Tunnelled External Versus Implanted Port Central Venous Catheters in Paediatric Oncology: a systematic review and meta-analysis.

Jonathan J Neville[1], Hinn Moe Aye[2], Nigel J Hall[1]*

1. Department of Paediatric Surgery, University Surgery Unit, University of Southampton, Southampton, UK
2. School of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland

*Corresponding author: Nigel Hall, n.j.hall@soton.ac.uk, University Surgery Unit, University Hospitals Southampton, Tremona Road, Southampton, SO16 6YD, United Kingdom

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JJN and NJH conceptualized the project. JJN and HMA collected and analysed the data. JJN and HMA drafted the manuscript. All authors revised the manuscript and approved the final version.

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Abbreviations:

CVC	Central venous catheter
PORT	Implanted port catheter
PRISMA	Preferred Reporting for Systematic Reviews and Meta-analysis
QoL	Quality of Life
OR	Odds Ratio
CI	Confidence Interval
RCT	Randomised Control Trial
PICC	Peripherally Inserted Central Venous Catheter

ABSTRACT

Objective: To evaluate and compare the complications associated with tunnelled external and implanted port (PORT) central venous catheters (CVCs) in children with cancer.

Design: A systematic review in accordance with PRISMA guidelines was performed (pre-registered on PROSPERO: CRD42022300869). MEDLINE, Web of Science and the Cochrane Library databases were searched.

Patients: Patients ≤18 years of age with haematological or solid malignancies.

Interventions: Studies comparing tunnelled external and PORT CVCs.

Main outcomes measures: Infection, mechanical failure, thrombosis, bleeding, acceptability, quality of life (QoL), cost, premature removal, and days from insertion to removal for any reason.

Results: Twenty-three observational studies met the inclusion criteria, representing 6,644 devices and 6,032 patients. Tunnelled external CVCs were associated with an increased risk for systemic infection (odds ratio [OR] 2.10, 95% confidence interval [CI] 1.59 – 2.77, p <0.001, 16 studies, 3,425 devices). There was no significant difference in the risk of localised infection (OR 1.15, 95% CI 0.66 – 2.01, p = 0.62, five studies, 979 devices). Tunnelled external CVCs were also associated with a significantly increased risk of mechanical complications (OR 2.47, 95% CI 1.21 – 5.05, p = 0.01, 11 studies, 2,187 devices) and premature device removal (OR 3.24, 95% CI 1.28 – 8.22, p = 0.01, six studies, 1,514 devices).

Conclusion: This study shows that PORTs associate with a reduced risk of infectious and mechanical complications, and a lower overall risk of removal, compared to tunnelled external CVCs in children with cancer. Further work is required to confirm these findings in a prospective randomised trial, and compare cost implications and acceptability to patients and caregivers.

SUMMARY

What is already known on this topic

Complications associated with central venous catheters (CVCs) in children with cancer are commonplace. The choice of CVC line is based on clinician and patient preference, the duration, nature and frequency of treatment, and the potential for CVC-associated complications.

What this study adds

This is the first systematic review and meta-analysis to compare tunnelled external to implanted port (PORT) CVCs in children with cancer. PORTs associate with a reduced risk of infectious and mechanical complications, and a lower overall risk of removal, compared to tunnelled external CVCs.

How this study might affect research, practice or policy

Clinicians should consider using PORT CVCs in children with cancer. Further prospective research is warranted to confirm these findings, and investigate quality of life and acceptability.

INTRODUCTION

Tunnelled external and implanted port (PORT) central venous catheters (CVCs) are commonly used in paediatric oncology as the repeated administration of irritant medications over a period of months requires safe and reliable long-term central venous access[1]. Tunnelled external catheters are channelled through the subcutaneous tissue away from the site of central venous puncture to a separate skin exit site. The line is stabilized and protected from the entry of microorganisms by a Dacron® cuff which fuses with subcutaneous tissues. Alternatively, catheters can be connected to a subcutaneous metal or plastic reservoir (a 'port') topped with a self-sealing silicone membrane. PORTs are entirely intracorporeal, with access to the reservoir achieved percutaneously with a non-coring needle. Because of the associated tissue reactions, cuffed tunnelled external and PORT CVCs both require surgical removal under local or general anaesthetic[2]. Tunnelled external CVCs are better suited to frequent access, and do not require a needle, whereas PORT CVCs provide better cosmesis, require less care, and allow for bathing and swimming[2,3].

CVC choice is based on clinician and patient preference, the duration, nature and frequency of treatment, and the potential for CVC-associated complications. Complications, such as bleeding, occlusion, migration or displacement, infection, venous thrombosis, and mechanical failure can result in premature line removal in 15 – 40% of cases[3–6].

There is a paucity of evidence comparing tunnelled external CVCs to PORTs in paediatric oncology patients. The aim of this systematic review was to compare and evaluate the complications associated with tunnelled external and PORT CVCs in children with cancer, in order to better inform clinicians, patients and their families, and identify areas of unmet research need.

METHODS

A systematic review of the literature and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[7].

The study protocol was specified in advanced and registered on PROSPERO (CRD 42022300869).

An electronic database search was performed of MEDLINE, Web of Science and the Cochrane Library from inception to December 2021 (Supplementary Table 1). Reference lists were also searched.

Prospective and retrospective studies investigating patients ≤18 years of age undergoing treatment for solid or hematological malignancies, that directly compared tunnelled external to PORT CVCs, were eligible for inclusion. Review articles, clinical guidelines and articles not published English were excluded. Studies comparing CVCs in patients with non-oncological or mixed oncological and non-oncological indications were also excluded.

Two reviewers (J.J.N. and H.M.A.) independently screened the titles and abstracts of each study identified from the literature search. Articles not meeting the inclusion criteria and duplicates were excluded. The full text of the remaining articles was assessed against predefined inclusion criteria. Data was then extracted by J.J.N. and validated by H.M.A. independently. Study design, patient population, CVC placement details, and clinical or device-related outcomes were extracted.

The outcomes recorded included: systemic and localised infection, mechanical failure, thrombosis, bleeding, acceptability, quality of life (QoL), financial cost, premature removal, and days from insertion to removal for any reason (line duration). Systemic infection was defined as CVC infection causing a physiological response, and/or proven bacteraemia or colonization of the line. Localised infection was port site or tunnel infection, or erythema at the exit site. Mechanical failure included line fracture, erosion, dislodgement, and occlusion. Premature removal was defined as the removal of a CVC prior to completion of treatment due to any complication.

Assessment of risk of bias

Each study was assessed for risk of bias using the ROBINS-1 tool[8]. The following domains were assessed: bias due to confounding, bias due to selection of participants, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result. Each domain was categorised as low, moderate or serious risk. The visualization tool Robvis was used to create traffic-light and weighted bar plots to illustrate the results of the assessment at a domain-level for each study[9].

Statistical analysis

The included studies variably used patient or device number as the denominator when reporting complication rate. Complication rate per 1,000 catheter days was also used. For the purposes of analysis device number was used as the unit of measure. When only patient number was reported, it was assumed that each patient received a single device. Complication rate per 1,000 catheter days was converted back to complication frequency using the total number of catheter days.

When appropriate data was available, meta-analysis was performed in Review Manager version 5.4. For dichotomous variables the odds ratio (OR) and 95% confidence interval (CI) were calculated. A random-effects model was used. Study heterogeneity was assessed using the Chi-squared test and I^2 statistic. For continuous variables the mean difference was calculated with 95% CI using a random-effects model.

RESULTS

Study selection and characteristics

In total, 2,839 publications were identified from electronic database searching (Figure 1). Duplicates and articles not published in English were removed, and 2,013 articles underwent title and abstract screening. Of these, 167 underwent full text review and 23 studies were

identified that met the inclusion criteria[10–31]. All studies were included. No studies were identified from reference list searching.

Of the 23 included studies, seven publications were prospective observational studies and 16 were retrospective cohort studies (Table 1). No randomised control trials (RCT) were identified. The total number of devices was 6,644 CVCs placed into 6,032 children.

Six studies included patients with only haematological malignancies[10,18,19,21,30,31]. The remaining 17 studies incorporated patients with both solid and haematological malignancies. Eight studies specified that the CVCs were inserted by surgeons[11,14,16,19,20,23,26,28]. In two studies lines were placed by surgeons or interventional radiologists (IR)[18,25]. In one study lines were inserted by surgeons or oncologists[15]. Otherwise, the operator was unspecified. Insertion technique was via the Seldinger/percutaneous technique in one study[18]. Both Seldinger/percutaneous or open cutdown was used in five studies[15,16,19,20,25]. Placement technique was unspecified in 17 studies. IR and oncologists all used the Seldinger/percutaneous technique for insertion. Sites of insertion were specified in nine studies and included the external and internal jugular, subclavian, facial and cephalic veins.

Prophylactic antibiotics were given in four studies (one with haematological disease only and three with solid and haematological malignancies)[16–18,23]. Antibiotics were explicitly stated as not given in two studies (both haematological malignancies only)[10,19]. Otherwise, antibiotic practice was unspecified.

Eight studies described stakeholder involvement in the decision-making process surrounding CVC type. Two studies stated the decision was parent-led[10,23]. In one study it was surgeon preference alone[24]. Choice was dictated by hospital policy in four, with three of these involving the parents in some form. One study described the decision as being shared between clinicians and parents[20].

Risk of bias within studies

Twenty-one studies were found to have moderate risk of bias and two studies were at serious risk of bias (Supplementary Figure 1)[28,31]. All the studies were assessed as at moderate or serious risk of bias due to confounding. This is due to the heterogeneity in diagnoses and variable treatments of CVC complications across the studies. One study is judged to be at serious risk of bias across three domains[31]. Most studies defined the outcome measurements and provided information on the analytical method (Supplementary Figure 2).

Infectious complications

Sixteen studies, including 3,425 devices, reported data for systemic infections and were included in meta-analysis (Figure 2)[11,13–21,23–27,30]. Tunnelled external CVCs were associated with a significantly increased odds ratio (OR) for systemic infection (OR 2.10, 95% CI 1.59 – 2.77, p <0.001). Moderate heterogeneity of studies was observed.

Subgroup analysis was performed comparing studies including children with haematological malignancies only to those including solid and haematological malignancies. The risk of systemic infection with a tunnelled external CVC was greater in the haematological malignancy group (OR 3.16, 95% CI 1.44 – 6.91, p = 0.004, 596 devices) compared to the solid and haematological malignancy group (OR 1.85, 95% CI 1.44 – 2.38, p <0.001, 2,829 devices).

Five studies reported data on localised infection, including 979 devices (Figure 3)[11,15,18,19,25]. Tunnelled external CVCs did not associate with an increased risk of localised infection (OR 1.15, 95% CI 0.66 – 2.01, p = 0.62). Heterogeneity was low.

Three studies discussed infectious complications of each CVC but could not be meta-analysed. Flynn *et al.* compared catheter-associated bloodstream infections between CVC types, but no denominators were provided[29]. They observed that PORTs had a significantly higher rate of recurrent infection (OR 10.00, 95% CI 3.10 – 33.30, p < 0.001). Similarly, Hord and colleagues reported inpatient and outpatient catheter-associated bloodstream infections

across 15 centres[12]. There was a lower incidence of infection in PORTs, compared to tunnelled external and peripherally-inserted CVCs (PICC) in both settings (inpatient: PORTs 1.48 per 1,000-line days and tunnelled external CVCs 3.51 per 1,000-line days; outpatient: PORTs 0.16 per 1,000-line days and tunnelled external CVCs 1.38 per 1,000-line days). Hooda and colleagues described their experiences switching from tunnelled external to PORT CVCs over a two-year period. They observed fewer infectious complications with PORTs but no formal statistical analysis was performed[31].

Mechanical complications and device removal

Mechanical complications were reported in 11 studies, totaling 2,187 devices (Figure 4; Supplementary Table 2)[11,14,15,18–21,25–27,30]. PORTs were associated with a significantly lower risk of mechanical complications (OR 2.47, 95% CI 1.21 – 5.05, p = 0.01). Study heterogeneity was moderate to high.

The included studies provided insufficient data regarding the CVC insertion technique to enable a subgroup analysis.

Six studies (1,514 devices) reported device removal rate due to complications of any kind (Supplementary Figure 3)[14,18,20,22,27,30]. Tunnelled external CVCs were associated with an increased risk of removal (OR 3.24, 95% CI 1.28 – 8.22, p = 0.01). Heterogeneity was moderate to high.

Mean time to device removal was reported in four studies[10,18,20,21]. PORTs were in place for a longer period compared to tunnelled external CVCs, however this was not significant (mean difference, 184.26 days, 95% CI -65.94 – 434.47 days, p = 0.15).

Other complications

The rate of venous thrombosis was reported in five studies, across 867 devices (Supplementary Figure 4)[18,25,26,28,32]. No significant difference in the rate of venous thrombosis was observed (OR 1.54, 95% CI 0.85 – 2.81, p = 0.16). Heterogeneity was low.

Significant bleeding on insertion was reported in one study[18]. There was no significant difference between tunnelled external and PORT CVCs (8.6% *versus* 8.3%, p = 0.666). No studies investigated financial cost.

Patient acceptability

No studies formally compared patient and caregiver acceptability of either CVC. Hooda *et al.* assessed the preference of 52 parents for either PICCs, tunnelled external CVCs or a PORT[31]. The authors do not document the results of this survey, but highlight that parents show "clear preference" for a PORT. No studies investigated QoL.

DISCUSSION

CVCs are necessary in children with cancer to facilitate long-term blood sampling and treatment. Complications are commonplace and influence the choice of CVC. In this meta-analysis we have shown that PORTs associate with significantly lower rates of systemic infection, mechanical complications and device removal for any reason compared to tunnelled external CVCs.

Similar findings have been observed in adult cancer patients. Kulkarni and colleagues showed that PORTs were superior to external CVCs in a meta-analysis of 30 studies[33]. A RCT comparing PORTs to tunnelled external CVCs and PICCs showed significantly fewer complications in the PORT group[34]. Acceptability was also investigated, with general QoL assessments favoring PICCs. However, device-specific questionnaires favored PORTs. PORTs were also shown to be more cost effective (£210 per catheter week for PORTs *versus* £257 for tunnelled CVCs). Formal assessment of the acceptability of CVC in adult cancer patients has shown that PORTs are perceived to offer a better QoL[35,36]. PICCs are less commonly inserted in the paediatric oncology population, and are often used for temporary access before inserting a tunnelled external or PORT CVC. Further work investigating the use of PICCs in children is warranted.

It is perhaps unsurprising that PORTs associate with a reduced risk of infection. Tunnelled external CVCs are often chosen in patients who require frequent access and the externalized portion of the tunnelled CVC offers a potential route for ingress of microorganisms. Mechanical complications may occur from the more frequent handling and usage of tunnelled external CVCs. Displacement was more frequent in the tunnelled external CVCs, compared to PORTs (Supplemental Table 2). There is a greater risk of accidental damage with an externalized device.

There is a paucity of literature covering the discussions between clinicians, patients and caregivers around the choice of CVC. Eight studies in this systematic review commented on which stakeholders were involved in this decision. Surgeon preference and hospital policy had a large impact on the choice of CVC, but six studies highlighted parental involvement. Wiener *et al.* reported the surgeon-perceived difficulty of 1,016-line insertions in children with cancer, and observed similar reported difficulty grades between tunnelled CVCs (mild 89.5%, difficult 9.5%, complex 1%) and PORTs (mild 90%, difficult 9.5%, complex 0.5%)[37].

PORTs may be less suitable for younger children, as they require access with a needle. Ross and colleagues reported outcomes in infants under one year of age who received a PORT. They observed a similar complication rate to that described in this study (30%)[38]. In this systematic review, insufficient data was available to conduct any subgroup analysis based on age.

Patients and caregivers should be actively involved in the decision-making process as the choice of line has an impact on the child's QoL. Ullman and colleagues explored the experiences of children <18 years of age with CVCs inserted for oncological and non-oncological indications[39]. Parents saw the lines as necessary, a theme that is echoed in adults[35,36]. Families were aware of, and concerned about, complications associated with CVCs. The main impacts on the child were distress associated with dressing changes and difficulties with certain activities of daily living (showering, bathing and playing). This study did

not investigate the decision-making process prior to insertion and also did not compare CVC types.

Strengths and limitations

This is the first systematic review and meta-analysis to compare tunnelled external and PORT CVC lines in children with cancer. The findings corroborate literature from adult cancer patients. A large cohort of children with solid and haematological malignancies have been included in the study and the findings are relevant to this group.

Across the studies included in this systematic review there will exist variation in CVC insertion techniques, antibiotic usage, catheter care regimes, and management of complications. Clinicians will have different thresholds for CVC removal. As such this study is limited by the heterogeneity of the evidence base. Subgroup analyses investigating the effects of patient age, CVC insertion technique, and CVC care regimen could not be performed due to insufficient data being reported in the included studies. The certainty of the evidence is low, and as such caution should be used when interpreting the pooled OR. When device number was unspecified, patient number and device number were assumed to be equal to facilitate statistical analysis. This assumption has been made in similar studies[33].

Further work

To date, no studies have formally assessed and compared patient and caregiver acceptability of different types of CVC. Given that patients are involved in the decision to insert a certain CVC, assessment of their perspectives is an important next step. It may be necessary to stratify patients based on age, and create and validate a new CVC-specific QoL questionnaire to ensure that the impacts of the CVC are measured independently of the underlying disease process. Both patients and their caregivers should be surveyed. Similarly, a cost analysis may be useful to understand the financial impact of each CVC on the healthcare system. Both QoL and cost could be analysed as part of a prospective RCT comparing tunnelled CVCs to PORTs

in children with cancer. This study would provide the best evidence for clinicians, patients, and families to guide decision making.

Conclusions

This systematic review and meta-analysis shows that the use of PORT CVCs in children with cancer associates with a reduced risk of infectious and mechanical complications, and a reduced rate of removal due to complications of any kind, when compared to tunnelled external CVCs. Whilst a prospective RCT comparing tunnelled external CVCs and PORTs, assessing complication rate, cost, and patient acceptability, would provide higher quality data on which to base decision making, we acknowledge this may be challenging to perform.

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FIGURES

TABLES

Table 1 – Characteristics of the included studies. RC – retrospective cohort study, PC – prospective cohort study, NS – not specified, PORT-implanted port.

Study	Location	Study Design	Study Quality Assessment	Patients Number (frequency male)	Devices Number	Indication	Frequency Tunnelled/ PORT	Frequency Insertions Open/ Percutaneous	Outcomes
Abbas *et al.* 2014	Saudi Arabia	RC	Moderate	148 (74)	199	Haematological malignancy	101/47	NS	Duration
Adler *et al.* 2006	Israel	PC	Moderate	281 (243)	419	Haematological and solid tumours	173/246	NS	Infection, mechanical, duration
Barrett *et al.* 2004	UK	PC	Moderate	NS	824	Haematological and solid tumours	745/77	NS	Failure/removal
Basford *et al.* 2003	Canada	RC	Moderate	67 (35)	98	Haematological and solid tumours	52/46	NS/41	Infection, mechanical
Beck *et al.* 2019	Germany	RC	Moderate	296 (149)	NS	Haematological and solid tumours	168/128	NS	Infection, mechanical, thrombosis
Bratton *et al.* 2013	USA	RC	Moderate	170 (NS)	144	Haematological and solid tumours	34/110	NS	Infection, mechanical, failure/removal
Chen *et al.* 2016	Canada	RC	Serious	104 (53)	147	Haematological and solid tumours	40/70	NS	Thrombosis
Flynn *et al.* 2003	USA	RC	Moderate	172 (96)	NS	Haematological and solid tumours	151/21	NS	Infection
Handrup *et al.* 2010	Denmark	PC	Moderate	98 (96)	98	Haematological malignancy	63/35	NS	Infection
Hooda *et al.* 2008	Pakistan	RC	Serious	92 (NS)	NS	Haematological malignancy	4/42	NS	Infection, acceptability

Hord *et al.* 2016	USA	PC	Moderate	1,113 (NS)	NS	Haematological and solid tumours	NS/NS	NS	Infection
Kelly *et al.* 2013	USA	RC	Moderate	123 (68)	NS	Haematological and solid tumours	23/102	NS	Infection
La Quaglia *et al.* 1992	USA	PC	Moderate	271 (149)	271	Haematological and solid tumours	229/42	NS	Infection, mechanical, failure/removal, duration
Mirro *et al.* 1989	USA	PC	Moderate	264 (172)	286	Haematological and solid tumours	204/82	228/58	Infection, mechanical
Newman *et al.* 2012	Israel	RC	Moderate	NS	328	Haematological and solid tumours	190/138	151/177	Infection
Park *et al.* 2021	South Korea	RC	Moderate	470 (290)	NS	Haematological and solid tumours	226/242	NS	Infection
Pektas *et al.* 2015	Turkey	RC	Moderate	106 (73)	203	Haematological malignancy	112/91	0/203	Infection, mechanical, thrombosis, failure/removal, duration, bleeding
Severien *et al.* 1991	USA	RC	Moderate	60 (33)	75	Haematological malignancy	45/25	NS	Infection, mechanical
Stammers *et al.* 2016	Canada	RC	Moderate	330 (152)	NS	Haematological and solid tumours	41/216	NS	Thrombosis
Wacker *et al.* 1992	Switzerland	RC	Moderate	69 (45)	93	Haematological and solid tumours	59/34	56/37	Infection, thrombosis, duration
White *et al.* 2012	UK	RC	Moderate	322 (165)	322	Haematological malignancy	68/254	NS	Infection, thrombosis, failure/removal, duration
Wurzel *et al.* 1988	USA	PC	Moderate	62 (43)	78	Haematological and solid tumours	33/45	NS	Infection
Yacobovich *et al.* 2015	Israel	RC	Moderate	262 (155)	463	Haematological and solid tumours	104/126	NS	Infection