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

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Aims: 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 2 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blood return and no obstructions, until the month of the 10th, when one participant in the group A receiving was withdrawn due to an absence of blood flow ($P = 0.587$).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. 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. The insertion must be performed with surgical intervention and under the strictest aseptic conditions.

Despite the manufacturer recommends a monthly check of port, evidence in the literature shows variability that must be investigated with clinical trials. 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.

Regarding port maintenance and solutions also, the disparity of locking protocols has been reported. Bertoglio in 2021 described the diversity of locking intervals in practice, questioning a need for changes to be made. Solinas et al described a 3-monthly port locking with saline, and...
Rasero et al presented prolonged washout intervals in patients with cancer and with no significant differences comparing plus or minus 45 days. A recent study with patients with colorectal cancer maintained their ports for up to 24 months following treatments, with washout intervals every 3 months. 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. Additional authors like Kuo et al, have reported that heparinization was comparably in safety and effectiveness at longer intervals between 3 flushes. Examining complications associated to management of the port, Dal Molin et al observed that ports used intermittently remained safe for long periods of time. 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.

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

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. Initially, the administration of heparin 500 IU (control) vs. 100 IU (experimental) demonstrated that lower dose was equally effective in central lines. All these previous studies were very heterogeneous both in methods and interventions.

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, effective, without the risk for infection or thrombosis.

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 with cancer, after receiving chemotherapy. We hypothesised that locking with heparin at four-month intervals and

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Fig. 1. CONSORT diagram.
Chi-squared tests for the association of participants' sociodemographic and health-related characteristics and their categorization in the study groups (Table 1). 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 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.

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 ICO, an onco-hematological day hospital (in 2 cancer centres Badalona and Hospitalat-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 Lópeuz-Briz 17 and a proportion of obstruction of 5%, with α = 5% and β = 20% (Graano 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 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 1

| Variables                          | Group A Heparin 2 months | Group B Heparin 4 months | Group C saline 2 months | p value<sup>a</sup> |
|-----------------------------------|--------------------------|--------------------------|-------------------------|---------------------|
| 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 (92.3%)              |                     |
| 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 (26.4%)               | 14 (36.8%)               | 14 (36.8%)              |                     |
| Private                           | 21 (46.3%)               | 24 (63.2%)               | 24 (63.6%)              |                     |
| Presence of companion (n = 111)   |                          |                          |                         | 0.367               |
| Yes                               | 6 (17.6%)                | 10 (25.5%)               | 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%)               |                     |

<sup>a</sup> Chi-squared and Anova tests.

### 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 (11.1%)     | 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.
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.

Table 3

| Time point (months) | Group A: Heparin 2 months | Group B: Heparin 4 months | Group C: Saline 2 months |
|---------------------|---------------------------|--------------------------|------------------------|
| 2 (n = 143)         | Yes: 47 | No: 0 | Yes: 45 | No: 0 | Yes: 45 | No: 0 |
| 4 (n = 134)         | Yes: 43 | No: 0 | Yes: 40 | No: 0 | Yes: 42 | No: 0 |
| 6 (n = 130)         | Yes: 39 | No: 0 | Yes: 39 | No: 0 | Yes: 41 | No: 0 |
| 8 (n = 122)         | Yes: 39 | No: 0 | Yes: 38 | No: 0 | Yes: 39 | No: 0 |
| 10 (n = 111)        | Yes: 38 | No: 0 | Yes: 37 | No: 0 | Yes: 38 | No: 0 |
| 12 (n = 119)        | Yes: 39 | No: 0 | Yes: 39 | No: 0 | Yes: 39 | No: 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* |
|--------------------------|------|-----|---------------------------------|--------|---------|
|                          | 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 | 3.30 | 7.84 – 9.86 | 0.65   | 0.57    |
| Group C: Saline 2 months (n = 39) | 8.40 | 3.87 | 6.92 – 9.87 | 0.91   | 0.36    |
| 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 | 0.07   | 0.92    |
| 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   | 0.02    |
| Group B: Heparin 4 months (n = 42) | 1.64 | 2.79 | 0.56 – 2.73 | 0.10   | 0.10    |
| 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   | 0.09    |
| 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 |        |         |

* Anova test for comparison of means.
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. 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 Lopez-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).11 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.
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Declaration of competing interest

None declared.

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References

1. Lucendo Villarín AJ, Noél Belda J. Prevention and treatment of extravasation of intravenous chemotherapy (Prevención y tratamiento de las extravasaciones de quimioterapia intravenosa). Enferm Clin. 2004 Jan 1;14(2):122–126.
2. Tipo de canalización de acceso venoso central PORT-A-CATH [Internet]. vol. 2, ENE Revista de Enfermería. 2008 [cited 2022 Feb 6]; p. 45–50. Available from: https://dialnet.sanitario.es/servlet/articulo?codigo=2923268.
3. Smith RN, Nolan JP. Central venous catheters. Internet BMJ. 2013 Jan 1;347. cited 2022 Feb 10 Available from: http://pubmed.ncbi.nlm.nih.gov/24217269/.
4. Bertoglio S, Solari N, Meszaros P, et al. Efficacy of normal saline versus heparinized saline solution for locking catheters of totally implantable long-term vascular access devices in adult cancer patients. Cancer Nurs. 2012;35(4):35–42.
5. Clari M, Spoto M, Franceschi G, et al. Short versus long timing of flushing of totally implantable vascular access devices: results from a systematic review and meta-analysis. Cancer Nurs. 2021;44(3):205–213.
6. Kefeli U, Dane F, Yumuk PF, et al. Prolonged interval in prophylactic heparin flushing for maintenance of subcutaneous implanted port care in patients with cancer. Eur J Cancer Care. 2009;18(2):191–194.
7. Bertoglio S. Extending the interval of flushing procedures of totally implantable vascular access devices in cancer patients: it is time for a change. J Vasc Access. 2021; 32(5):689–691.
8. Solinas G, Platini F, Trivellato M, Rigo C, Abalos G, Galeo AS. Port in oncology practice: 3-monthly locking with normal saline for catheter maintenance, a preliminary report. J Vasc Access. 2017;18(4):325–327.
9. Rasoer L, Golin L, Ditta S, Di Massimo DS, Dal Molin A, Frimont M. Effects of prolonged flushing interval in totally implantable vascular access devices (TIVADs). Jr J Nurs. 2018;27(8):54–510. https://doi.org/10.12968/jbn.2018.27.8.54.
10. Oh S-I, By-Y, Park R, Kim J-J, et al. Safety and feasibility of 3-month interval access and flushing for maintenance of totally implantable central venous port system in colorectal cancer patients after completion of curative intended treatments (Baltimore) [Internet]. Medicine. 2021 Jan 15;100(2), e24156. https://doi.org/10.1097/MD.00000000000024156 [cited 2022 13 Jan], Available from.
11. Ignatov A, Ignatov T, Tzan A, Smith B, Costa SD, Bischoff J. Interval between port catheter flushing can be extended to four months. Gynecol Obstet Invest. 2010 Aug;70(2):91–94.
12. Kuo YS, Schwartz R, Santiago J, Anderson PS, Fields AL, Goldberg GL. How often should a port-A-cath be flushed? How often should a port-A-cath be flushed? Internet Cancer Invest. 2009;23(7):582–585.
13. Dal Molin A, Clerico M, Baccini M, Guerretta L, Sartorello B, Rasero L. Normal saline versus heparin solution to lock totally implantable vascular access devices: results from a multicenter randomized trial. Eur J Oncol Nurs. 2015;19(6):638–643.
14. Goossens GA, Jeroine M, Janssens C, et al. Comparing normal saline versus diluted heparin to lock non-valved totally implantable vascular access devices in cancer patients: a randomised, non-inferiority, open trial. Ann Oncol. 2015;24(7):1892–1899.
15. Goossens GA, Vrebos M, Stats M, De Wever I, Fredericks L. Central vascular access devices in oncology and hematology considered from a different point of view: how do patients experience their vascular access ports? J Infus Nurs. 2005(28):1–67.
16. Eugnati D, Gloria C. Implanted port patency [Internet] Clin J Oncol Nurs. 2021; 25(2):169–173. Available from: https://pubmed.ncbi.nlm.nih.gov/3373937/.
17. Pizani A, Balduzzi D, Rupil A, et al. Maintaining patency in totally implantable vascular access devices (TIVAD): a time-to-event analysis of different lock irrigation intervals. Eur J Oncol Nurs. 2014;18(1):66–71.
18. Lopez-Briz E, Ry V, Jh B, S-B M, Cr R, B A. Heparin versus 0.9% sodium chloride locking solution for prevention of occlusion in central venous catheters in adults (Review). J Vasc Access. 2016 Jan 20(7), CD008462.
19. Conley SB, Buckley P, Magarace L, Hsieh C, Pedulla LV. Standardizing best nursing practice for implanted ports: applying evidence-based professional guidelines to prevent central line-associated bloodstream infections. J Infus Nurs. 2017;40(3):165–174.
20. Sona C, Prentice D, Schallom L. National survey of central venous catheter flushing in the intensive care unit. Crit Care Nurs. 2012 Feb 1;32(1):12–19.
21. Zhong Lei, Hai-Li W, Bo X, et al. Normal saline versus heparin for patency of central venous catheters in adult patients: a systematic review and meta-analysis. Crit Care. 2017;21(5).
22. Sharma SK, Mudgal SK, Gaur R, Sharma R, Sharma M, Thakur K. Heparin flush vs. normal saline flush to maintain the patency of central venous catheter among adult patients: a systematic review and meta-analysis. J Family Med Prim Care. 2019 Sep 30;8(9):2779–2792. https://doi.org/10.4103/jfmpm.jfmpm_669_19.
23. Dougherty L. Maintaining vascular access devices: the nurse’s role. Support Care Cancer. 1998;6(1):23–30.
24. Fornaro C, Piubeni M, Tovazzi V, et al. Eight-week interval in flushing and locking port-a-cath in cancer patients: a single-institution experience and systematic review. *Eur J Cancer Care*. 2019;28(2): e12978.

25. Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for Investigation with medicinal products and the Spanish Clinical Studies Registry. Access: https://www.aemps.gob.es/legislacion/espansa/investigac.

26. Dal Molin A, Rasero L, Guerretta L, Perfetti E, Clerico M. The late complications of totally implantable central venous access ports: the results from an Italian multicenter prospective observation study (star, open). *Eur J Oncol Nurs*. 2011;15(5): 377–381.

27. Pronovost PJ. Ensuring that guidelines help reduce patient harm. *J Oncol Pract*. 2013; 9(4):e172–173.

28. Kapucu S, Özkaraman AO, Uysal N, Bagcivan G, Şeref FC, Eloy A. Knowledge level on administration of chemotherapy through peripheral and central venous catheter among oncology nurses. *Asia-Pacific J Oncol Nurs*. 2017;4(1): 61–68.