



**Centre for Clinical Effectiveness**

Enhancing patient outcomes through clinical application of the best available evidence

**EVIDENCE CENTRE  
CRITICAL APPRAISAL**  
Series 2002: Therapy

## **Heparin flushing of peripherally placed central venous catheters**

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## **SUMMARY STATEMENT**

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Muggli, EE (2002). Heparin flushing of peripherally placed central venous catheters. [Online]. Available from <http://www.med.monash.edu.au/healthservices/cce>

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## REQUEST

Is there evidence that flushing long-term intravenous access devices with heparin is more effective than flushing with normal saline? If so, what strength heparin is indicated?

## REQUESTED BY

Mr Steve Guinea, Clinical Teacher, Continuing education, Dandenong Hospital.

## METHODOLOGY

### Search Strategy

The Centre for Clinical Effectiveness defines the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to pre-defined National Health and Medical Research Council (NHMRC, 2000) criteria (see Appendix 1).

First, we search for systematic reviews, evidence based clinical practice guidelines, health technology assessments and randomised controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalisable or have other methodological difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Such studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

### Details of Evidence Request

Patients (Subjects): Adults or children with peripherally inserted central venous catheters

Intervention: Intermittent flushing with heparin

Comparisons: Intermittent flushing with Saline

Outcomes: Catheter patency or incidence of catheter occlusion

### Search terms

(see Appendix 2 for exact search strategy)

Patient (Subject): central venous catheterisation, PICC

Intervention: heparin

Comparison: N/A

Outcome: patency, occlusion

## **Resources Searched**

We searched the following databases and Internet websites:

The Cochrane Library (CD-ROM) 2001 Issue 1

Medline (OVID)- 1966 to December April, Week1 2002

CINAHL (OVID)- 1982 to April 2002

Current Contents (OVID)- 1993 Week 26 to 2002 Week 16

PubMed National Library of Medicine, accessed 15 April, 2002

PREMEDLINE (OVID)- April 15, 2002

Australasian Medical Index- accessed 15 April, 2002

National Guideline Clearinghouse- accessed 15 April, 2002

## **Refinements, Searching & Reporting Constraints**

We included items of evidence that were available to us on 15 April, 2002. Critical appraisal was performed on the subset of studies published in English.

## RESULTS

From our sources we identified 6 potentially relevant articles. We obtained the full text of these articles to determine their relevance.

After examination of the 6 articles, the following were excluded as follows:

Reason for exclusion	Number
Level IV evidence	
Narrative reviews	1
Foreign language articles	1
Means of heparin administration other than intermittent flushing or inappropriate control group	2
<b>Total</b>	<b>4</b>

2 articles then remained for appraisal. These studies are classified as follows:

Study Design	Number included
<b>Systematic reviews or meta-analyses</b>	<b>1</b>
Evidence-based clinical practice guidelines	0
Randomised controlled trials	0
Pseudo-randomised controlled trials	0
<b>Controlled trials, cohort or case-control analytic studies</b>	<b>1</b>
<b>Total</b>	<b>2</b>

Based on our refinements, searching and reporting constraints we are reasonably confident these articles represent the most relevant findings published to date.

### Summary of findings

Our search identified no articles with direct relevance to peripherally inserted central venous catheters and intermittent flushing of heparin. The two articles appraised in this report refer to central venous catheters, one of which is a systematic review of randomised controlled trials published in 1997. This review addressed 3 different forms of heparin prophylaxis: intermittent flushing, continuous infusion and subcutaneous injection. With regards to thrombotic catheter occlusion or formation of a fibrin sleeve on the outside of the catheter no significant improvement could be demonstrated when heparin was used instead of saline. Similarly, in the second study appraised, the authors concluded that saline might be just as effective as heparin-flushes to maintain patency of a central venous catheter.

One additional study which might be of interest was that of Hoffer et al (not appraised). This was a randomised controlled trial of valved versus clamped PICCs. Unfortunately only the clamped catheters were flushed with a heparin solution, so direct comparison was not possible, but the authors found that even with saline-flushed valved PICCs there was a significant reduction in catheter occlusion and catheter-related infection when compared with clamped catheters.

# EVIDENCE SUMMARIES

## Format

Evidence summaries are presented as spreadsheets attached to this report. Each spreadsheet contains the article citation, details of the study design, patient description, scientific validity of the article, results, and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewer.

## REFERENCES

### ARTICLES CRITICALLY APPRAISED FOR THIS REPORT

Randolph, A. G., D. J. Cook, et al. (1998). "Benefit of heparin in central venous and pulmonary artery catheters: a meta-analysis of randomized controlled trials." Chest 113(1): 165-71.

Stephens, L. C., W. D. Haire, et al. (1997). "Normal saline versus heparin flush for maintaining central venous catheter patency during apheresis collection of peripheral blood stem cells (PBSC)." Transfusion Science 18(2): 187-93.

### ARTICLES NOT CRITICALLY APPRAISED

Sterba, K. G. (2001). "Controversial issues in the care and maintenance of vascular access devices in the long-term/subacute care client." Journal of Infusion Nursing 24(4): 249-54.

Shah, P. and V. Shah (2001). "Continuous heparin infusion to prevent thrombosis and catheter occlusion in neonates with peripherally placed percutaneous central venous catheters." Cochrane Database Syst Rev (3): CD002772.

Gratadou, D., A. Elias, et al. (2001). "[Venous thrombosis from central venous catheterization in oncology]." Presse Medicale 30(6): 298-301.

Hoffer, E.K. (1999). "Prospective randomized comparison of valved versus nonvalved peripherally inserted central vein catheters." American Journal of Roentgenology 173(5): 1393-1398.

# APPENDIX 1

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## Levels Of Evidence

Based on "How to use the evidence: assessment and application of scientific evidence" (National Health & Medical Research Council, Canberra, 2000):

Level I		Evidence obtained from a systematic review (or meta-analysis) of all relevant randomised controlled trials.
Level II		Evidence obtained from at least one randomised controlled trial.
Level III	-1	Evidence obtained from pseudo-randomised controlled trials (alternate allocation or some other method).
	-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case control studies or interrupted time series with a control group.
	-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.
Level IV		Evidence obtained from case series, either post-test or pretest/post-test.

## APPENDIX 2

### Search strategy

	Search terms for MEDLINE, CINAHL, PREMEDLINE, Current Contents
1	Randomised controlled trial.pt
2	Controlled clinical trial.pt
3	Randomised controlled trials.sh
4	Random allocation.sh
5	Double blind method.sh
6	Single blind method.sh
7	Or/1-6
8	(animal not human).sh
9	7 not 8
10	Clinical trial.pt
11	Exp clinical trials/
12	(clin\$ adj25 trial\$).ti,ab
13	((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab
14	Placebos.sh
15	Placebo\$.ti,ab
16	Random\$.ti,ab
17	Research design.sh
18	Or/10-17
19	18 not 8
20	19 not 9
21	Comparative study.sh
22	Exp evaluation studies.sh
23	Follow up studies.sh
24	Prospective studies.sh
25	(control\$ or prospective\$ or volunteer\$).ti,ab
26	Or/21-25
27	26 not 8
28	27 not (9 or 20)
29	9 or 20 or 28
30	Exp Catheterization, Central venous/
31	Central catheter.tw

32	PICC.tw
33	Or/ 30-32
34	Exp HEPARIN/
35	Heparin.tw
36	34 or 35
37	33 and 36
38	Occlusion.mp
39	37 and 38
40	Patency.mp
41	37 and 40

\$ wildcard indicating truncation

	<b>Search terms for Pub Med</b>
1	(Heparin and catheter occlusion) AND (randomised controlled trial [PTYP] OR drug therapy[SH] OR therapeutic use [SH:NOEXP] OR random*[WORD])
2	(heparin and catheter) AND systematic[sb]
3	(heparin and catheter occlusion) AND systematic[sb]

	<b>Search terms for Cochrane Library</b>
1	Heparin and central next catheter

	<b>Search terms for Australasian Medical Index and National Guidelines Clearinghouse</b>
1	Heparin and catheter

<p><b>Evidence Summary Therapy/Intervention</b></p> <p><b>Heparin flushing of peripherally placed central venous catheters</b></p>	<p><b>Study 1</b></p> <p>Randolph AG, Cook DJ, Gonzales CA <i>et al.</i> (1998). Benefit of heparin in central venous and pulmonary artery catheters: a meta-analysis of randomised controlled trials. <i>Chest</i> 113: 165-171.</p>	<p><b>Study 2</b></p> <p>Stephens LC, Haire WD, Tarantolo S <i>et al.</i> (1997) Normal saline versus heparin flush for maintaining central venous catheter patency during apheresis collection of peripheral blood stem cells (PBSC). <i>Transfusion science</i> 18: 187-193.</p>
<p><b>STUDY DESIGN &amp; NHMRC LEVELS OF EVIDENCE</b></p>	<p>Level I – Systematic review</p>	<p>Level III-2 – Controlled clinical trial</p>
<p><b>DESCRIPTION:</b> Patients (subjects), Intervention, Comparisons, Outcomes, Inclusion &amp; Exclusion Criteria</p>	<p><b>Patients (subjects):</b> Adult or paediatric with central venous or pulmonary artery catheters  <b>Intervention:</b> prophylactic heparin infused through the catheter, given subcutaneously or bonded to the catheter  <b>Comparisons:</b> control group without saline  <b>Outcomes:</b> catheter patency, catheter thrombus or catheter-related vessel thrombosis, catheter colonisation, catheter-related bacteraemia, or septicaemia  <b>Inclusion Criteria:</b> Randomised controlled clinical trials with randomisation by individual patient.  <b>Exclusion Criteria:</b> Studies where more than 40% of observations were not reported after randomisation.</p>	<p><b>Patients (subjects):</b> Patients requiring peripheral blood stem cell transplantation because of marrow involvement by malignancy or prior marrow irradiations.  <b>Intervention:</b> 10-20ml saline flush of apheresis catheters, followed by 5ml of 100U/ml heparin  <b>Comparisons:</b> Catheters flushed with saline only.  <b>Outcomes:</b> Slow flow rate, radiographically demonstrated thrombotic occlusion and empiric urokinase injections.  <b>Inclusion Criteria:</b> Subjects (as above) were consecutively recruited from December 1994 to December 1995. A total of 86 catheters were evaluated. The control group consisted of a convenience sample of 33 women with breast cancer, the heparin group included 53 patients.  <b>Exclusion Criteria:</b> N/A</p>
<p><b>VALIDITY:</b> Methodology, rigour, selection</p>	<p><b>Focussed question:</b> This systematic review was conducted to “resolve and synthesize the conflicting literature, and to address the potential problem of type II error in interpreting individual studies”.  <b>Search strategy:</b> An appropriate search strategy was detailed, listing the source databases. Reference lists of potentially relevant articles were reviewed, package inserts of catheter kits were searched for published and unpublished references.</p>	<p><b>Randomisation:</b> Patients were not randomly allocated. (See inclusion criteria).  <b>All patients accounted for:</b> Yes.  <b>Patients treated equally:</b> N/A.  <b>Similar groups:</b> Yes, for age and mean duration of each apheresis course.  <b>Gender:</b> There were 33 subjects in the control group, all of which were female. Only 21 out of 53 subjects in the treatment group were female.</p>

	<p><b>Methodological Quality:</b> Out of 15 trials of heparin use in central venous catheters 12 met all the selection criteria and 2 out of 2 trials of heparin use in pulmonary artery catheters were also included. The authors “combined data from trials using various doses of prophylactic heparin, including unfractionated heparin dosing regimens of 1U/ml, 3U/ml, 50U q 12h, 5000 U intermittently, and 2500U daily of subcutaneous low molecular weight heparin”, and also heparin bonded catheters.</p> <p><b>Assessed validity:</b> Where data was pooled in the analysis, a test of heterogeneity of variance was performed. For all the results presented, the tests of heterogeneity were non-significant.</p>	<p><i>Number of apheresis procedures:</i> The control group had a total of 197 procedures and the heparin group had a total of 422 procedures.</p>
<p><b>RESULTS:</b> Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p><b>Relevant outcomes:</b> 3 trials included in the analysis used intermittent flushing of 50 U q 12 hrs, 5000U q 6 hrs and 5000U q 12hrs. However, the data presented came from a pooled analysis.</p> <p><b>Catheter thrombus or fibrin sheath:</b> There was a trend for heparin to be beneficial in preventing catheter thrombi or fibrin sleeves, however this did not reach significance (RR 0.66; 95% CI, 0.42, 1.05). Results from 4 trials.</p> <p><i>Catheter-related deep vein thrombosis:</i> “Prophylactic heparin significantly decreases central venous catheter-related thrombosis by 57% (RR 0.43; 95%CI, 0.23, 0.78)”. Results from 7 trials.</p> <p><i>Catheter colonisation:</i> “Heparin significantly decreases bacterial colonisation of the catheter (RR 0.18; 95% CI, 0.22, 0.87)”. Results from 3 trials.</p> <p><i>Catheter-related bacteraemia and sepsis:</i> “There was a strong trend for a reduction in catheter-related bacteraemia with use of heparin (RR 0.26; 95% CI, 0.07, 1.03)”. Results from 4 trials.</p>	<p>“In both groups, more than a third of the patients had at least one apheresis procedure interrupted by slow flow. Thrombotic catheter occlusion was objectively demonstrated by radiographic contrast injection in 21% of the catheters in the non-heparin group and 17% in the heparin group.”</p> <p>No significant differences were found between the heparin and non-heparin groups (p=0.08, log rank test).</p> <p><i>Other findings independent of flushing technique:</i> The only medications the study subjects received during the time period of stem cell collection the growth factors GM-CSF (259µg/M<sup>2</sup>) or G-CSF (10µg/kg). Radiographically demonstrated catheter thrombosis occurred in 22% of the 73 patients who received GM-CSF and in none of the patients who received G-CSF (13 patients) (p=0.05, Fisher’s exact test).</p>

<p><b>AUTHOR(S) CONCLUSIONS:</b> Limitations, implications for practice and research</p>	<p>"In this systematic review, we found that prophylactic use of heparin significantly decreases central venous catheter-related thrombosis, decreases bacterial colonisation of the catheter, and may decrease catheter-related bacteraemia.</p>	<p>"Prophylaxis against catheter thrombosis with heparin-flushes is clearly inadequate and no more efficacious than saline flushing. The focus of prophylaxis must be directed toward altering coagulation at the most frequent site of thrombotic occlusions- the blood flowing on the outside of the catheter tip". Systemic anticoagulation should particularly be considered for patients who are at increased risk of forming thrombotic catheter occlusions (such as the study subjects who received GM-CSF).</p>
<p><b>OUR COMMENTS:</b> Opportunity for bias, weakness and strength</p>	<p><b>Potential for bias:</b> The methodology of the systematic review is designed to minimise bias. <b>Weakness/es:</b> Although pooled data from different studies showed no significant heterogeneity, the studies combined utilised a variety of methods of heparin delivery and it is unclear if intermittent flushing is as effective as continuous infusion. The studies in this review have not addressed the complications associated with unfractionated heparin such as autoimmune thrombocytopenia. <b>Strength/s:</b> This is a well designed review of the best available evidence</p>	<p><b>Potential for bias:</b> Blinding of subjects or investigators was not mentioned. Study groups were not entirely comparable. Treatment was not randomly allocated. <b>Weakness/es:</b> Findings should be interpreted with caution because the study design was very open to bias. <b>Strength/s:</b> This study included concurrent controls. Several clearly defined and relevant outcomes were measured. <b>Other:</b> The reported total number of subjects and the number of subjects in the control and heparin groups differ in the abstract and the full text of the article. No explanation was given.</p>

## EXPLANATION OF TERMINOLOGY USED IN SPREADSHEET

**Level of evidence:** A hierarchy of study evidence that indicates the degree to which bias has been eliminated in the study design.

**Focussed question:** The review should address a clearly focused issue, in terms of the population studies, the intervention given and the outcomes considered.

**Search strategy:** A description of methods used to identify relevant studies from various computer databases and other sources.

**Systematic review:** The process of systematically locating, appraising and synthesising evidence from scientific studies in order to obtain a reliable overview.

**Intervention:** A therapeutic procedure such as treatment with a pharmaceutical agent, surgery, a dietary supplement, a dietary change or psychotherapy.

**Randomisation:** A process of allocating participants to treatment or control group within a controlled trial by using a random mechanism, such as coin toss, random number table or computer-generated random numbers. Study subjects have an equal chance of being allocated to an intervention or control group; thus, the two groups are comparable. Randomisation ensures that the results are not biased by the selection of particular types of patients to receive a specific therapy.

**Blinding:** Blinding or masking is a process used in epidemiological studies and clinical trials in which the observers and the subjects have no knowledge as to which treatment group's subjects are assigned. It is undertaken in order to minimise bias occurring in patient response and outcome measurement.

**All patients accounted for:** Once patients are randomly allocated to a specific group and withdraw before study conclusion, they have to be accounted for in order to ensure that patients withdrawing from the study are not significantly different from those continuing in the study. The final analysis should be conducted on an intention-to-treat basis, which includes the results of withdrawn patients in the analysis.

**Patients treated equally:** To be able to attribute any difference in the observed outcome to the intervention, study patients need to be treated equally in every way except for the intervention being evaluated.

**Similar groups:** Baseline characteristics of patients that are also likely to affect results should be evenly distributed between the intervention and control groups. Following proper randomisation, patients' attributes would be expected to be equally distributed between groups.

### Validity:

Of measurement: an expression of the degree to which a measurement measures what it purports to measure; it includes construct and content validity.

Of study: the degree to which the inferences drawn from the study are warranted when account is taken of the study methods, the representativeness of the study sample, and the nature of the population from which it is drawn (internal and external validity, applicability, generalisability).

**Type I error:** The error of rejecting a true null hypothesis; declaring a difference when there is not.

**Type II error:** The error of failing to reject a false null hypothesis; declaring a difference does not exist when in fact it does.

**Test of heterogeneity:** Test of constancy of variance across factors in the groups under study.

**Potential for bias:** Bias is a systematic deviation of a measurement from the 'true' value leading to either an over (or under) estimation of the treatment effect. Bias can originate from many different sources (including allocation of patients, measurement, interpretation, publication and review of data).