ORIGINAL RESEARCH

DOI: 10.37047/jos.2019-73122

The Comparison of Central Venous Port Catheters in Gastrointestinal Cancer Treatment

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ABSTRACT Objective: Patients with solid cancers frequently suffer from thrombosis, which is associated with considerable cost, morbidity, and mortality. The infusional chemotherapy regimen, especially in gastrointestinal cancers, has a long-term need for central venous catheterization. Implantable ports (IP) are increasingly used for the administration of chemotherapy and supportive treatment to cancer patients. **Material and Methods:** In this study, we evaluated the factors affecting the port thrombosis in gastrointestinal cancers. The patients with gastric, colorectal and pancreatic cancer were included in the study. **Results:** There were 113 patients with IP locations on subclavian and 7 on femoral veins. IP thromboses were detected in 10 patients. One of the patients had two thrombosis sites on both femoral and subclavian veins. The median time duration from the placement of the port to thrombosis was 4 months. There were 9 patients who underwent treatment with low molecular weight heparin, while one patient received warfarin treatment. There were ten non-port events related to thrombosis events. There was a significant difference between port thrombosis due to location ($p<0.0001$). This study showed increased thrombotic events in femoral IPs. Pulmonary embolization due to port thrombosis was not observed. Time to thrombose was significantly shorter in femoral IPs ($p=0.04$). **Conclusion:** Although femoral IPs have been reported to be safe for the use of breast cancers, great attention must be paid for the utilization of femoral IPs in gastrointestinal cancers. Prospective and larger trials are needed to confirm the results of the present study.

Keywords: Implantable ports; gastrointestinal cancer; colon cancer; port thrombosis; gastric cancers

The infusional chemotherapy regimen, especially in gastrointestinal cancers, has a long-term need for central venous catheterization. Implantable ports (IP) are increasingly used for the administration of chemotherapy and supportive treatment to cancer patients. The IPs may be complicated with thrombosis in both upper and lower extremities, during placement or long-term follow-up which is associated with treatment delay, increasing financial burden, morbidity and mortality.[1-6] IP thrombosis is mostly seen in the first three months and rarely seen beyond this period.

The most preferred location for IPs is the subclavian vein, which is implanted by the Seldinger technique via a cephalic vein.[7] In appropriate patients, femoral IPs can also be used.[8] The main cause of thrombosis is considered to be direct vascular damage.[4,9,10] There are mainly three mechanisms of IP thrombosis. The first mechanism is an acute reaction of clotting, which is induced with a fibrin sheath and is related to the subsequent risk of thrombosis. The second mechanism is the lumen thrombosis of the catheter, which may be thawed with thrombolytic agents. Blood vessel thrombosis is the most severe

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Peer review under responsibility of Journal of Oncological Sciences.

Received: 13 Jul 2019 ***Received in revised form:*** 24 Oct 2019 ***Accepted:*** 16 Dec 2019 ***Available online:*** 10 Feb 2020

complication and is the third mechanism of IP thrombosis.[11-13] The cancer patients tend to have vascular thrombosis due to procoagulant activities of cancer cells and increased platelet aggregation. Moreover, induced inflammation, impaired fibrinolysis and decreased levels of coagulation inhibitors increase the thrombosis risk.[14] Although, there is an increased risk of thrombosis in a cancer patient with port implementation, all current guidelines advise against anticoagulant prophylaxis.[1-3,5,15]

This may be attributed to a high annual incidence of thrombotic events (0.5-20%), achieving minor benefit from the treatment and increasing cost of the treatment.[16-18]

However, the studies investigating the port thrombosis are very heterogeneous. Moreover, the studies have not described the types of chemotherapy used, including biological agents such as bevacizumab. In this study, we evaluated the factors that affect the port thrombosis in gastrointestinal cancers.

MATERIAL AND METHODS

PATIENTS

In this cross-sectional study, patients with gastrointestinal cancer diagnosis between 2013 and 2019 were retrospectively analyzed. The patients with other types of organ cancer and without IPs were excluded. Also, the patients who had less than 3 months of follow-up and did not receive chemotherapy after port implementation, were not included. The demographic characteristics, smoking status, comorbid conditions, port thrombosis side and localization, chemotherapy types, and biologic agents were recorded.

STATISTICS

The statistical analysis was performed with SPSS software (Statistical Package for the Social Sciences, version 22.0, SPSS Inc, Chicago, IL). Descriptive data were presented as either the mean or median for continuous variables. Frequencies and percentages were reported for categorical variables. Pearson's chi-squared (X^2) test was used to assess the association in categorical variables.

ETHICS

The study was approved by the ethics committee at Afyonkarahisar Health Sciences University Faculty of Medicine and carried out according to the principles of the Declaration of Helsinki and all applicable regulations.

RESULTS

Out of the total of 1827 gastrointestinal cancer patients, 154 patients with IP were evaluated. A total of 120 patients enrolled in the study and 34 patients were either lost to follow-up or were excluded due to insufficient data. There were two patients who were using anticoagulants after mitral valve replacement and were inappropriate to study. The mean age of the patients was 59.9 years (range 32-81). There were 72 males and 48 female patients in the study population. The number of patients with the diagnosis of colorectal, gastric and pancreatic cancer was 97 (80%), 22 (18%) and 1 (2%), respectively. There were 5 patients with a history of thrombosis before cancer diagnosis. The frequencies of the diagnosis of type 2 diabetes (DM), hypertension (HT), and coronary artery disease (CAD) were 18, 30, and 6, respectively. The majority of IPs was located on the subclavian (113) vein and 7 were on the femoral vein. There were 13 IPs that were placed on the left side of the body while 117 were implemented on the right. Patient characteristics are shown in Table 1.

Only 10 IP thromboses were detected in our study. There was one patient with two thromboses on both femoral and subclavian veins. The median time duration from the placement of the port to thrombosis was four months. A total of nine patients were treated with low molecular weight heparin, while one patient received warfarin treatment. There were 10 non-port cases related to thrombotic events. There was a significant difference between port thrombosis due to the location ($p<0.0001$). Out of seven IP thromboses, there were six on femoral location and four out of 113 patients were on subclavian veins. There was no pulmonary embolization due to port thrombosis. Time to thrombose was significantly shorter in femoral IPs ($p=0.04$) (Table 1).

TABLE 1: The characteristic features of the patients due to port location.

		Subclavian IP	Femoral IP	P value
Age		60	72	0.38
Gender	Male/Female	69/44	3/4	0.34
Smoking status		37/113	1/7	0.35
DM		18/113	0/7	0.49
HT		30/113	0/7	0.27
CAD		6/113	0.7	0.79
Thrombose history		5/113	0/7	0.82
IP Thrombose		4/113	6/7	<0.000
Non-IP Thrombose		10/113	0/7	0.41
Chemotherapy	Folfox	31	3	0.11
	Folfiri	19	2	
	Folfoxiri	3	0	
	mDCF	9	0	
	Flot	1	1	
	5-FU	6	0	
	>1	44	1	
Biologic Agents	None	44	3	0.7
	Anti-VEGF	34	3	
	Anti-EGFR	15	0	
	Both	18	1	
Time to thrombose		7.5 mo	1 mo	0.04

Folfox: 5-Fluorouracil, Leucovorin, Oxaliplatin; Folfiri: 5-Fluorouracil, Leucovorin, Irinotecan; Folfoxiri: 5-Fluorouracil, Leucovorin, Irinotecan, Oxaliplatin; Flot: 5-Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel; mDCF: 5-Fluorouracil, Leucovorin, Cisplatin, Docetaxel; 5-FU: 5-Fluorouracil; Anti-VEGF: Anti-Vascular Endothelial Growth Factor (Bevacizumab); Anti-EGFR: Anti-Epidermal Growth Factor Receptor (Cetuximab, Panitumumab).

The differences between the patient characteristics, comorbidities, chemotherapy regimens, and biologic agents were not statistically significant among the groups.

DISCUSSION

In this study, it was observed that femoral IPs were significantly more prone and took lesser time to thrombose than the subclavian IPs.

In a meta-analysis, the rate of symptomatic catheter thrombosis was reported to be 0.5-20% and pulmonary embolism due to IP thrombosis ranged 1-5%.[16,19] The thrombosis rate in subclavian IPs was 3.5% and these results were comparable with the literature. The thrombosis rates were very high in femoral IPs, which was found to be 85%. In a single-center study, the rate of IP thrombosis was observed to be 5.9%, and that of the lower extremity was 4.6%.[20]

In a study published in 2008, the results of 86 patients showed the rate of femoral IPs thrombosis as 3.5%. The patients in that study had undergone a bilateral mastectomy. The low rates of thrombosis and local complications in femoral IPs in that study were encouraging. The wide difference of IP thrombose between that study, and ours may be attributed to the type of cancer, tumor localization, types of chemotherapy, and use of biologic agents.[19] A total of four out of six patients received anti-VEGF agents in femoral IP thrombosis. This rate was two out of four in subclavian IP thrombosis. Although the VEGF use was more in femoral IP thrombose, the event rates were lower to have a precise decision.

The thromboembolic events due to IP thrombosis were reported to be low, and these results were comparable to the current literature. There was no pulmonary thromboembolism related to IP thrombosis. Port-related complications, such as infection or

bleeding were not observed. Our study did not analyze the risk factors for the pulmonary embolism. Khorana et al. identified that the site of cancer, increased white blood cell counts, and low hemoglobin levels were the risk factors for thromboembolism.[20] This result was confirmed by ONCOPIP study.[21]

Although French ONCOPIP study showed that the median time to thrombose in IPs was 45 days (range 23-99 days), it was observed to be longer in our study.[21] Especially, subclavian IPs took a median time of 7.5 months to thrombose while femoral IPs had a shorter time to thrombotic events. The wide difference may be related to low patient numbers. Also, in our study, the subjects with only gastrointestinal cancers were studied which might influence the results. Moreover, in ONCOPIP study, there were no femoral IPs, which made our results difficult to compare with that study. The only risk factor for catheter thrombosis in that study was cephalic vein insertion. On the contrary, ongoing antiplatelet treatment was associated with decreased thrombose risk.[21] In our study, routine prophylaxis with low molecular weight heparin (LMWH) was not used. The LMWH prophylaxis for IP thrombosis has been investigated in large trials. In a database study, Akl et al. reported that routine prophylaxis may have a beneficial or detrimental effect.[22] Compatible with this literature in a meta-analysis, the utility of the LMWH in preventing IP thromboses cannot be proven.[23]

LIMITATIONS OF THE STUDY

The present study was retrospective and cross-sectional, which made data evaluation limited. Also, our data were limited in covering all gastrointestinal cancer types. The cancer types were mainly gastric and colorectal, and the patients with the pancreas and biliary system cancers were very few in number. The use of multi-drug regimens and multiple steps of chemotherapy made it hard to evaluate the thrombose-drug relationship.

CONCLUSION

Our study showed increased thrombotic events in femoral IPs. Even though femoral IPs have been reported to be safe for the use in breast cancers, great attention must be paid for their utilization in gastrointestinal cancers. Prospective and larger trials are required to confirm the results of the present study.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** İsmail Beypınar, Mükremin Uysal; **Design:** İsmail Beypınar; **Control/Supervision:** Mükremin Uysal, Murat Araz; **Data Collection and/or Processing:** İsmail Beypınar, Dilek Beypınar; **Analysis and/or Interpretation:** İsmail Beypınar, Dilek Beypınar; **Literature Review:** İsmail Beypınar; **Writing the Article:** İsmail Beypınar; **Critical Review:** Murat Araz, Hacer Demir; **References and Fundings:** İsmail Beypınar; **Materials:** İsmail Beypınar.*

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