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Experimental study of antimicrobial polymeric composition with hemostatic effect in treatment of implant associated infection

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Introduction Management of infection associated with surgical implants comprise local application of antimicrobial agents. The purpose of the in vivo experimental study was identification of an optimal antimicrobial polymeric composition with hemostatic effect for local wound application and assessment of its influence on clinical and morphological changes in implant-associated infection caused by staphylococcus in rabbit femur. **Materials and methods** A composition exhibiting minimal bleeding time was identified in the first experiment using six experimental samples with different concentration of tranexamic acid (TXA) and polyvinylpyrrolidone (PVP) implanted in the soft tissue wound of the rat liver (n = 18). Peri-implant infection caused by staphylococcus was simulated in the rabbit femur in the second experiment. Infected wire was implanted in the intramedullary canal of control animals (n = 9). The wire was steeped in gentamicin-containing sample selected in the first experiment before it was used for experimental animals (n = 9). Histologic assessment of the wire placement site was performed at 14, 21 and 28 days. **Results** Minimal bleeding time was recorded with the sample containing 25 mg of TXA in 1 mL of 10 % PVP aqueous solution. 8 mg/mL of gentamicin was added to the sample tested. Both groups showed histological signs of inflammation at 14 days of implantation being more evident in controls with fibrinopurulent inflammation and microabscesses. Inflammatory infiltration was more expressed in controls at 21 days and was characterized by a great number of plethoric vessels. A capsule with leucocytes and fibrin clots was observed in the intramedullary canal. Experimental animals exhibited fading signs of inflammation with delicate fibrous tissue and moderate mononuclear infiltration formed. Signs of bone regeneration were detected in both groups at 28 days apart from persistent inflammation being secondary to decompactization. However, bone trabeculae were noted to recover in controls with evident inflammation featuring extensive erythrocyte clusters, necrotic bone fragments, granulated tissue and evident leucocyte infiltration. **Conclusion** The experimental study allowed identifying PVP and TXA based composition as most effective for hemostasis estimating dynamics in perifocal reactions with the use of gentamicin-containing sample to prevent osteomyelitis in implantation of experimental animals. The findings showed prospectiveness of further research of the polymeric composition with antimicrobial and hemostatic effects.

Keywords: implant-associated infection, periprosthetic joint infection, deep surgical site infection, polymeric composition, local antimicrobial therapy, hemostatic effect

Trauma and orthopaedic surgery is inextricably linked with metal constructs intended either for temporary or permanent usage in fracture repair and joint replacement. Presence of implant is characterized by specificity of pathogenesis in the development of infection often resulting in chronic condition. The incidence of periprosthetic joint infection (PJI) which is a particular case of implant-related infection (IRI) is between 0.3 % and 3.0 % for primary arthroplasties [1, 2] and between 5 to 15 % for arthroplasty revision surgery [3, 4]. The rate of infection recurrence after revision arthroplasty in PJI patients is very high and ranges from 23 to 36 % [5, 6]. Chronic infection at the implant site is characterized by microbial biofilm (MBF) formed on the surface of the implant [7]. Radical surgical debridement with removal of infected construct is intended to remove MBF from the wound, whereas systemic antimicrobial therapy is aimed at eradication of free planktonic bacteria including biofilm debris circulating in the flow during and after surgical intervention.

Although pathophysiology of infectious process is well understood the complex surgical treatment with debridement of suppurative nidus, removal of metal construct and systemic antimicrobial therapy may fail and result in infection recurrence in 10–35 % of the cases [8, 9]. Local antimicrobial therapy is deemed to be an important constituent of complex management of PJI cases. Antibiotic impregnated spacers have been integrated in two-stage protocol of treatment and are a gold standard for the repair of post-debridement tissue defects [10]. The technology allows solution of two important goals: maintain motion in the infected segment and additionally provide a local antimicrobial effect. Review of many years' application of antimicrobial cement spacers allowed identification

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of several disadvantages. First, effective antibiotic elution occurs during the first 24–72 hours of spacer implantation [11]. Second, total antimicrobial release from the spacer surface is about 10 % [12]. Third, spacer removal leads to greater bone loss.

In recent years, biodegradable delivery carriers were developed and evaluated for delivery of local antibiotics in treatment of PJI patients. Carriers were presented by bone autologous graft, bioceramics, natural polymers, synthetic polymers and composites [13, 14, 15]. The products were shown to experimentally provide high concentrations of local antibiotics having anticipated degradation period and no systemic toxicity. In addition to antimicrobial effect of biodegradable carriers the possibility of its combination with hemostatic capacity is being explored. Local blood loss at early postoperative period is associated with considerably aggressive surgery, systemic thromboprophylaxis and application of drainage systems. The above factors lead to reduction in local antimicrobial effect of spacer increasing risk of infection for postoperative wound. Studying a combination of local antimicrobial and hemostatic effects in one antimicrobial composition to be used locally for PJI patients can yield satisfying results.

The purpose of the in vivo experimental study was identification of an optimal antimicrobial polymeric composition with hemostatic effect for local wound application and assessment of its influence on clinical and morphological changes in implant-associated infection caused by staphylococcus in rabbit femur.

MATERIAL AND METHODS

The studies conducted with two types of experimental animals were approved by Local Ethic Board of the Vreden Russian Research Institute of Trauma and Orthopaedics. The procedures were performed in compliance with Guide to the care and use of experimental animals and Directive 2010/63/EU of the European Parliament and of the Council of the European Union on the protection of animals used for scientific purposes.

The first experiment was carried out on 23 Wistar rats weighing 200-250 g and comprised two series: preliminary (n = 8) and index (n = 15). Bleeding was simulated with surgical intervention under intravenous anesthesia (Ketamine, Relanium) in aseptic conditions. Midline laparotomy was produced in anesthetized animals after aseptic processing of the surgical field with a small part of liver localized. Then it was marginally resected cutting off a fragment of 1 x 0.5 cm with scissors. Cotton pellet soaked in 1 mL of testable solutions with hemostatic properties or saline solution (in 7 control animals) was applied to liver wound. Spontaneous hemostasis in parenchymal wound of the rat liver was determined using different combinations of tranexamic acid (TXA) and saline solution or tranexamic acid and polyvinylpyrrolidone (PVP) (Table 1). Postoperative wound was treated with antiseptic and sutured with Monamit 2-0 thread layer by layer. No dressing was applied.

Table 1

Details of testable sample solutions with hemostatic properties and number of experimental animals

№ of sample	Sample composition	Series of experiments (number of animals)	
		preliminary	index
TXA solutions			
1	5 mL (250 mg) TXA: 5 mL H2O = 2.5 % TXA solution	1	–
2	5 mL (250 mg) TXA:10 mL H2O = 1.65 % TXA solution	1	–
3	5 mL (250 mg) TXA: 15 mL H2O = 1.25 % TXA solution	1	–
TXA and PVP solutions			
4	5 mL (250 mg) TXA + 1 g PVP + H2O up to 10 mL	1	5
5	5 mL (250 mg) TXA + 2 g PVP + H2O up to 10 mL	1	5
6	5 mL (250 mg) TXA + 0.5 g PVP + H2O up to 10 mL	1	–
7	Saline solution	2	5
Total:		8	15

One experimental animal (rat) was used in preliminary series of the first experiment (n = 8) to test each of the 6 samples. Minimal bleeding time was determined with samples № 1–3, and most effective TXA concentration tested with samples № 4–6 containing different PVP content. Sample № 6 exhibited maximal bleeding time and was excluded from the series. The remaining two samples (№ 4 and № 5) were explored in index series of the first experiment (15 rats) in comparison to controls (saline solution) including 5 experimental animals for each. The sample that exhibited minimal bleeding time was employed in the second experiment. In addition to TXA and PVP, Gentamycin (8 mg/mL), commonly used in orthopaedic practice for local antimicrobial therapy in bone cement [16] and polymer compositions [17], was also applied.

The second experiment was carried out on 18 Chinchilla rabbits weighing 3–3.5 kg. Acute Staphylococcus infection of the implanted femur was simulated in all experimental animals. The left hind limb of anesthetized animals was fixed following aseptic treatment of the surgical field. An incision was produced at the greater trochanter of the left femur layer by layer. Intramedullary canal was perforated from the top of greater trochanter with 1.2 K-wire 3 cm in length that was pre-incubated in 0.5 mL of microbial suspension of daily culture *S. aureus* (MSSA) 10^6 CFU/mL. The infected implant was taken out of incubation medium and introduced into the canal by the whole wire length following exposure of intramedullary canal in control animals (n = 9). Experimental animals (n = 9) had the infected wire implanted in a similar manner. Prior to implantation the infected wire was placed in 2 mL of the study polymer composition for three seconds and then introduced into intramedullary canal. Postoperative wound was treated with antiseptic after initial phase and adaptation sutures applied with Monamit 2–0 thread. No dressing was used. Animals of both groups received systemic antimicrobial therapy including intramuscular injections of Ceftriaxone 250 mg administered daily for 7 days. After 14, 21 and 28 days of implantation, animals were sacrificed by overdose of thiopental sodium and material was histologically evaluated. An incision of 0.7-1.0 cm was produced at the site of greater trochanter in aseptic conditions and metal construct was isolated in an acute and blunt way. The removed femoral segment was placed in medium with 10 % formaldehyde solution and used for histological assessment.

Morphological evaluation. Experimental material was fixed in 10 % formaldehyde solution (pH 7.4), decalcified in 25 % salt solution of Trilon B organic acid during 72 hours, dehydrated in alcohol of increasing concentrations using *Microm* STR-120 Spin Tissue Processor (Micron Technology, U.S.A.) and embedded in paraffin with the *Leica* paraffin embedding station (Germany). Microscopic sections (5-7 mkm thick) were obtained with the *Leica* sledge microtome (Germany) and colored by hematoxylin and eosin according to manufacturer's protocol (Bio-Vitrum, Russia) using *Raffaello Advanced* automatic linear stainer (DIAPATH, S.p.A., Italy). Measurement analysis and microscopic imaging were produced with Leica light microscope and incorporated Nikon E950 digital camera (Japan) with 40, 100, 200 and 400 times magnification.

RESULTS

Identification of hemostatic effect Minimal time of spontaneous arrest of bleeding from the rat's parenchymal liver wound was identified for sample № 1 containing 2.5 % of antifinbrinolytic in preliminary series of the first experiment with 3 testable samples of TXA in saline solution (Table 2). From 3 samples with 2.5 % of TXA combined with different PVP content maximal bleeding time was determined for sample № 6 that was excluded from the study. An evident hemostatic effect was identified with sample № 4 containing 250 mg of TXA and 1 g of PVP in 10 mL solution in index series of the first experiment on rats (Table 3).

Table 2

Bleeding time with the use of TXA samples

Sample number	Bleeding time (seconds)
1	244
2	409
3	445
4	196
5	363
6	750
Control	380 460

Table 3

Bleeding time with the use of samples № 4 and № 5

Series №	Bleeding time (seconds)		
	sample 4	sample 5	control
1	149	123	372
2	128	184	126
3	205	211	190
4	146	134	486
5	201	247	214
Mean ±	**166 ± 9**	**180 ± 13**	**278 ± 37**

Study of morphological changes Signs of inflammation being more evident in controls with fibrinopurulent inflammation combined with micro abscesses were observed in both groups of animals after 14 days of implantation of infected construct (**Fig. 1, a**). Control animals demonstrated decompactization and focal necrotic and necrobiotic changes in the cortical bone, bifurcated bone matrix, isolation and resorption of necrotic fragments (**Fig. 1, b**). Initial signs of bone formation were identified on cortical surface. Subacute inflammation, moderate inflammatory, primarily mononuclear infiltration in the lumen of intramedullary canal and the developing fibrous capsule delimiting the wire were observed in the experimental group after 14 days of implantation (**Fig. 1, c**). Clusters of structured protein masses – hyaline thrombus (**Fig. 1, d**) – were likely to result from local antifibrinolytic effect of TXA in the composition. Pattern of cortical changes was similar to that observed in controls: decompactzation, foci of necrosis and necrobiosis, bifurcated bone matrix and resorbed cortical fragments (**Fig. 1, b**).

Inflammatory signs of a different degree were revealed in the study groups after 21 days of implantation. Inflammatory infiltration was more evident in controls and was characterized by multiple vessels full of blood (**Fig. 2, a**). A capsule containing leukocytes and fibrin clots was noted in the intramedullary canal (**Fig. 2, b**). Experimental group showed signs of fading inflammation with delicate fibrous tissue and moderate mononuclear infiltration being developed (**Fig. 2, c**). Newly formed osteoid trabeculae were observed in the lumen of the intramedullary canal (**Fig. 2, d**).

In addition to signs of persistent inflammation secondary to decompactization signs of regeneration and restructuring with elements of lamellar bone tissue were observed in both groups of animals after 28 days of implantation (**Fig. 3, a**). However, restitution of bone trabeculae occurred in presence of evident inflammation with multiple vessels full of blood, necrotic bone fragments and granulated tissue with expressed leukocyte infiltration in controls (**Fig. 3, b**). Experimental group showed evident signs of bone formation with erratic thickening and compactization of bone trabeculae in presence of residual inflammatory events (**Fig. 3, c**). A fibrous bar was visualized in the cavity of intramedullary canal after 28 days of implantation (**Fig. 3, d**).

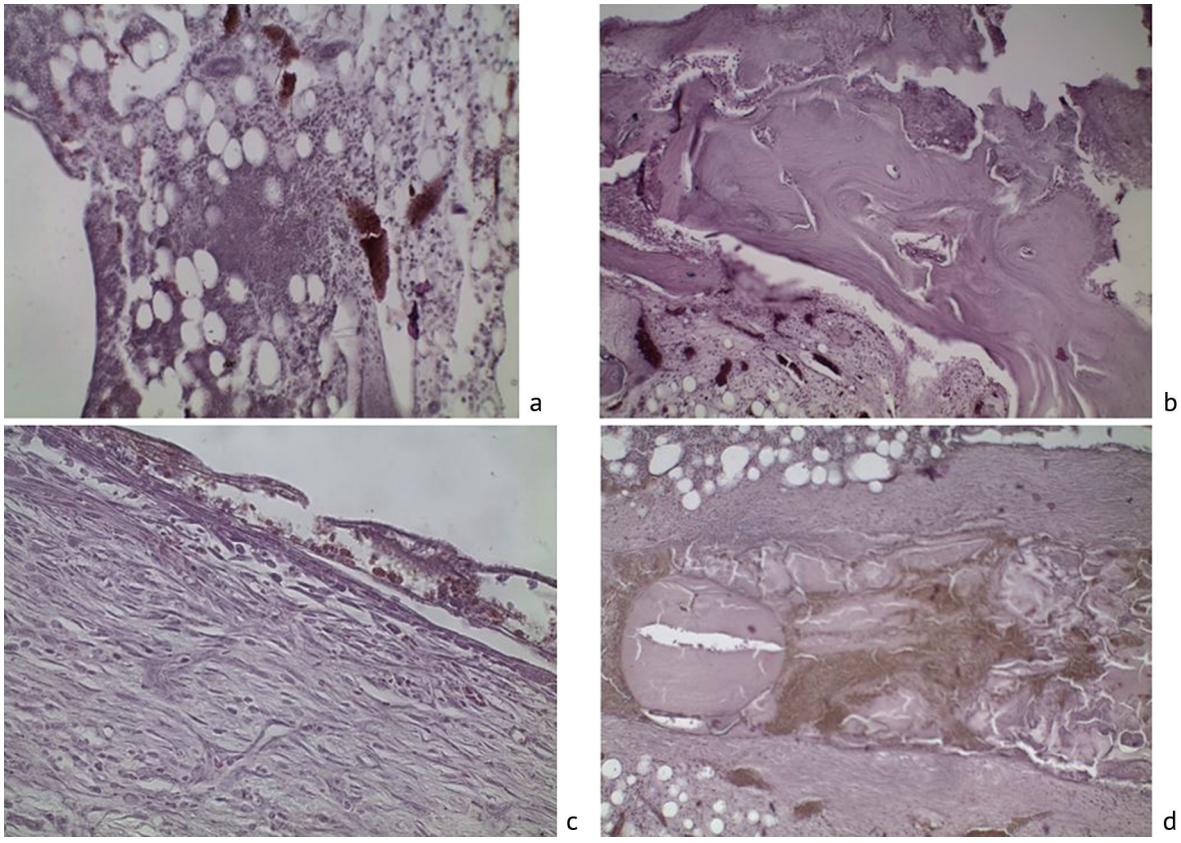

Fig. 1 Microphotograph of femoral section after 14 days of infected K-wire implantation in control (***a, b***) and experimental (***c, d***) groups: (a) micro abscess in intramedullary canal seen in the center of the picture (× 200 magnification); (***b***) necrobiotic changes in the cortical bone (× 100 magnification); (***c***) spongy fibrous tissue with weak mononuclear infiltration (× 100 magnification); (d) hyaline thrombus, clusters of structured proteins masses in the cavity off the wire seen in the center of the picture to the left (× 100 magnification). Stained with hematoxylin and eosin

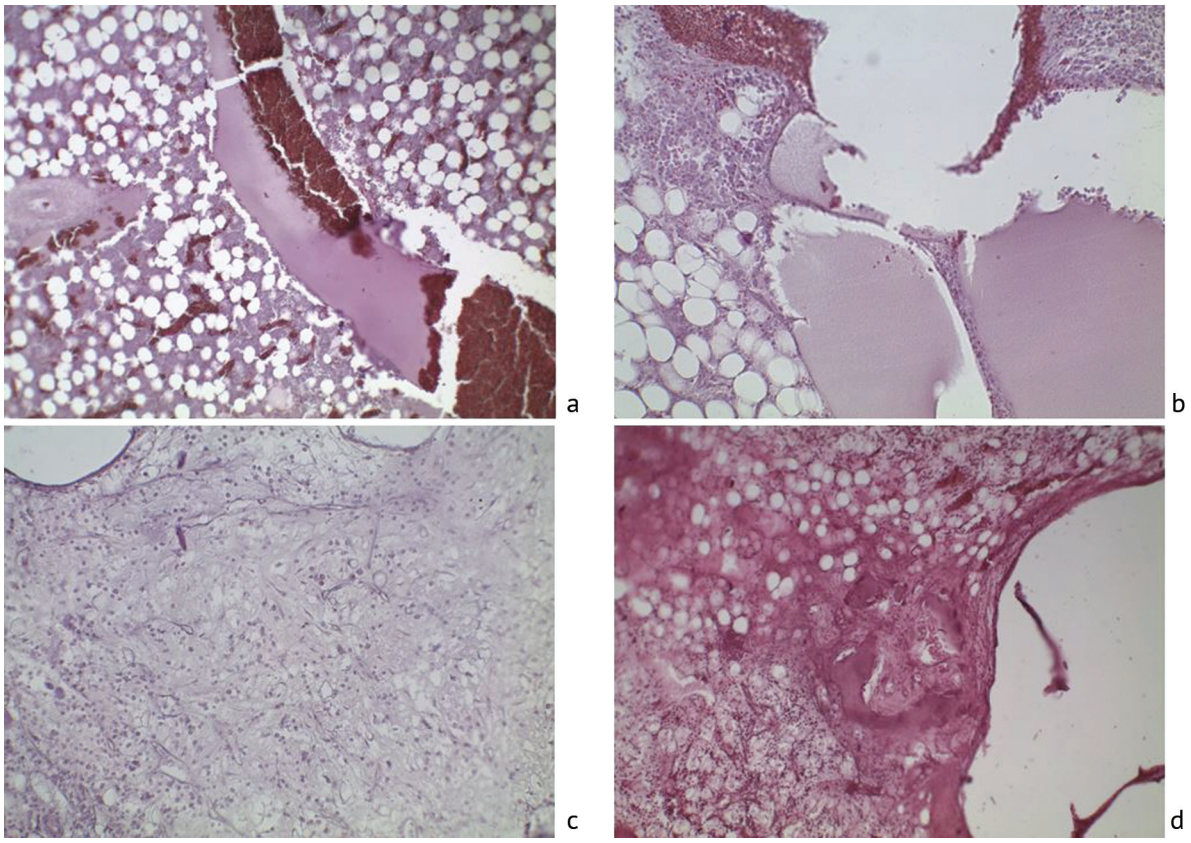

Fig. 2 Microphotograph of femoral section after 21 days of infected K-wire implantation in control (***a, b***) and experimental (***c, d***) groups: (***a***) leukocyte infiltration, vessels full of blood (× 100 magnification); (***b***) capsule with hemorrhage and leukocyte infiltration (× 200 magnification); (***c***) mononuclear infiltration of delicate fibrous tissue (× 200 magnification); (***d***) clusters of osteoids with small bone trabeculae seen in the center of the picture (× 200 magnification). Stained with hematoxylin and eosin

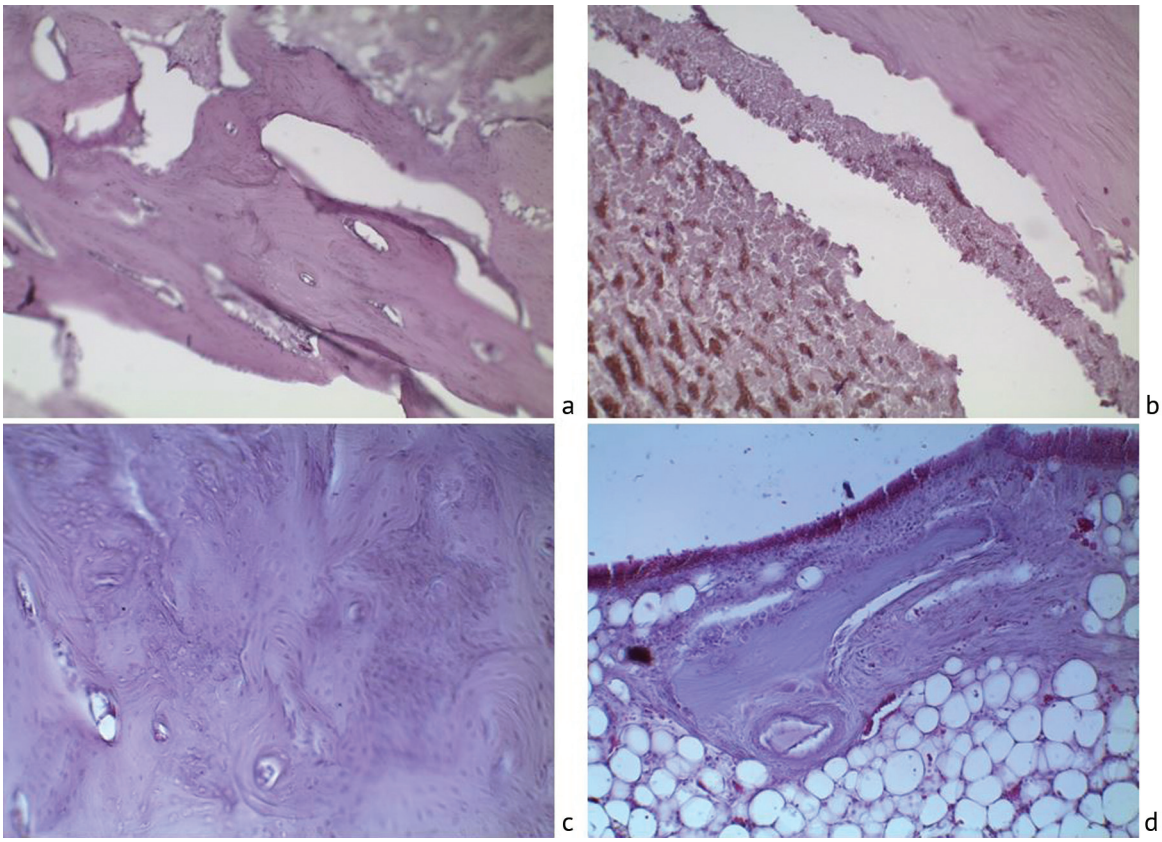

Fig. 3 Microphotograph of femoral section after 28 days of infected K-wire implantation in control (***a, b***) and experimental (***c, d***) groups: (***a***) decompactization of cortical bone (× 200 magnification); (***b***) necrotic bone fragments (at the top), vessels full of blood, leukocyte infiltration (× 100 magnification); (***c***) erratic thickening of cortical bone (× 100 magnification); (***d***) a fibrous bar formed at a margin (× 100 magnification). Stained with hematoxylin and eosin

DISCUSSION

Failures in treatment of infected cases associated with orthopaedic implants can be ascribed to ineffective systemic antimicrobial therapy with appropriate debridement of purulent focus provided and infected construct removed. Antibiotic treatment may be inadequate or ineffective in patients with poorly vascularized sclerotic tissues or evident scarry changes at the site of operative intervention following repeat surgeries, in particular. Moreover, normal doses of systemic antibiotics may be insufficient to breach the MBF produced by the infecting bacteria [18]. Despite a wide local use of antibiotics mixed with bone cement in treatment of patients with orthopaedic infection, only 10–20 % is reported to be actually released from spacer [12]. In our earlier series, the maximal length of antimicrobial activity of bone cement samples impregnated with gentamicin and vancomycin was shown to be released in vitro within 3 days for MRSA, 4 days for *MSSA* and *E. Coli*, and 5 days for *K. Pneumoniae* [19]. Short-term elution of antibiotic from cement spacer can definitely lead to ineffective local antibacterial therapy (ABT) and recurrence of infection. Techniques intended to improve efficacy of ABT are continuously being developed to combat orthopaedic infection. Local administration of catheter antibiotic infusion is offered for chronically infected cemented THR and débridement of bone-ingrown cementless THR [20]. A resorbable, biocompatible hydrogel, able to release antibacterial and antibiofilm agents, can be applied on implants to prevent infection occurrence in an in vitro model of peri-prosthetic infection [21]. However, the problem has not been fully resolved.

The antimicrobial composition containing gentamicin and TXA is integrated in a range of antibiotic applications in complex treatment of the cohort of patients. Currently, polymethylmethacrylate (PMMA) is the most widely used bone cement material for loading antibiotics, gentamicin, in particular, and represents the current standard as an antibiotic delivery vehicle in orthopaedic surgery. Bioresorbable materials with gentamicin include antimicrobial formulations: collagen sponges, antimicrobial gels, bone allografts and calcium-based granules. Systemic usage of TXA has become a routine practice in prophylaxis of intra- and postoperative blood loss including orthopaedic interventions. There are studies being performed to explore local application of TA. The largest patient cohort review showed the efficacy of intra-articular TXA administration during total knee arthroplasty in reducing both blood loss and transfusion requirements in the absence of surgical drains [22].

CONCLUSION

The experimental study allowed identifying PVP and TXA based composition as most effective for hemostasis, estimating dynamics in perifocal reactions with the use of gentamicin-containing sample to prevent osteomyelitis in experimental animals with infected construct implantation. Sustainable hemostatic effect was detected with polymer antimicrobial composition containing 25 mg of TXA in 1 mL of 10 % PVP solution. The sample exhibited the least time of parenchymal bleeding from rat liver tissue wound. Treatment of the infected construct with polymer composition improved femoral intramedullary canal involved with infectious agent showing less signs of inflammation in experimental animals. Fibrin degradation products found in the experimental group only indicated to antifibrinolytic activity of TXA in the study composition. Bone reorganization was shown to be more intensive with the use of polymer antimicrobial composition revealing less extensive areas of necrosis and necrobiosis. The findings suggest prospectiveness of further research of the new polymeric antimicrobial composition.

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