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Effects of heparin catheter-sealing solution for implantable venous access ports on D-dimer levels in older cancer patients

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Abstract. – OBJECTIVE: To investigate the effects of different concentrations of heparin catheter-sealing solution for implantable venous access ports (VAPs) on D-dimers (D-D) in older cancer patients.

PATIENTS AND METHODS: A total of 208 older cancer patients who received intravenous chemotherapy for the first time were randomly divided into four groups: the normal saline group, the low concentration heparin group (25 U/ml), the medium concentration heparin group (50 U/ml), and the high concentration heparin group (75 U/ml), with 52 patients in each group. VAPs were sealed by the positive pressure technique every day before and after perfusion, as well as at the end of a course of chemotherapy when the butterfly needle was removed. The patients were followed-up for three courses of chemotherapy, and comparisons of the clinical effects were conducted.

RESULTS: Before treatment and at the end of follow-up, no significant differences among groups were found in platelet count, prothrombin time, thrombin time, or activated partial thromboplastin time ($p>0.05$). At the end of follow-up, the high concentration heparin group had reduced fibrinogen (FIB) and increased D-D compared with the other groups, and the differences were statistically significant ($p<0.05$). The other three groups showed no significant differences in FIB or D-D before treatment or at the end of follow-up ($p>0.05$). The high concentration heparin group had higher local bleeding rate, while the saline group had higher partial and complete prevalence of blockage compared with the other groups. The differences were statistically significant ($p<0.05$).

CONCLUSIONS: 25-50 U/ml heparin catheter-sealing solution had little effect on blood circulation and coagulation. Additionally, it did not increase the risk of local bleeding or thrombotic blockage.

Key Words:
Implantable venous access port, Heparin catheter-sealing solution, Geriatric oncology, D-dimer.

Introduction

Implantable venous access ports (VAPs) and peripherally inserted central catheters (PICCs) are two main central venous catheterization techniques with broad clinical applications. They significantly reduce outer periphery phlebitis and local tissue necrosis caused by chemotherapy drugs, as well as the prevalence of hematoma, infection, and bleeding caused by repeated needle punctures[1,2]. VAPs can be implanted beneath the skin for long periods of time. Paleczny et al[3] indicated that VAPs are safer than PICCs. They cause few catheter-related complications, require simple care, and are well accepted by patients. Heparin is the most commonly used catheter-sealing solution. Whether repeated application of heparin has an impact on the coagulation system of cancer patients during chemotherapy, and whether the effect is related to the concentration of heparin remain controversial issues. According to some scholars[4],

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sealing solutions that contain very low amounts of heparin do not have effects on blood circulation and the coagulation system. However, others have proposed that because cancer patients are hypercoagulable, and chemotherapy can worsen disorders of blood coagulation, heparin-sealing solutions may promote coagulation[5]. Regarding PICCs, the effects of heparin on PICC patency, the prevalence of thrombotic blockage, and bleeding are well studied[6]. The aim of this study was to evaluate the clinical effects of heparin on patients implanted with VAPs, using a randomized controlled trial study design, to provide insights on the application of heparin in cancer patients with VAPs.

Patients and Methods

Patients

A total of 208 patients with advanced non-small-cell lung cancer who were receiving intravenous chemotherapy for the first time in our hospital from January 2014 to June 2016 were selected for this study. They were implanted with VAPs and signed the informed consent. Inclusion criteria: 1. Patients were between 50 and 75 years old and had Karnofsky Performance *Score* (KPS) $\geq$ 80 points; 2. Patients underwent at least three courses of chemotherapy; 3. Patients had no primary blood diseases, nor severe coagulopathy during chemotherapy. Exclusion criteria: 1. Patients had severe diseases, such as of the heart, liver, kidney, lung, and brain, or other organ dysfunctions; 2. Patients had serious nutritional disorders and required repeated intravenous administration of nutrients and intravenous transfusion; 3. Patients had catheter-related issues, such as dislocation, blockage (non-thrombotic), phlebitis, local infection, and puncture failure. Patients were randomly divided into four groups: the saline group, the low concentration heparin group (25 U/ml), the medium concentration heparin group (50 U/ml), and the high concentration heparin group (75 U/ml). Each group included 52 cases. The saline group included 32 males and 20 females, with mean age of 58.9 ± 7.5 years. The low concentration heparin group included 30 males and 22 females, with mean age of 61.2 ± 8.3 years. The medium concentration heparin group included 33 males and 19 females, with mean age of 60.8 ± 7.9 years. The high concentration heparin group included 34 males and 18 females, with mean age of 63.3 ± 8.5 years. There were no significant differences in age or sex between the four groups. The study was approved by the Ethics Committee of The Second Hospital of Dalian Medical University. Signed written informed consents were obtained from all participants before the study.

Research Methods

Gemcitabine or paclitaxel combined with cisplatin (Yangzijiang, Taizhou, China) were used for chemotherapy. One course lasted for 21 days. There was a 21-day interval between courses. The vital signs, blood indexes, liver and kidney functions, and blood coagulation indexes [platelet count (PLT), coagulation zymogen time (PT), thrombin time (TT), activated partial thromboplastin time (APTT), fibrinogen (FIB), and D-dimer (D-D)] of patients were closely monitored during both chemotherapy and intervals to evaluate the safety of chemotherapy. Symptomatic treatments were given promptly. The interval time was extended as needed. The implanted VAPs were three-way-valve VAPs (Bard Access Systems, Salt Lake City, UT, USA). The implantation was carried out by physicians in the operating room. The patients were in the supine position with elevated shoulders. The subclavian vein was punctured. All operations were performed strictly in accordance with the operating rules of intravenous infusion established by the Infusion Nurses Society (INS). This passage was used for chemotherapy, blood transfusion, and delivery of high concentrations of nutrients. Routine blood collections and perfusion were not performed through VAPs. Before and after daily infusion, as well as at the end of one course of chemotherapy when the butterfly needle was removed, the VAPs in the saline group were pulsed rinsed with 20 ml saline solution and then sealed with 5 ml saline solution with the positive pressure technique. The VAPs in the other three groups were pulsed rinsed with 20 ml saline solutions, then sealed with 5 ml heparin solutions of different concentrations with the positive pressure technique.

Observational Indexes

Six indicators of coagulation, and the prevalence of local bleeding and thrombotic blockage were compared before treatment and at the end of the follow-up. A total of 3 ml venous blood was drawn and analyzed with a Hitachi 7300 automatic biochemical analyzer (Hitachi, Tokyo, Japan) to test the indicators of coagulation. The reference range for PLT was $100\text{-}300\times10^9$/l. The reference range for PT was 12-16 s. The reference range for TT was 16-18 s. The reference range for APTT

was 35-45 s. The reference range for FIB was 2-4 g/l. The reference rang for D-D was < 200 μg/l. Local bleeding criteria: bleeding was observed at the puncture site, or bleeding occurred 72 h after it had previously stopped. Thrombotic blockage criteria: If no blood could be withdrawn and great resistance was felt when pulsed intravenous saline rinses were conducted. After confirmation by X-ray that the catheter was in the correct position and the head was in the correct direction, 5 ml urokinase (5000 U/ml) was used for thrombolysis (three times for 20 min per thrombolysis). If blood could still not be withdrawn and resistance was still felt with the saline rinse, patients were observed for 24 h. A complete blockage occurred if afterward still no blood was withdrawn and there was resistance with the saline rinse. The catheter was removed. If no blood was withdrawn and the saline rise was performed with or without resistance, 5 ml urokinase was used for thrombolysis 1-3 times. A partial blockage was recorded if blood could then be withdrawn.

Statistical Analysis

SPSS20.0 software (Version X; IBM, Armonk, NY, USA) was used for data analysis. Measurement data are presented as mean ± standard deviation. Comparisons among groups were by one-way ANOVA. Pairwise comparisons were by the LSD-*t* test. The paired *t*-test was used for intra-group comparisons. Count data are presented as number (%). Comparisons among groups were by χ^2-test. $p<0.05$ was considered statistically significant.

Results

Comparison of Coagulation Indexes.

Before treatment and at the end of follow-up, there were no differences between groups in PLT, PT, TT, or APTT ($p>0.05$). Compared with the other groups, at the end of follow-up, the high concentration heparin group had reduced FIB and elevated D-D levels. The differences were statistically significant ($p<0.05$). The FIB and D-D levels in the other three groups were comparable both before treatment and at the end of follow-up ($p>0.05$) (Table I).

Comparisons of the Prevalence of Local Bleeding and Thrombotic Blockage

The high concentration heparin group had a higher rate of local bleeding compared with the other groups. The saline group had a higher rate of partial and complete thrombotic blockage compared with the groups sealed with heparin. The differences were statistically significant ($p<0.05$) (Table II).

Discussion

The prevention of catheter blockage is an important part of VAP care. Blockages[7,8] can be induced by increased intrathoracic pressure, the formation of blood clots during blood reflux, improper catheter sealing, increased blood reflux caused by frequent upper limb movements, endogenous coagulation resulting from vascular

Table I. Comparison of coagulation indexes.

Group		Saline	Low con. heparin	Medium con. heparin	High con. heparin	F	p
PLT (×10⁹/l)	Before treatment	242.6±56.9	256.8±62.3	236.9±64.5	251.7±72.2	0.263	0.845
	End of follow up	156.9±45.5	148.2±46.8	162.3±42.7	166.9±51.2	0.212	0.869
PT (s)	Before treatment	14.5±3.6	14.8±3.9	15.2±4.4	15.3±4.5	0.296	0.821
	End of follow up	14.6±3.9	14.7±4.2	14.9±4.3	15.4±4.8	0.419	0.675
TT (s)	Before treatment	16.5±2.2	16.3±2.4	17.2±2.6	17.1±2.5	0.323	0.758
	End of follow up	16.6±2.3	16.8±2.5	17.2±2.6	17.3±2.7	0.356	0.721
APTT (s)	Before treatment	42.1±4.5	43.6±4.6	44.5±4.8	40.8±4.3	0.421	0.768
	End of follow up	43.6±4.4	45.2±4.6	44.8±4.5	42.5±4.7	0.369	0.845
FIB (g/l)	Before treatment	2.6±0.4	2.5±0.3	2.7±0.6	2.7±0.5	0.069	0.963
	End of follow up	2.8±0.6	2.7±0.7	2.6±0.8	2.3±0.4	3.245	0.036
D-D (μg/l)	Before treatment	356.5±76.8	364.5±72.4	372.2±82.4	349.8±76.5	0.465	0.598
	End of follow up	342.3±65.2	352.2±64.3	364.7±59.8	478.5±89.7	3.958	0.031

PLT: platelet count; PT: Prothrombin Time; TT: Thrombin time; APTT: activated partial thromboplastin time; FIB: Fibrinogen; D-D: D-Dimer.

Table II. Comparisons of the incidence of local bleeding and thrombotic blockage [cases (%)].

Group	Saline	Low con. heparin	Medium con. heparin	High con. heparin	χ^2	*p*
No.	52	52	52	52		
Bleeding	2 (3.8)	4 (7.7)	5 (9.6)	11 (21.2)	9.150	0.027
Partial blockage	16 (30.8)	8 (15.4)	7 (13.5)	6 (11.5)	8.252	0.041
Complete blockage	13 (25.0)	6 (11.5)	5 (9.6)	4 (7.7)	8.254	0.041

endothelial injuries caused by continuous contact of the catheter tip with the vein wall, and coagulopathy in cancer patients with hypercoagulability which can be further worsened by chemotherapy. Additional causes of blockage include precipitation of small particles in the catheter lumen wall resulting from the interaction of different drugs, deposition and solidification of high concentrations of nutrient macromolecules such as fat emulsion on the catheter wall, and improper flushing. Clinically, 10-100 U/ml heparin is commonly used to seal VAP catheters. Saline can be used when patients have platelet or clotting abnormalities[9]. Humphries et al[10] indicated that heparin can effectively prevent catheter blockage. Also, it might exert a synergistic anti-tumor effect with chemotherapy drugs. Heparin could not reduce catheter blockage in adult patients, although it had better effects in newborns. Furthermore, regular replacement of the heparin cap during chemotherapy intervals can increase catheter patency[11]. Some studies suggested that[12] low concentrations of heparin (less than 75 U/ml) do not increase the rate of local bleeding. However, the repeated use of heparin in cancer patients undergoing chemotherapy can increase the overall concentration of heparin in blood, and might have a great impact on blood circulation and coagulation[13,14]. Heparin can reduce blood FIB, increase D-D, and enhance fibrinolysis. Heparin can also decrease PLT and extend other indicators of coagulation such as PT, TT, and APTT[10,15-17]. In this study, we found no significant differences between groups in PLT, PT, TT, or APTT before treatment or at the end of follow-up. However, the high concentration heparin group had lower FIB and higher D-D concentrations than the other groups at the end of follow-up. A higher local bleeding rate was found in the high concentration heparin group compared with the other groups. The saline group showed increased rates of partial and complete blockage compared with the groups with different concentrations of heparin. These results suggested that 25-50 U/ml heparin catheter-sealing solution had few effects on blood circulation and coagulation. It did not increase the risk of local bleeding or catheter blockage.

Conclusions

VAP catheters are made from advanced silicone material. They have good biocompatibility and cause minimal irritation and damage to the vascular endothelium, thereby reducing the risk of phlebitis and thrombosis[15]. Proper care and procedures are critical for extending catheter life, reducing catheter-related complications, and minimizing the suffering of patients[16]. The fact that patients have large differences in coagulation parameters might make them react differently to heparin. Additionally, the long-term use of a single concentration of heparin might have adverse effects[10,17]. Determining how to dynamically adjust the concentration of heparin requires further research.

Conflict of interest

The authors declare no conflicts of interest.

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