Central venous access sites for the prevention of venous thrombosis, stenosis and infection in patients requiring long-term intravenous therapy (Review)

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[Intervention Review]

Central venous access sites for the prevention of venous thrombosis, stenosis and infection in patients requiring long-term intravenous therapy

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Editorial group: Cochrane Anaesthesia Group.
Publication status and date: Edited (no change to conclusions), published in Issue 2, 2008.
Review content assessed as up-to-date: 16 April 2007.

Citation: Hamilton HC, Foxcroft D. Central venous access sites for the prevention of venous thrombosis, stenosis and infection in patients requiring long-term intravenous therapy. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD004084. DOI: 10.1002/14651858.CD004084.pub2.

ABSTRACT

Background

Central venous access (CVA), in which a large bore catheter is routed through a vein in the neck, upper chest or femoral area, is needed to give drugs that cannot be given by mouth or via a conventional cannula in the arm.

Objectives

To establish whether either the jugular, subclavian or femoral CVA routes result in a lower incidence of venous thrombosis, venous stenosis or infection related to CVA devices.

To determine whether the circumference of a long-term central venous access device influences the incidence of venous thrombosis, venous stenosis or infection related to CVA devices.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2006, Issue 4), MEDLINE, CINAHL, EMBASE (from inception to December 2006), reference lists of identified trials, and bibliographies of published reviews. We also contacted researchers in the field. There were no language restrictions.

Selection criteria

We included randomized controlled trials comparing central venous catheter insertion routes.

Data collection and analysis

Two authors assessed potentially relevant studies. We resolved disagreements by discussion. Relevant outcomes were: venous thrombosis, venous stenosis, infection related to CVA devices, mechanical complications (e.g misplaced catheter, minor bleeding, haematoma).

Main results

We considered 83 studies for inclusion in the review. Six studies appeared eligible but five were subsequently excluded because they did not randomize participants for either site of access or catheter circumference size. One study was a high quality block randomized controlled trial. Allocation concealment was good and randomization was by a central computer. In all, 293 patients were randomized to a femoral or a subclavian CVA group. Results from this one trial were as follows

1. Catheter-related infectious complications

Infectious complication (colonization with or without sepsis: the relative risk (RR) was 4.57 (95% confidence interval (CI) 1.95 to 10.71) favouring subclavian over femoral access.

Major infectious complications (sepsis with or without bacteremia): the RR was 3.04 (95% CI 0.63 to 14.82) favouring subclavian access.

Colonized catheter (greater than 103 colony-forming units/mL of gram positive microorganisms): the RR was 3.65 (95%CI 1.40 to 9.56) favouring subclavian access.

Colonized catheter (greater than 103 colony-forming units/mL of gram negative microorganisms): the RR was 5.41 (95% CI 1.61 to 18.15) favouring subclavian access.

2. Catheter-related mechanical complications

Overall complications (arterial puncture, minor bleeding, haematoma, misplaced catheter): the RR was 0.92 (95% 0.56 to 1.51) favouring subclavian access.

3. Catheter-related thrombotic complications

Catheter-related thromboses (fibrin sleeves, major and complete thrombosis): the RR was 11.53 (95% CI 2.80, to 47.52) favouring subclavian access.

Authors' conclusions

Subclavian CVA is preferable to femoral CVA. Further trials of subclavian versus femoral or jugular CVA are needed. Research on the impact of catheter circumference on catheter-related complications is required.

PLAIN LANGUAGE SUMMARY

Central venous access sites to prevent venous blood clots, blood vessel narrowing and infection in patients requiring long-term intravenous therapy

Central venous access (CVA) involves a large bore long-term use catheter routed through a vein in the neck, upper chest or groin (femoral) area, to give drugs that cannot be given by mouth or via a conventional needle (or tube (cannula) in the arm over the longer term. This review examined whether there was any evidence to show that CVA through any one site (neck, upper chest or femoral area) was better than any other. Results from one high quality randomized trial indicated that the upper chest area was better than the femoral area because of a lower risk of infection and blood clots forming on the catheter tip. No studies compared the neck access site with other sites so no conclusions can be drawn about the relative advantages or disadvantages of access in the neck.

BACKGROUND

Central venous access (CVA), in which a large bore catheter, or venous access device (VAD) is placed in a vein in the neck, groin or upper chest, is needed to give drugs that cannot be given by mouth or via a conventional cannulae in the arm. Drugs administered via these catheters include chemotherapy, intravenous feeding, drugs

acting on the heart and blood vessels, blood products and other agents. These treatments may need to be continued for a long time and therefore, a reliable, safe administration route is essential. CVA may also be required in intensive care settings to assess venous and cardiac function.

To gain CVA a silicone or polyurethane tube is passed into the venous system, often either via the subclavian vein in the shoulder, the jugular vein in the neck or less commonly via the femoral vein in the groin. The distal tip of the central venous catheter (CVC) is ideally positioned in the lower third of the superior vena cava (SVC, the largest vein in the upper chest) or the inferior vena cava if a femoral approach is used.

Concerns have arisen over the number of patients in whom the vein that the catheter is in becomes blocked by a blood clot (thrombosis) or by narrowing of the vessel (stenosis) around the catheter. One third of all thromboses of the upper extremity are related to intravenous catheters (Yellin 1996). The clinical picture of central venous thrombosis is recognized by the development of pain and swelling of the neck and arm and a positive venogram, which is performed by administering a radio-opaque dye into the affected vein (Alhimyary 1996). Prognosis for patients with catheter-related venous thrombosis is good in uncomplicated cases (Hye 1996). However, certain clinical groups for example patients with malignant disease, appear to be at a greater risk of developing venous thrombosis and warfarin is used to reduce the risk of thrombus formation within the vein that the CVC is in (Bern 1990). Severe cases of venous thrombosis, involving virtual total occlusion of the SVC, can be life threatening and involve

high-cost therapy, prolonged hospital stay and lifelong anticoagulant therapy, which incurs considerable healthcare costs and inconvenience to patients.

Whilst considerable research has been performed on the subject of catheter-related sepsis (CRS) (Raad 2002), and a number of studies have compared the risks of infection between subclavian and jugular venous cannulation, there does not appear to be as much research evidence on whether the subclavian or jugular route is preferable in the avoidance of venous thrombosis or stenosis. A recent review and meta-analysis (Reusch 2002) of non-randomized studies published up to the year 2000 reported that there were significantly more arterial punctures with jugular access compared with subclavian access, but that there were significantly fewer malpositions with jugular access. There was no evidence of any difference in the incidence of haemato- or pneumothorax and vessel occlusion in this review (Reusch 2002). The authors concluded that selection bias couldnot be ruled out.

There is considerable observational data that the femoral insertion site is associated with higher rates of catheter-related sepsis (CRS) and thrombosis (Goetz 1998; Lorente 2005). This data is inconsistent (Deshpande 2005), hence, the need for

well-designed clinical trials.

This systematic review assessed the evidence from controlled trials on whether the incidence of venous thrombosis, venous stenosis or infection related to CVA devices varies with the site of access and the circumference of the catheter used.

OBJECTIVES

1. To establish whether either the jugular, subclavian or femoral CVA routes result in a lower incidence of venous thrombosis, venous stenosis or infection related to CVA devices.

2. To determine whether the circumference of a long-term central venous access device influences the incidence of venous thrombosis, venous stenosis or infection related to CVA devices.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) or controlled clinical trials (CCTs).

Types of participants

We included adults over 16 years of age with any disease process requiring proposed long-term intravenous therapy. We excluded those trial participnats requiring short-term intravenous therapy via the central venous route. We included patients receiving anticoagulation agents (warfarin, fragmin or full heparin) in this review but planned to undertake subgroup analysis on this group.

Types of interventions

CVCs implanted for long-term use (intended to be in situ for at least one month). Immediate complications related to short term central venous cannulation performed in acutely unwell patients in whom aetiology may be multi factorial were excluded. We included:
1. any CVC facilitating the administration of intravenous therapy via the central venous route;
2. polyurethane and silicone plastic catheter materials;
3. any size CVC ;
4. CVCs with any number of lumens;
5. only CVCs inserted via the subclavian, jugular or femoral veins on either the left or right side.

Types of outcome measures

Primary outcomes

1. Venous thrombosis
2. Venous stenosis
3. Infection related to CVA devices
4. Mechanical complications (e.g. catheter fracture)

Secondary outcomes

1.Mechanical complications (e.g. misplaced catheter, minor bleeding, haematoma) that were related to insertion rather than long-term use

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2006, Issue 4), MEDLINE (1966 to December 2006), EMBASE (1980 to December 2006) and CINAHL (1982 to December 2006) for RCTs and CCTs relating to CVA via the subclavian, jugular and femoral venous access routes. We used the Cochrane highly sensitive search strategies I and II, adapted for all databases (Higgins 2005).

For specific information regarding our search strategies please see Appendix 1 (CENTRAL); Appendix 2 (Ovid MEDLINE); Appendix 3 (EMBASE) and Appendix 4 (CINAHL)

Searching other resources

We searched bibliographies of published trials and conference proceedings.

We contacted prominent authors in the field and manufacturers of cannulae for knowledge of unpublished trials.

We did not undertake any hand searching of entire journals for the first version of this review.

We did not impose any language or date restrictions.

Data collection and analysis

We independently extracted data using a data extraction checklist and discussed conclusions. We resolved any disagreements through discussion. We assessed the quality and validity of trials using a standardized methodological checklist (Schulz 1995). We contacted trial authors for missing data, where appropriate. For categorical outcomes, estimators included relative risk and absolute risk difference. Studies were examined with the fixed-effect method, using the Cochrane statistical package Review Manager (RevMan 4.2). If studies demonstrated significantly heterogeneity the random-effects method was applied. Sub-group analyses assessing the impact of different sized VADs, materials of VADs, influence of disease process, influence of vessels being on either the right or left side, stenosis and the influence of catheter tip position on thrombotic events and infections were planned if adequate information was available.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

We identified over 500 studies that were screened for inclusion in the review, based on titles and abstracts, This was reduced to 83 on a second screen by another author. We obtained and examined these 83 studies of which only six appeared eligible for inclusion in the review. These six studies were further assessed using the data extraction proforma and process, but five were subsequently excluded (Darouiche 1999; Pemberton 1996; Raad 1997; Safdar 2002; Timsit 1996) because they did not randomize participants by site of access or catheter circumference size and therefore, they could not be included in this review. Only one study (Merrer 2001) was included in this review. This study was a randomized controlled trial conducted between December 1997 and July 2000 at eight intensive care units (ICUs) in France. Four ICUs were in university-affiliated hospitals and the remaining four were in general hospitals. Only patients undergoing their first central venous catheterization during the ICU stay were eligible for the study. The eight ICUs participated in the study for a mean duration of 25 months (range 9 to 32 months). The mean duration of catheter placement was 9.3 days (SD = 6.2) for patients randomized to a femoral insertion group compared with 11.0 days (SD = 6.3) for patients randomized to a subclavian insertion group. Merrer 2001defined major complications as:

- catheter-related infection: catheter-related clinical sepsis with or without bloodstream infection;
- catheter-related mechanical complications: those complications requiring a specific therapeutic process (e.g. pneumothorax necessitating chest tube insertion or haemorrhage requiring blood transfusion or a surgical procedure);
- cathter-related thrombotic complications: complete thrombosis of subclavian or axillary veins for subclavian catheters and femoral or iliac veins for femoral catheters.

Risk of bias in included studies

The study by Merrer 2001 was a high quality block-randomized controlled trial in eight clinical treatment centres. Allocation concealment was good and randomization was by a central computer. Randomization was performed in blocks of six participants, with stratification according to centre and number of lumens. All caregivers and other research personnel were blinded to the randomization schedule and the block size. A total of 1402 eligible patients were not randomized because of exclusion criteria or patient refusal. In all, 293 patients were randomized to either a femoral or a subclavian central venous access group. Baseline characteristics were similar for patients in both groups. Catheterization was attempted in 289 of 293 patients and these patients were evaluated for mechanical complications. Of the 293 patients, 270 (93.4%) had their catheter tip cultured and were evaluated for infection complications. Amongst the 19 patients with no catheter tip culture, 7 catheters could not be inserted, 4 were grossly contaminated during removal, and 8 were removed without notification to the investigator. A smaller number of 223 (77.2%) patients were evaluated for thrombotic complications by ultrasound. Of the 66 patients in whom ultrasound was not performed, 41 died before catheter removal or ultrasound examination, 10 were discharged from hospital before examination was performed and the examination was refused or not done in 15 patients (including 7 unsuccessful catheter insertions).

Effects of interventions

As only one study was included in this review a meta-analysis was not performed. The study by Merrer 2001 reported several outcome measures that are included in this review.

Catheter-related infectious complications

Outcome 01: Infectious complications (colonization with or without sepsis): the relative risk (RR) was 4.57 (95% confidence interval 1.95 to 10.71) favouring subclavian access over femoral.
Outcome 02: Major infectious complication (sepsis with or without bacteremia): the RR was 3.04 (95% CI 0.63 to 14.82) favouring subclavian access.
Outcome 03: Colonized catheter (>10^3 colony-forming units/mL of gram positive microorganisms): the RR was 3.65 (95% CI 1.40 to 9.56) favouring subclavian access.
Outcome 04: Colonized catheter (>10^3 colony-forming units/mL of gram negative microorganisms): the RR was 5.41 (95% CI 1.61 to 18.15) favouring subclavian access.

Catheter-related mechanical complications

Outcome 01: Overall complications (arterial puncture, minor bleeding, haematoma, misplaced catheter): the RR was 0.92 ()5% CI 0.56, 1.51) favouring subclavian access over femoral access.

Catheter-related thrombotic complications

Outcome 01: Catheter-related thromboses (fibrin sleeves, major and complete thrombosis): the RR was 11.53 (95% CI 2.80, to 47.52) favouring subclavian access over femoral access.

DISCUSSION

One study (Merrer 2001) reported a high quality randomized controlled trial of catheter-related complications comparing femoral with subclavian access. The results of this single trial favour subclavian access for reduced infectious and thrombotic complications.

The study by Merrer 2001 also reported several analyses over and above the analysis provided in this Cochrane review. Using a stepwise Cox proportional hazards model, the risk of infection was increased by femoral insertion (hazards ratio (HR) =4.83; 95% CI 1.96 to 11.93), but decreased when the catheter was used for systemic antibiotic therapy (HR = 0.41; 95% CI 0.18 to 0.93). In multivariate logistic regression analysis, factors significantly associated with occurrence of a mechanical complication were: duration of catheter insertion attempt (per additional minute, odds ratio (OR) =1.05; 95% CI 1.03 to 1.08), catheter insertion at two of the participating centres (OR = 4.52; 95%CI 1.81 to 11.23) and catheter insertion during the night (OR = 2.06; 95% CI 1.04 to 4.08). The only risk factor for thrombotic complications identified in a multivariate logistic regression analysis was insertion at the femoral site (OR = 14.42; 95%CI 3.33 to 62.57).

An important characteristic of Cochrane reviews is that they focus on randomized controlled trials as providing the best evidence of effectiveness and, where possible, meta-analytic synthesis or pooling of results from individual trials. In a randomized trial, the only difference between the patients, or people, in the groups being compared is that which is of most interest, the intervention(s) under investigation. Thus, any differences in the outcomes of the people in the groups being compared will be due to either the interventions they were allocated to receive or to chance variations that will always exist between groups of people. In part because of these chance variations, the results of a single trial will rarely be sufficient. Most trials are too small and their results are not sufficiently robust against the effects of chance Ioannidis 2005. Therefore, the results from the Merrer 2001 study need to be interpreted cautiously, and further trials conducted. However, in the absence of further evidence it is probably reasonable to prefer subclavian to femoral access.

We found no studies that directly compared jugular with subclavian central venous access in a randomized controlled trial, leaving open the possibility of selection bias in the non-randomized studies meta-analysed by Reusch 2002. No studies were found that compared catheter-related complications according to catheter circumference size.

AUTHORS' CONCLUSIONS

Implications for practice

1. Based on evidence from one high quality randomized controlled trial, subclavian central venous access is preferable to femoral access because of lower risks of infectious and thrombotic complications.

Implications for research

1. We did not find any trials of subclavian versus jugular central venous access, so more evidence on whether the subclavian or the jugular access route is optimal is required.

2. We did not find any trials that examined the impact of catheter circumference on catheter-related complications. Further research is required to address this issue.

ACKNOWLEDGEMENTS

We would like to thank Drs'Duncan Young, Andrew Smith, Nathan Pace, Richard Hall, Christopher J Crnich and Bernard Coronel for their help and editorial advice during the preparation of this protocol and review.

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References to studies excluded from this review

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Raad 1997 *{published data only}*

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Yellin AE, Hood DB, Weaver FA. Axillo-subclavian vein thrombosis. In: Wilson SE editor(s). *Vascular access: principles and practice*. 3rd Edition. St Louis: Mosby, 1996: 104–9.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Merrer 2001

Methods	Randomized controlled trial
Participants	289 patients in 8 intensive care units in France receiving a first central venous catheter
Interventions	Randomized to femoral (N = 145) or subclavian (N = 144) access with a 15-or 16- cm long polyurethane standard central venous catheter inserted by a staff physician or a supervised resident physician
Outcomes	Rate and severity of mechanical, infectious and thrombotic complications
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Darouiche 1999	This study reported outcome by site of access but did not randomize by site. All catheters had similar lumen size
Pemberton 1996	This study compared sepsis between patients randomized to receive either standard or antiseptic catheters. There was no randomization by site of access. All catheters had similar lumen size
Raad 1997	This study randomized by catheter type rather than site of access. All catheters had similar lumen size
Safdar 2002	This study pooled results from two earlier RCTs but neither of these two earlier studies randomized by site of access or provided information about lumen size
Timsit 1996	This study compared tunneled versus non-tunneled catheters for jugular access only. There was no randomized comparison with other access sites. Although different lumen size catheters were used no information was provided about outcomes related to catheter circumference size within tunneled and non-tunneled groups. No further information from the authors has been obtained

DATA AND ANALYSES

Comparison 1. Femoral versus subclavian access: catheter-related infectious complications

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infectious complications (colonization with or without sepsis)	1	270	Risk Ratio (M-H, Fixed, 95% CI)	4.57 [1.95, 10.71]
2 Major infectious complication (sepsis with or without bacteremia)	1	270	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.63, 14.82]
3 Colonized catheters: gram-positive microorganisms	1	270	Risk Ratio (M-H, Fixed, 95% CI)	3.65 [1.40, 9.56]
4 Colonized catheters: gram-negative microorganisms	1	270	Risk Ratio (M-H, Fixed, 95% CI)	5.41 [1.61, 18.15]

Comparison 2. Femoral versus subclavian access: catheter-related mechanical complications

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total insertion complications (arterial puncture, minor bleeding, haematoma, misplaced catheter)	1	289	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.56, 1.51]

Comparison 3. Femoral versus subclavian access: catheter-related thrombotic complications

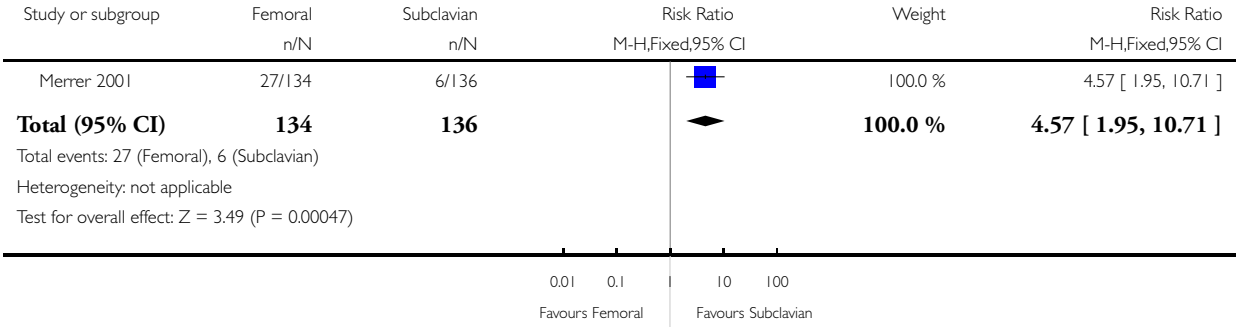
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Catheter-related thromboses (fibrin sleeves, major and complete)	1	223	Risk Ratio (M-H, Fixed, 95% CI)	11.53 [2.80, 47.52]

Analysis 1.1. Comparison 1 Femoral versus subclavian access: catheter-related infectious complications, Outcome 1 Infectious complications (colonization with or without sepsis).

Review: Central venous access sites for the prevention of venous thrombosis, stenosis and infection in patients requiring long-term intravenous therapy

Comparison: 1 Femoral versus subclavian access: catheter-related infectious complications

Outcome: 1 Infectious complications (colonization with or without sepsis)

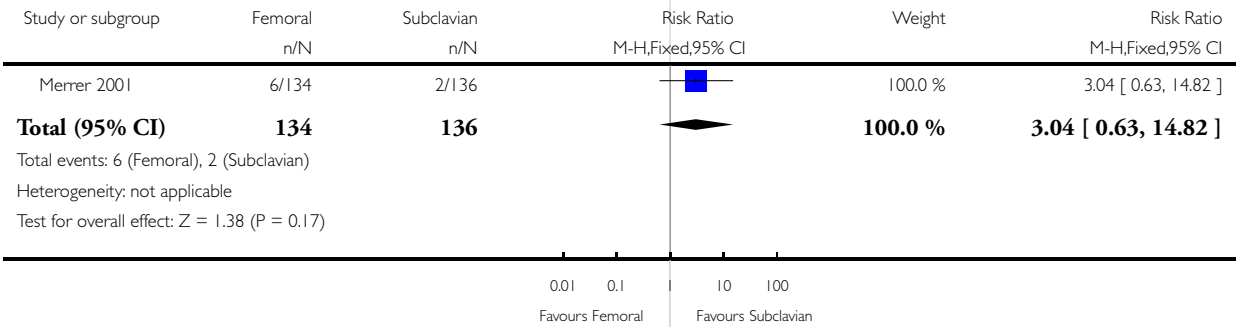


Analysis 1.2. Comparison 1 Femoral versus subclavian access: catheter-related infectious complications, Outcome 2 Major infectious complication (sepsis with or without bacteremia).

Review: Central venous access sites for the prevention of venous thrombosis, stenosis and infection in patients requiring long-term intravenous therapy

Comparison: 1 Femoral versus subclavian access: catheter-related infectious complications

Outcome: 2 Major infectious complication (sepsis with or without bacteremia)



Analysis 1.3. Comparison 1 Femoral versus subclavian access: catheter-related infectious complications, Outcome 3 Colonized catheters: gram-positive microorganisms.

Review: Central venous access sites for the prevention of venous thrombosis, stenosis and infection in patients requiring long-term intravenous therapy

Comparison: 1 Femoral versus subclavian access: catheter-related infectious complications

Outcome: 3 Colonized catheters: gram-positive microorganisms

Study or subgroup	Femoral n/N	Subclavian n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Merrer 2001	18/134	5/136		100.0 %	3.65 [1.40, 9.56]
Total (95% CI)	**134**	**136**		**100.0 %**	**3.65 [1.40, 9.56]**
Total events: 18 (Femoral), 5 (Subclavian)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.64 (P = 0.0083)					

Analysis 1.4. Comparison 1 Femoral versus subclavian access: catheter-related infectious complications, Outcome 4 Colonized catheters: gram-negative microorganisms.

Review: Central venous access sites for the prevention of venous thrombosis, stenosis and infection in patients requiring long-term intravenous therapy

Comparison: 1 Femoral versus subclavian access: catheter-related infectious complications

Outcome: 4 Colonized catheters: gram-negative microorganisms

Study or subgroup	Femoral n/N	Subclavian n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Merrer 2001	16/134	3/136		100.0 %	5.41 [1.61, 18.15]
Total (95% CI)	**134**	**136**		**100.0 %**	**5.41 [1.61, 18.15]**
Total events: 16 (Femoral), 3 (Subclavian)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.74 (P = 0.0062)					

Analysis 2.1. Comparison 2 Femoral versus subclavian access: catheter-related mechanical complications, Outcome 1 Total insertion complications (arterial puncture, minor bleeding, haematoma, misplaced catheter).

Review: Central venous access sites for the prevention of venous thrombosis, stenosis and infection in patients requiring long-term intravenous therapy

Comparison: 2 Femoral versus subclavian access: catheter-related mechanical complications

Outcome: 1 Total insertion complications (arterial puncture, minor bleeding, haematoma, misplaced catheter)

Study or subgroup	Femoral n/N	Subclavian n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Merrer 2001	25/145	27/144		100.0 %	0.92 [0.56, 1.51]
Total (95% CI)	**145**	**144**		**100.0 %**	**0.92 [0.56, 1.51]**
Total events: 25 (Femoral), 27 (Subclavian)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					

Analysis 3.1. Comparison 3 Femoral versus subclavian access: catheter-related thrombotic complications, Outcome 1 Catheter-related thromboses (fibrin sleeves, major and complete).

Review: Central venous access sites for the prevention of venous thrombosis, stenosis and infection in patients requiring long-term intravenous therapy

Comparison: 3 Femoral versus subclavian access: catheter-related thrombotic complications

Outcome: 1 Catheter-related thromboses (fibrin sleeves, major and complete)

Study or subgroup	Femoral n/N	Subclavian n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Merrer 2001	25/116	2/107		100.0 %	11.53 [2.80, 47.52]
Total (95% CI)	**116**	**107**		**100.0 %**	**11.53 [2.80, 47.52]**
Total events: 25 (Femoral), 2 (Subclavian)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.38 (P = 0.00071)					

APPENDICES

Appendix 1. CENTRAL

Search terms
1 thromb* in Clinical Trials
2 fibrin* in Clinical Trials
3 occlu* in Clinical Trials
4 block* in Clinical Trials
5 stenos* in Clinical Trials
6 infect* in Clinical Trials
7 (#1 or #2 or #3 or #5 or #6)
8 central near venous in Clinical Trials
9 CVA* in Clinical Trials
10 jugular* near subclavian* in Clinical Trials
11 jugular* near femoral* in Clinical Trials
12 subclavian* near femoral* in Clinical Trials
13 (#8 or #9 or #10 or #11 or #12)
14 (#7 and #13)

Appendix 2. Ovid MEDLINE

Search terms
1 RANDOMIZED CONTROLLED TRIAL.pt.
2 CONTROLLED CLINICAL TRIAL.pt.
3 RANDOMIZED CONTROLLED TRIALS.sh.
4 RANDOM ALLOCATION.sh.
5 DOUBLE BLIND METHOD.sh.
6 SINGLE BLIND METHOD.sh.
7 or/1-6
8 CLINICAL TRIAL.pt.
9 exp CLINICAL TRIALS/
10 (clin$ adj25 trial$).ti,ab.
11 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
12 PLACEBOS.sh.
13 placebo$.ti,ab.
14 random$.ti,ab.
15 RESEARCH DESIGN.sh.
16 or/8-15
17 7 or 16
18 (ANIMALS not HUMAN).sh.

(*Continued*)

19 17 not 18

20 thromb$.ab,ti.
21 fibrin$.ab,ti.
22 occlu$.ab,ti.
23 block$.ab,ti.
24 stenos$.ab,ti.
25 infect$.ab,ti.
26 or/20-25

27 (central adj5 venous).ti,ab.
28 CVA$.ti,ab. (1581)
29 (jugular$ adj25 subclavian$).ti,ab.
30 (jugular$ adj25 femoral$).ti,ab.
31 (subclavian$ adj25 femoral$).ti,ab.
32 or/27-31

33 26 and 32
34 19 and 33

Appendix 3. EMBASE

Search terms

1 random$.ab,ti.
2 placebo.ab,ti.
3 ((singl$ or doubl$ or trebl$ or tripl$) and (blind$ or mask$)).mp.
4 (cross-over$ or crossover$).tw.
5 randomized controlled trial/
6 phase-2-clinical-trial/
7 phase-3-clinical-trial/
8 double blind procedure/
9 single blind procedure/
10 crossover procedure/
11 Latin square design/
12 exp PLACEBOS/
13 multicenter study/
14 or/1-13
15 limit 14 to human

16 thromb$.ab,ti.
17 fibrin$.ab,ti.
18 occlu$.ab,ti.
19 block$.ab,ti.
20 stenos$.ab,ti.
21 infect$.ab,ti.

(*Continued*)

22 or/16-21

23 (central adj5 venous).ti,ab.
24 CVA$.ti,ab. (1581)
25 (jugular$ adj25 subclavian$).ti,ab.
26 (jugular$ adj25 femoral$).ti,ab.
27 (subclavian$ adj25 femoral$).ti,ab.
28 or/23-27

29 22 and 28
30 15 and 29

Appendix 4. CINAHL

Search terms
1 random$.mp.
2 clin$.mp.
3 trial$.mp.
4 (clin$ adj2 trial$).ti,ab.
5 exp Single-Blind Studies/
6 exp Clinical Trials/
7 exp Double-Blind Studies/
8 exp Triple-Blind Studies/
9 exp random assignment/
10 exp meta analysis/
11 allocate$.ti,ab.
12 or/1-11
13 thromb$.ab,ti.
14 fibrin$.ab,ti.
15 occlu$.ab,ti.
16 block$.ab,ti.
17 stenos$.ab,ti.
18 infect$.ab,ti.
19 or/13-18
20 (central adj5 venous).ti,ab.
21 CVA$.ti,ab. (1581)
22 (jugular$ adj25 subclavian$).ti,ab.
23 (jugular$ adj25 femoral$).ti,ab.
24 (subclavian$ adj25 femoral$).ti,ab.
25 or/20-24
26 19 and 25
27 12 and 26

WHAT'S NEW

Last assessed as up-to-date: 16 April 2007.

Date	Event	Description
23 January 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 3, 2007

Date	Event	Description
17 April 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Hamilton

Co-ordinating the review: Hamilton and Foxcroft

Undertaking manual searches: Hamilton and Foxcroft

Screening search results: Hamilton and Foxcroft

Organizing retrieval of papers: Hamilton and Foxcroft

Screening retrieved papers against inclusion criteria:

Appraising quality of papers: Hamilton and Foxcroft

Abstracting data from papers: Hamilton and Foxcroft

Writing to authors of papers for additional information:

Providing additional data about papers: Hamilton and Foxcroft

Data management for the review: Hamilton and Foxcroft

Entering data into Review Manager (RevMan 4.2): Foxcroft

RevMan statistical data: Foxcroft

Double entry of data: (data entered by person one:Foxcroft)

Interpretation of data: Foxcroft

Statistical inferences: Foxcroft

Writing the review: Hamilton and Foxcroft

Performing previous work that was the foundation of the present study: Hamilton

Guarantor for the review (one author) Foxcroft

Person responsible for reading and checking review before submission: Foxcroft

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Oxford NHS R&D Consortium, UK.
- Oxford Brookes University, UK.
- Oxford Radcliffe Hospitals NHS Trust, UK.

External sources

- Oxfordshire Health Services Research Committee, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Bacterial Infections [*prevention & control]; Catheterization, Central Venous [adverse effects; *methods]; Constriction, Pathologic [prevention & control]; Femoral Vein; Jugular Veins; Subclavian Vein; Venous Thrombosis [*prevention & control]

MeSH check words

Humans