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Brief Communication

Outcome of perioperative hemostatic management in patients with hemophilia without inhibitors undergoing 161 invasive or surgical procedures

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Abstract

Perioperative management of persons with hemophilia (PWH) is a challenge for surgeons and hematologists. Reductions in mortality rate and complications have been achieved since the introduction of clotting factor concentrates (CFCs), which improve hemostatic control. However, there is no clear consensus on the optimal dosing of CFC administration. The aim of this study was to evaluate the outcome of PWH without inhibitors in patients undergoing invasive or surgical procedures. A total of 161 procedures, including 57 major and 104 minor ones were retrospectively reviewed. The characteristics of PWH, age at procedure, duration and total amount of CFC administration during the perioperative period, hemostatic adequacy, and complications were summarized. The study showed a low rate of bleeding (1.2%), infection (0%), thromboembolic event (0%), and inhibitor development (0%). The results revealed the doses and duration of CFC administration for several major and minor procedures which were capable of achieving excellent hemostatic control.

Keywords: Blood coagulation factors; General surgery; Hemophilia

1. Introduction

Hemophilia A (HA) and hemophilia B (HB) are inherited bleeding disorders that result from the absence or deficiency of clotting factors VIII and IX, respectively. Perioperative management of persons with hemophilia (PWH) is a challenge for surgeons and hematologists. The mortality rate was reported to be up to 66% in PWH undergoing minor and major surgery in the mid-20th century.[1] A reduction in the mortality rate to 4.5% was achieved due to improvements in hemostatic control using clotting factor concentrates (CFCs) during the perioperative period.[2] However, PWH with surgical intervention still have a higher risk of bleeding, delayed wound healing, and postoperative infections.[3] These complications are mainly caused by insufficient CFC administration during the perioperative period. Since CFC is widely available in most developed countries, some studies have reported the effectiveness of individual CFC replacement therapy for PWH undergoing invasive or surgical procedures.

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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However, the dose and duration of CFC administration for the procedures remain controversial.[4,5] The World Federation of Hemophilia (WFH) devised a guideline for PWH undergoing surgery for both resource-constrained and uncontrained countries.[6] In Taiwan, patients with hemophilia are added to the "registry of catastrophic illness patients", which is maintained by the Bureau of National Health Insurance. Each newly diagnosed case of hemophilia is certified by clinicians, and the patient is then eligible to receive free treatment with CFCs, which includes the perioperative period. The aim of this study was to evaluate the outcome of perioperative hemostatic management in PWH without inhibitors according to the guideline of the WFH.

2. Methods

The study was approved by the hospital's Institutional Review Board. In this consecutive case study, data from all moderate and severe hemophilia patients undergoing invasive or surgical procedures at a single hemophilia comprehensive care center for the period 2011 to 2016 were evaluated retrospectively. PWH who had been diagnosed with an inherited or acquired hemostatic defect other than hemophilia, had a present or past history of inhibitors, had a diagnosis of cirrhosis, or had a low platelet count were excluded. Procedure type was classified as either major or minor. Major procedures referred to major orthopaedic surgery, major abdominal surgery (e.g., bowel resection and colon tumor removal), spinal surgery, and other surgery involving significant risk of large volume blood loss or blood loss into a confined anatomical space. Extraction of impacted third molars was also considered major surgery. Minor procedures generally referred to interventions such as removal of intravenous access devices, cardiac catheterization, transcatheter arterial chemoembolization, intra-articular therapy, or endoscopy with biopsy. When the classification was difficult to make according to the abovementioned criteria, location of the procedure and level of surgical invasiveness were used to establish whether it was major or minor.

The target peak levels of clotting factor before major procedures were 100 IU dL^{-1} and 80 IU dL^{-1} for HA and HB patients, respectively, but before total joint replacement the target peak level was 120 IU dL^{-1}. Before minor procedures, the target peak level of clotting factor was 80 IU dL^{-1}. Trough level was examined after procedure, and CFC dose after surgery was administered according to the recommendation of WFH guideline to maintain the desired trough level.[6] However, the duration of CFC administration was extended to 21–28 days after certain types of major procedures, e.g., spinal surgery, total joint replacement, and intestine resection. All CFCs used for the procedures were recombinant factor concentrates, which were administered by bolus infusion. The hemostatic response to surgery with clotting factor was reviewed using a four-point scale (i.e., excellent, good, fair, poor/none) via patients' operation notes and medical records between the 3rd and 5th day after operation, in accordance with the WFH guidelines.

3. Results

A total of 80 HA and 9 HB patients undergoing invasive or surgical procedure were enrolled. Among the enrolled PWH, 70 (87.5%) HA and 5 (55.5%) HB patients had a severe type. Twelve (15.0%) of the HA patients were on prophylactic therapy, and all were younger than 18 years old. Of the HB patients, only one (11.1%) was on prophylactic therapy. None of the enrolled PWH had human immunodeficiency virus infection, but 10 (12.5%) HA and 3 (33.3%) HB patients had hepatitis C virus infection.

Among these 89 PWH, data from a total of 161 procedures, including 57 major and 104 minor procedures, were retrospectively reviewed. The characteristics of PWH, age at procedure, duration and total amount of CFC administration during the perioperative period, hemostatic adequacy, and complications are summarized and listed in Table 1.

The time of drainage removal was determined according to the patient's condition, following standard surgical protocols. Three patients with total joint replacements received transfusions of red blood cells during the operation, but otherwise blood component transfusion was not needed in any of the other procedures during perioperative period. Adjunctive therapy with antifibrinolytic agents was used in 4 of the patients undergoing a major procedure, including one total joint replacement and 4 ureter stone removal, and all patients who received dental management.

No thromboprophylactic therapy was used during the perioperative period, except for patients who underwent cardiac catheterization, who received half the standard dose of heparin. None of the PWH experienced a thromboembolic event after the procedures. In addition, none developed inhibitors of coagulation factors during the follow-up period of more than three months after the procedures.

Acute and delayed bleeding occurred in 2 of 161 (1.2%) procedures. Three complications were noted. One patient with severe HA developed pyogenic arthritis 3 weeks after total knee replacement. The cause was associated with non-sterile intravenous CFC infusion at home. The second complication was arterial aneurysm 2 months after ankle fusion surgery in a patient with moderate HA. It may have been caused by arteriole injury during surgery and lower intensity of CFC coverage after surgery. During the 3-year period of conservative follow-up, the aneurysm shrank in size and no further complications developed. The third complication was renal subcapsular hematoma 2 weeks after ureteral stone extraction to ameliorate hydronephrosis and hydroureter in a patient with severe HA. This could have resulted from transient indwelling of the double J stent after removal of the renal stone with lower trough level of CFC maintenance. The hematoma resolved without further intervention, but 2 months of prophylactic CFC therapy was applied as a precaution.

4. Discussion

Several reports have shown that PWH undergoing abdominal surgery, urological surgery or bone fracture management with adequate CFC administration and

Table 1
Procedure type, characteristics, clotting factor use and outcome in patients with hemophilia undergoing 161 procedures.

	n	Age at procedure (years)	Severe hemophilia n (%)	Clotting factor use		Adequancy of hemostasis[b] (n)	Complication (n)
				Duration (days)	Total amount (IU)/kg[a]		
Hemophilia A	145						
Major procedure	49						
Total joint replacement	9	53 (35-60)	9 (100 %)	26 (25- 28)	1280 (1187-1332)	E (8), G (1)	Pyogenic arthritis (1)
Spinal fusion	1	52	1 (100 %)	28	1285	E	
Ankle fusion	1	53	0 (0 %)	21	998	E	Arterial aneurysm (1)
Ligament reconstruction	3	12 (8-34)	2 (66.7 %)	21 (17-22) 790 (688- 873)	E		
Intestinal resection	2 24 (0-47)	1 (50 %)	20 (18-21)	955 (-1147-3058)	E		
Colon tumor removal	1	59	1 (100 %)	14	723	E	
Ureter stone removal	3	51 (49-59)	3 (100 %)	14	888 (557-1093)	E (2), G (1)	Renal hematoma (1)
Pyogenic arthritis debribment	3	46 (46-48)	3 (100 %)	14	741 (616-897)	E	
Chemoport insertion	2	10 (8-12)	2 (100%)	14	802 (-366-1970)	E	
Varicose ligation	1	19	1 (100 %)	14	676	E	
Hernia repair	3	45 (13-46)	1 (100 %)	10 (9-12)	440 (374-501)	E	
Soft tissue tumor resection	1	34	0 (0 %)	10	373	G	
Deep wound with closure	5	48 (4-86)	1 (20 %)	7 (5-10)	315 (173-398)	E	
Tooth extraction with incision	12	30 (10-50)	6 (50 %)	7 (7-10)	340 (327-345)	E	
Eyelid surgery	1	7	1 (100 %)	9	284	E	
Minor procedure	96						
Gastroendoscope with biopsy	6	37 (12-59)	5 (83.3 %)	3 (3-5)	263 (228-290)	E	
Double J stent removal	3	50 (51-53)	3 (100 %)	3	185 (147-222)	E	
TAE	7	58 (57-62)	7 (100 %)	4 (3-5)	269 (255-278)	E	
Radiofrequency ablation	3	60 (60-62)	3 (100 %)	4 (3-5)	276 (231-320)	E	
Chemoport removal	4	12 (10-17)	4 (100%)	4 (3-5)	254 (228-269)	E	
Cardiac catherization	2	9 (8-10)	2 (100%)	3	241 (-96-577)	E	
Intraarticular therapy	68	41 (17-54)	60 (88.2 %)	1 (1-2)	51 (55-62)	E	
Internal fixation removal	1	59	0 (0 %)	7	288	G	
Bone marrow biopsy	1	46	1 (100%)	3	208	E	
ESWL	1	51	1 (100%)	5	258	E	
Hemophilia B	16						
Major procedure	8						
Pseuotumor removal	1	21	1 (100%)	14	855	E	
Hemorrhoid ligation	1	48	0 (0 %)	10	570	G	
CAPD tube insertion	1	30	1 (100%)	14	770	E	
Tooth extraction with incision	5	31 (21-62)	3 (60%)	5 (3-7)	396 (267-480)	E	
Minor procdure	8						
Gastroendoscope with biopsy	2	40 (31-48)	0 (0 %)	3	242 (95-387) E		
Intraarticular therapy	6	52 (49-54)	6 (100 %)	1 (1-2)	80 (66-101)	E	

[a] Data are expressed as median with 95 % confidence interval.
[b] Adequacy of hemostasis according to the guideline of World Federation of Hemophilia; E = excellent; G = good; CAPD = Continuous Ambulatory Peritoneal Dialysis; ESWL = Extracorporeal shock wave lithotripsy; TAE = Transcatheter Arterial Embolization.

interdisciplinary cooperation in a comprehensive hemophilia center have the same risk of developing postoperative complications as non-hemophiliacs.[7–10] However, perioperative administration of CFC in hemophilia patients could result in either underdosing or overdosing, leading to risk of bleeding complications or unnecessary costs, respectively. To date, there is little evidence indicating how best to determine whether the recommended levels of clotting factor are adequate. In addition, the current guideline for the recommended level and duration of CFC use is simply classified into two categories, major and minor surgery. However, surgery types in PWH, as well as in the general population, are diverse. With such a broad range of surgeries currently available, it is therefore a considerable challenge to select the optimal treatment strategy for PWH. Depending on the procedure being performed, the CFC dose per infusion, the number of infusions and duration required to maintain hemostasis during the perioperative period, and the anticipated complications may vary widely. Therefore, a coordinated approach with an interdisciplinary cooperation between surgeons and hematologists can guarantee timely and individualized CFC replacement.

The study highlights a lower rate of bleeding, infection, thromboembolic events, and inhibitor development during the perioperative period. Moreover, these findings indicate the doses and duration of CFC administration for several major and minor procedures which could achieve excellent hemostatic control. However, specific treatment guidelines for different invasive or surgical procedures need to be devised based on large cohort or case series studies.

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