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Original Article

Evidence on port-locking with heparin versus saline in patients with cancer not receiving chemotherapy: A randomized clinical trial

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ABSTRACT

Objective: To assess the safety and efficacy of port-locking with heparin every 2 months vs. every 4 months and vs. saline solution every 2 months in patients with cancer not receiving active chemotherapy. The hypothesis stated that locking with heparin at four-month intervals and saline at two-month intervals would not increment > 10% of port obstructions.

Methods: Multicentre, phase IV parallel, post-test control group study took place at the two chemotherapy units of oncology hospitals. Included patients with cancer with ports that completed the chemotherapy treatment but still having port maintenance care or blood samples taken up to four months. A sample of 126 patients with cancer in three arms was needed to detect a maximum difference of 10% for bioequivalence on the locking methods. Consecutive cases non-probabilistic sampling and randomized to one of the three groups; group A: received heparin 60 IU/mL every two months (control) vs. group B heparin every four months and vs. saline every two months in group C. Primary variables were the type of locking regimen, port obstruction, and absence of blood return, port-related infection, or venous thrombosis during the study period. Clinical and sociodemographic variables were also collected.

Results: A total of 143 patients were randomly assigned; group A, 47 patients with heparin every 2 months, group B, 51 patients with heparin 4 months, and group C, 45 patients with saline every 2 months. All participants presented an adequate blood return and no obstructions, until the month of the 10th, when one participant in the group A receiving was withdrawn due to an absence of blood flow ($P = 0.587$).

Conclusions: Port locks with heparin every 4 months or saline every 2 months did not show differences in safety maintenance, infection, or thrombosis compared to heparin every 2 months.

Introduction

Most patients with cancer require a long-term central venous catheter (ports) to receive highly irritating chemotherapy or multiple blood samples to control hematological parameters and monitor the disease responses.[1,2] A port allows for bloodstream, it is made of silicone and strategically situated below subcutaneous tissue. The reservoir or titanium portal is connected to a catheter introduced into the venous flow, in adults preferably in one of the jugulars veins, subclavian, or cephalic.[2] The insertion must be performed with surgical intervention and under the strictest aseptic conditions.[3]

Despite the manufacturer recommends a monthly check of port, evidence in the literature shows variability that must be investigated with clinical trials.[4] A recent systematic review and meta-analysis showed a widespread practice in oncology with longer flushing intervals, while ports were out of use, to adapt the patients' comfort, safety and hospital visits.[5]

Regarding port maintenance and solutions also, the disparity of locking protocols has been reported.[6] Bertoglio in 2021 described the diversity of locking intervals in practice, questioning a need for changes to be made.[7] Solinas et al described a 3-monthly port locking with saline[8], and

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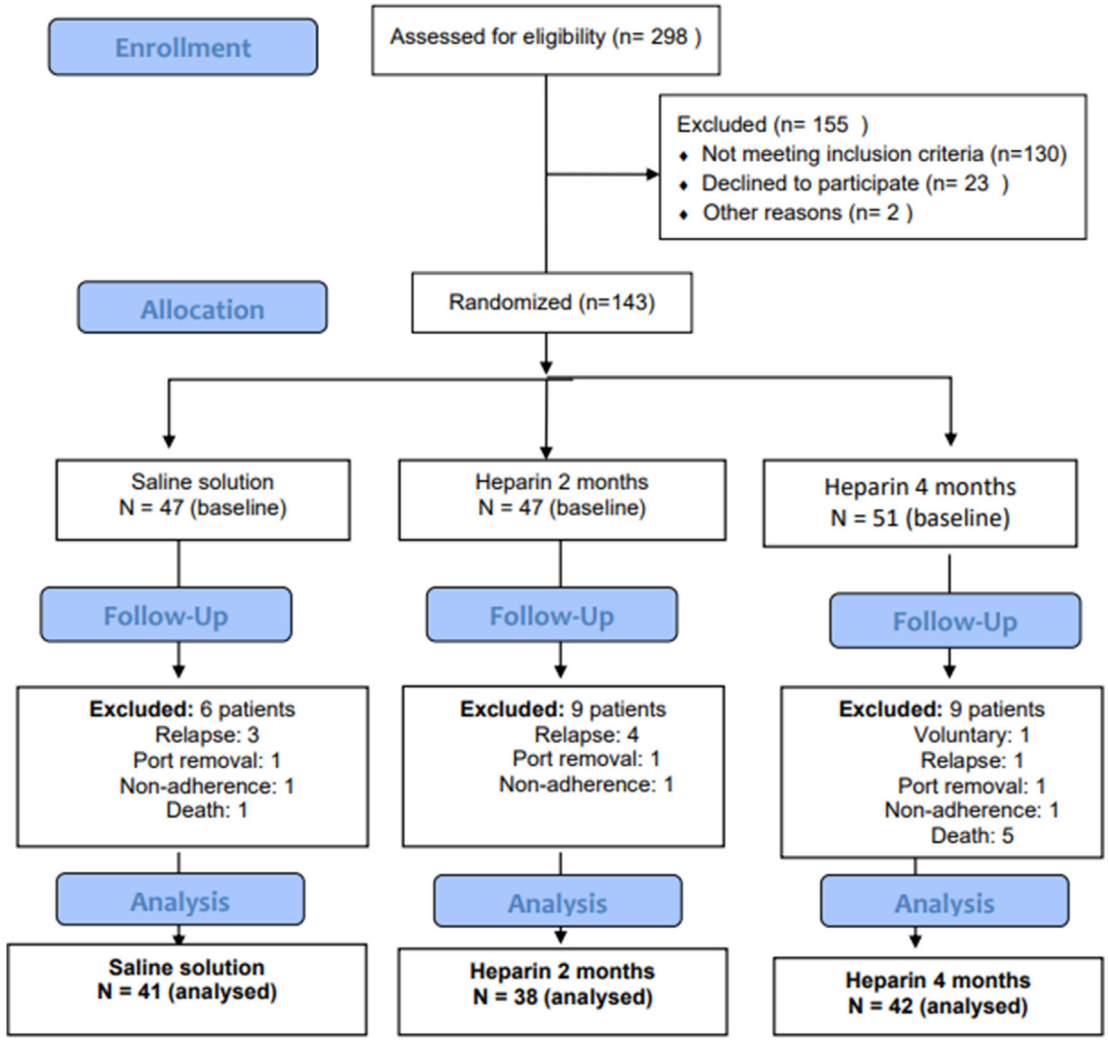

Fig. 1. CONSORT diagram.

Rasero et al presented prolonged washout intervals in patients with cancer and with no significant differences comparing plus or minus 45 days.[8,9] A recent study with patients with colorectal cancer maintained their ports for up to 24 months following treatments, with washout intervals every 3 months.[10] Four locking periods in 349 ports were studied by Ignatov et al, and up to four months did not result in more complications than shorter intervals; moreover, it was a safe clinical practice and drastically reduces costs.[11] Additional authors like Kuo et al, have reported that heparinization was comparably in safety and effectiveness at longer intervals between 3 flushes.[12] Examining complications associated to management of the port, Dal Molin et al observed that ports used intermittently remained safe for long periods of time.[13] A recent systematic review and meta-analysis also showed the extended practice of longer intervals for flushing while ports were out of use, advising for caution.[5]

Goosens et al demonstrated saline effectivity vs. heparin to lock ports without functional problems.[14,15] In peripheral catheters, saline was as effective as heparin.[12,16] Variables as infection and thrombosis were equivalents with heparinization every 6 weeks vs. 4 weeks and with different concentrations of heparin.[6] Italian researchers achieved the same conclusions with heparinization every 4 weeks vs. every 8 weeks and no statistically significant differences for occlusion,[17] and when comparing heparin with saline in a Cochrane systematic review, the best option was saline, although with limitations due to small sample size.[18,21]

Another question raised is the variability of care for ports and the use of heparin for patency described in intensive care units and patients with cancer.[19–21] Initially, the administration of heparin 500 IU (control) vs. 100 IU (experimental) demonstrated that lower dose was equally effective in central lines.[22] All these previous studies were very heterogeneous both in methods and interventions.[19,23]

Protocol at our cancer centre establishes that ports are locked using 3 mL of heparin, always with a positive pressure technique to lock without halting the inflow of the heparin solution and might be checked at least every two months, which has been proved equally safe,[5] effective,[8] without the risk for infection or thrombosis.[7,15,24]

This study aims to assess the safety and efficacy of port locking using heparin every two months vs. every four months and vs. saline every two months in patients ports with cancer, after receiving chemotherapy. We hypothesised that locking with heparin at four-month intervals and

Table 1
Sociodemographic and health-related characteristics of participants by group.

Variables	Group A Heparin 2 months	Group B Heparin 4 months	Group C Saline 2 months	*P* value[a]
Age, years, mean ± SD ($n = 143$)	63.5 ± 10.0	62.4 ± 10.9	62.7 ± 9.6	0.870
Gender ($n = 143$)				0.982
Men	22 (46.8%)	23 (45.1%)	21 (46.7%)	
Women	25 (53.2%)	28 (54.9%)	24 (53.3%)	
Cancer type ($n = 143$)				0.430
Breast	14 (29.8%)	11 (21.6%)	8 (17.8%)	
Bowels	18 (38.3%)	20 (39.2%)	22 (48.9%)	
Oesophagus-stomach	6 (12.8%)	8 (15.7%)	4 (8.9%)	
≥ 2 sites	4 (8.5%)	4 (8.5%)	6 (13.3%)	
Others	5 (10.6%)	8 (15.0%)	5 (11.1%)	
History of thrombosis ($n = 139$)				0.959
Yes	3 (6.5%)	4 (7.7%)	3 (7.0%)	
No	43 (93.5%)	46 (88.5%)	40 (93.0%)	
Type of catheter ($n = 97$)				0.789
High pressure	15 (48.4%)	18 (50.0%)	17 (56.7%)	
Low pressure	16 (51.6%)	18 (50.0%)	13 (43.3%)	
Insertion site ($n = 140$)				0.235
Right jugular	8 (38.1%)	11 (22.0%)	12 (26.7%)	
Right subclavian	11 (52.3%)	34 (68.0%)	27 (60.0%)	
Left jugular	0 (0.0%)	2 (4.0%)	0 (0.0%)	
Left subclavian	2 (9.6%)	3 (6.0%)	6 (13.3%)	
Distance between residence and health centre ($n = 141$)				0.579
<25 km	39 (83.0%)	43 (86.0%)	41 (93.2%)	
25–50 km	6 (12.8%)	4 (8.0%)	2 (4.5%)	
>50 km	2 (4.3%)	3 (6.0%)	1 (2.3%)	
Transportation mode ($n = 109$)				0.999
Public	12 (36.4%)	14 (36.8%)	14 (36.8%)	
Private	21 (63.2%)	24 (63.2%)	24 (63.6%)	
Presence of companion ($n = 111$)				0.367
Yes	6 (17.6%)	10 (25.6%)	5 (13.2%)	
No	28 (82.4%)	29 (74.4%)	33 (86.8%)	
Dependents ($n = 110$)				0.621
Yes	5 (14.7%)	4 (10.5%)	7 (18.4%)	
No	29 (85.3%)	34 (89.5%)	31 (81.6%)	
Employment activity ($n = 123$)				0.587
Disability	8 (20.6%)	14 (32.5%)	9 (22.0%)	
Retired	23 (59.0%)	23 (53.5%)	24 (58.5%)	
Active	6 (15.4%)	5 (11.6%)	3 (7.3%)	
Unemployed	2 (5.1%)	1 (2.3%)	5 (12.2%)	

[a] Chi-squared and Anova tests.

saline every two-month intervals would not increase more than 10% the port obstructions compared to heparin locking every two months.

Methods

Study design

This comparative phase IV post-market study used a multicentre, open-label, parallel design with the post-test control group. It took place at the ICO, an onco-hematological day hospital (in 2 cancer centres Badalona and Hospitalet-Barcelona, Spain).

Participants

Participants were patients with oncological ports who were not on active chemotherapy but were receiving care for port maintenance follow-up in the chemotherapy unit and were having their blood taken from once a month or up to every four months. The calculated sample size was 126 patients, for three study arms ($n = 42$ per arm), to detect a maximum difference of 10% for bioequivalence of the locking methods, based on the study performed by López-Briz[17] and a proportion of obstruction of 5%, with $\alpha = 5\%$ and $\beta = 20\%$ (Granmo 7.12).

Participants were recruited by cancer nurses with non-probabilistic sampling according to a consecutive presentation at the day hospitals, and they were enrolled after signing informed consent. Random number tables were used to allocate participants to one of the three treatment arms. The control group followed the centre's protocol and received a heparin solution of 60 IU (3 mL of Fibrillin®) every two months. The intervention groups received either the same locking solution every four months or a saline solution (10 mL) every two months. Fibrillin® is a product composed of Heparin sodium 20 IU/mL, recommended in the vascular access guidelines.

Inclusion and exclusion criteria

Inclusion criteria were oncological patients with a thoracic port; not receiving active therapy; undergoing not more than one blood extraction every four months; aged 18 years or older; any gender or diagnosis. Exclusion criteria were having a cognitive or neurological deficit; a history of catheter occlusion; a port with no blood flow at recruitment; a double-lumen port; a non-thoracic port or non-adherence to the 12-month safety follow-up for any reason.

Study variables

The primary explanatory variable was the type of locking regimen used, while the outcome variables were port occlusion; the absence of blood flow through the catheter; port-related infection diagnosed by a positive blood culture drawn through the port and simultaneously through a peripheral vein; and the presence of venous thrombosis or pulmonary emboli over follow-up. Secondary variables were gender, age, weight, height, body mass index (BMI), cancer type, vein of catheter insertion, anticoagulant or anti-platelet drug treatment at baseline, history of thrombosis, type of catheter, insertion site, the distance between residence and health centre, transportation mode, presence of companion, dependents, employment activity.

Data collection and tools

Patients who met the inclusion criteria were informed of the study and signed their voluntary consent to participate. Afterward, they were randomized to one of the three study arms under the supervision of the head of clinical research in the centre, using computerized random number tables, balanced in sequences of six cases. Follow-up visits to check patency were then programmed at the day hospital according to the study arm, using a personalized appointment sheet and with the study's reference nurse. At the beginning of the study, it was evaluated that the secondary variables previously described. At each visit, patients were assessed for a pre-defined set of potential complications, and any adverse events were recorded in a logbook. Patients were followed for one year. That is, patients receiving maintenance care every two months had at least six follow-up visits, while those following the four-month protocol were assessed at three-time points. In case of an absence of blood flow or the presence of an obstruction, the institutional protocol was applied (heparin flush) and the re-establishment of patency (or not) was recorded in the logbook. In case of permanent obstruction, the

Table 2
Reasons for exclusion, by study group ($n = 24$).

	Voluntary	Relapse	End of use	Non-adherence	Exitus
Group A: Heparin 2 months ($n = 9$)	0 (0.0%)	4 (44.4%)	1 (11.2%)	4 (44.4%)	0 (0.0%)
Group B: Heparin 4 months ($n = 9$)	1 (11.1%)	1 (11.1%)	1 (11.1%)	1 (11.7%)	5 (55.6%)
Group C: Saline 2 months ($n = 6$)	0 (0.0%)	3 (50.0%)	1 (16.6%)	1 (16.6%)	1 (16.6%)

Chi-squared $P = 0.065$.

Table 3
Patency and blood flow at assessment time points, by study arm.

	Time point (months)													
	Baseline ($n = 143$)		2 ($n = 143$)		4 ($n = 134$)		6 ($n = 130$)		8 ($n = 122$)		10 ($n = 111$)		12 ($n = 119$)	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Group A: Heparin 2 months	47	0	47	0	45	0	43	0	39	0	39	1	38	0
Group B: Heparin 4 months	51	0	–	–	45	0	–	–	42	0	–	–	42	0
Group C: Saline 2 months	45	0	45	0	44	0	42	0	41	0	38	0	39	0

Chi-squared $P = 0.587$.

Table 4
Evaluation of post-treatment model in 3 groups.

	Mean	SD	95% confidence interval for mean		*F*	*P* value[a]
			Min	Max		
Appropriateness of the N of visits (0 = completely inappropriate, 10 = very appropriate)						
Group A: Heparin 2 months ($n = 38$)	7.74	3.07	6.53	8.96	1.15	0.32
Group B: Heparin 4 months ($n = 42$)	8.85	2.30	7.94	9.76		
Group C: Saline 2 months ($n = 39$)	8.40	2.67	6.92	9.87		
Quality of life (0 = no effect, 10 = very large effect)						
Group A: Heparin 2 months ($n = 38$)	2.00	2.53	1.00	3.00	0.57	0.57
Group B: Heparin 4 months ($n = 42$)	2.43	3.14	1.21	3.65		
Group C: Saline 2 months ($n = 39$)	1.47	2.80	-0.08	3.02		
Pain caused by the maintenance care (0 = no pain, 10 = a lot of pain)						
Group A: Heparin 2 months ($n = 38$)	0.78	1.31	0.26	1.30	2.47	0.92
Group B: Heparin 4 months ($n = 42$)	1.64	2.79	0.56	2.73		
Group C: Saline 2 months ($n = 39$)	0.33	0.82	-0.12	0.79		
Effect on working life (0 = no change, 10 = large change)						
Group A: Heparin 2 months ($n = 38$)	0.37	1.15	-0.08	0.82	0.10	0.90
Group B: Heparin 4 months ($n = 42$)	0.54	1.92	-0.24	1.32		
Group C: Saline 2 months ($n = 39$)	0.36	1.34	-0.41	1.13		

[a] Anova test for comparison of means.

patient was withdrawn from the study and referred to the radiology unit of reference for follow-up. Likewise, patients with an absence of blood flow were also withdrawn and restored to the centre's care protocol. Any manipulation of the port was done under the strictest aseptic conditions, following the indications of the institution protocol. At the last visit, it was evaluated the appropriateness of the number of visits, quality of life, pain caused by the maintenance care, and effect on working life.

Ethical considerations

The board of the research ethics committee at the study centres approved the study categorized as ICO-PAC-2016-01. Participants were always kept informed of the project through oral and written communications. Informed consent and other documents, considered class III documentation according to Spanish legislation on the protection of personal and digital data (Organic Law 3/2018 of 5 December), were safeguarded by the research team of the onco-hematological day hospitals. In addition, all bioethical and legal norms were followed, including the Declaration of Helsinki, the Spanish Royal Decree on clinical drug trials (1090/2015 of 4 December), the regulations established by the drug research ethics committee, and the Spanish Registry of Clinical Trials by Ministry of Health and the Spanish Agency for Drug & Medications (AEMPS) on data January 11, 2016 and good clinical practice guidelines.[25]

Data analysis

Data were processed using the SPSS statistical programme (v. 24.0, Spanish version), and descriptive and inferential analyses were performed. Prior to the bivariable analysis, we assessed the normality of the distribution of variables in the sample using the Kolmogorov–Smirnov test. The chi-squared test was used in the inferential analysis to compare the detection of complications according to the locking regimen. The student t and Anova tests were also applied to compare study groups.

Results

In total, 143 patients were recruited: 47 in group receiving saline every two months, 45 in the group receiving heparinization every two months, and 51 in the group receiving heparinization every four months (CONSORT flow diagram, Fig. 1). Participants' mean age was 62.9 (standard deviation [SD] 10.2) years, and 53.8% ($n = 77$) were women. The most prevalent cancer were bowel (42.0%, $n = 60$) and breast (23.1%, $n = 31$), oesophageal-stomach cancer (12.6%, $n = 18$). A history of deep vein thrombosis or pulmonary thromboembolism was present in 7.2% ($n = 10$) of the participants. Regarding the type of ports, 51.5% ($n = 50$) were high pressure models; 51.4% ($n = 72$) were inserted in the right subclavian vein, and 22.1% ($n = 31$) in the right jugular vein. Most participants (87.2%, $n = 123$) lived within 25 km of the study centre, and 63.3% ($n = 69$) participants used a private vehicle to travel to the health centre; 36.7% ($n = 40$) patients used public transport. Most patients (81.1%, $n = 90$) presented to their maintenance visits alone. Over half (56.9%, $n = 70$) were retired, while a minority were either not working due to disability (25.0%, $n = 31$) or unemployed (6.7%, $n = 8$). Just 11.4% ($n = 14$) were actively employed. Table 1 presents the characteristics of participants by study arm.

There were 24 withdrawn ports: 33.3% ($n = 8$) due to relapse, 25.0% ($n = 6$) due to death or non-adherence to the study protocol, and 12.5% ($n = 3$) due to end of use for ports (Table 2). All the patients in follow-up presented blood flow and showed no obstructions until month 10, whereas one patient (0.8%) had the port withdrawn due to an absence of blood flow ($P = 0.587$). Table 3 shows the distribution of control visits and patency by study arm.

There were no statistically significant differences between groups in terms of the perceived appropriateness of the number of visits or patients' quality of life (Table 4).

Discussion and conclusions

Our results indicated the equivalence for safety and efficacy of both; the saline lock every two months and the heparin lock every four months compared to the standard heparin lock every two months. These findings are consistent with those reported in other studies that similarly concluded that heparinization every six weeks is just as effective as regimens of every four weeks with different concentrations of heparin.[5,11,25] Evidence in literature shows variability in the intervals for heparinization of central venous catheter (CVC). Kefeli et al, comparing variables as infection and thrombosis with 1,000U of heparin every 6 weeks vs. 500U every 4 weeks over one-year maintenance period, concluded that heparinization every 6 weeks was just as effective as every 4 weeks with different concentrations of heparin.[6] Similarly, like the Italian study by Palese et al, we have observed no significant differences in occlusion rates between groups.[17] The assessment of four different heparinization intervals concluded that heparinization every four months is a safe clinical practice that does not result in a higher rate of complications than shorter intervals, and it drastically reduces costs.[11]

Finally, the most recent Cochrane reviews by Zhong et al and by López-Briz et al, are in keeping with our results, report that the use of heparin for maintaining intermittent catheters may have little to no effect on the duration of the catheter's patency.[18,21] The use of higher concentrations of heparin, similarly, did not yield conclusive results or show any evidence of difference in the safety of maintenance methods about the risk of sepsis, mortality, or hemorrhage.[5,26]

In summary, the study demonstrated that ports can be locked either with heparin every 4 months or with saline every 2 months compared to the standard of heparin every 2 months according to no differences in infection, thrombosis, and occlusion rates.

Implications for practice

The implications of these results are only circumscribed to the adult population. However, there is still little evidence on the best approach for maintaining port patency in children (Zhong et al, 2017).[21] Another important implication for oncology nurses' practice is the need to continue training both patients and nurses in best practice and management with ports and central lines.[27,28]

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Authors' contributions

Melania Cia-Arriaza, Sandra Cabrera-Jaime and Paz Fernández-Ortega: Conceptualization, Methodology, Recruitment supervision, Analysis and Writing-Reviewing and Editing, Project Administration.

Rosario Cano-Soria R, Mireia Manzano-Castro, Margarita Domínguez-Gómez, Maria Dolores Prieto-Arenas, Maria Ángeles Benito-Yagüe, Adela Sánchez-Martín and Cristina González-Alonso: Data recruitment and patients' participation at the multicenter institutions.

Declaration of competing interest

None declared.

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