilizing crystal violet with 33% acetic acid as described above.

2.4.4. Confocal Laser Scanning Microscopy (CLSM). Overnight culture of ST1792-sfGFP was serially diluted 1:1000 in groups 1, 2, 3, 4, 5, and 6 with TSBG. 500 μ l of bacteria suspension were incubated with cover glass overnight in 24-well tissue culture plate at 37°C. The cover glasses were washed gently 3 times with NS and imaged by CLSM. The ST1792-sfGFP showed green fluorescence.

3. Results

3.1. The Colonization on the Surface of Implant Were Increased by Continuous Use with TXA In Vivo. Mice with a single local injection of tranexamic acid during the perioperative period showed no significant difference in *Staphylococcus aureus* colonization of tissue and implant sample after 3 and 7 days (Figures 1(a) and 1(b)). Although mice with continuous local injection of tranexamic acid for 3 days showed no significant increase of bacterial colonization in tissue (Figure 1(c)), there was significant higher CFU counting from implant (Figure 1(d)). The experimental results suggested that the continuous local injection of tranexamic acid can promote biofilm formation.

3.2. Influence of Tranexamic Acid on the Growth of *Staphylococcus aureus*. For analysis of the influence of tranexamic acid on bacterial growth curve, tranexamic acid with clinically used concentration (10 mg/ml) and high concentration (50 mg/ml) was used. Compared to the medium without tranexamic acid, the medium containing tranexamic acid with clinically used concentration (10 mg/ml) has no influence on bacterial growth. Bacterial growth was inhibited by tranexamic acid with high concentration (50 mg/ml) (Figure 2). It showed that tranexamic acid has no antibacterial capacity in concentration of clinical use.

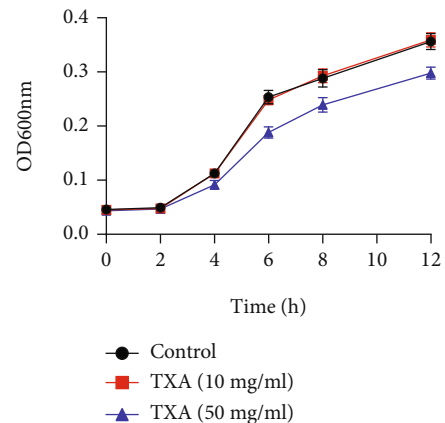


FIGURE 2: Bacterial growth curve of *Staphylococcus aureus* ST1792 cultured separately in TSB medium containing 10% SF (Blank, 10 mg/ml TXA and 50 mg/ml TXA).

3.3. The Influence of Tranexamic Acid on the Bacterial Aggregation in Different Media. The aggregation of *Staphylococcus aureus* inhibited by tranexamic acid with clinically used concentration (10 mg/ml) in TSB medium. The inhibitory effect was attenuated in tranexamic acid with high concentration (50 mg/ml) (Figure 3(a)). However, the anti-aggregation capacity of tranexamic acid disappears when cultured in TSB medium containing 10% SF (Figure 3(b)). The results suggested that inhibitory effect of tranexamic acid on bacterial aggregation attenuated in the microenvironment of the prosthetic joint.

3.4. The Individual and Mutual Inhibition for Biofilm Formation of *Staphylococcus aureus* by Tranexamic Acid and Plasmin. Whether on 96-well plates or UHMWPE washer, the biofilm formation of *Staphylococcus aureus* was slightly inhibited by tranexamic acid (Figures 4(a) and 4(b)). Biofilm formation was inhibited more significantly by tranexamic acid in high concentration (50 mg/ml) with the inhibitory ability of bacterial growth. When plasmin was added into the culture medium, the biofilm formation was significantly inhibited. However, the antibiofilm formation ability of plasmin was inhibited by tranexamic acid; thus, the culture medium exhibited a weak antibiofilm formation effect.

3.5. Tranexamic Acid Offset the Inhibition of Biofilm Formation with Plasmin via CLSM. Biofilm formed obviously in TSBG with 10% SF by ST1792 and slightly inhibited with TXA (10 mg/ml). The inhibitory effect of TXA at high concentration (50 mg/ml) was more obvious. However, the biofilm disappeared after PLM was added, and it can be found that antibiofilm formation function of plasmin is much stronger than TXA in TSBG with 10% SF (Figure 5). The weak antibiofilm formation function exhibited in medium when acting simultaneously with tranexamic acid and plasmin. The results of CLSM provide further confirmation that tranexamic acid offsets the inhibition of biofilm formation with plasmin.

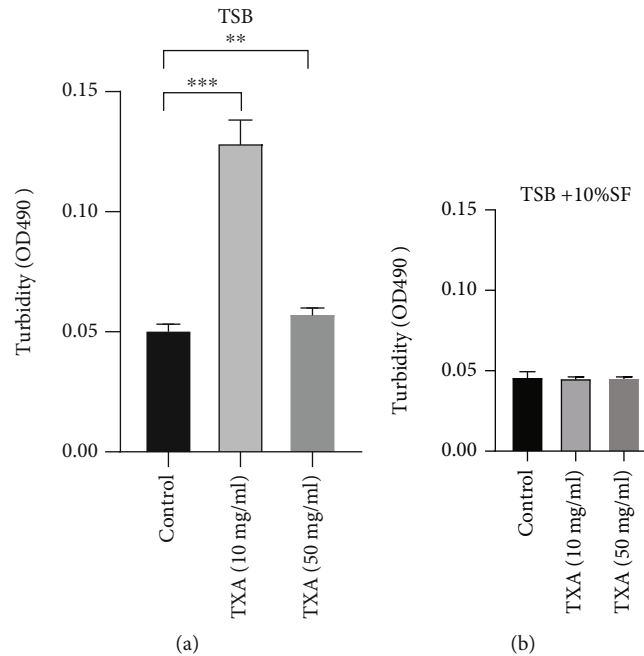


FIGURE 3: Tranexamic acid shows difference of inhibiting bacterial aggregation in TSB with or without SF. (a) The turbidity of medium supernatant increased in TSB medium containing TXA ($n = 6$). (b) No significant difference of the turbidity was observed in TSB medium containing SF and TXA. $**P < 0.01$, $***P < 0.001$. Error bars represent standard deviations.

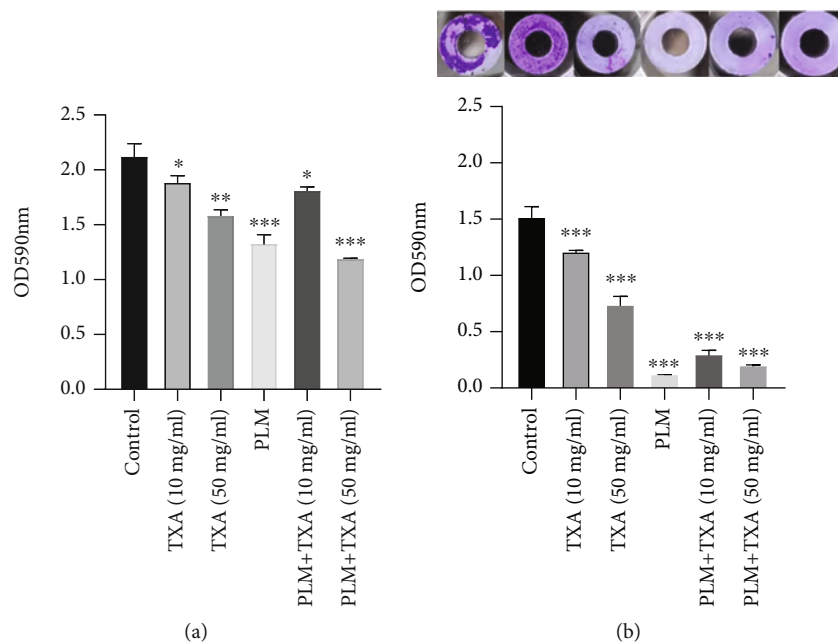


FIGURE 4: Inhibitory effect of biofilm formation with tranexamic acid were observed in 96-well tissue culture plate (Figure 4(a)) and on the surface of UHMWPE washer (Figure 5(b)). Biofilm formation inhibited more obviously by plasmin and the inhibition of plasmin were reversed by tranexamic acid. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. Error bars represent standard deviations.

4. Discussion

Mice studies with staphylococcal sepsis or septic arthritis showed increasing severity and mortality of infection by treatment with tranexamic acid; however, the mice were

infused with tranexamic acid at a dose of 700-800 mg/kg every 8 hours [14] which was much higher dosage than that for clinical use [14], and previous study had proposed that high-dose tranexamic acid caused significant cytotoxicity [20]. In present study, we constructed *Staphylococcus aureus*

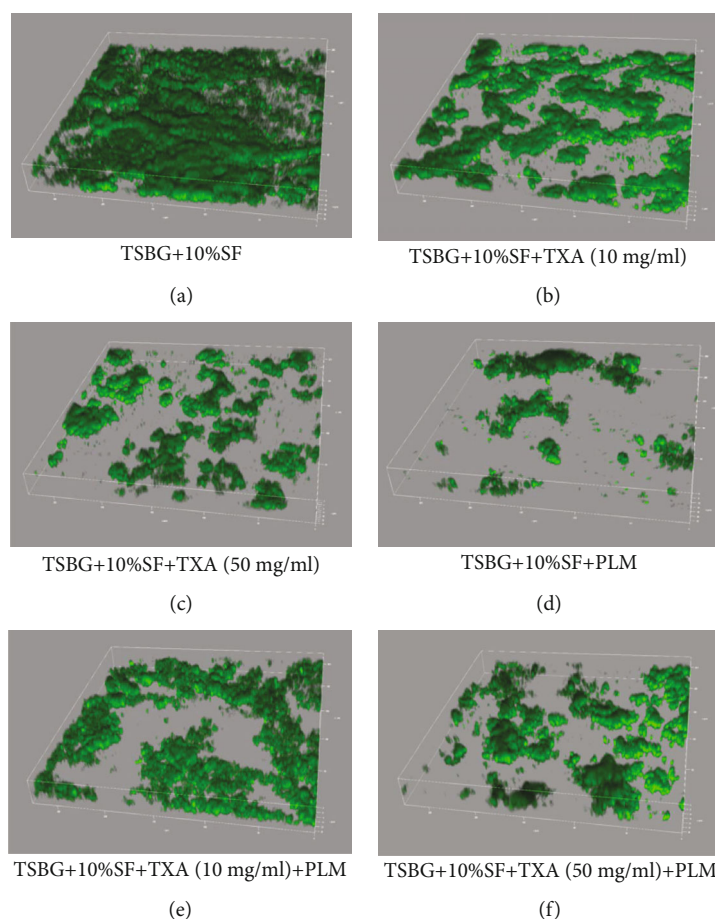


FIGURE 5: CLSM results of biofilm forming with ST1792-sfGFP. (a) Biofilm formation of *Staphylococcus aureus* in TSBG medium containing 10% SF. (b) Biofilm formation was inhibited by tranexamic acid (10 mg/ml). (c) Biofilm formation was significantly inhibited by tranexamic acid (50 mg/ml). (d) Biofilm formation was significantly inhibited by plasmin. (e, f) Tranexamic acid offset the inhibition of biofilm formation with plasmin.

prosthetic joint infection model with topical tranexamic acid at 10 mg/kg which dose was similar with that using clinically and found that continuous local injection of tranexamic acid promoted biofilm formation in vivo.

Clinically, a single local injection of tranexamic acid is commonly used in joint replacement surgery, and the safety of this method is well documented [15, 16, 18]. In our in vivo experiments, it was observed that a single local injection of tranexamic acid did not aggravate *Staphylococcus aureus* infection. However, for patients bleeding after joint implanted surgery, we hope to explore the feasibility of continuous local injection of tranexamic acid. With the help of mice model, continuous local injection of tranexamic acid was observed to promote the formation of *S. aureus* biofilm, which is the potential risk of using tranexamic acid. Continuous local injection of tranexamic acid is not recommended for clinical treatment.

In order to clarify action of tranexamic acid against *Staphylococcus aureus*, bacterial growth, aggregation, and biofilm formation has been studied in vitro experiment. Results indicated no influence of tranexamic acid with clinical concentration (10 mg/ml) on *Staphylococcus aureus*

growth. However, tranexamic acid showed inhibitory function on aggregation and biofilm formation of *Staphylococcus aureus*. The function of antibacterial aggregation disappeared in microenvironment containing synovial fluid. High concentration of TXA (50 mg/ml) showed inhibition of bacterial growth and relatively stronger function of antibiofilm formation, but the significant cytotoxicity exhibited in the high concentration of TXA which was not used in clinically cases [20].

We can observe some special phenomenon in bacteria aggregation experiments. In the infected setting, polysaccharide-based aggregates and biofilms can be regarded as different phases of the same process. Aggregate seeding biofilms, while biofilms dispersing into free floating aggregates [21]. The aggregates can enhance the protection from phagocytosis and be more tolerant to antibiotic treatment [22]. Therefore, the supernatant of bacteria in TSB with TXA had higher turbidity, which proves that the clinical concentration of TXA can inhibit bacteria aggregation, and the high concentration of TXA can inhibit the growth of *Staphylococcus aureus*, resulting in lower turbidity. However, tranexamic acid's inhibitory ability on bacterial aggregation

disappeared in synovial fluid environment, which may be related to the complex joint microenvironment, and further research is needed.

The primary target of action for tranexamic acid was plasmin [2]. The double-sided effect of plasmin in the process of *Staphylococcus aureus* infection has been shown in previous studies. On one hand, plasmin can act in a proinflammatory manner via triggering chemotaxis and cytokine release [23], and the histones in neutrophil extracellular traps (NETs) cleaved by plasmin, which lead to protection of *Staphylococcus aureus* in vivo [24]. Therefore, plasmin showed the function of promoting infection. On the other hand, fibrin-containing bacterial biofilms were decomposed by the specifically targeting fibrin function of plasmin, and the antibiotic efficiency were greatly improved [22, 25]. Thus, plasmin showed the function of inhibiting infection.

In this study, the significant antibiofilm function of plasmin was found in experiments compared with tranexamic acid. The obvious inhibitory effect of plasmin on *Staphylococcus aureus* biofilm formation was mentioned in previous studies [22], but this significant antibiofilm function of plasmin inhibited by tranexamic acid. Therefore, the increased colonization of *Staphylococcus aureus* made it easier to form biofilms by tranexamic acid on the surface of implant. While tranexamic acid promoted biofilm by inhibiting plasmin, it also inhibited the degradation of histones in NETs. Therefore, one single local injection has not shown to promote infection in vivo, but continuous use of tranexamic acid in vivo has shown increased *Staphylococcus aureus* colonization, which suggested the potential risk of topical tranexamic acid.

There are still some limitations in this study. Although the clinical used concentration of tranexamic acid has been applied to avoid the cytotoxicity caused by high concentration, the viewing time of mouse model was relatively short and the effect of continuous topical tranexamic acid for a longer time has not been tested. The influence of tranexamic acid on antibiotic sensitivity of *Staphylococcus aureus* has not been explored in the present study. Although *Staphylococcus aureus* ST1792 was used in terms of strains, the response of various *Staphylococcus aureus* subtypes to tranexamic acid has not been verified.

5. Conclusions

In summary, here, we clarified the function of topical tranexamic acid use with *Staphylococcus aureus*. Continuous topical injection of tranexamic acid promoted biofilm formation of *Staphylococcus aureus* which has potential risks to patients undergoing total joint replacement. Although it has clinical safety for using one single local injection of tranexamic acid, it is recommended to use antibiotics in combination with topical using of tranexamic acid in clinic to minimizing the rate of infection.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors have no conflicts of interest.

Authors' Contributions

Zhang, Feiyang, Dong, Wenjun, and Wang, Fengyan contributed equally to this work.

Acknowledgments

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