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Original Article

Postoperative Low Molecular Weight Heparin-induced Infection in Gastrointestinal Cancer Patients. A 2-year Single Centre Experience

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Abstract

Introduction: Patients with gastrointestinal cancer are at high risk of developing thrombosis and postoperative infection. Anticoagulation therapy for such patients is provided by low molecular weight heparin (LMWH) and elastic stockings. The latter, however, is linked to immunoregulatory activities and immunosuppression in vivo and in vitro.

Aim: Therefore, the present study aimed to examine the link between LMWH and infection in patients with gastrointestinal cancer.

Materials and methods: The study is a retrospective report of 51 patients operated on at the Second Department of Surgery at Metaxa Cancer Hospital. The sample was divided into groups based on the presence or absence of diabetes and preoperative anticoagulation therapy. Afterwards, the data were statistically analysed.

Results: The results of the study show a statistically significant correlation between LMWH and infection. Moreover, the risk of infection increases by 13.3% for each day of heparin intake. The theory of this correlation is explained in detail.

Conclusions: The findings of the present study raise an essential question about postoperative management of cancer patients. However, the study sample size is rather small so further studies with larger sample size are required to give greater credence to results.

Keywords

cancer, HIT, infection, LMWH, PF4

INTRODUCTION

Cancer is a genetic disease driven by mutations and activation or deactivation of genes.[1,2] It is the second leading cause of death worldwide.[3,4] Colorectal and stomach cancers are estimated to be the second and the third most common causes of death of cancer patients followed only by lung cancer, with estimated 862000 and 783000 deaths, respectively, in 2018 according to statistics provided by the World Health Organization.

The immune system of a cancer patient is usually unable to fight the disease mainly because of the activation of immune checkpoints.[5] Moreover, cancer patients are prone to infections due to many other factors including age, lymphocyte defects, malnutrition, obstruction due to primary or metastatic disease, different interventions (including surgery), disruption of anatomical barriers and iatrogenic immunosuppression.[6,7]

Furthermore, cancer patients have an increased general risk of venous thrombosis.[8-10] After abdominal surgery because of cancer, patients are at more than six-fold risk of thrombosis, much higher compared to the four-fold risk for abdominal surgery due to other reasons.[11] According to the recent guidelines by the National Institute of Health and Care Excellence (NICE)[12], patients after abdominal surgery for cancer should use intermittent pneumatic compression or pharmacological thromboprophylaxis and elastic stockings, based on the patients' individual factors. Patients receiving anticoagulants at home should receive 'bridging anticoagulation' therapy before surgery.[13] The list of recommended pharmacological thromboprophylactic agents includes the low molecular weight heparins (LMWH). The mechanism of action these heparins use is to bind to antithrombin (AT), thus inhibiting the typical cascade of coagulation.[14] Recent studies have shown that LMWH has immunoregulatory functions and leads to immunosuppression.[15-17]

Regarding this term, an important question arises, namely, whether the LMWH during the postoperative hospitalization of gastrointestinal cancer patients is linked to infection, which the presents study aims to answer.

MATERIALS AND METHODS

Data collection

An initial application with the protocol of the study was submitted to the Metaxa Cancer Hospital Ethics Committee.

After the approval of the Ethics Committee, a filtration of the surgical book was done, where the ID numbers of the patients operated for gastrointestinal tract pathology were selected. After that, filtration of the histopathological archive was made based on the same ID numbers. From the archive, we selected only patients with gastrointestinal tract cancer operated on in the Second Department of Surgery at Metaxa Cancer Hospital between January 1, 2017 and December 31, 2018. Using the patient ID number, the folders of patients were retrieved from the comprehensive hospital archive. Of the 810 surgeries performed in this period, we found only 82 patients that were eligible according to the histopathological diagnosis.

In order to proceed with the data collection, two things were necessary: firstly, the file of the patient and secondly, the nursing file, usually saved at the back of the big patient file. Inclusion criteria from the files were: 1) demographics (sex and age); 2) nursing file (days of LMWH intake, days of antibiotic intake; 2) Patient's file (other pathologies, anticoagulant intake prior surgery, days of hospitalization and cultivation's outcome), and 4) blood screening tests.

If one of the two files was missing making it impossible to retrieve the information as mentioned above, the patient was considered ineligible.

Out of these 82 eligible patients, only 51 patients (23 females and 28 males) were included either because of missing or incomplete nursing file or because of a missing patient's file.

Then these 51 patients were divided into four categories based on whether or not they had diabetes and on the reception of anticoagulants at home:

1. Patients with diabetes receiving no anticoagulant therapy at home.
2. Patients without diabetes but receiving anticoagulant therapy at home.
3. Patients without diabetes receiving no anticoagulant medication.
4. Patients with diabetes receiving anticoagulant therapy.

Blood tests were conducted two days before surgery as preoperative screening and on the first day after surgery. All patients received LMWH injection 6 hours after surgery. Group 2 and 4 received bridging anticoagulation therapy when recommended. Adjuvant therapy before surgery was not administered to the patients. The patients' characteristics are shown in **Table 1**.

Outcome measures

The primary target outcome was to find whether there was a correlation between LMWH and infection. Secondary outcomes were the correlations between age, sex, days of hospitalization, days of LMWH, white blood cell count preoperatively, and at postoperative day 1, platelets count preoperatively, and at postoperative day 1 and duration of antibiotic intake.

Statistical analysis

The data we collected were saved as Excel tables and statistically analysed using JASP v. 0.8.5.1 and Stata/IC v 15.1 by two independent individuals. Logistic regression and correlation analysis were performed for the four categories separately and the whole sample. The p value was considered statistically significant at $p<0.05$.

RESULTS

Heparin and infection

According to the logistic regression analysis, there was a statistically significant difference between positive cultivation for the diagnosis of infection and heparin for the entire

Table 1. Patients' characteristics

	Total (N=51)	Group 1	Group 2	Group 3	Group 4
Age (yrs)	67.63	66.8	73.5	65.8	71.5
Sex	23 F : 28 M	4 F : 2 M	1 F : 3 M	17 F : 14 M	1 F : 9 M
Days of hospitalization	19.63	20.7	31	17.5	21.1
Days of heparin	16.02	17.2	31.5	12.9	18.8
Infection / Cultivation +/-	19 + / 32-	3+ / 3-	2+ / 2-	10 + / 21-	4+/ 6-
Duration of antibiotic intake, days	12.16	14	27.3	10.1	11.5
Preoperative WBC count x 10^9/L	7.69	7.87	6.8	7.81	7.6
Postoperative WBC count ax 10^9/L	10.34	10.44	10.91	10.56	9.82
Preoperative PLT count x 10^9/L	293.6	338.3	242.5	296.5	278.1
Postoperative PLT count x 10^9/L	264.7	317.2	226.5	257.5	270.6

WBC: white blood cell; PLT: platelets; F: female; M: male

sample of the study (p=0.031) **(Tables 2a, 2b)**. Moreover, for every other day of heparin intake, the risk of infection increased by 13.3%. There was no statistically significant difference between the four separate categories or their combinations. However, there was a slightly sensitive result in group 3 **(Table 3)**.

Correlation analysis

The correlation analysis showed positive correlations between days of heparin intake and age, days of hospitalization and antibiotic intake, while the antibiotic intake was positively correlated with the days of hospitalization **(Table 4)**.

On the other hand, there was a negative correlation between the WBC count at the first postoperative day and age, days of hospitalization, days of heparin, and antibiotic intake **(Table 5)**. PLT count had no correlations with the other groups.

T-test

The T-paired test was performed for the preoperative and immediately postoperative WBC and PLT count. The results showed that there was a significant difference between the preoperative and postoperative data **(Table 6)**.

Table 2a. Logistic regression analysis: days of heparin and infection according to Stata/IC version 15.1

Infection - days of heparin	p value	OR	95% CIs
Total sample	0.031	1.133	1.012-1.269
Group 1	0.271		
Group 2	0.298		
Group 3	0.075	1.156	0.985-1.357
Group 4	0.628		

Table 2b. Logistic regression analysis: according to JASP for infection and days of heparin intake

Model summary									
Model	**Deviance**	**AIC**	**BIC**	**df**	**χ^2**	**p**	**McFadden R^2**	**Nagelkerke R^2**	**Tjur R^2**
H_0	68.31	70.310	72.242	50					
H_1	58.24	62.238	66.101	49	10.072	0.002	0.147	0.243	0.133

Coefficients				
	Estimate	**Standard Error**	**z**	**p**
(Intercept)	2.287	0.862	2.655	0.008
Days heparin	-0.125	0.058	-2.159	0.031

Note. Infection level '2' coded as class 1.

Table 3. JASP logistic regression analysis for group 3

Coefficients				
	Estimate	**Standard Error**	**z**	**p**
(Intercept)	2.525	1.171	2.156	0.031
Days heparin group 3	-0.145	0.082	-1.778	0.075

Note. Infection group 3 level '2' coded as class 1.

Table 4. Positive correlation analysis for the entire group

		Age	**Days of hospitalization**	**Days of heparin**
Days of hospitalization	Pearson's r	0.137		
	p value	0.168		
Days of heparin	Pearson's r	0.245	0.927	
	p value	0.042	<0.001	
Days of antibiotics	Pearson's r	0.103	0.842	0.882
	p value	0.236	<0.001	<0.001

Table 5. Negative correlation matrix for the entire group

		WBC	**WBC1**
WBC at the 1st postoperative day	Pearson's *r*	0.575	—
	p value	1.000	—
Age	Pearson's *r*	0.121	-0.253 *
	p value	0.802	0.037
Days of antibiotic intake	Pearson's *r*	0.042	-0.246 *
	Days of hospitalization	0.614	0.041
Days of LMWH intake	Pearson's *r*	-0.031	-0.306 *
	p value	0.415	0.015
Days of hospitalization	Pearson's *r*	-0.051	-0.338 **
	p value	0.361	0.008

Table 6. T-paired test

Paired samples t-test					
-			**t**	**df**	**p**
Pre-op PLT	-	Post-op PLT	4.785	50	<0.001
Pre-op WBC	-	Post-op WBC	-5.429	50	<0.001

Descriptives				
	N	**Mean**	**SD**	**SE**
Pre-operative PLT	51	293.608	87.178	12.207
Post-operative PLT	51	264.686	82.704	11.581
Pre-operative WBC	51	7.694	2.862	0.401
Post-operative WBC	51	10.432	4.464	0.625

WBC: white blood cell; PLT: platelets

DISCUSSION

Infection is defined as 'the invasion and multiplication of microorganisms such as bacteria, viruses, and parasites that are not normally present within the body'. Health care-associated (HCA) infection is one of the most common adverse events during the period of patient's care.[18]

Overall, the health care-associated infections in developed countries range from 3.5% to 12%, while the same rate for the low and middle-income countries ranges from 5.7% to 19.1%. The factors contributing to health care-associated infections are listed below:[18-20]

1. High-risk procedures
2. Immunosuppression
3. Prolonged and inappropriate use of devices and antibiotics
4. Inappropriate prevention methods

Recently, about half of the registered infections in cancer patients have been caused by Gram-positive bacteria, including enterococci, streptococci and staphylococcus aureus.[21] In the past, the majority of the infections were caused by Gram-negative bacteria.[6]

Surgical site infection (SSI) is one of the most common types of HCA infections in low and middle-income countries. It affects on average between 11.8/100 and up to 1/3 of the operated patients.[22] The European Centre for Disease Prevention and Control has shown that SSIs are more frequent after colon surgery (9.5% per 100).[23] In this regard, Serra-Aracii et al.[24] reported rates of 23.1% and 27.6% of SSIs after elective surgery for colon and rectal cancer, respectively, while Ozmen et al.[25] reported a SSI rate of 19% after elective surgery for gastric cancer.

Bloodstream infections (BSI) are another category of common infections among oncological patients. Reports suggest that the incidence of BSIs in cancer patients could reach 17%.[26] It prolongs not only the hospital stay but also increases the mortality rates, costs and further delays cancer therapy. Bos et al.[27] compared the mortality rate of patients with and without cancer, to conclude that the BSI 90-day mortality rate was significantly higher among cancer patients. According to Islas-Muñoz B et al.[28], BSIs mortality reached a rate up to 70% when inappropriate therapy was given.

Cancer patients have an increased risk of thrombosis.[29] This is caused by one or more of the Virchow triad's factors (venous stasis, intravascular coagulation from malignant cells, and endothelial injury). More often than not, cancer patients have all three factors. Despite the fact that oncological patients have an enhanced risk of thrombosis, it is not equally dangerous for all types of tumors and patients. Therefore, there are predicting score systems to evaluate the risk of thrombosis.[30] Recent studies suggest that pharmacological anticoagulation therapy and its extended use is superior for cancer patients, undergoing abdominal or pelvic surgeries.[11,31,32]

The recent guidelines for anticoagulation therapy suggest that cancer patients should be protected from thrombosis with LMWH and/or elastic stockings.[10,12] LMWH's mechanism of action is to inhibit the final step of the anticoagulation cascade, thus activating the AT III, which inhibits the factor Xa.[33] Moreover, it is believed that heparin protects the entirety of vessel walls from endothelial injury, inhibits the cell production and relocation, as well as cancer growth. Furthermore, heparin has immunoregulatory functions as well as it binds to cytokines and growth factors such as tumor necrosis factor (TNF) and extracellular matrix proteins (ECM), thus regulating the leukocytes.[15-17]

It is believed that LMWH reduces the risk of cancer-associated thrombosis (CAT).[34] However, it is associated with quite severe adverse events, as it is the heparin-induced thrombocytopenia (HIT). As reported by Ahmed et al.,[35] HIT is present in two different types – I and II. The first is non-immune, usually present in the first days of LMWH use, without clinical symptoms, while the PLT count is rarely under 100000/mm^3. Type II appears as a response to a few immune mechanisms with the contribution of T and B-cells, where antibodies against the LMWH's molecules are developed as anti-platelet factor 4/heparin (PF4, CXC 4) antibodies.[36]

PF4 is saved within platelet α-granules and discharged when platelets are being activated.[37] PF4 plays a part in inflammatory responses by attraction and promotion of monocytes and neutrophils and modulation of B and T cells, in the control of hematopoiesis and reduction of angiogenesis and tumor growth.[38]

The formation of PF4/heparin antibodies is unusual among healthy individuals, but it is observed in inflammation, cardiopulmonary and orthopedic surgery, suggesting that platelet and endothelial activation play a significant role.[39,40] There is a belief that prior antigen exposure, lead to early appearance (4-5 days) of 'isotype-switched antibodies'.[41,42] Moreover, it is cleared that PF4 binds to bacterial lipopolysaccharides and platelets.[41,43] Krauel et al.[41] reported that either type of bacteria (gram-positive and negative) compete with the LMWH's molecules to bind to the PF4, thus explaining that each type of bacteria could be a source of PT4/heparin antibodies.[44-46] On the other hand, Maharaj et al.[47] showed that hospitalized patients with sepsis and bacteremia had increased levels of antibodies compared to those with fungemia.

Studies with healthy individuals and patients with inflammation showed that the latter category had seven times more elevated rate of appearance of PF4/heparin antibodies than control/healthy subjects. The latter is supported by Kelton et al.[48] where control sample was exposed to heparin without surgery and displayed PF4/heparin antibodies and Grigorian et al.[49], who reports that patients with HIT developed infection more often compared to those who have no HIT.

Finally, another study of immunosuppressed patients showed that there was no profound HIT event, even though a few patients developed PF4/heparin antibodies.[50] The latter is also supported by Katz et al.[51], who linked the PF4 to immunosuppression in vitro and in vivo in mice.[51,52] These

findings are also reviewed previously by Quere et al. and Livingston et al.[51,53,54], where the histamine and H2 receptor agonist activate T-suppressive cells, modification of lymphokines, and inhibition of antibody production in vitro and in vivo.[51,55-59]

The current study shows that LMWH is linked to infection with the rate of infection increases by 13% every other day. There is a statistically significant difference between preoperative and postoperative numbers of WBC count and PLT count. The limitation of the study is that the number of patients per category was not equal and for a few groups- insufficient, so it could not be found whether the subgroups are linked to LMWH-induced infection; therefore, this problem needs further studies. The results of the study, though, are explained as a theory that cancer patients, who are themselves immunosuppressed, might also develop subclinical or clinical HIT type I, which is linked, on the other hand, to infections. However, as we had only a small number of patients, further studies are needed to give greater credence to results.

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Послеоперационная низкомолекулярная гепарин-индуцированная инфекция у больных раком желудочно-кишечного тракта. Двухлетнее моноцентрическое исследование

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Резюме

Введение: Пациенты с раком желудочно-кишечного тракта имеют высокий риск развития тромбоза и послеоперационной инфекции. Антикоагулянтная терапия для таких пациентов обеспечивается низкомолекулярным гепарином (НМГ) и эластичными чулками. Однако последние связаны с иммунорегуляторной активностью и иммуносупрессией in vivo и in vitro. Таким образом, настоящее исследование направлено на изучение взаимосвязи между НМГ и инфекцией у пациентов с раком желудочно-кишечного тракта.

Материалы и методы: Исследование представляет собой ретроспективный доклад о 51 пациентах, прооперированных во Втором хирургическом отделении онкологической больницы „Метакса". Пациенты были разделены на группы в зависимости от наличия или отсутствия диабета и предоперационной антикоагулянтной терапии. После этого данные были проанализированы статистически.

Результаты: Результаты исследования показывают статистически значимую корреляцию между НМГ и инфекцией. Кроме того, риск заражения увеличивался на 13.3% на каждый день введения гепарина. Подробно объясняется теория этой корреляции.

Заключение: Результаты настоящего исследования поднимают важный вопрос о предоперационном подходе к онкологическим больным. Однако размер выборки исследования довольно невелик, поэтому необходимы дополнительные исследования с большим размером выборки, чтобы обеспечить большую надёжность результатов.

Ключевые слова

рак, ХИТ, инфекция, НМГ, PF4