# A PROSPECTIVE STUDY OF THE INCIDENCE OF CENTRAL VEIN THROMBOSIS IN PATIENTS ON HOME PARENTERAL NUTRITION. ANALYSIS OF FACTORS RELATED TO THIS COMPLICATION

## Principal investigator

Dr. Cristina Cuerda (ESPEN member) on behalf of the ESPEN Home Artificial Nutrition and Chronic Intestinal Failure Working Group

## Institute and location

Nutrition Unit
Hospital General Universitario Gregorio Marañón
Doctor Esquerdo 46
28007 Madrid
Spain
Tel: +34915868541
Fax: +34915868540
E-mail: mcuerda.hgugm@salud.madrid.org

## Background

The thrombotic complications of central catheters include occlusion of the catheter by thrombi and thrombosis of the vein associated with the central line (1). There is some confusion in the literature about these terms and the strategies that can be used for their prevention.

Catheter thrombosis refers to the occlusion of the lumen of the catheter by thrombi. This is the most frequent type of catheter occlusion. Strategies for the prevention of catheter thrombosis should focus on maintaining patency by keeping blood out of the catheter using two main interventions: catheter flushing and the use of antireflux needleless connectors and valves (2). There are three important components in the flushing protocol for maintaining the patency of vascular catheters: the volume of solution, the flush solution, and the flushing technique. The volume of flush solution recommended must be at least 120% the volume of the catheter (3). The flush/lock solution may be a compound of saline or include anticoagulant agents, such as heparin, EDTA, citrate. Although the use of heparin lock of the CVC line has been recommended to prevent catheter occlusion (4,5), its efficacy and safety have not been demonstrated. Indeed, many groups do not recommend this practice because of the risk of infection associated with the manipulation of the catheter (6).
In peripheral vascular accesses, saline and heparin are equally efficient at maintaining the permeability of the catheter (I, Cochrane) (7-10). Some studies support the use of saline flush instead of heparin for long-term central catheters (11-13).

Central vein thrombosis (CVT) manifests as oedema and increased filling of superficial veins of the territory drained by that vein (14), although is often asymptomatic. The prevalence of symptomatic CVT is around 0.027 cases/catheter/year (95% CI, 0.02-0.034) (1), but the prevalence of asymptomatic CVT (ACVT) is unknown. A prevalence of ACVT of 11-44% has been reported in studies on cancer patients with long-term central catheters (15), and most cases were diagnosed in the first weeks after catheterization, although none of the studies was performed in patients on home parenteral nutrition (HPN). However, most of the data in the literature are quite old, especially taking into account current changes in the practice of HPN (different types of lipid emulsions, all-in-one solutions).

Computed tomography, venography or Color Doppler Duplex Sonography (CDDS) can confirm the diagnosis of CVT. Although venography is the standard method for diagnosis, it is invasive and carries a risk of nephrotoxicity and allergic reactions to iodinated contrast agents; therefore, it cannot be used as a screening tool in asymptomatic patients. CCDS is an accurate method for the diagnosis of ACVT, with a sensitivity ranging from 78% to 100%, and specificity ranging from 82% to 100% (15).

The pathogenesis of CVT is multifactorial and includes the following: a) vessel injury during the procedure of insertion, b) venous stasis due to indwelling of the device and damage to the endothelium caused by infusion of parenteral nutrition with a high osmolality, and c) mechanical rubbing of the catheter against the vessel wall. Hypercoagulability related to cancer or another underlying disease may also contribute to the risk. The incidence may be higher in patients with inflammatory bowel disease (4). Catheter-related infection may also contribute to the pathogenesis of thromboembolic complications. The type of catheter (material, thickness), catheter tip, and location (this complication is higher in those catheters located in the femoral vein) are also important factors (16). In addition, highly concentrated glucose solutions increase the risk. The ESPEN guidelines on parenteral nutrition recommend an insertion technique associated with minimal damage to the vein, such as ultrasound guidance (grade C), choice of a catheter with the lowest calibre compatible with the infusion therapy needed by the patient (grade B), and appropriate position of the tip of the catheter in the proximity of the atrio-caval junction (grade B), for prevention of catheter-related CVT.

CVT is a severe complication of HPN and is responsible for the loss of central venous accesses in these patients. It is important to remember that one of the criteria of HPN failure before intestinal transplantation is considered, is the presence of two CVT.

In order to prevent CVT, several practices have been proposed: the inclusion of heparin in the HPN formula, and anticoagulation with different drugs (low-molecular-weight heparin, warfarin) and doses.

Heparin added to the HPN solution is probably only efficient to prevent venous thrombosis with certain doses (3 units/ml) (4,17), but not with lower doses (1 unit/ml) (16). A meta-analysis and a systematic review that studied the efficacy of heparin in preventing venous thrombosis revealed different results. In the meta-analyses, the use of prophylactic heparin decreased the incidence of thrombosis and infections in patients with a central catheter (5). However this meta-analysis included studies with heparin flush/lock, heparin in the parenteral nutrition bag, and subcutaneous heparin. The systematic review included only studies in which heparin was added to the bag of parenteral nutrition, and found this treatment useless (18).

Adverse effects of heparin are common and include bleeding, thrombocytopenia, metabolic bone disease, and hair loss. Autoimmune-mediated heparin-induced thrombocytopenia occurs in 2.7% of patients exposed to unfractionated heparin, which greatly increases the risk of thrombotic events (5).

Another approach to decreasing the incidence of venous thrombosis has been the use of oral anticoagulants and subcutaneous heparin.

Oral anticoagulants (warfarin) at low doses may protect against CVT in patients with long-term central catheters for HPN (19,20) and chemotherapy (21). Warfarin has also been administered safely in children on long-term parenteral nutrition and seems to prolong catheter survival (22). Furthermore, low- molecular-weight heparin seems to be effective in the prevention of CVT in patients receiving chemotherapy (23). In a prospective randomised study it was as effective as warfarin in cancer patients (24). There have been several systematic reviews and meta-analyses on the value of thromboprophylaxis in patients with long-term central venous catheters, although the results are contradictory (18, 25-27). Moreover, most of the patients included in these studies had cancer and were not receiving HPN.

Based on these studies, the ASPEN guidelines recommend the use of low doses of anticoagulants in patients on long-term parenteral nutrition (B) (28), and the ESPEN guidelines recommend prophylaxis with a daily dose of low-molecular-weight heparin (100 IU/kg) for high risk patients only (grade C) (29,30).

These recommendations should balance the benefits and risks (bleeding, thrombocytopenia, bone disease, hair loss) of these treatments. However, it will be impossible to resolve outstanding issues until the prevalence of CVT is known in these patients.

## Working hypothesis and aims of the research

### Hypotheses

- CVT , especially ACVT is a frequent complication in patients on HPN
- This complication is underreported in the clinical management of these patients
- We can identify some factors related to the prevention of this complication: choice of the appropriate catheter, location, catheter care, use of antithrombotic therapy in some cases

### Aims

The aims of this prospective, multi-centre, multi-national, open-label study are:

- Primary aim: to know the incidence of CVT in patients starting treatment with HPN. The approach adopted will be one of serial studies with CDDS.
- Secondary aim: to investigate the impact of different variables (catheter care, type of catheter, location, patient characteristics, antithrombotic therapy) on the development of CVT

.

This study will help us to know the true incidence of CVT in HPN and to identify the factors related to the development of CVT. This knowledge would help us to value the risks and benefits of antithrombotic therapy in these patients. Loss of central venous access is a cause of HPN failure in some patients, and an indication for intestinal transplantation.

## Study design and methods

### Type of study

Prospective, multi-centre, multi-national, open-label study

### Number of patients to be included

We will include 100 patients for an expected incidence of CVT of 15% (± 7%, 95% CI, alpha risk 0.05).

One of the problems of the study will be the enrolment of patients, as the incidence of HPN in Europe is low, 3 patients/$10^6$ inhabitants /year (data from a 1997 survey). That is why we need a multi-national, multi-centre study. Given the long experience of the members of the study we calculate that at least 100 patients will be recruited during the study period. We will call for participation in the study via e-mail to groups with HPN patients in different countries through the local contact (member of the HAN-CIF ESPEN group).

One possible limitation of the study would be that the number of patients with CVT was too low to establish any correlation with the study variables (type of catheter, catheter care, antithrombotic treatment). In this case, it would be necessary to include more patients.

Another weakness could be the loss of patients during the study (because of weaning HPN treatment or other reasons), although this is resolved if we include the data on an intention-to-treat basis.

### Inclusion criteria

All the following criteria are required:

- Patients starting HPN through a central tunnelled catheter or port-a-cath
- Intestinal failure due to a benign disease
- Possibility of follow-up during the study (12-month period)
- Informed consent signed

**Exclusion criterion**

- Presence of CVT at baseline in patients with a catheter inserted before the start of the protocol. (The presence of previous CVT in other veins won't be an exclusion criterion, and will be included in the patient filling form)
- Diagnosis of an active cancer disease

**Definitions**

- **Symptomatic venous thrombosis:** thrombosis of the vein associated with the catheter (manifests as oedema and increased filling of superficial veins of the territory drained by that vein)
- **Asymptomatic venous thrombosis:** thrombosis of the vein associated with the catheter found accidentally during CDDS
- **Criteria of venous thrombosis in the CDDS:** CDDS is the standard method of screening in asymptomatic patients. The diagnostic criteria are as follows:
  - visualization of an intraluminal thrombus (location, extension)
  - flow void on CDDS
  - dampened, nonpulsatile, and nonphasic flow on duplex sonography.

**Schedule of data collection**

Patients will be invited to participate by their HPN clinician. The patients' clinical care will not be affected by a decision not to participate. Patients will be included in the study after signing the informed consent.

The inclusion period will extend from 1st April 2010 to 31st March 2011.

The first CDDS will be performed after catheter insertion for HPN (baseline), and repeated at 7th day (if possible), 3rd , 6th and 12th month thereafter. Patients with catheters inserted before the enrolment will be included if there is not CVT (in the vein of the catheter) at the first CDDS evaluation (baseline) and they will follow the same schedule.

Patients will be followed for 12 months. At enrolment the investigator will include the following data: etiology of the intestinal failure, catheter, HPN, flushing/lock technique,

anticoagulation and use of the catheter for infusion of drugs or blood extraction (see attached excel file). These variables will be checked at each visit. The investigators will fill out the results of the CDDS evaluations and will communicate the onset of any symptomatic thrombotic complication during the study (including type and date).

**Study chronogram**

| | Baseline | $7^{th}$ day (not mandatory) | $3^{rd}$ month | $6^{th}$ month | $12^{th}$ month |
|---|---|---|---|---|---|
| Clinical evaluation | + | + | + | + | + |
| Doppler | + | + | + | + | + |

**Statistical evaluation**

We will analyse data on an intention-to-treat. Quantitative variables will be expressed as the mean $\pm$ SD, or median and interquartile range. Qualitative variables will be expressed as frequencies and percentages. We will use the $\chi^2$ or Fisher's exact test to study the association between qualitative variables. We will study the incidence of venous thrombosis using Kaplan- Meier curves. The level of significance will be set at 5%. Data will be analysed using the SPSS-16 package.

**Administration and data management**

All completed questionnaire (excel file enclosed) will be returned to the PI. Results will be shared with the ESPEN HAN-CIF group and other collaborators. Results will be submitted as abstracts to ESPEN and other PEN societies as appropriate and a manuscript prepared for Clinical Nutrition. All of the collaborators will be recognised authors in order of the number of patients recruited.

**Research Network**

The PI has the support of clinical colleagues in Spain (is in charged of the Spanish Committee for Home Artificial Nutrition, NADYA group, a working group of the Spanish Society for Parenteral and Enteral Nutrition, SENPE).

The study has the support of the members of the ESPEN HAN-CIF committee and colleagues in their respective clinical nutrition societies. The framework for carrying out the study will consist of a group of colleagues identified through the working of the committee and by knowledge of other international collaborators. The infrastructure of the group will help on the enrolment of new HPN patients, otherwise this study will be impossible to perform due to the low prevalence of HPN worldwide. The PI has sent an application for financial support for this study at the ESPEN EBM grants 2010.

**Timeline of the project**

Patients starting on HPN that fulfil the inclusion criteria will be recruited from1st April 2010 until 31st March 2011. The study will finish in March 2012. The results will be analyzed and published.

**Study registration**

The PI will register the study at Clinicaltrials.gov.

**Questionnaire:** (find enclosed the excel file)

To be completed for each patient

Hospital:

Phsysician (responsible):

**Patient**

- Date of birth:
- Name: Initials
- Etiology of intestinal failure (disease):
- Indication of HPN (short bowel, obstruction..):
- Date of starting protocol (informed consent date):

**Patient history**

Previous central catheters: YES/NO

If YES: Were any of them located in the current vein? YES/NO

If YES: Date and indication for withdrawal

Previous catheter-related thrombotic complications: YES/NO

If YES: date, type (catheter thrombosis, central vein thrombosis)

Previous thrombotic episodes (not related to catheter): YES/NO

If YES: type (venous/arterial), location

Previous catheter-related infection: YES/NO

If YES: date, type according to the CDC definition (exit site infection, tunnel infection, pocket infection, catheter-related bloodstream infection) (for definitions see Appendix I)

**Current catheter**

- Type: tunnelled/port-a-cath
- Internal diameter:
- Internal volume:
- Number of lumens:
- Material:
- Vein of location:
- Date of insertion:

- Tip location:
- Method of insertion: blind venipuncture, surgical cutdown, radiographically guided cannulation, ultrasound guided cannulation

**HPN**

- Date patient starts HPN:
- Number of bags per week:
- Infusion time:
- Composition: volume, all-in-one, without lipids, lipids once per week, other solutions
- Use of pump for HPN: YES/NO
- Person taking care of the catheter at home: patient, caregiver, home care company

**Other uses for the catheter:**

Is the catheter used for infusing drugs? YES/NO

If YES, what type?

Iron

Antibiotics

Specify

Is the catheter used for extracting blood samples? YES/NO

**Flushing/lock technique:**

1. Saline and heparin
2. Only saline
3. Only heparin
4. Others (specify): sterile water, etanol, antibiotic, taurolidin, citrate, citrulin..

If your answer is 1.or 3., please complete the characteristics of the heparin flush/lock:

Volume of infusion:

Concentration (units/ml):

Do you withdraw heparin before the infusion of the HPN bag: YES/NO

If your answer is 1.or 2., please complete the characteristics of the saline flush:

Volume of infusion:

If your answer is 4., please complete the characteristics of the flush/lock:

Volume of infusion:

Type: sterile water, etanol, antibiotic, taurolidin, citrulin, citrate..

Do you withdraw the liquid of the lock before the infusion of the HPN bag: YES/NO

**Anticoagulation:**

Do you use oral anticoagulants?

1. Yes
2. No

If your answer is 1., what is your INR target?:

Do you use low-molecular-weight heparin?

1. Yes
2. No

Do you use heparin in the HPN bag?

1. Yes
2. No

If your answer is 1., what dose/concentration of heparin do you use in the bag?:

**Study chronogram:**

| | Baseline | $7^{th}$ day (not mandatory) | $3^{th}$ month | $6^{th}$ month | $12^{th}$ month |
|---|---|---|---|---|---|
| Clinical evaluation | | | | | |
| Doppler | | | | | |
| Infection/occlusion/venous thrombosis | | | | | |

**Appendix I**

Definitions for catheter-related infections (Centers for Disease Control and Prevention. Guidelines for the Prevention of Intravascular catheter-related infections. MMWR 2002; 51(No. RR-10): 1-29).

- **Exit site infection:** erythema or induration within 2 cm of the catheter exit site, in the absence of concomitant bloodstream infection (BSI) and without concomitant purulence.
- **Tunnel infection:** tenderness, erythema, or site induration > 2 cm from the catheter site along the subcutaneous tract of a tunnelled catheter, in the absence of concomitant BSI.
- **Pocket infection:** purulent fluid in the subcutaneous pocket of a totally implanted intravascular catheter that might or might not be associated with spontaneous rupture and drainage or necrosis of the overlaying skin, in the absence of concomitant BSI.
- **Catheter-related BSI:** bacteremia/fungemia in a patient with an intravascular catheter with at least one positive blood culture obtained from a peripheral vein, clinical manifestations of infections (i.e., fever, chills, and/or hypotension), and no apparent source for the BSI except the catheter. One of the following should be present: a positive semiquantitative (> 15 CFU/catheter segment) or qualitative (> $10^3$ CFU/catheter segment) culture whereby the same organism (species and antibiogram) is isolated from the catheter segment and peripheral blood; simultaneous quantitative blood cultures with a $\geq$ 5:1 ratio CVC versus peripheral; differential period of CVC culture versus peripheral blood culture positivity of > 2 hours.

## BIBLIOGRAPHY


1. Howard L, Ashley C. Management of complications in patients receiving home parenteral nutrition. Gastroenterol 2003; 124: 1651-61.
2. Ryder M. Evidenced-based practice in the management of vascular access devices for home parenteral nutrition therapy. JPEN 2006; 30: S82-93.
3. Intravenous Nursing Society. Infusion nursing standards of practice. J Infusion Nurs 2000; 23(6suppl): S53-4.
4. Williams NMA, Wales S, Scout NA, Irving MH. The incidence and management of catheter occlusion in patients on home parenteral nutrition. Clin Nutr 1993; 12: 344-9.
5. Randolph AG, Cook DJ, Gonzales CA, Andrew M. Benefit of heparin in central venous and pulmonary artery catheters: a meta-analysis of randomized controlled trials. Chest 1998; 113(1): 165-71.
6. Stephenson J. Can a common medical practice transform candida infections from benign to deadly? JAMA 2001; 28: 2531-2.
7. Steiger E. Consensus statements regarding optimal management of home parenteral nutrition (HPN) access. JPEN 2006; 30: S94-5.
8. Garrelts JC, LaRocca J, Ast D, Smith DF, Sweet DE. Comparison of heparin and 0,9% sodium chloride injection in the maintenance of indwelling intermitent i.v. devices. Clin Pharm 1989; 8(1): 34-9.
9. Peterson FY, Kirchhoff KT. Analysis of the research about heparinized versus nonheparinized intravascular lines. Heart Lung 1991; 20: 631-42.
10. Goode CJ, Titler M, Rakel et al. A meta-analysis of effects of heparin flush and saline flush: quality and cost implications. Nurs Res 1991; 40: 324-30.
11. Bozzetti F, Mariani L, Boggio Bertinet D, et al. Central venous catheter complications in 447 patients on home parenteral nutrition: an analysis of over 100.000 catheter days. Clin Nutr 2002; 21 (6): 475-85.
12. Smith S, Dawson S, Hennessey R, Andrew M. Maintenance of the patency of indwelling central venous catheters: is heparin necessary? Am J Pediatr Haematol Oncol 1991; 13(2): 141-3.
13. Shang E, Geiger N, Sturm MD, Post S. Heparin complication in parenteral nutrition via intravenous port system. Clin Nutr 2003; 22(1): S77.

14. Pennington CR. Central vein thrombosis during home parenteral nutrition. Clin Nutr 1995; 14(Suppl 1): 52-5.
15. Gaitini D, Beck-Razi N, Haim N, Brenner B. Prevalence of upper extremity deep venous thrombosis diagnosed by color doppler duplex sonography in cancer patients with central venous catheters. J Ultrasound Med 2006; 25: 1297-303.
16. Bozzetti F, Scarpa D, Terno G, et al. Subclavian vein thrombosis due to indwelling catheters: A prospective study on 52 patients. JPEN 1983; 7: 560-2.
17. Fabri PJ, Mirtillo JM, Ruberg RL, et al. Incidence and prevention of thrombosis of the subclavian vein during total parenteral nutrition. Surg Gynecol Obstet 1982; 155: 238-40.
18. Klerk CPW, Smorenburg SM, Büller HR. Thrombosis prophylaxis in patient populations with a central venous catheter. A systematic review. Arch Intern Med 2003; 163: 1913-21.
19. Bern MM, Bothe A, Bristian B, et al. Prophylaxis against central vein thrombosis with low dose warfarin. Surgery 1986; 99: 216-21.
20. Veerabagu MP, Tuttle-Newhall J, Maliakkal R, Champagne C, Mascioli EA. Warfarin and reduced central venous thrombosis in home total parenteral nutrition patients. Nutrition 1995; 11(2): 142-4.
21. Bern MM, Lockich J, Wallach SR, et al. Very low doses of warfarin can prevent thrombosis in central venous catheters. Ann Intern Med 1990; 112: 423-8.
22. Newall F, Barnes C, Savoia H, Campbell J, Monagle P. Warfarin therapy in children who require long-term total parenteral nutrition. Pediatrics 2003; 112: 386-8.
23. Monreal M, Alastrue A, Rull M, et al. Upper extremity deep venous thrombosis in cancer patients with venous access devices—prophylaxis with a low molecular weight heparin (Fragmin). Thromb Haemost 1996; 75(2): 251-3.
24. Mismetti P, Mille D, Laporte S, et al. Low-molecular-weight heparin (nadroparin) and very low doses of warfarin in the prevention of upper extremity thrombosis in cancer patients with indwelling long-term central venous catheters: a pilot randomized trial. Haematologica 2003; 88: 67-73.
25. Kirkpatrick A, Rathbun S, Whitsett T, Raskob G. Prevention of central venous catheter-associated thrombosis: a meta-analysis. Am J Med 2007; 120: 901-10.

26. Rawson KM, Newburn-Cook CV. The use of low-dose warfarin as prophylaxis for central venous catheter thrombosis in patients with cancer: a meta-analysis. Oncol Nurs Forum 2007; 34(5): 1037-43.
27. Cunningham MS, White B, Hollywood D, O'Donnell J. Primary thromboprophylaxis for cancer patients with central venous catheters, a reappraisal of the evidence. Br J Cancer 2006; 94: 189-94.
28. ASPEN Board of directors. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN 2002; 26: 1SA-137.
29. Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN guidelines on parenteral nutrition: central venous catheters (access, care, diagnosis and therapy of complications). Clin Nutr 2009; 28: 365-77.
30. Staun M, Pironi L, Bozzetti F, Baxter J, Forbes A, Joly F, Jeppesen P, Moreno J, Hébuterne X, Pertkiewicz M, Mühlebach S, Shenkin A, Van Gossum A. ESPEN guidelines on parenteral nutrition: home parenteral nutrition (HPN) in adult patients. Clin Nutr 2009; 28: 467-79.