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Percutaneous central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates (Review)

Ainsworth S, McGuire W

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[Intervention Review]

Percutaneous central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates

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ABSTRACT

Background

Neonatal parenteral nutrition may be delivered via peripheral cannulas or central venous catheters (umbilical or percutaneous). As the result of complications associated with umbilical catheters, many neonatal units prefer to use percutaneous catheters after initial stabilisation. Although they can be difficult to place, these catheters may be more stable than peripheral cannulae and require less frequent replacement. These delivery methods may be associated with different risks of adverse events, including acquired invasive infection and extravasation injury.

Objectives

To determine the effects of infusion of parenteral nutrition via percutaneous central venous catheters versus peripheral cannulae on nutrient input, growth and development and complications among hospitalised neonates receiving parenteral nutrition in terms of adverse consequences such as bacteraemia or invasive fungal infection, cardiac tamponade or other extravasation injuries.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 5), MEDLINE (1966 to June 2015) and EMBASE (1980 to June 2015), as well as conference proceedings and previous reviews.

Selection criteria

Randomised controlled trials that compared delivery of intravenous fluids (primarily parenteral nutrition) via percutaneous central venous catheters versus peripheral cannulae in hospitalised neonates.

Data collection and analysis

We extracted data using standard methods of the Cochrane Neonatal Group, with separate evaluation of trial quality and data extraction by two review authors.

Main results

We found six trials recruiting a total of 549 infants. One trial showed that use of a percutaneous central venous catheter was associated with a smaller deficit between prescribed and actual nutrient intake during the trial period (mean difference (MD) -7.1%, 95% confidence interval (CI) -11.02 to -3.2). Infants in the percutaneous central venous catheter group needed significantly fewer catheters/cannulae (MD -4.3, 95% CI -5.24, -3.43). Meta-analysis of data from all trials revealed no evidence of an effect on the incidence of invasive infection (typical risk ratio (RR) 0.95, 95% CI 0.72 to 1.25; typical risk difference (RD) -0.01, 95% CI -0.08 to 0.06).

Authors' conclusions

Data from one small trial suggest that use of percutaneous central venous catheters to deliver parenteral nutrition increases nutrient input. The significance of this in relation to long-term growth and developmental outcomes is unclear. Three trials suggest that use of percutaneous central venous catheters decreases the number of catheters/cannulae needed to deliver nutrition. No evidence suggests that percutaneous central venous catheter use increases risks of adverse events, particularly invasive infection, although none of the included trials was large enough to rule out an effect on uncommon severe adverse events such as pericardial effusion.

PLAIN LANGUAGE SUMMARY

Percutaneous central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates

Review question: In newborn infants receiving parenteral nutrition, does delivery into deep veins (via percutaneous central venous catheters) versus superficial veins (via peripheral cannulae) affect nutrition, growth and development, and adverse events including infection or skin damage?

Background: Preterm or sick newborn infants are often fed with special nutrient solutions delivered directly into the veins. These solutions can be given into a superficial vein through standard, short (peripheral) cannulae or into a large deep vein via long (central) catheters.

Study characteristics: We found six small randomised controlled trials (enrolling 549 infants in total) that addressed this question. The trials generally were of good methodological quality, although study findings may be biased by the inability to blind caregivers and investigators to the type of intervention provided.

Key results: These trials provided only limited evidence on the effects of the interventions on nutrition. Analysis of data from three trials revealed that infants in the percutaneous central venous catheter group needed about four fewer catheters or cannulae during hospitalisation. Combined data from all trials showed no evidence of an effect on risk of bloodstream infection.

Conclusions: Use of central venous catheters has been thought to increase the risk of bloodstream infection in newborn infants, but this review of randomised trials found no evidence that this was the case. More trials are needed to determine which method is better for improving nutrition and growth and development in newborn infants.

BACKGROUND

Description of the condition

Appropriate methods of feeding neonates vary with gestational age and clinical state. Some neonates, particularly those who are preterm or sick, are slow to tolerate the introduction of enteral feeds because of delayed gastric emptying and intestinal peristalsis. As early postnatal nutrition may affect important outcomes, including long-term neurodevelopment, these infants often receive parenteral (intravenous) nutrition during the period of establishment of enteral nutrition (Wilson 1997; Thureen 2001). Parenteral nutrition may also be delivered during periods when enteral nutrition is not possible, as when maternal expressed breast milk is lacking or when feeding is specifically contraindicated because of gastrointestinal disease such as necrotising enterocolitis. As modern perinatal care has improved the survival rate of preterm and sick newborn infants, the number of infants who require prolonged parenteral nutrition has increased.

Description of the intervention

Parenteral nutrition usually consists of a glucose and electrolyte solution. More nutritionally complete formulations - "total parenteral nutrition" - can include an amino acid solution with minerals and vitamins, in addition to fat, as the principal non-protein energy source. Solutions are infused via short narrow-gauge peripheral venous cannulae or by means of longer central venous catheters that extend into larger veins such as the venae cavae (Shaw 1973; Trotter 1996).

Central venous catheters

In neonatal practice, a central venous catheter is usually placed percutaneously for delivery of parenteral nutrition, although an umbilical venous or arterial catheter may also be used to deliver parenteral nutrition, particularly during the first week after birth. Surgical placement, in which a deep vein is surgically exposed before cannulation and for which the infant may require a general anaesthetic, is done less often. This review will focus on the specific comparison of percutaneous central venous catheters versus peripheral cannulae.

The most common complication associated with percutaneous central venous catheter use is nosocomial infection, which can include bacteraemia and invasive fungal infection. Micro-organisms can enter the bloodstream through the catheter entry site or, less commonly, via the catheter hub (Salzman 1993; Salzman 1995). Catheter-associated thrombosis can act as a nidus for infection (Thornburg 2008). It is often necessary to remove the catheter to clear the infection (Karlowicz 2002). Reported incidences of catheter-related invasive infection in the neonatal intensive care unit vary from 5% to nearly 40%, depending on the precise criteria used to define catheter-related infection and the population studied (Hruszkewycz 1991; Neubauer 1995; Garland 2008; Ohki 2008; Olsen 2009). Extremely low birth weight infants (birth weight < 1000 g) are particularly at risk. Additional putative risk factors include prolonged use of parenteral nutrition and insertion of the catheter after the first week of life (Mahieu 2001). However, it is uncertain whether percutaneous central venous catheter use further increases the risk of infection in an "at-risk" population (Sohn 2001).

Invasive infection increases the risk of mortality and a range of important morbidities, including the need for intensive care and mechanical ventilation, bronchopulmonary dysplasia, necrotising enterocolitis, retinopathy of prematurity, hepatic dysfunction and prolonged hospitalisation, and adds to the cost of neonatal care (Saint 2000; Mahieu 2001; Chapman 2003; Payne 2004; Adams-Chapman 2006; Hermans 2007; Lahra 2009; Johnson 2013). Bloodstream infection is associated with higher rates of several adverse neurodevelopmental outcomes, long-term disability, vision and hearing impairment and cerebral palsy (Stoll 2004; Shah 2008; Bassler 2009). Use of a percutaneous central venous catheter to deliver parenteral nutrition may be associated with iatrogenic injury, including embolism (air or thrombus) and infusate extravasation into tissue spaces. Cardiac tamponade following migration of the catheter tip to the pericardial space has been reported (Darling 2001).

Peripheral cannulae

Although it may be technically easier to site peripheral cannulae than to site central venous catheters, peripheral cannulae are less stable and may require more frequent replacement. Once placed, a central venous catheter should remain *in situ* longer than a peripheral cannula, thus reducing the number of potentially painful procedures to which the infant is exposed (Shaw 1973). The need for frequent replacement of a peripheral cannula might result in a significant cumulative period of interruption to the delivery of parenteral nutrition and in a nutrient deficit that can have long-term consequences for growth and development (Embleton 2001). Another concern with use of a peripheral cannula for delivering parenteral nutrition is the risk of extravasation injury. Subcutaneous infiltration of a hypertonic and irritant parenteral nutrition solution can cause local skin ulceration, secondary infection and scarring.

Why it is important to do this review

Given that the choice of route for delivery of parenteral nutrition may affect clinically important outcomes in neonates, such as growth and development, we systematically reviewed available evidence to determine whether this has implications for current practice or for future research.

OBJECTIVES

To determine the effects of infusion of parenteral nutrition via percutaneous central venous catheters versus peripheral cannulae on nutrient input, growth and development and complications among hospitalised neonates receiving parenteral nutrition in terms of adverse consequences such as bacteraemia or invasive fungal infection, cardiac tamponade or other extravasation injuries.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled trials using random or quasi-random participant allocation.

Types of participants

Neonates (newborn infants younger than 28 days at study entry) receiving parenteral nutrition and cared for in a hospital setting.

Types of interventions

Trials comparing parenteral nutrition delivered via percutaneously inserted central venous catheters versus peripheral cannulae. We did not include studies that compared delivery of parenteral nutrition via surgically placed central lines (when the vein is surgically exposed before cannulation) or via umbilical catheters. We did not specify a minimum duration for trials.

Types of outcome measures

Primary outcomes: nutrient input, growth and development

- Average daily input of parenteral calories (kcal/kg/d) and protein (g/kg/d) during trial period.
- Average daily proportion of prescribed parenteral calories and protein actually delivered during trial period.
- Short-term (before discharge from the hospital) growth: weight gain (g/kg/d), weight z-score at discharge, linear growth (mm/wk), head growth (mm/wk) and skinfold thickness growth (mm/wk).
- Long-term (after discharge from the hospital) growth: weight gain (g/kg/d), linear growth (mm/wk), head growth (mm/wk) and skinfold thickness growth (mm/wk).
- Neurodevelopmental outcomes during infancy and beyond, using validated assessment tools, such as Bayley Scales of Infant Development, and classifications of disability, including auditory and visual disability. Severe neurodevelopmental disability was defined as any one or combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70) or auditory and visual impairment.

Secondary outcomes: adverse events

- Death (all causes) before 28 days.
- Death (all causes) before discharge from hospital.
- Confirmed invasive bacterial infection as determined by:
  - culture from a normally sterile site: cerebrospinal fluid, blood (from peripheral sites, not from indwelling catheters), urine (obtained by sterile urethral catheterization or suprapubic bladder tap), bone or joint, peritoneum, pleural space or central venous line tip; or
  - findings on autopsy examination consistent with invasive bacterial infection.
- Confirmed invasive fungal infection as determined by:
  - culture from a normally sterile site: cerebrospinal fluid, blood (from peripheral sites, not from indwelling catheters), urine (obtained by sterile urethral catheterisation or suprapubic bladder tap), bone or joint, peritoneum, pleural space or central venous line tip;
  - findings on autopsy examination consistent with invasive fungal infection;
  - findings on ophthalmological examination consistent with fungal ophthalmitis or retinitis; or
  - pathognomonic findings on renal ultrasound examination: "renal fungal balls".
- Extravasation injury as determined by:
  - subcutaneous injury resulting in skin ulceration;
  - "deep" extravasation resulting in limb swelling; or
  - "central" extravasation-infusate in the pleural, peritoneal or pericardial space.
- Number of cannulae/catheters used per child to administer parenteral nutrition during the trial period.

Search methods for identification of studies

We used the standard search strategy of the Cochrane Neonatal Review Group.

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; current issue), MEDLINE (1966 to June 2015) and EMBASE (1980 to June 2015), using a combination of the following text words and Medical Subject Heading (MeSH) terms: [infant, newborn OR infant, premature OR infant, low birth weight OR infan* OR neonat*] AND [catheters, Indwelling OR catheterization, central venous OR central near3 cathet* OR central near3 cannul* OR central near3 line OR CVC OR CVL OR PCVC OR PICC].

We limited search outputs by applying relevant search filters for clinical trials, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We applied no language restrictions.

We searched ClinicalTrials.gov and Current Controlled Trials for completed or ongoing trials.

Searching other resources

We examined reference lists within previous reviews and included studies. We searched the proceedings of the annual meetings of the Pediatric Academic Societies (1993 to 2015), the European Society for Pediatric Research (1995 to 2014), the Royal College of Paediatrics and Child Health (2000 to 2015) and the Perinatal Society of Australia and New Zealand (2000 to 2015). Trials reported only as abstracts were eligible if information provided by the report, or through contact with study authors, was sufficient to fulfil the inclusion criteria.

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Group.

Selection of studies

We screened the titles and abstracts of all studies identified by the above search strategy, and two review authors independently assessed full articles for all potentially relevant trials. We excluded studies that did not meet all of the inclusion criteria and stated the reasons for exclusion. We discussed disagreements until we reached consensus.

Data extraction and management

Two review authors independently extracted data from each included study using a data collection form to aid extraction of information on design, methods, participants, interventions, outcomes and treatment effects. We discussed disagreements until we reached consensus. If data from trial reports were insufficient, we contacted the trialists to request missing information.

Assessment of risk of bias in included studies

We used the criteria and standard methods of The Cochrane Collaboration and the Cochrane Neonatal Group to assess the methodological quality of included trials (Higgins 2011). We requested additional information from trial authors to clarify methods and results as necessary. We evaluated and reported the following issues in 'Risk of bias' tables.

- Sequence generation (method used to generate the allocation sequence).
  - Low risk: any truly random process (e.g. random number table, computer random number generator).
  - High risk: any non-random process (e.g. odd or even date of birth, hospital or clinic record number).
  - Unclear risk: no or unclear information provided.
- Allocation concealment (method used to conceal the allocation sequence).
  - Low risk: e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes.
  - High risk: open random allocation (e.g. unsealed or non-opaque envelopes, alternation, date of birth).
  - Unclear risk: no or unclear information provided.
- Blinding (methods used to ensure blinding of participants, clinicians and caregivers and outcome assessors).
  - Low risk.
  - High risk.
  - Unclear risk.
- Incomplete outcome data (completeness of data including attrition and exclusions from the analysis for each outcome, and reasons for attrition or exclusion when reported): We will assess whether missing data are balanced across groups or are related to outcomes. When sufficient information is reported or supplied by the trial authors, we will reinstate missing data in the analyses. We will categorise completeness as follows.
  - Low risk: adequate (< 10% missing data).
  - High risk: inadequate (> 10% missing data).
  - Unclear risk: no or unclear information provided.

Measures of treatment effect

We analysed treatment effects in the individual trials by using Review Manager 5.3 and reported risk ratio (RR) and risk difference (RD) for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). We determined the number needed to treat for an additional beneficial outcome (NNTB) or for an additional harmful outcome (NNTH) for analyses with a statistically significant difference in the RD.

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials. An infant was considered only once in an analysis. We planned to exclude infants with multiple enrolments unless we obtained from the report or from investigators data related to the first episode of randomisation. If we could not separate data from the first randomisation, we planned to exclude that study, as we would not be able to address the unit of analysis issues that arise from multiple enrolments of the same infant.

We intended to conduct intention-to-treat analyses. However, if placement of the allocated catheter or cannula was unsuccessful, it may not have been possible to evaluate some outcomes for that infant.

The participating neonatal unit or section of a neonatal unit was the unit of analysis in cluster-randomised trials. We planned to analyse these using an estimate of the intra-cluster correlation coefficient derived from the trial (if possible), or from another source, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

If we identified cluster-randomised trials and individually randomised trials, we planned to combine the results from both only if we noted little heterogeneity between study designs, and if we considered interaction between effects of the intervention and choice of randomisation unit to be unlikely.

Dealing with missing data

We requested additional data from trial investigators if data on important outcomes were missing or were reported unclearly. When data were still missing, we examined the impact on effect size estimates in sensitivity analyses.

Assessment of heterogeneity

We examined treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We calculated the I-squared (I^2) statistic for each RR analysis to quantify inconsistency across studies and to describe the percentage of variability in effect estimates that may be due to heterogeneity rather than to chance. If we detected substantial or considerable heterogeneity (I^2 > 50%), we explored possible causes (e.g. differences in study design, setting, participants or interventions).

Assessment of reporting biases

When we suspected reporting bias, we contacted trial investigators to request missing outcome data. When this was not possible, and when the missing data were thought to introduce serious bias, we planned to explore in a sensitivity analysis the impact of including such trials in the overall assessment of results.

Data synthesis

We used the fixed-effect model in Review Manager 5.3 when conducting meta-analyses.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup comparisons.

- Preterm infants (< 37 weeks' gestation).
- Very low birth weight infants (< 1500 g).
- Extremely low birth weight infants (< 1000 g).

Sensitivity analysis

We planned sensitivity analyses to determine whether our findings are affected by inclusion only of studies using adequate methods (low risk of bias), defined as adequate randomisation and allocation concealment, blinding of intervention and measurement and less than 10% loss to follow-up.

RESULTS

Description of studies

We identified 13 studies for potential inclusion. Six of these, involving a total of 549 infants, fulfilled the inclusion criteria (Annibale 1995; Janes 2000; Ainsworth 2001; Wilson 2007; Barria 2007; Hosseini 2014; see Characteristics of included studies).

Included studies

The included studies were undertaken over the past two decades in neonatal intensive care units in North America (Annibale 1995; Janes 2000; Wilson 2007), the United Kingdom (Ainsworth 2001), Chile (Barria 2007) and Iran (Hosseini 2014). Average gestational age of participating infants was 26 weeks (Janes 2000), 27 weeks (Wilson 2007), 28 weeks (Ainsworth 2001 and Hosseini 2014), 29 weeks (Annibale 1995) and 31 weeks (Barria 2007). In all trials, infants were recruited within the first week after birth, and follow-up continued until the infant no longer required intravenous access for delivery of parenteral nutrition (i.e. when the infant tolerated enteral intake).

Four of the trials reported no data on the prespecified primary outcomes for this review: nutritional input, growth and development (Annibale 1995; Janes 2000; Wilson 2007; Barria 2007). We contacted the lead investigators for these trials to request the relevant data. Ainsworth 2001 reported the proportion of prescribed parenteral nutrition that was actually delivered during the trial period. All trials reported data on the incidence of bacteraemia or fungaemia. Three reported the number of insertion attempts and catheters required to maintain venous access, as well as the total duration of intravenous access (Annibale 1995; Janes 2000; Barria 2007). Wilson 2007 reported the number of skin punctures but not the duration of venous access. Data on neonatal deaths and deaths before hospital discharge were available for five trials (Janes 2000; Ainsworth 2001 ;Barria 2007; Wilson 2007; Hosseini 2014).

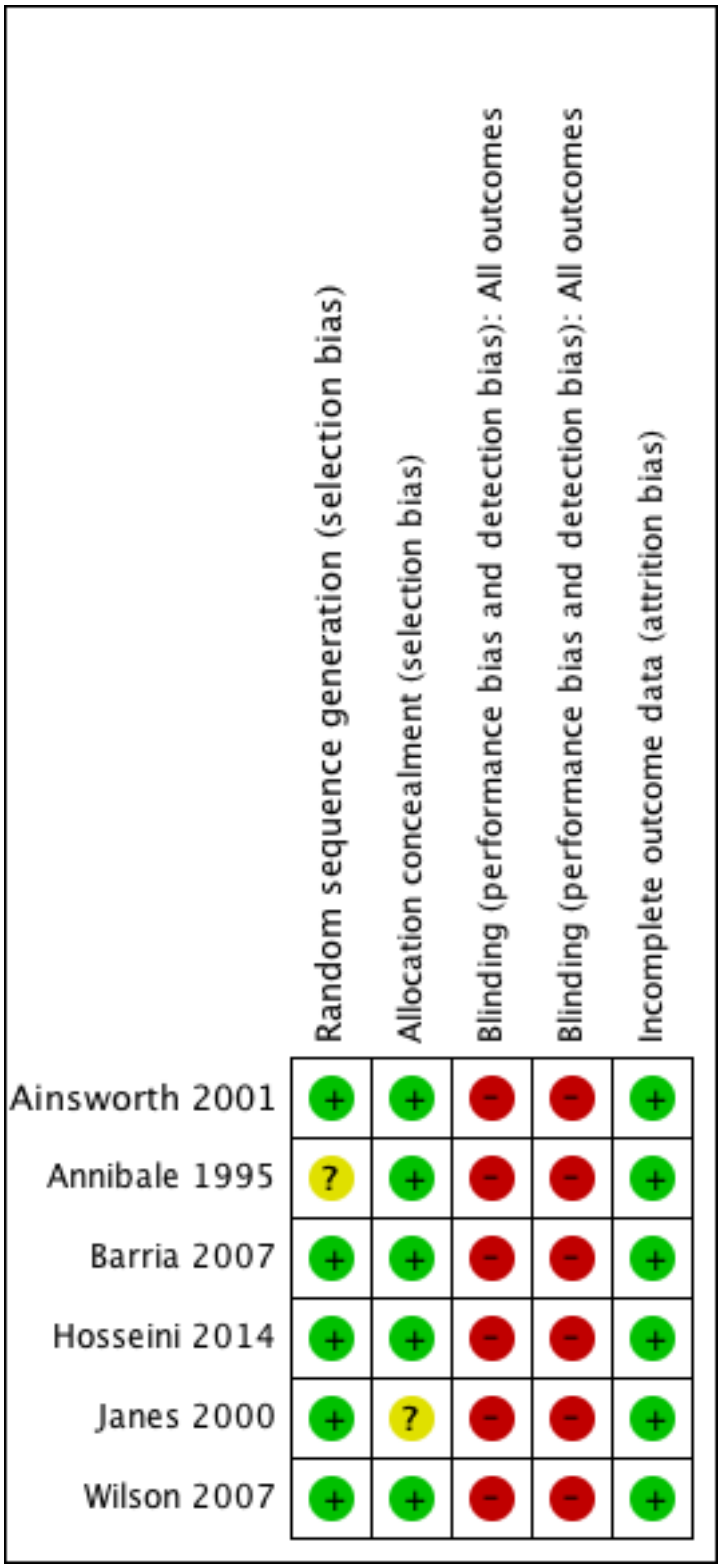
Excluded studies

Four of the excluded studies (Cairns 1995; Parellada 1999; Liossis 2003; Geffers 2010) reported outcomes between cohorts of infants who received parenteral nutrition via percutaneous catheters or peripheral cannulae. Although groups were matched in terms of gestation and birth weight, the potential for bias at selection of these groups was high. For example, clinicians may have been more likely to use a peripheral cannula for infants thought to require parenteral nutrition for a shorter duration. We excluded Schwengel 2004, as this study examined outcomes in paediatric surgical patients and enrolled participants of all age ranges from neonates through 14-year-olds. No stratification had been used in the study, and it was not possible for review authors to extract the neonatal data. The study by Childs 1995 looked at whether the tip of the central venous catheter was better placed centrally or peripherally. The study by Arnts 2014 compared complication rates between central venous catheters that had been inserted into umbilical or peripheral blood vessels (see Characteristics of excluded studies).

Risk of bias in included studies

See Characteristics of included studies and Figure 1.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Investigators in four trials concealed random allocation by using sealed opaque envelopes (Annibale 1995; Ainsworth 2001; Wilson 2007; Barria 2007). Hosseini 2014 used an Internet-based randomisation web site. Janes 2000 used a computer-generated block random number table to assign randomly eligible infants but did not describe the allocation concealment method used.

Blinding

No trials were able to blind caregivers or investigators to the intervention.

Incomplete outcome data

Follow-up appears complete for reported outcomes.

Effects of interventions

Percutaneous central venous catheters versus peripheral cannulae

Primary outcomes: nutrient input, growth and development

Average daily input of parenteral calories

No trials reported the average daily input of parenteral calories or protein during the trial period.

Average daily proportions of prescribed parenteral calories and protein actually delivered during the trial period (Outcome 1.1)

Ainsworth 2001 reported a statistically significant difference in the deficit of delivered parenteral nutrition (from that actually prescribed) during the trial period: 3.2% (standard deviation (SD) 6.8%) in the percutaneous central venous catheter group versus 10.3% (SD 7.2%) in the peripheral cannula group (MD -7.1%, 95% CI -11.02 to -3.2). Other trials did not report this outcome.

Short-term growth parameters

No trials reported short-term growth parameters (before discharge from the hospital).

Long-term growth parameters

No studies reported long-term growth parameters (after discharge from the hospital).

Neurodevelopmental outcomes

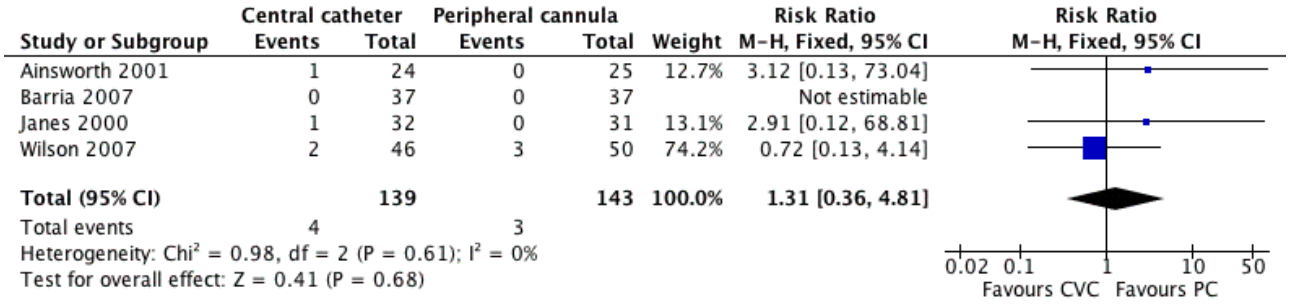
No studies reported neurodevelopmental outcomes during infancy and beyond.

Secondary outcomes: adverse events

Death (all causes) before 28 days (Outcome 1.2)

Three included trials reported this outcome (Janes 2000; Ainsworth 2001; Wilson 2007). The authors of a fourth study (Barria 2007) confirmed that none of the infants entered into the study died during the study period nor before discharge. Seven of a total of 282 infants recruited to the four studies died. No statistically significant differences in incidence of death before 28 days were reported by individual trials or on meta-analysis of the four trials (typical RR 1.31, 95% CI 0.36 to 4.81; typical RD -0.01, 95% CI -0.03 to 0.05) (Figure 2).

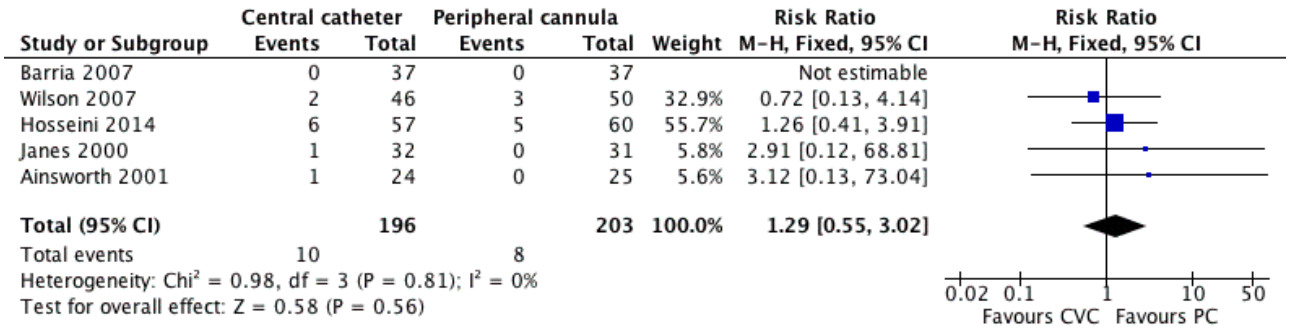
Figure 2. Forest plot of comparison: 1 Percutaneous central venous catheter versus peripheral cannula, outcome: 1.2 Death before 28 days (all causes).



Death (all cause) before discharge from the hospital (Outcome 1.3)

Data on death before discharge were the same in the four studies that reported death before 28 days. Hosseini 2014 reported death before discharge. No statistically significant differences in the incidence of death before 28 days were reported by individual trials or on meta-analysis of the four trials (typical RR 1.29, 95% CI 0.55 to 3.02; typical RD 0.01, 95% CI -0.03 to 0.06) (Figure 3).

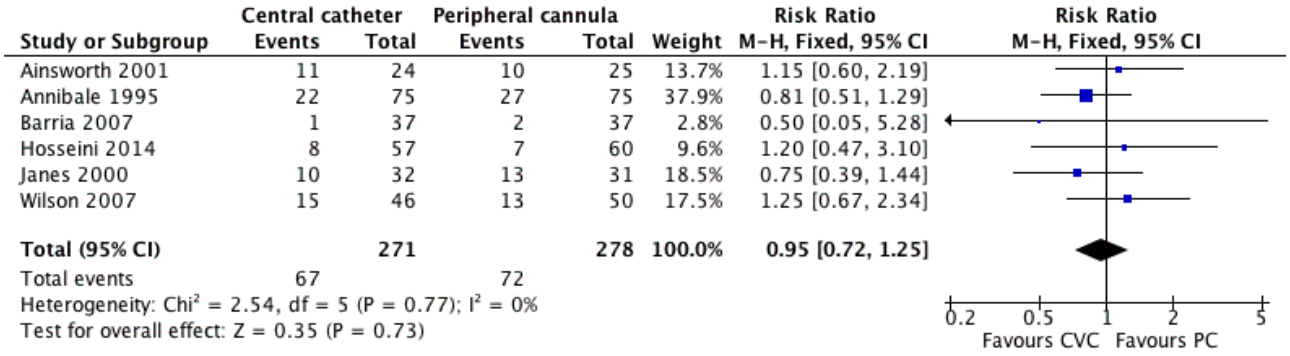
Figure 3. Forest plot of comparison: 1 Percutaneous central venous catheter versus peripheral cannula, outcome: 1.3 Death before hospital discharge (all causes).



Confirmed invasive bacterial or fungal infection (Outcome 1.4)

All trials reported bloodstream infection (sepsis). Meta-analysis of the data revealed no statistically significant differences between groups in the incidence of invasive infection (typical RR 0.95, 95% CI 0.72 to 1.25; typical RD -0.01, 95% CI -0.08 to 0.06) (Figure 4).

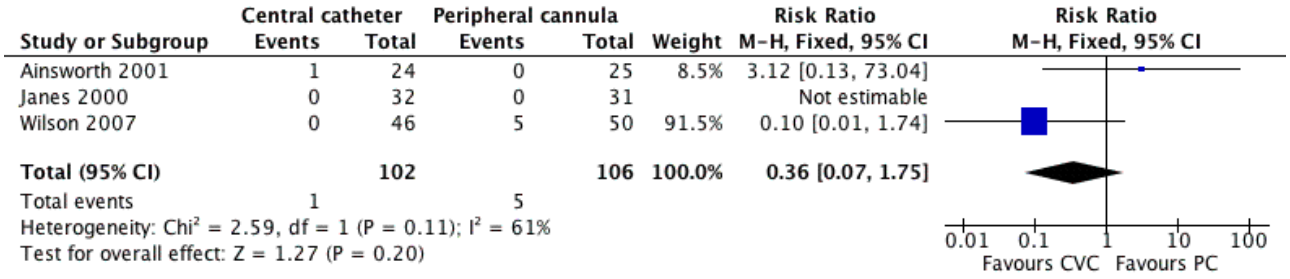
Figure 4. Forest plot of comparison: 1 Percutaneous central venous catheter versus peripheral cannula, outcome: 1.4 Invasive bacterial and fungal infections.



Extravasation injury (Outcome 1.5)

Three trials reported this outcome (Janes 2000; Ainsworth 2001; Wilson 2007). Meta-analysis of these trials revealed no statistically significant differences (typical RR 0.36, 95% CI 0.07 to 1.75; typical RD -0.04, 95% CI -0.09 to 0.02) (Figure 5).

Figure 5. Forest plot of comparison: 1 Percutaneous central venous catheter versus peripheral cannula, outcome: 1.5 Extravasation injury.

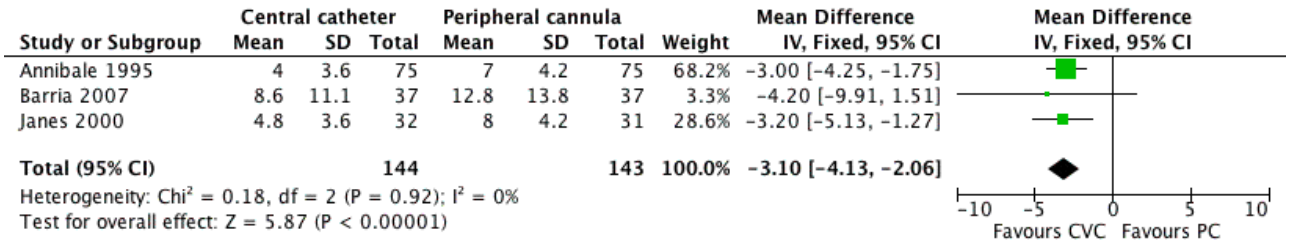


Barria 2007 reported the incidence of 'phlebitis', but this did not fulfil the criteria for extravasation injury. Hosseini 2014 reported 'phlebitis' (again not meeting the criteria for extravasation injury) in the peripheral cannula arm and one case of pericardial effusion in the central venous catheter arm. We contacted the lead investigator in the sixth trial to determine whether the data were available (Annibale 1995).

Numbers of cannulae/catheters per infant used to administer parenteral nutrition during the trial period (Outcome 1.6)

Meta-analysis of data from Annibale 1995, Janes 2000 and Barria 2007 shows a statistically significant reduction in the numbers of cannulae/catheters reported for the percutaneous central venous catheter group (MD -3.10, 95% CI -4.13 to -2.06) (Figure 6).

Figure 6. Forest plot of comparison: 1 Percutaneous central venous catheter versus peripheral cannula, outcome: 1.6 Numbers of cannulae/catheters per infant.



Wilson 2007 reported median values and ranges for the number of skin punctures; the median value (range) for skin puncture in the percutaneous central venous catheter group was 9 (one to 74) versus 14.5 (one to 111) in the peripheral cannula group. We contacted the authors of this study to request clarification regarding means and standard deviations for these data.

Data from the other two trials (Ainsworth 2001; Wilson 2007) are not available.

Subgroup analyses

Most infants participating in the five included trials were preterm. Subgroup analysis by birth weight was not possible.

DISCUSSION

Summary of main results

We found six randomised controlled trials that compared use of percutaneous central venous catheters versus peripheral cannulae for newborn infants who require parenteral nutrition. A total of 549 infants participated in these trials. Data from one trial suggest that use of percutaneous central venous catheters to deliver parenteral nutrition increases nutrient input. No trials assessed effects on growth nor long-term outcomes after hospital discharge. Three trials suggest that use of percutaneous central venous catheters decreases the numbers of catheters/cannulae needed to deliver nutrition. We found no evidence that percutaneous central venous catheter use increased the risk of adverse events, particularly invasive infection, although none of the included trials was large enough to rule out an effect on uncommon severe adverse events such as pericardial effusion.

Overall completeness and applicability of evidence

Only one of the six trials assessed nutrient input. Ainsworth 2001 found that infants randomly allocated to receive parenteral nutrition via peripheral cannulae had a statistically significantly higher nutritional deficit during the trial period when compared with infants who received nutrition via central venous catheters. The 7% difference in deficit, if accumulated over a period of one week, would result in loss of one-half of one day's nutrient requirements. The importance of this in relation to long-term growth and developmental outcomes is unclear. Nutritional deficits during this very critical period of brain growth may have adverse consequences for long-term neurodevelopmental outcomes. However, when enteral nutrition is introduced, catch-up growth may compensate for deficiencies experienced during the early neonatal period.

All trials reported the incidence of invasive (bloodstream) bacterial or fungal infection. Meta-analysis revealed no statistically significant differences, but this finding should be interpreted with caution, as no trials blinded caregivers and investigators to the nature of the intervention, and surveillance bias may have affected results. However, the direction of this bias is more likely to have caused a relative overestimation of the risk of infection in the percutaneous central venous catheter group because clinicians may have had a lower threshold for investigating or diagnosing infection in these infants. This situation is further compounded by the difficulty associated with diagnosing true invasive infection versus contamination of blood cultures with skin commensal organisms. Reported infection rates in the central venous catheter group might have been artificially high, as clinicians, already more concerned about risks of infection, might have attributed symptoms to organisms isolated in contaminated cultures. Although they are frequently blamed for increasing risk of invasive bacterial or fungal infection, percutaneous central venous catheters are not the only pieces of 'plastic' used in the high-risk neonate that bypass the body's innate defences. A high proportion of infants with percutaneous central venous catheters have or have had endotracheal tubes, nasogastric tubes or peripheral cannulae, as well as an immature gastrointestinal mucosa, which predisposes them to infection. Results of this meta-analysis and of three non-randomised cohort studies suggest no significant differences between invasive infection rates among infants receiving parenteral nutrition via central venous catheter or via peripheral cannula (Cairns 1995; Parellada 1999; Liossis 2003).

It is thought that percutaneous central venous cannulae are more stable than peripheral cannulae and therefore need to be replaced less frequently. We found evidence for this advantage. Three studies (Annibale 1995; Janes 2000; Barria 2007) found that mean numbers of cannulae/catheters used were statistically significantly lower in the percutaneous central venous catheter group than in the peripheral cannula group. On average, infants needed about four fewer cannulae/catheters during the trial period. Wilson 2007 reported the number of skin punctures required to maintain venous access. It is unclear whether these data show actual numbers of catheters or cannulae or whether they include 'failed' attempts. We need to obtain additional data from the lead investigator before we can assess whether this study should be included in future updates. Numbers of catheters/cannulae may indirectly reflect the number of painful procedures performed in these infants. However, it is not clear whether insertion of a catheter (usually through a larger-bore needle and technically more difficult) is more painful for the infant than is insertion of several peripheral cannulae over time. No study has specifically addressed the issue of pain, and none have used pain scores in this respect.

Quality of the evidence

The numbers of infants in these studies were too small to permit conclusions regarding the effects of catheters or cannulae on serious clinical adverse effects such as extravasation injury and cardiac tamponade, although one such case was reported by Hosseini 2014. Cartwright 2004 reported on use of 2186 catheters in one unit and found that, with careful adherence to policies for insertion, placement and aseptic precautions during times when the lines are accessed, percutaneous central venous catheters can be used safely to deliver parenteral nutrition in neonates.

Potential biases in the review process

Our main concern with the review process is the possibility that findings may reflect publication bias and other reporting biases. We attempted to minimise this threat by screening the reference lists of included trials and related reviews and by searching the proceedings of major international perinatal conferences to identify trial reports that are not (or are not yet) published in full form in academic journals. The meta-analyses that we performed did not include a sufficient number of trials for exploration of symmetry of funnel plots as a means of identifying possible publication or reporting bias.

AUTHORS' CONCLUSIONS

Implications for practice

Limited data from one small trial suggest that use of a percutaneous central venous catheter rather than a peripheral cannula is associated with a statistically significant smaller deficit in delivered parenteral nutrition. Use of percutaneous central venous catheters resulted in fewer painful procedures (venepunctures) than were seen with peripheral cannula use. We found no evidence of increased risk of adverse effects, particularly invasive infection.

Implications for research

Additional large and adequately powered randomised controlled trials are needed to determine whether use of percutaneous central venous catheters rather than peripheral cannulae to deliver parenteral nutrition provides important benefits for newborn infants. Trials should examine the effects of this intervention on growth and neurodevelopmental outcomes, particularly in very preterm infants for whom early nutritional intake may play an important role.

ACKNOWLEDGEMENTS

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REFERENCES

References to studies included in this review

Ainsworth 2001 *{published and unpublished data}*

* Ainsworth SB, Furness J, Fenton AC. Randomized comparative trial between percutaneous longlines and peripheral cannulae in the delivery of neonatal parenteral nutrition. *Acta Paediatrica* 2001;**90**(9):1016-20.

Annibale 1995 *{published data only}*

Annibale DJ, Bissinger RL, Husley TC, Headdon P, Ohning BL. Early percutaneous central venous catheterization (PCVC) in neonates. *Pediatric Research* 1995;**37**:1148.

Barria 2007 *{published and unpublished data}*

Barría RM, Lorca P, Muñoz S. Randomized controlled trial of vascular access in newborns in the neonatal intensive care unit. *Journal of Obstetric, Gynecologic and Neonatal Nursing* 2007;**36**(5):450-6.

Hosseini 2014 *{published data only}*

Hosseini MB, Jodeiri B, Mahallei M, Abdoli-Oskooi SH, Safari A, Salimi Z. Early outcome of peripherally inserted central catheter versus peripheral IV line in very low birth weight neonates. *Feyz, Journal of Kashan University of Medical Sciences* 2014;**17**(6):561-7.

Janes 2000 *{published and unpublished data}*

Janes M, Kalyn A, Pinelli J, Paes B. A randomized trial comparing peripherally inserted central venous catheters and peripheral intravenous catheters in infants with very low birth weight. *Journal of Pediatric Surgery* 2000;**35**(7):1040-4.

Wilson 2007 *{published data only}*

Wilson D, Verklan MT, Kennedy KA. Randomized trial of percutaneous central venous lines versus peripheral intravenous lines. *Journal of Perinatology* 2007;**27**(2):92-6.

References to studies excluded from this review

Arnts 2014 *{published data only}*

Arnts IJ, Bullens LM, Groenewoud JM, Liem KD. Comparison of complication rates between umbilical and peripherally inserted central venous catheters in newborns. *Journal of Obstetric Gynecologic and Neonatal Nursing* 2014;**43**(2):205-15.

Cairns 1995 *{published data only}*

Cairns PA, Wilson DC, McClure BG, Halliday HL, McReid M. Percutaneous central venous catheter use in the very low birth weight neonate. *European Journal of Pediatrics* 1995;**154**:145-7.

Childs 1995 *{published data only}*

Childs AM, Murdoch Eaton DG, Standring P, Puntis JW. A prospective comparison of central and peripheral vein access for parenteral nutrition in the newborn. *Clinical Nutrition* 1995;**14**:303-5.

Geffers 2010 *{published data only}*

Geffers C, Gastmeier A, Schwab F, Groneberg K, Rüden H, Gastmeier P. Use of central venous catheter and peripheral venous catheter as risk factors for nosocomial bloodstream infection in very-low-birth-weight infants. *Infection Control and Hospital Epidemiology* 2010;**31**(4):395-401.

Liossis 2003 *{published data only}*

Liossis G, Bardin C, Papageorgiou A. Comparison of risks from percutaneous central venous catheters and peripheral lines in infants of extremely low birth weight: a cohort controlled study of infants < 1000 g. *Journal of Maternal-Fetal & Neonatal Medicine* 2003;**13**:171-4.

Parellada 1999 *{published data only}*

Parellada JA, Moise AA, Hegemier S, Gest AL. Percutaneous central catheters and peripheral intravenous catheters have similar infection rates in very low birth weight infants. *Journal of Perinatology* 1999;**19**:251-4.

Schwengel 2004 *{published data only}*

Schwengel DA, McGready J, Berenholtz SM, Kozlowski LJ, Nichols DG, Yaster M. Peripherally inserted central catheters: a randomized, controlled, prospective trial in pediatric surgical patients. *Anesthesia & Analgesia* 2004;**99**:1038-43.

Additional references

Adams-Chapman 2006

Adams-Chapman I, Stoll BJ. Neonatal infection and long-term neurodevelopmental outcome in the preterm infant. *Current Opinion in Infectious Diseases* 2006;**19**(3):290-7. [PUBMED: 16645492]

Bassler 2009

Bassler D, Stoll BJ, Schmidt B, Asztalos EV, Roberts RS, Robertson CM, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009;**123**(1):313-8. [PUBMED: 19117897]

Cartwright 2004

Cartwright DW. Central venous lines in neonates: a study of 2186 catheters. *Archives of Disease in Childhood Fetal & Neonatal Edition* 2004;**89**:F504-8.

Chapman 2003

Chapman RL, Faix RG. Persistent bacteremia and outcome in late onset infection among infants in a neonatal intensive care unit. *The Pediatric Infectious Disease Journal* 2003;**22**(1):17-21. [PUBMED: 12544403]

Darling 2001

Darling JC, Newell SJ, Mohamdee O, Uzun O, Cullinane CJ, Dear PR. Central venous catheter tip in the right atrium: a risk factor for neonatal cardiac tamponade. *Journal of Perinatology* 2001;**21**:461-4.

Embleton 2001

Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of

current recommendations in preterm infants?. *Pediatrics* 2001;**107**:270-3.

Garland 2008

Garland JS, Alex CP, Sevallius JM, Murphy DM, Good MJ, Volberding AM, et al. Cohort study of the pathogenesis and molecular epidemiology of catheter-related bloodstream infection in neonates with peripherally inserted central venous catheters. *Infection Control and Hospital Epidemiology* 2008;**29**(3):243-9. [PUBMED: 18220483]

Hermans 2007

Hermans D, Talbotec C, Lacaille F, Goulet O, Ricour C, Colomb V. Early central catheter infections may contribute to hepatic fibrosis in children receiving long-term parenteral nutrition. *Journal of Pediatric Gastroenterology and Nutrition* 2007;**44**(4):459-63. [PUBMED: 17414144]

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Hruszkewycz 1991

Hruszkewycz V, Holtrop PC, Batton DG, Morden RS, Gibson P, Band JD. Complications associated with central venous catheters inserted in critically ill neonates. *Infection Control and Hospital Epidemiology* 1991;**12**:544-8.

Johnson 2013

Johnson TJ, Patel AL, Jegier BJ, Engstrom JL, Meier PP. Cost of morbidities in very low birth weight infants. *Journal of Pediatrics* 2013;**162**(2):243-49.e1.

Karlowicz 2002

Karlowicz MG, Furigay PJ, Croitoru DP, Buescher ES. Central venous catheter removal versus in situ treatment in neonates with coagulase-negative staphylococcal bacteremia. *The Pediatric Infectious Disease Journal* 2002;**21**:22-7.

Lahra 2009

Lahra MM, Beeby PJ, Jeffery HE. Intrauterine inflammation, neonatal sepsis, and chronic lung disease: a 13-year hospital cohort study. *Pediatrics* 2009;**123**(5):1314-9. [PUBMED: 19403497]

Mahieu 2001

Mahieu LM, De Muynck AO, Ieven MM, De Dooy JJ, Goossens HJ, Van Reempts PJ. Risk factors for central vascular catheter-associated bloodstream infections among patients in a neonatal intensive care unit. *The Journal of Hospital Infection* 2001;**48**:108-16.

Neubauer 1995

Neubauer AP. Percutaneous central i.v. access in the neonate: experience with 535 silastic catheters. *Acta Paediatrica* 1995;**84**:756-60.

Ohki 2008

Ohki Y, Yoshizawa Y, Watanabe M, Kuwashima M, Morikawa A. Complications of percutaneously inserted central venous catheters in Japanese neonates. *Pediatrics International* 2008;**50**(5):636-9. [PUBMED: 19261110]

Olsen 2009

Olsen AL, Reinholdt J, Jensen AM, Andersen LP, Jensen ET. Nosocomial infection in a Danish Neonatal Intensive Care Unit: a prospective study. *Acta Paediatrica* 2009;**98**(8):1294-9. [PUBMED: 19438843]

Payne 2004

Payne NR, Carpenter JH, Badger GJ, Horbar JD, Rogowski J. Marginal increase in cost and excess length of stay associated with nosocom surviving very low birth weight infants. *Pediatrics* 2004;**114**(2):348-55. [PUBMED: 15286215]

Saint 2000

Saint S, Veenstra DL, Lipsky BA. The clinical and economic consequences of nosocomial central venous catheter-related infection: are antimicrobial catheters useful?. *Infection Control and Hospital Epidemiology* 2000;**21**(6):375-80. [PUBMED: 10879567]

Salzman 1993

Salzman MB, Isenberg HD, Shapiro JF, Lipsitz PJ, Rubin LG. A prospective study of the catheter hub as the portal of entry for microorganisms causing catheter-related sepsis in neonates. *The Journal of Infectious Diseases* 1993;**167**:487-90.

Salzman 1995

Salzman MB, Rubin LG. Intravenous catheter-related infections. *Advances in Pediatric Infectious Diseases* 1995;**10**:337-68.

Shah 2008

Shah DK, Doyle LW, Anderson PJ, Bear M, Daley AJ, Hunt RW, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. *The Journal of Pediatrics* 2008;**153**(2):170-5. [PUBMED: 18534228]

Shaw 1973

Shaw JCL. Parenteral nutrition in the management of sick low birth weight infants. *Pediatric Clinics of North America* 1973;**20**:333-58.

Sohn 2001

Sohn AH, Garrett DO, Sinkowitz-Cochran RL, Grohskopf LA, Levine GL, Stover BH, et al. The Pediatric Prevention Network. Prevalence of nosocomial infections in neonatal intensive care unit patients: results from the first national point-prevalence survey. *Journal of Pediatrics* 2001;**139**:821-7.

Stoll 2004

Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-

birth-weight infants with neonatal infection. *JAMA* 2004;**292**(19):2357-65. [PUBMED: 15547163]

Thornburg 2008

Thornburg CD, Smith PB, Smithwick ML, Cotten CM, Benjamin DK Jr. Association between thrombosis and bloodstream infection in neonates with peripherally inserted catheters. *Thrombosis Research* 2008;**122**(6):782-5. [PUBMED: 17997477]

Thureen 2001

Thureen PJ, Hay WW Jr. Early aggressive nutrition in preterm infants. *Seminars in Neonatology* 2001;**6**:403-15.

Trotter 1996

Trotter CW. Percutaneous central venous catheter-related sepsis in the neonate: an analysis of the literature from 1990 to 1994. *Neonatal Network* 1996;**15**:15-28.

Wilson 1997

Wilson DC, Cairns P, Halliday HL, Reid M, McClure G, Dodge JA. Randomised controlled trial of an aggressive nutritional regimen in sick very low birthweight infants. *Archives of Disease in Childhood, Fetal and Neonatal Edition* 1997;**77**:F4-11.

References to other published versions of this review

Ainsworth 2004

Ainsworth SB, Clerihew L, McGuire W. Percutaneous central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD004219.pub2]

Ainsworth 2007

Ainsworth SB, Clerihew L, McGuire W. Percutaneous central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD004219.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ainsworth 2001

Methods	Randomised controlled trial
Participants	49 infants cared for in a regional neonatal intensive care unit, who, in the opinion of the attending clinician, were likely to need parenteral nutrition for longer than 5 days. Median gestation of recruited infants was 28 weeks Infants excluded: central venous catheter already *in situ* (except umbilical venous catheters removed at the time of recruitment). Percutaneous central venous catheter required for inotropic support Royal Victoria Hospital, Newcastle, UK: 1998 to 1999
Interventions	Delivery of parenteral nutrition via percutaneous central venous catheter (n = 24) or via peripheral cannula (n = 25)
Outcomes	• Episodes of "sepsis" - bacteraemia or fungaemia • Proportion of prescribed parenteral nutrition actually delivered
Notes	Infants in the 2 arms were of similar gestation, birth weight and age at randomisation. Infants in the percutaneous central venous catheter group were statistically significantly less likely to have had an umbilical line *in situ* and to have received parenteral antibiotics before randomisation This study was stopped earlier than was intended because interim analysis revealed a statistically significant difference between groups in nutrient delivery Additional details on study methods were provided by investigators

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated

Ainsworth 2001 *(Continued)*

Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up

Annibale 1995

Methods	Randomised controlled trial
Participants	150 neonates (< 6 days old) cared for in a large neonatal unit, who were thought likely to require intravenous access for ≥ 3 days. Exclusion criteria not stated Children's Hospital, Charleston, South Carolina, USA; before 1995
Interventions	Delivery of parenteral nutrition via percutaneous central venous catheter (n = 75) or via peripheral cannula (n = 75)
Outcomes	• Incidence of bacterial or fungal sepsis • Numbers of insertion attempts and catheters required for intravenous access (SD imputed from Janes 2000) • Duration of intravenous access
Notes	Trial reported in abstract form only. Lead investigator kindly provided further details of trial methods

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up

Barria 2007

Methods	Randomised controlled trial
Participants	74 neonates cared for in a single regional neonatal intensive care unit who were likely to require intravenous fluids for longer than 5 days. Median gestation of recruited infants was 31 weeks Infants excluded: congenital malformation, coagulopathy, skin injury at site of catheter/cannula insertion, requiring transfer to other unit for ongoing management NICU of Regional Hospital, Valdivia, Chile: April 2003 to January 2005
Interventions	Delivery of intravenous fluids (including parenteral nutrition) via percutaneous central venous catheter (n = 37) or via peripheral cannula (n = 37)
Outcomes	• Length of stay • Incidence of suspected bacterial or fungal sepsis • Incidence of proven (culture-positive) bacterial or fungal sepsis • Numbers of insertion attempts and catheters required for intravenous access • Incidence of phlebitis
Notes	Infants were of similar gestation, birth weight and age at randomisation. Catheters/cannulae were used for intravenous ('clear') fluids and for parenteral nutrition (proportion of infants receiving parenteral nutrition slightly higher in central venous catheter arm) Percutaneous central venous catheters inserted by trained neonatal nurses with ≥ 3 years' experience with the procedure. Same trained nurses also responsible for dressing changes and line manipulations Umbilical venous catheters (if used) were removed before enrolment Additional details on study methods and results were provided by investigators

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation, with a sequence of 8 units per block
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up

Hosseini 2014

Methods	Randomised controlled trial
Participants	117 preterm neonates with birth weight < 1500 g

Hosseini 2014 *(Continued)*

	Mean birth weight of intervention and control groups: 1061 g and 1054 g, respectively Setting: Tabriz University of Medical Sciences, Tabriz, Iran
Interventions	Delivery of intravenous fluids via peripherally inserted central catheter (PICC) line (n = 57) vs peripheral cannula (n = 60)
Outcomes	• Duration of catheter/cannula use • Incidence of catheter-related infection • Mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Internet-based randomisation website
Allocation concealment (selection bias)	Low risk	Internet-based randomisation website
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up

Janes 2000

Methods	Randomised controlled trial
Participants	63 infants of birth weight < 1251 g, cared for in a neonatal intensive care unit and likely to require intravenous maintenance fluids or total parenteral nutrition at 1 week of age, or when umbilical venous catheter was removed Children's Hospital and St Joseph's Hospital, Hamilton, Ontario, Canada: before 2000
Interventions	Delivery of parenteral nutrition via percutaneous central venous catheter (n = 32) vs via peripheral cannula (n = 31)
Outcomes	• Incidence of bacterial or fungal sepsis • Numbers of insertion attempts and catheters required for intravenous access • Courses of antibiotics • Duration of intravenous access
Notes	Random allocation was achieved by using a "computer-generated block random number table" Additional details on study outcomes were provided by investigators

Janes 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, block random number table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up

Wilson 2007

Methods	Randomised controlled trial
Participants	96 infants of birth weight < 1251 g or gestation < 32 weeks at birth, cared for in a neonatal intensive care unit and likely to require intravenous maintenance fluids or total parenteral nutrition until ≥ 5 days of age Memorial Hermann Children's Hospital, Hamilton, Houston, USA: between 2000 and 2002 Mean gestation 27.1 (central venous catheter) and 27.2 (cannula) weeks, mean birth weight 914 g and 971 g, respectively
Interventions	Delivery of parenteral nutrition via percutaneous central venous catheter (n = 46) vs peripheral cannula (n = 50)
Outcomes	• Incidence of bacterial or fungal infection • Mortality • Numbers of insertion attempts and catheters required for intravenous access • Extravasation episodes
Notes	Infants were of similar gestation, birth weight and age at randomisation Percutaneous central venous catheters were inserted by a team of trained neonatal nurses. Same trained nurses were responsible for dressing changes and line manipulations No prophylactic antibiotics were used Umbilical venous catheters (if used) were removed before enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated

Wilson 2007 *(Continued)*

Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up

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

Study	Reason for exclusion
Arnts 2014	Not a randomised controlled trial. Matched historic cohorts
Cairns 1995	Not a randomised controlled trial. Matched historic cohorts
Childs 1995	Comparison of percutaneous central venous catheters for which tip is sited in a peripheral vein or in a central vein (not percutaneous central venous catheters vs peripheral cannulae)
Geffers 2010	Not a randomised controlled trial
Liossis 2003	Not a randomised controlled trial. Matched historic cohorts
Parellada 1999	Non-randomised comparison of infants with percutaneous central venous catheters and matched controls with peripheral cannulae
Schwengel 2004	Randomised trial of percutaneous central venous catheters vs peripheral cannulae in neonates and children (ages ranging from neonatal through 14 years) without stratification by age. We are seeking relevant subgroup data from the trial authors

DATA AND ANALYSES

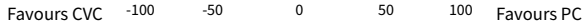
Comparison 1. Percutaneous central venous catheter versus peripheral cannula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Percentage deficit in nutrient delivery per infant	1	49	Mean Difference (IV, Fixed, 95% CI)	-7.10 [-11.02, -3.18]
2 Death before 28 days (all causes)	4	282	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.36, 4.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Death before hospital discharge (all causes)	5	399	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.55, 3.02]
4 Invasive bacterial and fungal infections	6	549	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.72, 1.25]
5 Extravasation injury	3	208	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.07, 1.75]
6 Numbers of cannulae/catheters per infant	3	287	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-4.13, -2.06]

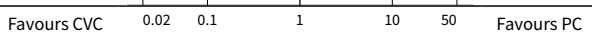
Analysis 1.1. Comparison 1 Percutaneous central venous catheter versus peripheral cannula, Outcome 1 Percentage deficit in nutrient delivery per infant.

Study or subgroup	Central catheter N	Central catheter Mean(SD)	Peripheral cannula N	Peripheral cannula Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Ainsworth 2001	24	3.2 (7.2)	25	10.3 (6.8)		100%	-7.1[-11.02,-3.18]
Total ***	**24**		**25**			**100%**	**-7.1[-11.02,-3.18]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.55(P=0)							



Analysis 1.2. Comparison 1 Percutaneous central venous catheter versus peripheral cannula, Outcome 2 Death before 28 days (all causes).

Study or subgroup	Central catheter n/N	Peripheral cannula n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ainsworth 2001	1/24	0/25		12.66%	3.12[0.13,73.04]
Barria 2007	0/37	0/37			Not estimable
Janes 2000	1/32	0/31		13.11%	2.91[0.12,68.81]
Wilson 2007	2/46	3/50		74.23%	0.72[0.13,4.14]
Total (95% CI)	**139**	**143**		**100%**	**1.31[0.36,4.81]**
Total events: 4 (Central catheter), 3 (Peripheral cannula)					
Heterogeneity: Tau^2=0; Chi^2=0.98, df=2(P=0.61); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					



Analysis 1.3. Comparison 1 Percutaneous central venous catheter versus peripheral cannula, Outcome 3 Death before hospital discharge (all causes).

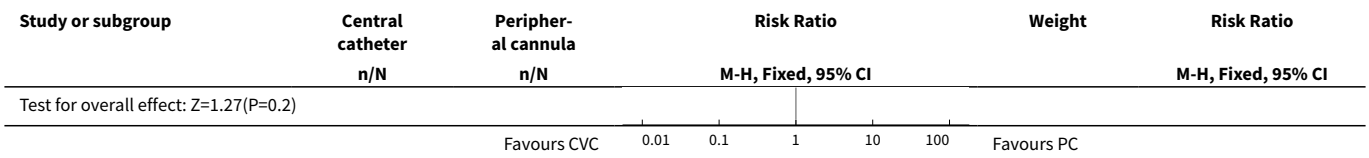
Study or subgroup	Central catheter n/N	Peripheral cannula n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Barria 2007	0/37	0/37			Not estimable
Wilson 2007	2/46	3/50		32.88%	0.72[0.13,4.14]
Hosseini 2014	6/57	5/60		55.71%	1.26[0.41,3.91]
Janes 2000	1/32	0/31		5.81%	2.91[0.12,68.81]
Ainsworth 2001	1/24	0/25		5.61%	3.12[0.13,73.04]
Total (95% CI)	**196**	**203**		**100%**	**1.29[0.55,3.02]**
Total events: 10 (Central catheter), 8 (Peripheral cannula)					
Heterogeneity: Tau^2=0; Chi^2=0.98, df=3(P=0.81); I^2=0%					
Test for overall effect: Z=0.58(P=0.56)					

Analysis 1.4. Comparison 1 Percutaneous central venous catheter versus peripheral cannula, Outcome 4 Invasive bacterial and fungal infections.

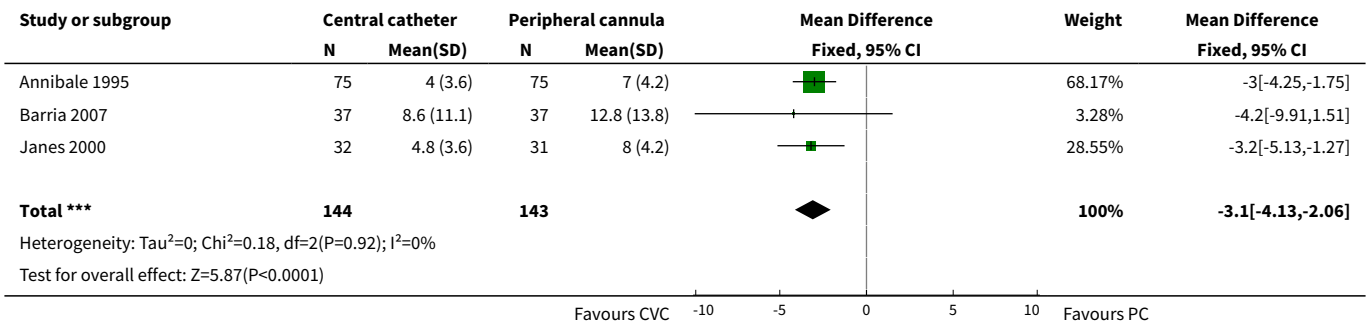
Study or subgroup	Central catheter n/N	Peripheral cannula n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ainsworth 2001	11/24	10/25		13.74%	1.15[0.6,2.19]
Annibale 1995	22/75	27/75		37.88%	0.81[0.51,1.29]
Barria 2007	1/37	2/37		2.81%	0.5[0.05,5.28]
Hosseini 2014	8/57	7/60		9.57%	1.2[0.47,3.1]
Janes 2000	10/32	13/31		18.53%	0.75[0.39,1.44]
Wilson 2007	15/46	13/50		17.48%	1.25[0.67,2.34]
Total (95% CI)	**271**	**278**		**100%**	**0.95[0.72,1.25]**
Total events: 67 (Central catheter), 72 (Peripheral cannula)					
Heterogeneity: Tau^2=0; Chi^2=2.54, df=5(P=0.77); I^2=0%					
Test for overall effect: Z=0.35(P=0.73)					

Analysis 1.5. Comparison 1 Percutaneous central venous catheter versus peripheral cannula, Outcome 5 Extravasation injury.

Study or subgroup	Central catheter n/N	Peripheral cannula n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ainsworth 2001	1/24	0/25		8.5%	3.12[0.13,73.04]
Janes 2000	0/32	0/31			Not estimable
Wilson 2007	0/46	5/50		91.5%	0.1[0.01,1.74]
Total (95% CI)	**102**	**106**		**100%**	**0.36[0.07,1.75]**
Total events: 1 (Central catheter), 5 (Peripheral cannula)					
Heterogeneity: Tau^2=0; Chi^2=2.59, df=1(P=0.11); I^2=61.4%					



Analysis 1.6. Comparison 1 Percutaneous central venous catheter versus peripheral cannula, Outcome 6 Numbers of cannulae/catheters per infant.



WHAT'S NEW

Date	Event	Description
19 March 2015	New citation required but conclusions have not changed	Our updated search of the literature through June 2015 led to inclusion of 1 additional trial (Hosseini 2014)
19 March 2015	New search has been performed	"Percutaneous central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates" - published in the Cochrane Database of Systematic Reviews, *The Cochrane Library*, Issue 3, 2007 (Ainsworth 2007)

HISTORY

Protocol first published: Issue 2, 2003
Review first published: Issue 2, 2004

Date	Event	Description
5 March 2007	New citation required but conclusions have not changed	Substantive amendments have been made

CONTRIBUTIONS OF AUTHORS

Sean Ainsworth (SA) and William McGuire (WM) developed the protocol for this review. All review authors screened the titles and abstracts of all studies identified by the search strategy. WM and SA screened the full-text report of each study identified as potentially relevant and extracted the data separately, compared data and resolved differences by consensus. SA and WM completed the final review.

DECLARATIONS OF INTEREST

Sean Ainsworth is the lead investigator for one of the included trials (Ainsworth 2001).

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Newborn; Catheterization, Central Venous [adverse effects] [*instrumentation]; Catheterization, Peripheral [adverse effects] [*instrumentation]; Extravasation of Diagnostic and Therapeutic Materials [etiology]; Infant, Extremely Low Birth Weight; Infant, Premature; Infant, Very Low Birth Weight; Parenteral Nutrition [adverse effects] [*instrumentation]; Randomized Controlled Trials as Topic

MeSH check words

Humans