


Prevention of Venous Thromboembolism After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Development of a Physiotherapy Program

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Abstract

Background: This study was to assess the risk of venous thromboembolism (VTE) in patients with peritoneal carcinomatosis (PC) and to evaluate the safety and feasibility of physiotherapy program to prevent VTE during cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). **Methods:** For VTE prevention, we developed a systematic physiotherapy program consisting of active exercises of both arms and legs, and intermittent pneumatic compression device to massage both legs. This physiotherapy was applied to all patients, and the VTE-related events were recorded and analyzed. **Results:** Cytoreductive surgery + HIPEC was performed on 466 patients with PC. All patients had highest VTE risk, with the median Caprini risk factor score being 11. During the 3-month observation period, 8 patients had 9 (1.9%) clinically symptomatic VTE events, including 8 (1.7%) deep vein thrombosis and 1 (0.2%) pulmonary embolism. Among those, 5 patients received pharmacological treatments with low-molecular-weight heparin, and the other 3 received physical exercises only. All these patients recovered well, and there was no mortality about VTE perioperatively. **Conclusions:** Patients with PC treated by CRS + HIPEC are at highest risk for VTE. The systematic physiotherapy program is safe and feasible to prevent VTE post CRS + HIPEC.

Keywords

venous thromboembolism, peritoneal carcinomatosis, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, physiotherapy

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Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE), are common complications of severe diseases and associated with increased morbidity and mortality.¹ Compared with cancer-free members of the general population, the incidence of VTE among patients with cancer is much higher (1.8% vs 0.8%), and the relative risk increases with advancing stage which can be up to 27.7-fold for stage IV cancer. Moreover, it is estimated that the risk of VTE among patients having cancer treated with chemotherapy is 16.2 times compared with general population, while 4.1 times for those undergone surgery.²

Peritoneal carcinomatosis (PC), which was once regarded as the terminal stage of cancer, now is treated by cytoreductive surgery (CRS) plus hyperthermic intraperitoneal

chemotherapy (HIPEC) in selected cases, because mounting clinical evidence from phase III clinical trials has demonstrated the superior efficacy and acceptable safety of this integrated strategy for PC from gastric cancer,³ colorectal cancer,⁴ and epithelial ovarian cancer.⁵ However, it remains a procedure with significant morbidity and mortality, including VTE and PE. One study reported 6 (10%) of 60 patients

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experiencing VTE,⁶ and another reported 25 (4.4%) of 562 patients were diagnosed with acute PE.⁷ Up to now, there has been no reports solely devoted to preventing VTE in patients with PC underwent CRS + HIPEC.

As a long-standing national PC treatment center, we have established specialized CRS + HIPEC protocols for patients with PC from gastrointestinal and pelvic cancers, and a series of experimental researches⁸ and clinical studies^{3,9-11} demonstrated the treatment advantages of this strategy. During the development, we have also paid particularly attention to preventing and treating major adverse events, including VTE. Over the past 3 years, a set of combined measures have been formulated to prevent DVT and PE in all patients having PC treated with CRS + HIPEC at our center. This study is to summarize our experience in developing this physiotherapy-based program.

Material and Methods

Design

Our institution is a university-based tertiary-referral cancer center and the only one education and training center on CRS + HIPEC to treat PC, authorized by Beijing Municipal Commission of Health. We have conducted a series of basic,¹² translational,¹³ and clinical¹⁴ studies on the diagnosis and treatment of PC. The current study was a retrospectively observational study; and the patient records were prospectively constructed into a comprehensive database. All patients and their authorized caretakers were well educated about the CRS + HIPEC procedures, and standardized informed consent forms were signed from the patients or their authorized caretakers. The study protocol was approved by the institutional review board and the ethics committee of Beijing Shijitan Hospital, Capital Medical University.

Patient Selection

From May 1, 2015, to March 1, 2018, 466 patients having PC treated with CRS + HIPEC at our hospital were enrolled into this retrospective study. All patients were pathologically diagnosed with PC and scheduled to undergo CRS + HIPEC procedure after detailed evaluation including general status, laboratory examinations, computed tomography scan, and dynamic imaging. Major inclusion criteria include: (1) Karnofsky performance status >50; (2) normal peripheral blood white blood cells count $\geq 3500/\text{mm}^3$ and platelet count $\geq 80\,000/\text{mm}^3$; (3) acceptable liver function, with bilirubin $\leq 2 \times$ the upper limit of normal (ULN) and aspartic aminotransferase and alanine aminotransferase $\leq 2 \times$ ULN; (4) acceptable renal function, with serum creatinine ≤ 1.5 mg/dL; and (5) cardiovascular pulmonary and other major organ functions can stand major operation; Major exclusion criteria include: (1) any lung metastasis, liver metastasis, or prominent retroperitoneal lymph node metastasis during preoperative workup and (2) imaging examination indicating mesenteric contracture.

Perioperative VTE Risk Evaluation

A major consideration in our preoperative management of patients with PC undergoing CRS + HIPEC is to assess the VTE risk. Two evaluation tools were used for this purpose.

The first is the Caprini risk factor score.¹⁵ This is a widely used system to evaluate the VTE risk, mainly based on clinical characteristics of the patients. For patients with PC, major risk factors are older age, cancer diagnosis, central venous access, chemotherapy, major surgery lasting over 3 hours, blood transfusion, and others.

The second is Doppler ultrasonography, which was performed on all patients before CRS + HIPEC. If a patient was preoperatively diagnosed as having DVT by Doppler ultrasonography, the intermittent pneumatic compression (IPC) device would not be applied intraoperatively, but the other physiotherapy methods were still used.

During postoperative period, patients with symptoms such as chest pain, dyspnea at rest, and calf swelling or pain were suspected VTE. And only for those suspected patients, computed tomography or Doppler ultrasonography was performed again. If a clot was seen obstructing a pulmonary vessel or lower extremities, PE or DVT was diagnosed.

Cytoreductive Surgery Plus HIPEC Procedure

All CRS + HIPEC procedures were conducted as described before¹⁶ by a designated team focusing on PC treatment. Briefly, maximal CRS was performed, including the curative or palliative resection of the primary tumor with acceptable margins, any involved adjacent structures, lymphadenectomy, peritonectomies where peritoneal surfaces were involved by tumor, according to the peritonectomy procedure developed by Sugarbaker,¹⁷ and after which the HIPEC was implemented by the open Coliseum technique with each drug dissolved into 3 L of heated saline with temperature $43^\circ\text{C} \pm 0.5^\circ\text{C}$, the duration of HIPEC for each drug was 30 minutes with a flow rate of 400 mL/min. The PC index (PCI) and completeness of cytoreduction (CC) were calculated according to the Sugarbaker criteria.¹⁸

Postoperative Physiotherapy for VTE Prevention and Treatment

A VTE prevention program is developed based on the characteristics of the procedure and guidelines,^{19,20} including physiotherapy and pharmacological treatments.

For patients without clinically significant VTE symptoms preoperatively, physiotherapy program is considered as the key prophylactic measures, as summarized in Table 1.

For the prevention of DVT, the dorsiflexion–plantarflexion exercise of the feet with the maximal force can activate both the leg muscles and accelerate the returning blood circulation in the deep veins of both legs. Such exercise is repeated at least 20 times every 8 hours. In addition, we also use IPC device to prevent DVT, from day 1 to 10 after surgery for 20 minutes twice a day.

Table 1. Details of the Systematic Physiotherapy Program.

Time	Protocol	Frequency
Intraoperation	IPC	For every operation
POD 1-2	IPC Dorsiflexion– plantarflexion exercises of the feet	>20 minutes, twice a day >20 times, every 8 hours
POD 3-7	Upper body exercise ^a All measures above Standing up and slow walking	>20 times, every 8 hours >3 minutes, every 8 hours
POD 7-10	All measures above Walking	>30 minutes, twice a day

Abbreviations: IPC, intermittent pneumatic compression; POD, postoperation day.

^aIncluding chest-expanding exercise, arm adduction–abduction exercise, washing face, combing hair, and so on

For the prevention of PE, the chest-expanding exercise could significantly activate the thoracic pump to accelerate the returning blood circulation in both the superior vena cava and inferior vena cava and also accelerate pulmonary circulation. This exercise contains 2 parts. First is the arm up-down exercise, in which the patient extends straight both arms and move arms up overhead as high as possible and then slowly let down. Second is the arm adduction–abduction exercise, in which the patient extends straight both arms and makes the arms adduction and abduction movements. Such exercise is repeated at least 20 times every 8 hours.

For patients with clinically significant VTE, based on the international guidelines,²⁰ pharmacological treatments are implemented, with 4100 AXaIU low-molecular-weight heparin (LMWH) subcutaneously injected twice a day to reduce platelet aggregation for 7 to 10 days.

Screening of the Symptomatic VTE Events

Attentions are especially paid to symptoms such as chest pain, dyspnea at rest, and calf swelling or pain, highly indicating VTE. If calf swelling or pain occurs, the circumference of both legs 10 cm under the patella is measured. Other parameters are reexamined, including vital signs, ultrasound, blood oxygen saturation, chest computed tomography scan, and blood coagulation function including D-dimer. When distinguished from acute coronary syndrome, pneumonia, artery dissection, and pleural effusion, and image examination finding thrombogenesis in the pulmonary artery or lower limb venous, the patient is eventually diagnosed with symptomatic VTE.

Follow-Up

All patients received regular follow-up every month for 3 months. Several different follow-up ways were used: routine outpatient clinical visit, telephone contact, e-mail contact, and WeChat instant communication. Among them, WeChat instant communication was the most efficient and most widespread in

China, which could reach everyone with a cellphone. A WeChat follow-up software was designed and used to update our patients' information. At the clinic, the follow-up package includes physical examination, coagulation function, and Doppler ultrasonography or chest computed tomography scan if necessary. The overall follow-up rate is 100%.

End Point of the Study

The primary end point of the study was the symptomatic VTE. The secondary end point of the study was the safety and feasibility of this systematic physiotherapy program.

Statistical Analysis

Data including clinical information, laboratory results, surgical reports, medical imaging reports, and pathology reports were all collected and analyzed using Microsoft Office 2016 and Statistical Package for Social Science (SPSS, IBM Corporation, SPSS, Armonk, New York). Continuous data were expressed as median and range, analyzed by *t* test; and category data were presented as number and percentage, analyzed by χ^2 test.

Results

The Clinic-Demographic Characteristics

The CRS + HIPEC procedures have been performed on 466 patients with PC, including 25 (5.4%) patients from gastric cancer, 100 (21.5%) from colorectal cancer, 82 (17.6%) from gynecological malignancies, 121 (26.0%) from pseudomyxoma peritonei, 35 (7.5%) from malignant mesothelioma, 16 (3.4%) from primary peritoneum, 55 (11.8%) from retroperitoneal sarcoma, and 32 (6.9%) from miscellaneous malignancies (Table 2). There were 178 (38.2%) male and 288 (61.8%) female patients; 39 (8.4%) patients had prior history of VTE, of which 16 (3.4%) had chemoprophylaxis, and 33 (7.3%) patients were diagnosed as asymptomatic DVT before surgery. The median age was 55 years.

Major CRS + HIPEC Information

The duration of CRS + HIPEC was 10.0 hours (range: 1.6–19.5). The median PCI was 23 (range: 0–39); 257 (60.1%) patients achieved complete or nearly complete cytoreduction, defined as CC score of 0 or 1. The HIPEC regimens used were cisplatin 120 mg and mitomycin C 30 mg in 123 (26.5%) patients; docetaxel 120 mg and mitomycin C 30 mg in 27 (5.8%) patients; or cisplatin 120 mg and docetaxel 120 mg in 259 (55.8%) patients. Of the 466 patients in this study, 429 (92.1%) required intraoperative blood infusion, including 48 (10.3%) patients receiving autologous transfusion.

Evaluation of VTE by Caprini Risk Factor Score

All patients received VTE assessment according to the Caprini's criteria, which defined total score ≥ 5 as the highest risk.¹⁵

Table 2. Demographic Characteristics.^a

Items	Value
Gender (male/female), %	
Male	178 (38.2)
Female	288 (61.8)
Age (years)	55 (10-81)
Karnofsky performance score	90 (50-100)
Prior history of VTE, %	39 (8.4)
Prior history of VTE chemoprophylaxis, %	16 (3.4)
VTE of ultrasound preoperatively, %	33 (7.2)
Caprini risk factor score	11 (9-17)
Primary tumor, %	
Carcinoma of the stomach	25 (5.4)
Carcinoma of the colorectum	100 (21.5)
Pseudomyxoma peritonei	121 (26.0)
Malignant peritoneal mesothelioma	35 (7.5)
Carcinoma of ovary	73 (15.7)
Carcinoma of other gynecology	9 (1.9)
Primary peritoneum	16 (3.4)
Retroperitoneal sarcoma	55 (11.8)
Others ^b	32 (6.9)
Vascular invasion, %	108 (23.9)

Abbreviation: VTE, venous thromboembolism.

^aData are presented as n (%) or median (range).

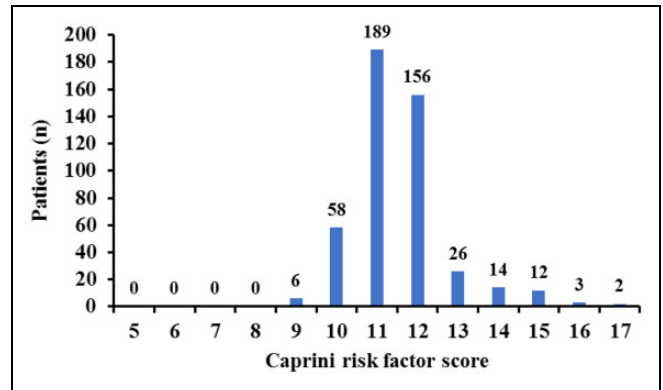
^bIncluding 2 hepatocellular carcinoma, 1 pancreatic carcinoma, 4 carcinoma from small intestine, 4 gastrointestinal stromal tumor, 1 carcinoma from biliary duct, 2 carcinoma of gallbladder, 2 breast carcinoma, 1 carcinoma from lung, 1 carcinoma from bladder, 1 hemangiopericytoma, 1 inflammatory myofibroblastic tumor, 1 carcinosarcoma, 2 neurofibroma, 1 schwannoma, 3 neuroectodermal, 1 aggressive angiomyxoma, 1 carcinoma from urachus, 1 angiomyolipoma, 1 Ewing sarcoma.

Table 3. Major Risk Factors in this Study.

Factors	Score	n (%)
Age, years		
<40	0	59 (12.7)
40-59	1	241 (51.7)
60-74	2	152 (32.6)
≥75	3	14 (3.0)
Cancer	3	466 (100.0)
Central venous access	1	466 (100.0)
Present cancer or chemotherapy	3	466 (100.0)
Major surgery lasting over 3 hours	5	462 (99.1)
Blood transfusion	1	429 (92.1)
History of venous thromboembolism	3	39 (8.4)
History of major surgery	1	14 (3.0)

According to this evaluation criteria, the most common risk factors in these patients were major surgery lasting over 3 hours (99.1%), present cancer or chemotherapy (100.0%), central venous access (100.0%), and blood transfusion (92.1%). Other less common risk factors such as history of major surgery and history of VTE are listed in Table 3.

The distribution of total Caprini risk factor score was from 9 to 17 (Figure 1). There were 409 (87.8%) patients in the risk score 9 to 12 group, and 57 (12.2%) patients in the risk score 13 to 17 group.

**Figure 1.** The Caprini risk factor score of the patients in this study.**Table 4.** Comparison of Patients Having VTE With Non-VTE Patients on Major Risk Factors.

Factors	VTE (n = 22)	No-VTE (n = 444)	P value
Age, years			.929
<40	2	57	
40-59	12	229	
60-74	7	145	
≥75	1	13	
Cancer	22	444	–
Central venous access	22	444	–
Present cancer or chemotherapy	22	444	–
Major surgery lasting over 3 hours	22	440	.655
Blood transfusion	22	407	.158
History of venous thromboembolism	5	34	.013
History of major surgery	3	11	.019

Abbreviation: VTE, venous thromboembolism.

Note: The aim of boldface is to show number highlight, because the P value have statistical significance.

Venous Thromboembolism-Related Clinical Outcomes and Risk Factor Analysis

There were 9 (1.9%) clinically symptomatic VTE events occurred in 8 patients during the 3-month perioperative period. The 9 clinically symptomatic VTE events included 8 (1.7%) DVT and 1 (0.2%) PE. Among the 8 patients with clinically symptomatic VTE, 5 patients received pharmacological treatments with LWMH. For the other 3 patients with Doppler ultrasonography confirmed small DVT, we just encourage the patients to perform standardized physical exercises only, and these patients also recovered well. For the only 1 patient with PE, she was in sound condition during the extended follow-up for 6 months. There was no mortality about VTE perioperatively.

We also conducted comparison study on major risk factors between the patients with VTE and without VTE (Table 4). The occurrence of VTE had a correlation with history of VTE ($P = .013$) and history of major surgery ($P = .019$), but no correlation with age, major surgery lasting over 3 hours, and blood transfusion.

Table 5. The Literature-Reported VTE Data on Patients Having PC Treated With CRS + HIPEC.

Reference	Year	Patient, n	Age, years	Operation Duration, hour	Blood Loss, mL	PCI	CC 0-1, n (%)	VTE, n (%)	DVT, n (%)	PE, n (%)
Witkamp et al ²⁶	2001	46	56 (34-76)	10 (5.5-18)	13,000 (1600-55 000)	NA	NA	NA	NA	3 (6.5)
Verwaal et al ⁴	2003	48	53 (28-69)	8.1 (5.3-12.8)	3900 (500-30 000)	NA	39 (81.3)	NA	NA	2 (4.2) ^a
Ahmad et al ²⁷	2004	33	49 (26-72)	8.3 (4.1-14.8)	650 (100-3300)	NA	NA	NA	1 (3.0)	NA
Glehen et al ²⁸	2004	506	51 (16-81)	NA	NA	NA	377 (74.5)	NA	NA	2 (0.4) ^b
Kusamura et al ²⁹	2006	205	52 (22-76)	8.9 (4.0-22.0)	NA	NA	182 (88.8)	NA	NA	1 (0.5)
Moran et al ³⁰	2006	100	52 (32-74)	NA (3-18)	NA	NA	65 (65.0)	NA	5 (5.0)	4 (4.0)
Smeenk et al ³¹	2006	103	57 (30-77)	9.0 (4.5-18.0)	8000 (300-55 000)	NA	87 (84.5)	10 (9.7) ^b	NA	NA
Hagendoorn et al ³²	2009	49	55 (40-76)	7.7 (5.0-11.5)	1420 (150-5500)	NA	NA	NA	1 (2.0) ^c	NA
Kerscher et al ³³	2010	109	54.1 ^d	6.63 (4-12)	NA	21.2 ^d	53 (48.6)	NA	NA	2 (1.8) ^b
Canda et al ³⁴	2013	115	53.4 (20-82)	6.0 (2.0-12.0)	NA	14.7 (3-28)	NA	NA	1 (0.9)	1 (0.9)
Votanopoulos et al ³⁵	2013	925	NA (11-82)	NA	NA	NA	NA	26 (2.8) ^e	17 (1.8)	9 (1.0)
Wagner et al ³⁶	2013	282	NA	NA (6.5-12.5)	NA (400-2500)	NA (8-18)	230 (81.6)	4 (1.4) ^b	NA	NA
Jimenez et al ³⁷	2014	202	53 (25-80)	NA	NA	NA	170 (84.2)	NA	NA	5 (2.5) ^b
Konigsrainer et al ³⁸	2014	90	55 (18-76)	7.6 (0.6-17.9)	NA	20 (3-39)	62 (68.9)	NA	NA	7 (7.7)
Shen et al ³⁹	2014	27	52.2 ^d	NA	NA	NA	NA	2 (7.4) ^a	NA	NA
Spiliotis et al ⁴⁰	2014	100	NA	NA	NA	NA (3-39)	86 (86.0)	NA	NA	6 (6.0)
Beckert et al ⁴¹	2015	381	55 (14-77)	7.6 (0.6-17.9)	NA	20 (1-39)	263 (69.0)	27 (7.1)	10 (2.6)	17 (4.5)
Coccolini et al ⁴²	2015	54	54.5 ^d	8.85 ^d	NA	10.1 (1-28)	54 (100.0)	NA	1 (1.9) ^{b,e}	1 (1.9) ^{b,e}
Huang et al ²⁵	2015	800	53 ^d	NA	NA	NA (2-31)	765 (95.6)	43 (5.4)	NA	NA
Lord et al ⁴³	2015	512	56 (24-82)	NA	NA	NA	512 (100.0)	NA	57 (11.1)	9 (1.8)
Randle et al ⁴⁴	2015	935	NA (11-87)	NA (4-25.6)	NA (50-6500)	NA (0-39)	NA	28 (3.0)	NA	NA
Spark et al ²⁴	2015	30	53.3 ^d (25-71)	10.1 ^d	NA	NA	21 (70.0)	NA	3 (10.0) ^b	2 (6.7)
Baumgartner et al ⁴⁵	2016	247	53 (20-86)	6.7 (3.3-13.3)	250 (10-4000)	14 (0-29)	235 (95.2)	NA	NA	8 (3.2) ^f
Dagbert et al ⁴⁶	2016	39	58.2 ^d	5.1 ^d	NA	15.1 ^d	38 (97.4)	NA	NA	5 (12.8) ^g
Martin et al ⁴⁷	2016	203	NA	5.1 (5.1-8.3) ^h	300 (200-600) ^h	NA (6-18)	173 (85.2)	14 (6.9)	NA	NA
Sargant et al ⁴⁸	2016	201	55	NA	NA	NA	NA	NA	10 (5.0) ⁱ	4 (2.0)
This study	2018	466	55 (10-81)	10.0 (1.6-19.5)	600 (0-6100)	23 (0-39)	257 (60.1)	23 (4.9)	22 (4.7)	1 (0.2)

Abbreviations: CC, completeness of cytoreduction; CRS, cytoreductive surgery; DVT, deep vein thrombosis; HIPEC, hyperthermic intraperitoneal chemotherapy; NA, not available; PC, peritoneal carcinomatosis; PCI, peritoneal carcinomatosis index; PE, pulmonary embolism; VTE, venous thromboembolism.

^aWithin 3 months after surgery.

^bGrades 3-5 according to the National Cancer Institute's Common Toxicity Criteria.

^cGrades 2-5.

^dAverage.

^eWithin 1 month after surgery.

^fWithin 2 months after surgery.

^gOnly for those underwent splenectomy.

^hInterquartile range.

ⁱIncluding 2 atrial thromboses.

Discussion

Venous thromboembolism is a common complication of severe diseases associated with increased morbidity and mortality and the second leading cause of cancer death.²¹ The incidence of VTE was 1.6% among patients with common cancer²² and with an estimated annual percentage increase of 4.0% (95% confident interval, 2.9-5.1).²³ Due to advanced stage, extensive surgery, chemotherapy, blood transfusion, and central venous access, patients with PC who underwent CRS + HIPEC are more prone to developing VTE. In studies focusing on CRS + HIPEC to treat peritoneal metastases, the incidence of symptomatic DVT ranged from 0.9% to 11.1%, and of PE from 0.5% to 12.8% (Table 5). Moreover, the mortality owing to PE could be as high as 3.3%.²⁴ Huang et al²⁵ even found that the incidence of DVT and PE was from 0.9% to 9.3%. Therefore, it is very important to enhance vigilance on VTE complications in patients with PC and adopt active perioperative prophylaxis.

According to the Chinese guidelines, IPC or graded compression stocking is recommend for all hospitalized patients with cancer, alone with unfractionated heparin or LWMH or factor Xa inhibitor for those with Carprini risk factor score ≥ 3 .¹⁹ However, in the international guideline, mechanical methods are not recommended as monotherapy (Grade IIC), while pharmacological prophylaxis of LMWH once a day post-operatively and continued at least 7 to 10 days is recommended (Grade 1A).²⁰ However, the practical importance of physical exercise has not been paid enough attention among clinicians.

In this study of 466 patients, the incidence of VTE (1.9%) is much lower than that of 10.0% compared with another similar retrospective study by Lanuke et al.⁶ The difference was that, in their study, all patients received prophylactic pneumatic sequential compression stockings and subcutaneous unfractionated heparin, but patients in our center all had IPC device combined with physiotherapy, and heparin was only used for those with VTE. This interesting result strongly suggest the key

role of physiotherapy in VTE prevention. Just as van Stralen et al.⁴⁹ concluded that regular sports activities could reduce the risk of VTE.

There is sound pathophysiological evidence to support physiotherapy in VTE prevention. According to the classical theory,⁵⁰ sluggish venous blood flow, hypercoagulability, and blood vessel wall injury are the 3 major contributors to thrombosis. The rationale of this physiotherapy program is to intervene 2 of the 3 factors. First, activating calf muscle pump and thoracic pump to increase blood velocity to prevent venous stasis. Stein et al⁵¹ demonstrated that ankle exercise increased venous blood velocity no matter in supine or sitting positions. Caldwell et al⁵² found upper body exercise could also increase lower extremity venous blood flow in healthy volunteers and in patients with acute DVT. Second, alterations in plasma coagulation factors to decrease blood clotting. Jahangard et al⁵³ found short-term aerobic training could reduce fibrinogen, von Willebrand factor antigen, plasminogen activator inhibitor-1 activity and antigen, and increase prothrombin time, partial thromboplastin time, tissue plasminogen activator activity, and antigen in sedentary postmenopausal women. Moreover, Chen et al⁵⁴ found that low-load resistance exercise plays an advantageous role in preventing thrombogenesis by reducing inflammatory process.

In addition to the effectiveness, this systematic physiotherapy program has several obvious advantages compared with other prophylactic measures. First, all hospitalized patients can easily master the key points, so it provides better compliance and higher practicability. Second, it can bring positive psychological benefits. These series of upper and lower extremity exercises under the instruction and encouragement of the treating physician or nurse have produced positive psychological feedback to the patients. They could feel a sense of control over their disease, still being an active part in the recovery process and being in close and active contact with the physicians and the nurses. Third, in some countries, some heparin drugs specific for VTE therapy are not easily accessible and can be costly, but this strategy is almost free, which means better social economic benefits.

In summary, this retrospectively observational study demonstrated the safety and feasibility, and potential beneficial effects of physiotherapy program integrating upper and lower extremity exercises on the prevention of VTE among patients having PC treated with CRS + HIPEC. The study also demonstrated the key role of early exercises after surgery in thromboprophylaxis. Randomized trials are warranted to validate this physiotherapy program.

Conclusions

Patients treated with CRS + HIPEC are at highest risk of developing VTE. The systematic physiotherapy program including dorsiflexion–plantarflexion exercise of the feet, and chest-expanding exercises is safe and feasible to prevent VTE in such patients. Randomized controlled trials are warranted to evaluate the efficacy of the systematic physiotherapy program.

Authors' Note

Xin-Bao Li and Kai-Wen Peng contributed equally to this work.

Declaration of Conflicting Interests

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Ethical approval

Ethical approval to report this case series was obtained from Beijing Shijitan Hospital, Capital Medical University.

Informed Consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

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