Totally implantable venous access devices – 20 years' experience of implantation in cystic fibrosis patients

T JAMES ROYLE¹, RUTH E DAVIES², MARK X GANNON¹

¹Department of Vascular Surgery and ²West Midlands Adult Cystic Fibrosis Centre, Heartlands Hospital, Heart of England NHS Foundation Trust, Birmingham, UK

ABSTRACT

INTRODUCTION Totally implantable venous access devices (TIVADs) are widely used to provide long-term, central venous access for antibiotic delivery in cystic fibrosis patients. However, few studies have demonstrated long-term follow-up with large cohorts.

PATIENTS AND METHODS This is a retrospective review of TIVADs implanted in cystic fibrosis patients by vascular surgeons at a tertiary referral centre, using an open venous cut-down technique, from March 1986 to July 2006. The cephalic vein was preferentially chosen for line placement, in the deltopectoral groove, under fluoroscopic control. TIVAD performance (life-span or survival) and complications were evaluated. Data were extracted by review of a local database (data collated prospectively since 1986), with supplementation from electronic patient records and medical notes.

RESULTS In total 165 TIVADs in 109 patients (34 males, 75 females) were reviewed. Median survival was 1441 days (range, 6–4440 days). Cumulative patency was 146,072 catheter-days. No immediate intrathoracic complications (pneumothorax, haemothorax, nerve injury) occurred. There were 3 early and 82 late complications, namely: occlusion (33 TIVADs; median age 510 days), infection (23 TIVADs; median 376 days), leakage (16; median 283 days), pain or discomfort (6), venous thrombosis (5), extravasation/skin necrosis (1), vegetation in right atrium (1). Overall incidence of complications was 0.58 per 1000 catheter-days.

CONCLUSIONS This study concurs with others that TIVADs are safe and effective, with a favourable life-span in cystic fibrosis patients if well looked after in a specialist centre. Complications of infection, leakage and occlusion do occur. Using an open, venous cut-down technique with fluoroscopic control avoids any immediate intrathoracic complications.

KEYWORDS

Totally implantable venous access devices – Cystic fibrosis – Venous cut-down

CORRESPONDENCE TO

T James Royle, Department of General Surgery, Harefield Hospitals NHS Trust, The County Hospital, Union Walk, Hereford HR1 2ER, UK
T: +44 (0)1432 355444; E: jamesroyle@doctors.org.uk

Totally implantable venous access devices (TIVADs) are widely used to provide long-term, intermittent central venous access for the administration of intravenous antibiotics, chemotherapeutic agents, and other treatments. They are used in a variety of disease groups, and in both children and adults.

Since TIVADs appeared in the early 1980s,^{1–5} a number of reports have been published in oncology and other patient groups. Some studies have compared percutaneous and open techniques,^{4–9} others specifically discussing TIVADs in cystic fibrosis patients.^{10–12} However, few such studies have demonstrated long-term follow-up with large cohorts. A Cochrane review in 2003¹⁵ identified a lack of randomised, controlled trials on TIVADs.

Vascular surgeons at Birmingham Heartlands Hospital, UK, have been inserting TIVADs using open venous cut-down since 1986, for both adults and children with cystic fibrosis, and severe asthma patients. The West Midlands Adult Cystic Fibrosis Centre, based at Heartlands Hospital, has looked after over 250 TIVADs in cystic fibrosis patients, including a number of devices previously inserted in patients at Birmingham Children's Hospital, UK. Many of these patients have subsequently had replacement TIVADs inserted at Heartlands Hospital. A total of 175 TIVADs have been inserted in cystic fibrosis patients over the age of 16 years at Heartlands Hospital.

The aims of this study were to review: (i) long-term outcomes of TIVADs (patency, or survival) in a cystic fibrosis

adult patient cohort; and (ii) complications such as infection and occlusion, particularly with respect to incidence and median time to occurrence.

Patients and Methods

Method of TIVAD insertion

All of the TIVADs in this study were placed using an open venous cut-down technique, usually under general anaesthetic. Dissection onto the vein, and pouch creation for the portal, can be performed through the same 4-cm long incision. If the vein is small, various techniques are available to the vascular surgeon to help cannulate the vein. In this cohort, if the vein was too under-sized or thrombosed, the surgeon performed an open dissection of a suitable alternative vein such as the external jugular, as described by Di Carlo *et al.*⁶ Other veins used were the internal jugular, subclavian, basilic, and long saphenous (at the groin). The principal steps of the open approach (cephalic vein) are well documented elsewhere^{7,9} and surgeons at Heartlands Hospital essentially use this standard technique.

Study design

In this retrospective, single-centre study, we reviewed all TIVADs inserted at Birmingham Heartlands Hospital, UK for adult patients with cystic fibrosis, over a 20-year period (March 1986 to July 2006).

Data on all TIVADs looked after at the West Midlands Adult Cystic Fibrosis Centre have been prospectively collated since 1986 by clinical nurse specialists. These data were updated for the study using the electronic patient record and patients' medical notes where possible.

The following parameters were recorded: age, sex, date inserted, age at insertion of TIVAD, and complications. Patency, or life-span, for each TIVAD was calculated in days from the date inserted to the date that the TIVAD was no

longer functioning, or to the date the patient died with the TIVAD *in situ* and functioning.

Inclusion/exclusion criteria

The data for many of the TIVADs inserted elsewhere were incomplete; therefore, all TIVADs inserted in other hospitals have been excluded. All those inserted in paediatric cystic fibrosis patients at Heartlands Hospital were also excluded because the paediatric department did not keep a detailed database of TIVADs inserted in cystic fibrosis patients. Of the 175 TIVADs inserted in patients over the 16 years, 10 were excluded as data were inadequate, leaving 165 for analysis.

Statistical analysis

Kaplan–Meier survival analysis (SPSS® v.14.0 for Windows®; SPSS Inc., Chicago, IL, USA) was used to produce survival tables and estimate median survival for TIVADs. This is an elegant solution to the problem of variable follow-up, to account for TIVADs that were still patent when the patient died, or those that were functioning at transplantation or at the time of analysis. For this analysis, we are considering TIVAD failure rather than patient mortality. Thus an 'event' (usually when a patient dies) represented the date on which a TIVAD failure occurred (patency *n* days), and a TIVAD that was functioning at the time of the patient's death, or at heart–lung transplant, was considered 'censored' (patency *n*+ days). All TIVADs that were still functioning at the time of analysis (usually patients alive at the end of follow-up) were also censored (patency of *n*+ days).

For each type of complication, median time from insertion to the complication occurring was estimated (range included) and frequency of early (< 30 days' post-insertion) or late (> 30 days) occurrences was tallied.

Median was used rather than mean in all analyses because the distribution of the data is skewed to the right

Table 1 Summary of complications

Complication	Early (< 30 days)	Late (> 30 days)	Median age (days [range])	Incidence (/1000 days)
Occlusion	0	33	510 [42–4440]	0.23
Infection	1	22	376 [21–2054]	0.16
Leak	1	15	283 [21–2668]	0.11
Pain/discomfort	1	5	540 [8–1614]	0.04
Venous thrombosis	0	5	507 [60–1125]	0.03
Extravasation/skin necrosis	0	1		0.007
Vegetation in right atrium	0	1		0.007
Total	3	82	N/A	0.58

(positive skew), with a small number of TIVADs surviving much longer than the majority. If mean was used, these few cases would have falsely enhanced the average longevity.

Finally, incidence of each complication was expressed as a unit per 1000 days.

Results

A total of 165 TIVADs were analysed in 109 patients. The mean age at insertion was 24.7 years (range, 16–48 years). Fifty-seven patients had two or more TIVADs; one patient has had seven devices inserted. Of the 165 TIVADs, 76 have stopped functioning (most of these removed), 43 are currently functioning in living patients (the longest functioning catheter was 3202 days at the time of analysis), and 46 were functioning at the time the patient died, or had a transplant. This represents a total cumulative experience of 146,072 patent catheter-days. This value is important both as a reflection of the significant experience that the specialist nurses have accumulated in TIVAD maintenance, but also as the figure used to calculate the incidence of a complication expressed per 1000 days.

Life-span

The duration of function ranged from 6 to 4440 days, with a median survival of 1441 days (Fig. 1).

Complications

There were no immediate complications, such as pneumothorax, arterial puncture, haemothorax, or nerve injury. All complications relate to the device, rather than technical

operative or postoperative complications. Some occurred 'early' (within the first month), the vast majority occurred from 1 month or later (Table 1). The overall incidence of complications was 0.58 per 1000 catheter-days. All of the complications led to failure of the TIVAD or cessation of its use; all were then removed, except one occluded TIVAD that was left *in situ*. Six patients declined to have a replacement TIVAD once they had experienced a problem or failure.

Occlusion

Occlusion occurred in 33 TIVADs in 25 patients, with an incidence of 0.23 per 1000 catheter-days. The age range of TIVAD at occlusion was 42–4440 days, with a median age of 510 days.

In some TIVADs that were slow to flush or partially occluded, thrombolysis was injected into the lumen of the catheter. If a thrombus-collagen sleeve was adherent to the catheter, stripping the catheter by interventional radiological techniques was sometimes performed. These techniques had some success but, in the majority, occlusion still eventually occurred.

Infection

Twenty-three TIVADs in 18 patients became infected, with an incidence of 0.16 per 1000 catheter-days. Of 18 patients with infected TIVADs, 10 had diabetes. TIVAD age range at infection was 21–2054 days, with a median age of 376 days. Five patients had two infected TIVADs.

Table 2 shows the frequency of micro-organisms cultured (whether this was a central or peripheral blood sample, or from a catheter tip, was not always recorded in the

Table 2 Micro-organisms cultured from peripheral blood or from central blood via TIVAD catheter

Micro-organism	(n)
<i>Candida</i> spp.	8
<i>Staphylococcus epidermidis</i>	5
<i>Ochrobacter anthropi</i>	2
<i>Klebsiella</i> spp.	1
<i>Diphtheroid</i> spp.	1
<i>Maltophilia</i> spp.	1
<i>Alcaligenes</i> spp.	1
Unknown	4

database). The most common organisms were *Candida* spp. and *Staphylococcus epidermidis*. Infection did not occur with *Pseudomonas aeruginosa* or *Staphylococcus aureus*.

Leakage

Sixteen TIVADs leaked in 13 patients. The incidence was 0.11 per 1000 catheter-days. The age range of TIVAD when leakage occurred was 21–2668 days with a median age of 283 days.

Leakage was demonstrated radiologically on linogram. In most cases, contrast could be seen leaking into the subcutaneous tissue from a kink in the catheter, usually where redundant (excessive) catheter was coiled near the connected port. It seems likely that the kink in the catheter led to a split or small fracture. However, this is distinctly different from 'fractures' where a distal portion of the catheter fragments and migrates via the central veins into the heart, or even pulmonary vessels. It is well known that 'pinch-off' syndrome can lead to fracture of catheters.^{4,9,14,15} 'Pinch-off' is thought to occur when a catheter is inserted into the subclavian vein too medially via a percutaneous Seldinger approach and becomes compressed between the first rib, clavicle and costoclavicular ligament. All TIVADs in this cohort were inserted by open cut-down; a few were placed directly in the subclavian vein, but into the middle or lateral third, well away from the costoclavicular ligament. Catheter fragmentation and subsequent migration did not occur in any TIVAD in this cohort.

It has been suggested¹¹ that a leak may occasionally be caused by forcibly injecting at higher pressure into an already occluded catheter so that the catheter becomes detached from the portal or, alternatively, the line fractures. However, of those TIVADs that leaked, concurrent occlusion was only documented in one case, and the median age of catheter when leakage occurred is approximately half that of the occlusion group.

Other complications

Pain or discomfort usually occurred late as a consequence of another problem with the TIVAD, for example, blockage. Only one patient experienced pain within 30 days of insertion; in this case, the pain occurred at 8 days' postoperatively, and the TIVAD was difficult to access.

There were five cases of venous thrombosis: two cases of internal jugular vein thrombosis, two axillary vein thromboses (one infected) and one thrombosis in a peripheral vein in the arm. These patients were all treated with thrombolysis and anticoagulation.

Extravasation of the portal occurred in one patient. This is extremely uncommon but has only occurred with titanium devices that we no longer use. A number of TIVADs by various manufacturers have been used by the department, but we have been using Chemosite® single-lumen TIVADs since 2000. A comparative analysis of the performance of different TIVADs was not possible as insufficient or inaccurate data were recorded in operation notes: surgeons often wrote 'vascuport' irrespective of the actual brand used.

In one patient, a vegetation on the catheter tip developed. As one would expect, this occurred because the tip of the catheter was residing in the right atrium.

Discussion

Method of insertion

A significant contribution to the literature has been from Di Carlo and colleagues,^{4–6} and others⁹ attempting to establish that, for implantation of TIVADs, open venous cut-down is superior to percutaneous Seldinger technique. The latter has been the more popular and commonly practised technique because it can be performed by radiologists, oncologists or other clinicians. Open-cut-down is limited by the availability of surgical expertise.

The main reason we believe the open cut-down is the right approach, particularly in cystic fibrosis patients, is that it is quicker to perform than the Seldinger technique (15–75 min)^{4,6,8} and is much more controlled, eliminating the risk of arterial injury, nerve injury, haemothorax and pneumothorax, as our results demonstrate. Pneumothorax is a serious complication in any patient; in a cystic fibrosis patient, the risk of potentially grave consequences is inevitably higher.¹⁶

Anaesthetic considerations

The open approach is more commonly performed using local anaesthetic, with or without sedation.^{4,7,11} At Heartlands Hospital, both general and local anaesthesia is used for open cut-down implantation in cystic fibrosis patients, based on patient preference. Any procedure with local anaesthetic requires a calm and relaxed patient who will remain still for a significant length of time, and anxiety can steadily increase, particularly if the procedure is pro-

longed by technical difficulty, or a second incision is required to access an alternative vein. Cystic fibrosis patients generally have poor lung function; thus, using sedation with local anaesthetic is not ideal.

We have found that cystic fibrosis patients do very well with a short, light, general anaesthetic (usually self-ventilating with a laryngeal mask airway), and this seems to be the normal practice in some other cystic fibrosis centres.¹⁰

Complications

Some authors have quoted absolute complication rates, as a percentage of all TIVADs, and compared their figures with those of other studies. Such comparison is of limited value. The majority of 'complications' are not directly related to the implantation procedure, whether open or Seldinger, and are simply a reflection of the fact that TIVADs have a limited life-span in different patient groups. If a cohort of TIVADs is followed up for long enough, the majority will fail through infection, occlusion or leakage.

It is, therefore, much more meaningful to describe the 'incidence' of complications (e.g. infection rate per 1000 patent catheter-days) and compare this with other cohorts. Unfortunately, for the reasons stated above, and because other authors have used mean rather than median values, we are unable to produce such a comparison table. Comparing the median time before infection occurs is also more useful than the proportion of catheters that became infected, as the former may be a reflection of nursing practice or how meticulously the patients look after their TIVAD. Obviously, there would be multiple confounders and patient factors that may make such comparison problematic, particularly if one was comparing a mixed oncology cohort in Italy⁴ with a UK cystic fibrosis cohort, for example. Even within cystic fibrosis populations, the likelihood of infection may be related to frequency of infective exacerbations, hospitalisations, or diabetic status. Such detailed subgroup or multivariate analysis is beyond the scope of this study.

Similarly, incidence or median time to occlusion, may be related to how well TIVADs are maintained, the frequency of flushes and solution used. The flushing regimen used at Heartlands Cystic Fibrosis Centre is 5 ml of 100 IU/ml heparin solution every 4–6 weeks. One might suggest that early occlusion could be explained by technical variability or surgical experience. If the catheter was an incorrect length and, therefore, kinked in the subcutaneous tissue, it might cause early occlusion or leakage but this is a fairly simple technical point. If the catheter tip is placed too high in the superior vena cava, or resting against the vessel wall this may also predispose to occlusion¹⁷ but the surgeon cannot control for that beyond the tip's position on fluoroscopy at operation. The only other technical factor that may explain early failure is the choice of Seldinger over open cut-down, in particular the described 'pinch-off' phenomenon with the former technique

and possible sequelae of catheter fracture/fragmentation, leakage and catheter migration.

Our study could be improved with a comparative cohort of TIVADs inserted through a radiologically guided Seldinger technique. Heartlands Hospital does not currently offer radiologically guided TIVAD insertion and, for the reasons already stated, we are not convinced this a safe alternative. Future studies should include TIVADs inserted in under-16-year-olds, if data collection is expanded.

What this study adds

Munck *et al.*¹² published a study in 2004 of the largest number of TIVADs in cystic fibrosis patients to date (452 TIVADs in 315 patients). However, this study gathered data across 36 cystic fibrosis centres, largely conducted by paper questionnaire; this may equate to roughly 12.6 TIVADs per centre on average, and possibly large variability of after-care protocols for TIVAD maintenance. Approximately half of these TIVADs were implanted percutaneously, and half surgically (it is not stated whether local or general anaesthesia was used). Only 5% were implanted in the cephalic vein.

Our study, therefore, makes a valuable contribution as the largest single cohort of TIVADs from one regional UK cystic fibrosis centre, all of which were implanted by open surgical cut-down technique. With 20 years' follow-up and 146,072 patent catheter-days (over 400 years) this also reflects the considerable experience that our cystic fibrosis clinical nurse specialists have accumulated. Over the years, they have developed and improved the protocols for after-care of the TIVADs to maximise the potential life-span and avoid early failures.

Conclusions

Allowing for the limitations discussed, this study demonstrates excellent results, with a median life-span for all TIVADs of almost 4 years (1441 days), and very low incidence of complications (0.58 per 1000 days). We believe that much of this success is due to the clinical nurse specialist-led after-care and maintenance of TIVADs, both at the cystic fibrosis centre, and also by the patients themselves at home. Most importantly, this study proves the reliability, safety and consistency of the open cut-down technique for insertion of TIVADs using the cephalic (or alternative) vein, and thus avoiding serious peri-operative intrathoracic complications, as well as other complications of the Seldinger approach such as 'pinch-off' syndrome and its sequelae.

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