Chitosan dressings achieve better femoral hemostasis after percutaneous procedures in patients with structural heart disease

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Abstract：AIM: To evaluate the efficacy and safety of chitosan dressings used for femoral hemostasis as an adjunct to manual compression in patients with structural heart disease undergoing cardiac catheterization. **METHODS:** Two hundred patients with structural heart disease undergoing cardiac catheterization were 1∶1 randomized for manual compression using regular or chitosan dressings. All patients were catheterized with a 6 Fr or 7 Fr sheath. Time to achieve hemostasis and incidence of minor and major bleeding were compared between groups. **RESULTS:** Time to achieve hemostasis was (4.0±1.5) and (7.6±2.5) min and the incidence of minor and major bleeding was 3% and 11%, respectively, in chitosan and regular dressings groups ($P<0.05$). Errhysis developed in 3%, and 3% of patients, respectively, in chitosan and regular dressings groups, but hematoma (n=4) and bleeding (n=4) were only observed in regular dressings group. Multiple regression models showed that the time to hemostasis was not associated with age, body mass index, blood pressure, blood platelet count and international normalized ratio in regular dressings group but was positively associated with mean blood pressure in chitosan dressings group. CONCLUSIONS: Compared with regular dressings, chitosan dressings significantly decrease the time to achieve hemostasis and lower the total incidence of hemorrhage.

[Key words]: haemostasis; artery; chitosan; structural heart disease

With the advent of various interventional devices and interventional therapies, many heart and vascular diseases can benefit from interventional therapy. In recent years, the interventional therapy for congenital heart disease, valvular heart disease and other structural heart diseases have also made considerable progress and are

gradually replacing the surgical thoracotomy, becoming the preferred treatment for patients. In cardiovascular interventional therapy, although many blood vessels such as the radial artery [1] and the ulnar artery [2] can be used as the interventional operating pathway, the trans-femoral artery is still the primary pathway for the above operation. Especially in structural heart diseases, majority of the cases need both the femoral artery and femoral vein as the operating pathway. However, the traditional manual compressing hemostasis needs to be applied for a long time and is prone to complications like hemorrhaging, hematoma and false aneurysm [3]. Chitosan, as the de-ethanoyled product of chitin, has the effect of promoting the coagulation of the blood, but there have been a few reports of using this method to assist hemostasis after femoral artery puncture in patients with structural heart disease. However, the involved diseases and the number of cases are limited [4]. This study aims at investigating the assisting effects of chitosan hemostatic dressings in femoral artery compressing hemostasis in patients with structural heart disease and exploring the related factors influencing the assisting effects of the hemostatic dressings.

1. Subjects and methods

1.1 Materials: the chitosan hemostatic dressings (produced by Daxon Biomedical(Suzhou) Co., Ltd) made from chitin fiber materials with the specifications of 5 × 6 cm, disinfected for use.

1.2 Subjects: 200 cases of patients with structural heart disease who must undergo interventional femoral artery puncture operations were selected and randomly divided into experimental and control groups, with 100 cases in each group. In the hemostasis of manual compression on femoral artery, chitosan hemostatic dressings were added for the experimental group while the traditional manual compression method was applied for the control group. All the patients received the related clinical assessment before the experiment. The inclusion criteria were patients with structural heart disease needing to puncture the femoral artery for interventional therapy or examination, using the 6-7F arterial sheath. Exclusion criteria were as follows: 1. Non local anesthetized patients; 2. Patients who were using coagulation affecting drugs before the interventional operation so that the international normalized ratio (INR) of prothrombin time > 2.5; 3.Various physiological or pathological factors leading to the impossibility of normal observation or the presence of potential risks; 4. Patients who have undergone repeated femoral artery puncture procedure, repeated replacement of the femoral artery sheath or need a huge arterial sheath; 5. Platelet count $< 8 \times 10^9$ / L; 6. Patients with coronary heart disease and diabetes.

1.3 Methods: All operations were conducted with the informed consent of patients by the designated personnel. The control group applied the traditional hemostasis methods: a small amount of blood spouted after unplugging the arterial sheath to prevent the thrombosis stranding in the artery; the artery puncture site was immediately compressed and 3 min later slightly relaxed to observe the occurrence of errhysis; if it occurred, continue the compression, and thereafter observe every 1 min until no more errhysis occurred when the hand almost completely relaxed; the compression time was recorded. The wound was bandaged with gauze and compressed with a sandbag (1kg) for 6 hours; the gauze was removed after the patient has been in a supine position for 24 hours, and then the patient can move freely. The experimental group received the following hemostasis: the arterial sheath was unplugged and a small amount of blood spouted; the arterial puncture point was immediately compressed with the left hand while the skin puncture point was exposed; the chitosan hemostatic dressings were moderately soaked with the spouted blood without thrombosis by the right hand and the skin puncture site was pressed with the chitosan hemostatic dressings using mild force; the compression time was recorded. Patients were allowed to do moderate activities in bed after 4 hours of sandbag (1kg) compression; the wound was observed for the occurrence of bleeding or hematoma; the bleeding complications were recorded.

1.4 Analysis: The measurement data were represented by mean ± standard deviation. The measurement data were compared with unpaired t test, whereas the count data were compared by the chi-square test. Multiple regression analysis was conducted with compression hemostasis time as the dependent variable and age, body mass index, mean blood pressure, platelet count and INR as the independent variables. SPSS 13.0 statistical software was used for the statistical analysis; P <0.05 represented a statistically significant difference.

2. Results

2.1 Basic data: The two groups of patients had no statistically significant differences in age, sex ratio, body weight, the distribution of disease types, the proportion of interventional therapy and inspection and clinical laboratory tests (see Table 1).

2.2 Compression time and complications: The compression hemostasis time of the experimental group and the control group were respectively 4.00 ± 1.49 min and 7.60 ± 2.46 min (P = 0.000), and the incidences of all complications were respectively 3%

and 11% (P = 0.049). In the experimental group, only 3 patients had a small amount of errhysis, noticeable from for the red stain on part of the bandaging gauze; no bleeding complications that must be treated or distal arterial thromboembolism had occurred. In the control group, in addition to 3 cases of errhysis, 4 cases of bleeding and 4 cases of hematoma were observed. The patients stopped bleeding after receiving compression hemostasis again; 3 cases of hematoma were treated by a drug for external application and in 1 case the hematoma disappeared after the extravasated blood was drawn out with a hematoma puncture.

2.3 Factors affecting the compression time: The multivariate regression analysis of forced entering (Table 2) showed that in the control group the compression time had no significant relationship with age, body mass index, mean blood pressure, platelet count and INR (F = 0.598; P = 0.701); whereas in the experimental group the compression time was correlated with the above factors (F = 8.914; P = 0.004). Further step-by-step analysis showed that the compression time was positively correlated with mean blood pressure (B = 0.037; t = 2.986, P = 0.004).

3. Discussion

Compared with coronary heart disease with very high incidence, patients with structural heart disease are a special group. Different from patients with coronary artery disease who often have hypertension, high cholesterol and hyperglycemia, the majority of patients with structural heart disease are young, coupled with digestive function affected by long-term poor cardiac function, thus, a few of them are overweight or obese. This characteristic can be seen from the body mass index of the patients in this study. Before the interventional operation, patients with coronary heart disease often need large doses of anti-platelet drugs, such as aspirin and clopidogrel, which may affect the platelet activation of the chitosan, whereas patients with structural heart disease almost do not use drugs before the interventional operation. In addition, different from coronary heart disease only puncturing the artery, regardless of the interventional therapy or interventional examination, structural heart disease always punctures both the femoral artery and the femoral vein. The above characteristics of structural heart disease suggest that although the incidence of coronary heart disease is low, the independent exploration of compression hemostasis in femoral artery of these patients has a unique significance. This study showed that the chitosan hemostatic dressing had a good hemostatic effect after the femoral artery puncture in patients with structural heart disease because it not only shortened the compression time but also significantly reduced vascular complications.

Although it has always been discussed, the various compression hemostasis methods after interventional therapy and examination of heart and vascular disease [5-8]patients, the manual compression hemostasis is still the most basic and safe way. Various assisting haemostasis methods, including compression hemostasis devices and vascular suture devices, have been produced [9, 10], but all of these methods have some defects due to the anatomical characteristics of the femoral artery. The operation of vascular suture devices is tedious; with a certain degree of failure rate, it does not reduce the incidence of complications. Due to the special anatomy of the femoral artery area, compression hemostasis devices are often difficult to fix; various reasons easily cause the displacement of the compression device, thus to lead to failure of the operation. Chitosan, made from chitin fiber materials, achieves the effect of blood coagulation by absorbing the proteins in blood cells and the blood via the positive ammonium ion electrons in glycosaminoglycan class and activating the platelets; meanwhile this porous material can also increase the contact area between the platelets and the poly-amino glucose thus promoting blood coagulation [11]. Animal studies showed [12, 13] that chitosan can be effectively used for traumatic hemostasis to improve the survival rate of animals with severe liver injuries. In the United States and Europe, chitosan has been approved for use in hemostatic bandages and various hemostatic agents. This study shows that chitosan can significantly shorten the hemostasis time, but it is difficult to explain in the multiple regression analysis that showed that the compression hemostasis time was positively correlated with blood pressure after using chitosan hemostatic dressings. The hemostasis time was not significantly correlated with physiological factors, such as blood pressure and body mass index, when using the traditional methods, which seemed irrational. Clinically, the compression time usually had to be extended with the increase in the patients' weight, blood pressure and other factors. We believe that the reason for this phenomenon is that the compression hemostasis time is affected by a variety of physiological and pathological factors so that the affecting strength of every single factor is diluted; chitosan has the function of absorbing the proteins in blood cells and blood and activating the platelets actually eliminating the influence of factors of the small amount of platelets or long INR; meanwhile the blood pressure, as a mechanical factor, reveals the function of compression hemostasis, which reflects the mechanism of the reaction of chitosan.

The inadequacies of this study are: ① because of medical ethics and cost issues, this study did not carry out pathologic research and laboratory examination of the patients after compression hemostasis; ② the majority of the patients with congenital

heart disease are children or infants, fearful of the patients losing consciousness of patients when they undergo general anesthesia or for noncompliance in the observation of patients who are too young, this study did not include this kind of patients; ③ for care requirements, the patients in the experimental group only moved their lower limbs in bed 4 hours after the compression bandage but did not take free ambulation; the time to take real ambulation is the same as the control group - after 24 hours; ④ the dosage of heparin is also an important factor affecting the compression time, but this study did not take it as an independent variable for the regression analysis. The main reason for heparin not being included in the analysis is that the dosage of heparin is disproportionate to the post-operative residual anti-coagulant effect. Clinically, the dosage of heparin is related to three factors - the weight of the patient, the interventional operation mode and the operation time. The greater the weight, the larger the dosage of heparin. The dosage of heparin for interventional therapy is larger than that for interventional examination, but what is more important is the operation time. Due to the short half-life of heparin, the length of the operation time will significantly affect the efficacy of heparin towards the end of the operation; and with the extension of the operation time, the dosage of heparin should be correspondingly increased. Therefore, the total amount of heparin used at the end of surgery cannot substitute for anticoagulant efficacy. For fear of increasing the costs for the patients, this study did not carry out the detection of activating coagulation time before removing the arterial sheath after the surgery has been completed.

In conclusion, this study shows that the application of chitosan hemostatic dressings can significantly reduce the compression time and reduce bleeding complications after femoral artery puncture, but the study is only a preliminary exploration of this haemostasis. In the future, it will be studied how to combine this material with existing hemostatic devices to achieve the effect of saving time and effort while at the same time reducing the braking time and vascular complications for patients.

Table 1. Comparison of basic data between the experimental group and the control group

	Experimental group	Control group	Value of *P*
Gender (male / female)	61/39	72/28	0.099
Age (years)	38.1±18.8	30.0±17.0	0.450
Height (cm)	161±11	161±10	0.656
Body weight (kg)	56.0±12.9	58.1±12.0	0.221
Body mass index (kg/m^2)	21.38±4.07	22.20±3.76	0.143
Systolic pressure (mmHg)	122±15	125±17	0.119
Diastolic pressure (mmHg)	75±12	74±10	0.412
Mean blood pressure (mmHg)	91±12	91±11	0.837
Platelet ($\times 10^9$ / L)	202±52	197±45	0.413
International normalized ratio	0.99±0.28	0.98±0.10	0.904
Intraoperative dosage of heparin	3803±1050	3794±1344	0.958
Size of the artery sheath (6F / 7F)	98/2	97/3	1.000
Type of disease (congenital / rheumatic heart disease)	87/13	84/16	0.547
Type of operation (interventional therapy / examination)	75/25	78/22	0.167