Pakistan Veterinary Journal

ISSN: 0253-8318 (PRINT), 2074-7764 (ONLINE)
DOI: 10.29261/pakvetj/2023.056

RESEARCH ARTICLE

Protective Effect of Locally Prepared Hemostatic Dressing on Hemorrhagic Groin Injury: Commensurate Power to Stop Bleeding but Greater Security

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ARTICLE HISTORY (22-169)

Received:	May 19, 2022
Revised:	July 5, 2023
Accepted:	July 12, 2023
Published online:	July 28, 2023

Key words:
Uncontrolled hemorrhage
Hemostatic dressing
Zeolite Dressing
Standard gauze

ABSTRACT

Uncontrolled hemorrhage remains the leading cause of trauma-related death. The QuikClot is the most popular hemostatic device; however, it also shows severe security hidden dangers. This study aimed to evaluate the efficacy and safety of the self-developed Zeolite Dressing in a rabbit model of hemorrhagic groin injury. A complex hemorrhagic groin injury model was prepared in the right femoral artery of 96 rabbits by lacerating at a half depth and a subsequent 30-second spontaneous hemorrhage, and security was evaluated at the appointed time (1 and 3 weeks after operation). Experimental rabbits were randomly divided into four groups (12 males and 12 females in each group), including sham-operated control group without vascular injury (Con), standard gauze dressing (SD) group, QuikClot (QC) group and Zeolite Dressing (ZD) group. Vascular suture operation and postoperative debridement were thoroughly performed after hemostasis. The results showed that bleeding times of QC and ZD groups were significantly shorter than that of SD group ($p<0.001$), and there was non-significant difference between QC and ZD groups. Similarly, total blood loss was significantly reduced after the intervention of QC or ZD compared with SD group ($p<0.001$). No obvious toxic reaction was recorded 3 weeks after the treatment in both ZD and QC groups. A high wound temperature (maximum temperature was 96.6±27.9°C) and the "cooked meat like" pathological changes in the skin and muscle were only found in QC group. In conclusion, Zeolite Dressing exhibited a commensurate power to stop bleeding with higher safety compared with QuikClot, indicating that it is a practicable alternative for treating severe hemorrhage.

To Cite This Article: Qu Y, Lu J, Shentu J, Yang X, Guo Z, 2023. Protective effect of locally prepared hemostatic dressing on hemorrhagic groin injury: Commensurate power to stop bleeding but greater security. Pak Vet J, 43(3): 567-572. http://dx.doi.org/10.29261/pakvetj/2023.056

INTRODUCTION

Traumatic injury is a common cause of death and disability, in which approximately 40% of trauma-related deaths are due to bleeding (Eastridge *et al.*, 2019). Despite different advances in medical management, there is no ideal protective equipment (high effective hemostasis and no fever) for the field treatment of hemorrhages and uncontrolled bleeding remains one of the most challenging problems in emergency medicine (Caspers *et al.*, 2018).

An ideal hemostatic device for the first aid treatment requires the following conditions to be satisfied (Pusateri *et al.*, 2006): first, it can be applied to different types and degrees of wounds, with the ability to stop bleeding from large vessels (arterial and venous) in a very short time (Effectiveness); second, it should be free from any adverse effect to the tissue to which it is applied, and should not increase the risk of inflammation and infection (Safety); third, it should be simple and easy to use, both for medical workers and those with limited first aid training (Simplicity); fourth, it should be cost-effective, which is especially important in the military setting due to the enormous demand (Inexpensive).

Several medical dressings are effective in stopping bleeding (Hickman *et al.*, 2018) but most of them have certain drawbacks (Pusateri *et al.,* 2006). The most popular ones are the procoagulant chitosan-based bandage HemCon [HC], Tricol Biomedical Inc. (Englehart *et al.*, 2008; Kozen *et al.*, 2008). Zeolite Powder Dressing (QuikClot[QC]) (Kozen *et al.*, 2008), Combat

Gauze(QuikClot[QCG]) (Travers *et al*., 2016; Shiu and Keller, 2019), Granular Hemostatic Agent (Quikclot[GHA]) (Goddard and Evriviades, 2017), Z-Medica Corporation. HemCon is a user friendly hemostatic bandage, which can effectively control bleeding from various kinds of wounds and also offers a physical antibacterial barrier. It works largely through tissue adherence, resulting in mechanical isolation and protection from injury (Pusateri *et al*., 2006; Kozen *et al*., 2008; Arbel *et al*., 2011). Although there are no known side effects recorded in its use, relatively high cost of HemCon has become a major concern (Burkatovskaya *et al*., 2006; Pusateri *et al*., 2006; Arbel *et al*., 2011).

QuikClot is a granular zeolite powder that can selectively absorb various liquids and water in the blood, thereby the platelets, erythrocytes, and clotting factors are concentrated to play their role in hemostasis (Liang *et al*., 2019). Yet there is a strongly exothermic reaction resulting from the combination of QuikClot and blood, which may produce severe thermal tissue injury and consequently limit its application (Arnaud *et al*., 2008; Liang *et al*., 2019). Besides, when applied to a source of high-pressure arterial bleeding, the effectiveness of both HemCon and QuikClot was severely marred. Once the manual compression was removed, blood flow pressure would dislodge the chitosan pad and disperse the zeolite granules. Encouragingly, the bagged zeolite is reported to be less likely to be dispersed and associated with lower thermal risk, which might be a viable alternative for treating severe hemorrhages (Ahuja *et al*., 2006). Therefore, we were encouraged to develop a new-type bagged zeolite dressing.

It was hypothesized that QC was intense exothermic effect, SD, and Con hemostasis without fever. ZD was a mild exothermic molecular sieve, it reduced the heat of adsorption. Consequently, in the current study, we evaluated and investigated the hemostatic effect, safety and toxic reactions of QuikClot and Zeolite Dressing (Zeo-Innov Inc.) in a rabbit model of hemorrhagic groin injury.

MATERIALS AND METHODS

Experimental animals: The study was approved by the Animal Research Committee at Zhejiang University (Animal Study No:16NGYX001Rab), and animal care was provided following institutional guidelines. Ninety-six adult New Zealand white rabbits (48 for each sex), aged 3 months with body weight of 2.0-3.0kg, were used as the experimental subjects. Animals were housed singly under an air-conditioned environment with a 12-h light and dark cycle, maintained at constant temperature (21±5°C) and relative humidity (40-70%). All rabbits were fed a fixed standard laboratory chow daily and free access to water. Animals were observed daily for at least 1 week to ensure they were in good health at the experiment's outset that. Starvation treatment was performed the night before the test, yet potable water was provided as usual.

Study design: This study was designed as a randomized, controlled, unblinded, preclinical trial using a rabbit model of hemorrhagic groin injury. This complex animal model was built in the right femoral artery of rabbits by snipping in half depth, followed by a 30-second hemorrhage. Experimental rabbits were randomly divided into four intervention groups (12 male and 12 female rabbits in each group). The groups included i) sham-operated control group (no vascular injury, Con), ii) Standard Gauze (Winner Medical, Shenzhen, China) dressing (SD) group, iii) QuikClot (QC; Z-Medica Corporation, Connecticut, USA) group and iv) Zeolite Dressing (ZD) group. The Zeolite Dressing was self-developed by Zeo-Innov Inc. (Hangzhou, China). Zeolite Dressing was a mild exothermic molecular sieve; it reduced the heat of adsorption. The protocol suggested by the manufacturer was followed for usage and dosage of these experimental materials.

Modelling protocol: The animals were anesthetized by intravenous injection of 30mg/kg pentobarbital sodium (Sigma-Aldrich, Missouri, USA). Following hair removal, cleaning and disinfection of the right groin and surrounding area, the right femoral artery was exposed. The femoral artery was lacerated with ophthalmic scissors at an incision depth of 1/2, and a subsequent 30-second spontaneous spraying hemorrhage was created, oppressed hemostasis operation was then performed with the experimental medicated dressings, as described above.

The hemostatic time and total blood loss were recorded. The hemostatic time, or bleeding time, was recorded by observing every 30 seconds until the bleeding was successfully controlled. The amount of blood loss was obtained by gently suctioning the blood that oozed from the dressings into a container, and the weight difference of the same surgical dressing before and after hemostasis was added to the weight of blood gathered. The temperature changes near the wound was also monitored closely. Vascular suture operation and postoperative debridement were performed after hemostasis.

Four animals (2 for each sex) in each group were randomly selected for histopathological examination to observe the microscopic changes in skin, muscles, blood vessels and nerves at the wound site, and survival rates of the remaining 20 rabbits in each group were observed at 3h after operation. At the appointed times (1 and 3 weeks after operation), the remaining half of animals in each group were randomly selected, and detected indicators after anesthesia after 3 weeks of recovery. Investigation items included routine hematological parameters (Sysmex XT-2000i, Japan), serum biochemistry parameters (Roche Cobas C311, Switzerland), coagulation indicators (Sysmex CA-1500, Japan), visceral organs weight (spleen, thymus, kidney, heart, renicapsule, liver) and organ coefficients. Relative Organ Weights (g/kg) were determined as the weight of corresponding organ (g) divided by body weight of the animal (kg).

Statistical analysis: Data were analyzed using IBM SPSS Statistics 25.0 (Armonk, NY, USA), and are presented as means±SD. Levene's test was performed to determine the homogeneity of variance, and when equal variances were assumed, one-way analysis of variance (ANOVA) was used to analyze the statistical difference among test groups. The Fisher's Least Significant Difference (LSD) test was applied to compare two groups; when equal variances were not assumed, the Kruskal-Wallis H test was applied.

RESULTS

Hemostatic effect: The results of the present study showed that both QC and ZD dressings exhibited a strong

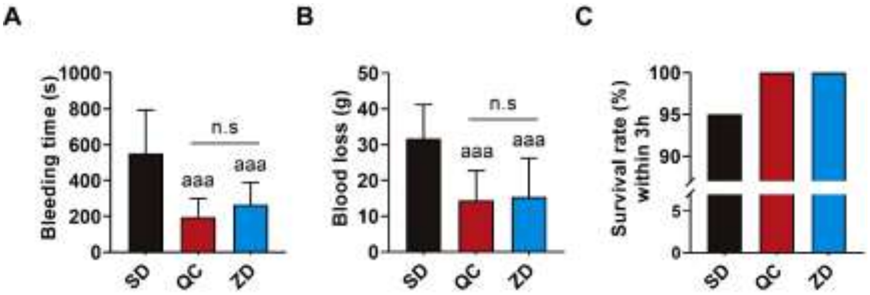

Fig. 1: Showing hemostatic effects of three dressings: (A) Bleeding time (*n* =24); (B) Total blood loss (*n* =24); (C) Survival rate within 3 hours (*n* =20). aaa, *p*<0.001 compared with SD group.

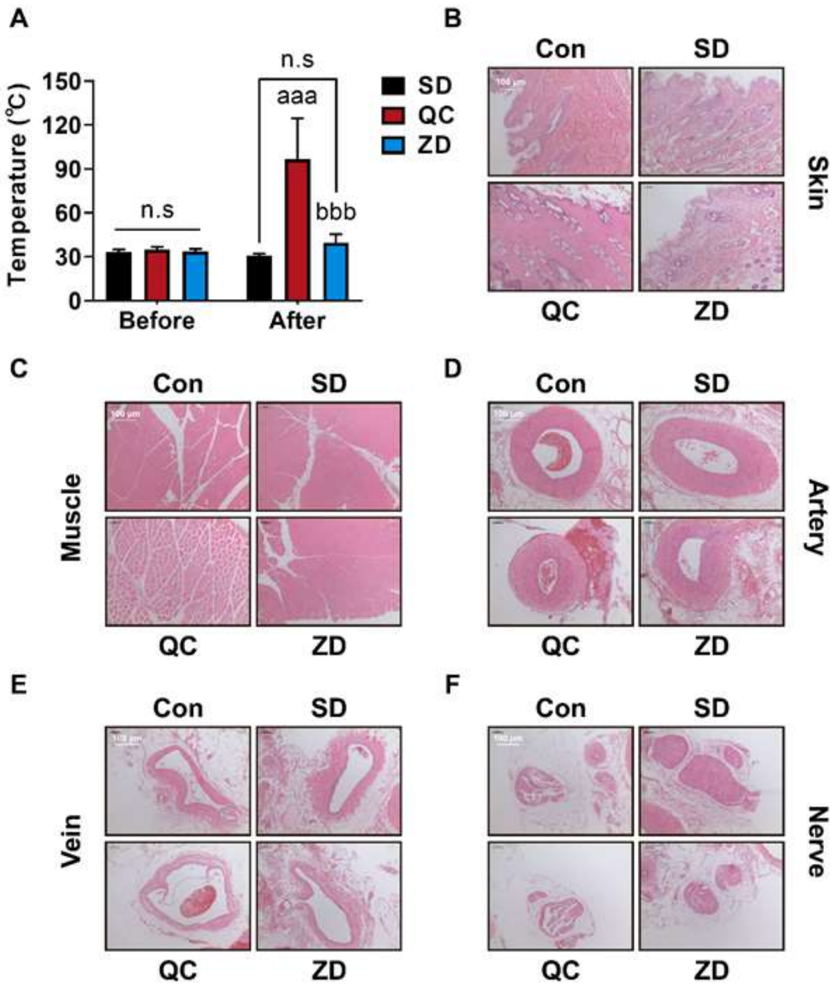

Fig. 2: Showing safety of three dressings: (A) temperature changes near the wound; (*n* =5); (B, C, D, E and F) The typical histopathological images of the skin (B), muscle (C), femoral artery (D), femoral vein (E) and nerve (F) in the operation site. aaa, *p*<0.001 compared with SD group; bbb, *p*<0.001 compared with QC group

hemostasis effect, manifested by the dark brown, sturdy, and thick blood crust near the damaged vessel, while the scab from SD group was bright red and soft. Surprisingly, as shown in Fig. 1A, the bleeding times of QC and ZD groups were significantly shorter than that of SD group (*p*<0.001), and the difference between the former two groups was non-significant. Similarly, the results of total blood loss (Fig. 1B) revealed that the blood loss was significantly reduced after the protection and intervention of QC or ZD compared with SD group (*p*<0.001). Except 4 animals in each group for histopathological examination, within 3 hours after the operation, the survival rates of SD, QC and ZD groups were 95, 100 and 100%, respectively (Fig. 1C). There were no statistical differences in the survival rates of SD, QC and ZD group. Therefore, Zeolite Dressing from Zeo-Innov Inc. exhibited a strong hemostatic effect comparable to QuikClot.

Safety: In the present experiment, results showed that the maximum temperature of QC group was 96.6±27.9°C, while that of SD and ZD groups it was is 30.9±1.2 and 39.4±5.8°C, respectively (Fig. 2A), indicating that compared with the intense exothermic effect of QC, the heat release of ZD and SD groups was mild (*p*<0.001), There was significant difference between QC group compared to SD and ZD groups (*p*<0.001).

The results of histopathological examination demonstrated that Zeolite Dressing was safer in dealing with traumatic uncontrolled hemorrhage compared with QuikClot. Specifically, the “cooked meat like” pathological changes in the skin and muscle of QC group were visible by the naked eye, and under microscope the skin tissue appeared homogeneous red stained suggestive of coagulative necrosis, while necrosis of muscle fibers was also found (Fig. 2B and 2C). Furthermore, a lot of red blood cells and homogenous red staining substances were found around the femoral artery tissue of QC group (Fig. 2D). There were no conspicuous microscopic changes in nerve and vein tissues of QC group (Fig. 2E and 2F) and yet no

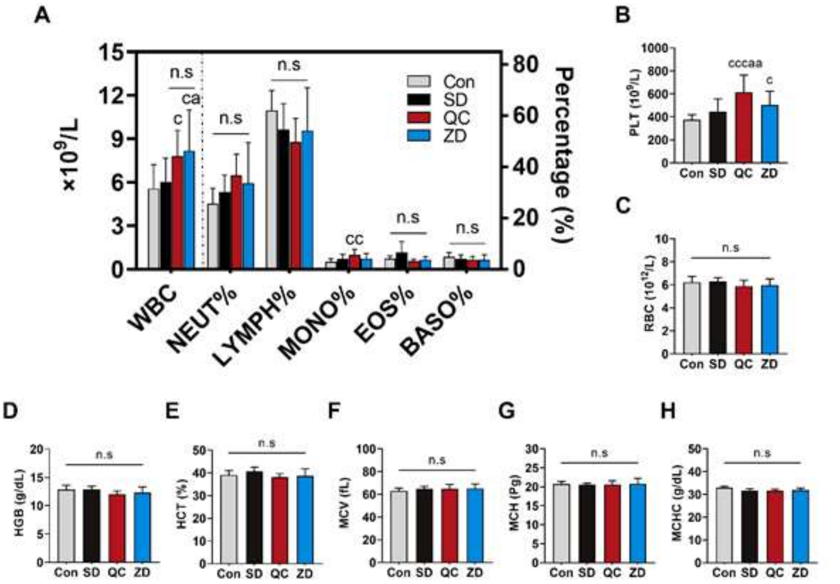

Fig. 3: Showing the toxic reaction of different dressings in terms of hematological parameters. (A, B, C, D, E, F, G and H) The results of complete blood count in animals of four groups at 3 weeks after surgery (*n* =10). c, *p*<0.05, cc, *p*<0.01 and ccc, *p*<0.001 compared with Control group; a, *p*<0.05 and aa, *p*<0.01 compared with SD group.

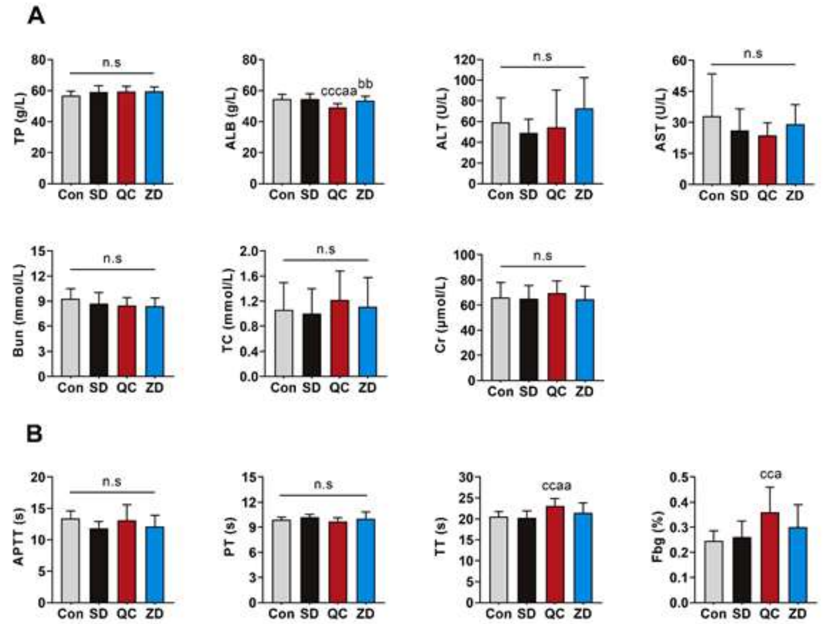

Fig. 4: Showing the toxic reaction of different dressings in terms of serum biochemistry and coagulation function. (A) Results of serum biochemical test of animals in four groups at 3 weeks after surgery (*n* =10). (B) Results of coagulation function test of animals in four groups at 3 weeks after surgery (*n* =10). cc, *p*<0.01 and ccc, *p*<0.001 compared with Control group; a, *p*<0.05 and aa, *p*<0.01 compared with SD group; bb, *p*<0.01 compared with QC group. TP: Total protein; ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; Cr: Creatinine; TC: Total cholesterol; APTT, Activated partial thromboplastin time; PT, Prothrombin time; TT, Thrombin time; Fbg, Fibrinogen.

obvious abnormality was found in all tested samples of other experimental groups. Another evidence of QC's side effects was that the femoral vessels of animals in QC group were far more difficult to suture than ZD and SDs groups after successfully controlled bleeding. Collectively, compared with QuikClot, Zeolite Dressing was found more safe than other dressings.

Toxic reactions: Due to the high similarity between the results of 1 and 3 weeks after operation in hematological and anatomical parameters, only the data from 3 weeks was given in this paper, which was considered to be more representative.

First, based on the results of total and differential white blood cell count, the levels of WBC of QC and ZD groups were significantly higher than Control and SD groups ($p<0.05$), while there was non-significant difference between QC and ZC dressing groups (Fig. 3A). The platelets count of QC and ZD groups was higher than Control ($p<0.001$) and SD groups ($p<0.01$), with no difference between QC and ZD groups (Fig. 3B), which indicates a compensatory increase caused by blood loss. Moreover, the proportions of NEUT, LYMPH, MONO, EOS and BASO fluctuated slightly within a certain range, and compared with Control group there was no difference in RBC, HGB, HCT, MCV, MCH and MCHC for SD, QC and ZD groups (Fig. 3C-H).

Next, regardless of the statistical significance, the levels of TP, ALT, AST, Bun, TC and Cr in serum of QC and ZD groups fluctuated in the normal range (Fig. 4A), which was of non-toxicological significance. However, the level of ALB for QC group was significantly lower than Con, SD and ZD groups. Results also showed that thrombin time of QC group was significantly longer than that of Con and SD groups, indicating a slower activation rate of fibrinogen; similarly, a lower level of fibrinogen was found in QC group, which would lead to the reduced hemostatic material fibrin. All this suggests that the coagulation function of animals in QC group was relatively weak (Fig. 4B), though without clinicopathologic significance. Taken together, both Zeolite Dressing and QuikClot did not cause obvious toxic reactions regarding hematological parameters.

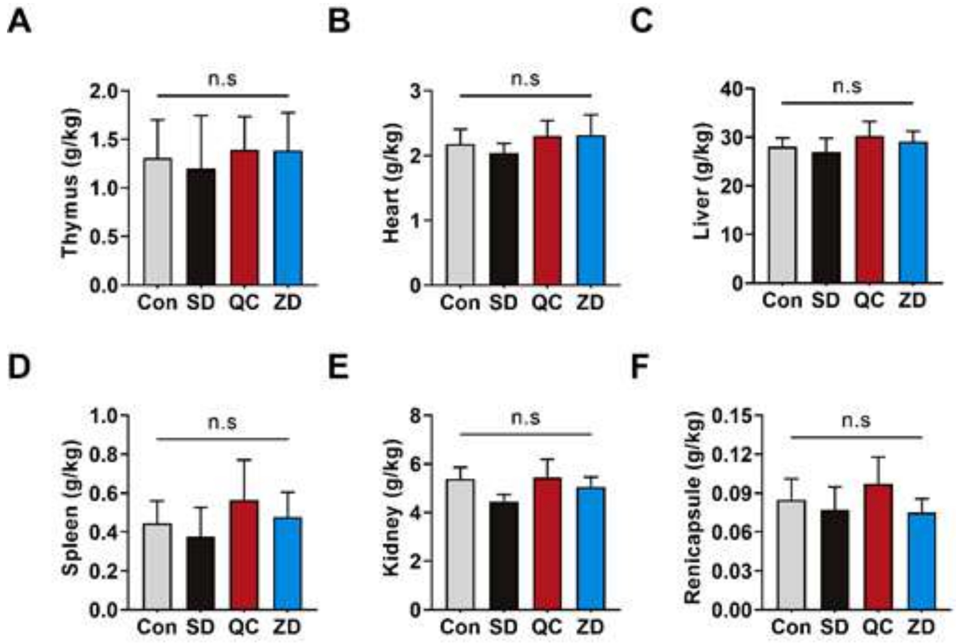

Fig. 5: Showing relative weight of different organs at 3 weeks after surgery (n =10).

Encouragingly, the results of gross anatomy showed that compared with the sham operation group (Con), the relative organ weight coefficient of SD, QC and ZD groups did not differ significantly (Fig. 5A-F). This indicates that both Zeolite Dressing and QuikClot did not cause any toxic effect in terms of relative weight of different organs included in the study.

DISCUSSION

Traumatic injury is a common cause of death and disability, with about 5 million deaths worldwide each year (Krug *et al.*, 2000), and uncontrolled bleeding remains the leading cause of early traumatic death (Schochl *et al.*, 2012). QuikClot hemostatic granules have been used by the U.S. military in Afghanistan and Iraq wars, and achieved good hemostasis effect in battle wounds (Alam *et al.*, 2003; Rhee *et al.*, 2008; Ran *et al.*, 2010). QuikClot has been reported to produce severe tissue injury and necrosis, consequently limiting its application (Hurtado and Wisenbaugh, 2005; Wright *et al*., 2004; Smith *et al*., 2013; Bennett, 2017). The intense exothermic increased burn hemostasis, but inhibited thrombin activity. Zeolite is an inorganic silico-aluminate material, with more than 200 zeolites with different structures in nature (Derakhshankhah *et al*., 2020). The structure and composition of zeolite was different, so the exothermic reaction degree was different. Zeolite Dressing was a mild exothermic molecular sieve. Besides that, another disadvantage of the zeolite granules is their quick dispersal by the high pressure of blood. Encouragingly, it has been reported that wrapping the zeolite granules with fabric bags can effectively prevent the heat damage, and maintain their integrality under the high pressure of blood, suggesting zeolite as a viable alternative for dealing with traumatic uncontrolled hemorrhage (Ahuja *et al.*, 2006). Therefore, we were encouraged to develop the bagged mild exothermic zeolite dressing.

In the present experiment, Zeolite Dressing exhibited a strong hemostatic effect comparable to QuikClot; yet an extremely high wound temperature, increased burn hemostasis, together with the "cooked meat like" macroscopic pathological changes and microscopic tissue necrosis, were only found in QC group, demonstrating the serious side effects of QuikClot. Another finding was that the femoral vessels of animals in QC group were far more difficult to suture than ZD group after the successfully controlled bleeding.

The heat release of ZD and SD groups was more mild, without burn hemostasis. Zeolite Dressing exhibited a strong hemostatic effect (without burn hemostasis) compared to QuikClot. Zeolite Dressing increased the concentration of platelets and clotting factors, enriched endogenous coagulation factors to form a protein corona, which in-turn activates the intrinsic coagulation pathway. In-situ generated thrombin with high activity on zeolite surface could accelerate the clotting progress and rapidly stop bleeding (Li *et al.*, 2014; Shang *et al.*, 2016; Shang *et al.*, 2021). The platelets and clotting factors of QC group was inactivated by strong exothermic reaction around the wound, resulting in extended healing time. In contrast, Zeolite Dressing (mild exothermic) could improve thrombin activity and healing. The level of ALB and Fbg of QC group was significantly lower than Con, SD and ZD groups. The results of total and differential white blood cell count, the levels of WBC of QC and ZD groups were significantly higher than Control and SD groups ($p<0.05$); nevertheless, these differences didn't make sense for toxicology study.

Interestingly, packaging the zeolite granules in fabric bags, without any change in chemical composition, could effectively eliminate the heat damage of tissue and maintain the integrity of zeolite granules so that a good hemostasis effect was maintained. Zeolite dressing was easy to debridement, which reduced operating time.

Conclusions: In a rabbit model of acute hemorrhagic groin injury, the locally prepared Zeolite Dressing exhibited a hemostatic effect comparable to QuikClot, and no toxic effects were noted after the treatment with both Zeolite Dressing and QuikClot. However, Zeolite Dressing was safer than QuikClot in dealing with uncontrolled traumatic hemorrhage, as the extremely high wound temperature together with the "cooked meat like" pathological changes were only found in QC group.

Acknowledgements: This project was supported by Hangzhou Science and Technology Development Program (No.20150633B49), China.

Authors contribution: YQ, JL, JS, XY and ZG conceived and designed the experiments; YQ, JL, XY and ZG performed the experiments; YQ, JL, XY and ZG analyzed the data; YQ, JL, XY and ZG contributed reagents/materials/analysis tools, while YQ, JL and JS prepared manuscript, and XY and ZG reviewed the manuscript.

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