A Survival Analysis of Ventricular Access Devices for Delivery of Cerliponase Alfa

Claudia L Craven[1]	MSc MRCS	claudia.craven@nhs.net
	ORCHID 0000-0002-6199-0090	
Paul Gissen[1,2]	PhD FRCPCH	p.gissen@ucl.ac.uk
Rebecca Bower[1]		rebecca.bower@gosh.nhs.uk
Laura Lee[1]		laura.lee@gosh.nhs.uk
Kristian Aquilina[1,2]	MD FRCS(SN)	kristian.aquilina@gosh.nhs.uk
Dominic NP Thompson[1,2]	FRCS(SN)	dominic.thompson@gosh.nhs.uk
	ORCHID 0000-0002-1114-9869	

Affiliations: 1. Great Ormond Street Hospital for Children NHS Foundation Trust London, WC1N 3JH, United Kingdom**.** 2. UCL Institute of Child Health, London, UK

Corresponding author: C L Craven, ORCHID 0000-0002-6199-0090, Great Ormond Street Hospital for Children NHS Foundation Trust London, WC1N 3JH, United Kingdom

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ABSTRACT

Introduction

Late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) is a rare autosomal recessive disease caused by tripeptidyl peptidase 1 (TPP1) enzyme deficiency. At this single centre, the medication cerliponase alfa is administered every two weeks via the intracerebroventricular (ICV) route. This requires the placement of a ventricular access device (VAD or reservoir) and frequent percutaneous punctures of this device, over the child's lifetime. In this study, we audit the longevity and survival of these VADs and examine the causes for device failure.

Methods

A single-centre survival analysis for VAD insertions and revisions (January 2014 – June 2020) was conducted. All children were receiving cerliponase alfa infusions through a VAD. Patient characteristics and complications were determined from a prospectively maintained surgical database and patient records. For VAD survival analysis, the defined endpoint was the point at which the device was removed or changed. Reservoir survival was assessed using Kaplan-Meier curves and Logrank (Cox-Mantel) test.

Results

A total of 17 patients had VADs inserted for drug delivery; median age at first surgery was 4 years 4 months (range 8 months - 15 years). 26 VAD operations were required amongst the 17 patients (17 primary insertions and 9 revisions), of which 12 VAD operations had an associated complication including CSF infection (n=6), with *Propionibacterium* and *Staphylococcus* species being the most prevalent, significant surgical site swelling preventing infusion (n=3), leakage/wound breakdown (n=2) and catheter obstruction (n=1). There were no complications nor mortality associated with VAD insertion. The median number of punctures for non-revised VADs (n=17) versus revised VADs (n=9) was 12.0 punctures (IQR 7.5-82.0) and 29.0 punctures (IQR of 6-87.5) respectively (p=0.70). The median survival of revisional reservoirs (n=9) was 301 days, compared to 2317 days for primary inserted (n=17) reservoirs (p=0.019).

Conclusion

In the context of the current interest in intrathecal drug delivery for rare metabolic disorders the need for VADs is likely to increase. Audit of medium to long term outcomes associated with these devices will hopefully have wider application, as well as potential implications for the development of new VAD technology. It also informs parent counselling prior to commencement of therapy and VAD implantation.

INTRODUCTION

Late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) is a rare autosomal recessive disease. It is a type of neuronal ceroid lipofuscinosis, also referred to as Jansky-Bielschowsky disease and is caused by tripeptidyl peptidase 1 (TPP1) enzyme deficiency. CLN2 is characterised by language delay, seizures, and progressive psychomotor decline [1]. There are an estimated 30-50 children living in the UK with CLN2 and diagnosis is usually around age 3-6 years, with a life expectancy ranging between 8 and 18 years [1,2].

Cerliponase alfa (Brineura, BioMarin (BMN)), a recombinant TPP1 enzyme replacement therapy, has been shown to slow down progression of the disease and was approved by FDA, EMA and NICE for treatment of CLN2 [3-5]. Long-term outcomes of this medication are currently being studied.

At the point of data collection, a total of 17 children with CLN2 received Cerliponase alfa at this single centre. Some of the infusions were given as part of a BMN Phase I/II trial, which has now been completed. The medication is administered as a 300mg dose via intracerebroventricular (ICV) infusion over 4 hours, every two weeks [3]. This requires the placement of a ventricular access device (VAD or reservoir) and frequent percutaneous punctures of this device.

ICV medication delivery via a reservoir has long been established as a safe and effective route [6]. However, few therapeutic regimens require such frequent punctures of the reservoir. This, in combination with the long infusion times, may increase the risk of failure due to infection or mechanical damage to the reservoir. Given the current interest in intrathecal drug delivery for rare metabolic disorders the need for VAD's is likely to increase [7-9]. In this study, we review the longevity and survival of the VADs used in the BMN trial and examine the causes for device failure. We aim to use this information when counselling patients and their parents for surgery.

METHODS

Study Design

We perform a single-centre survival analysis conducted for VAD insertions and revisions over a period of 5 years 6 months (January 2014 – June 2020).

Participants

Inclusion: Patients included in this survival analysis who received at infusions of cerliponase alfa via an ICV reservoir. The infusions were given every two weeks; each infusion is of 4 hours' duration.

Exclusion: Patients without a VAD or those not receiving infusions of cerliponase alfa every two weeks.

Reservoir placement

All patients underwent a preoperative high-resolution magnetic resonance imaging (MRI) scan for surgical planning. All procedures were performed under general anaesthesia by one of two consultant paediatric neurosurgeons at a single centre, with the exception of four devices that were inserted at other centres. Figure 1 summarises the key steps of reservoir insertion.

Catheters were placed in the ventricle under neuronavigation guidance with StealthStation S7 AxiEM navigation system (Medtronic, Inc., Dublin). Patients underwent skin preparation with 7.5% povidone-iodine and subsequent preparation with 2% chlorhexidine-gluconate (CHG) with 70% isopropyl alcohol. Antibiotic prophylaxis comprised a single dose of flucloxacillin and amikacin, dosed as per weight administered prior to skin incision.

A curvi-linear frontal incision was used. For primary insertions, the non-dominant side was chosen unless imaging characteristics (e.g. ventricular asymmetry suggested otherwise). For revision procedures in patients with a previous surgical site infection the contralateral side was used. A neuronavigation-planned burr hole near Kocher's point (mid pupillary line, anterior to the coronal suture) was drilled. Catheter trajectory was pre-planned using neuronavigation, with a selected target just superior to the ipsilateral foramen of Monro. Bactiseal® antibiotic impregnated ventricular catheters were used. No antibiotic soaking or intrathecal antibiotic was used. Catheter length was pre-determined from imaging, typically around 5.5cm. The guidance view function was used to place the catheter and puncture the ventricle. Cerebrospinal fluid (CSF) flow was confirmed, and a specimen sent for baseline cell count, gram stain and culture. Closure was performed in two layers with Vicryl suture material to the galea, and a continuous Monocryl layer to the skin.

Infusion technique

All patients underwent a post-operative check MRI, to confirm catheter position in the ventricle prior to drug delivery. Parents were advised to wash their child's hair before infusions. The standard dose of cerliponase alfa was 300mg delivered via an ICV device and infused at a rate of 2.5ml/per hour for 4 hours, every two weeks [3].

Practitioners wore sterile gloves and a gown for every ICV access. The patients' skin was carefully prepared with CHG with 70% isopropyl alcohol. The scalp was palpated to confirm the position of the reservoir and a 22G non-coring needle 24-25G was placed into the access device, and 1ml of CSF is aspirated and discarded. Care was taken not to perforate the bottom of the reservoir. If no CSF was aspirated, then the neurosurgical team was contacted to review and re-attempt device access. The drug delivery did not commence if CSF could not be readily aspirated. Another 1.5ml is aspirated and analysed for baseline cell count, gram stain and culture. A pre-flushed line was then connected, and the pump infusion checked prior to securing the port needle. Considering the long infusion (4 hours), the needle was secured with steri-strips and hair clips, and when needed a port cover/posey placed over the needle and a head bandage applied. After the 4-hour infusion, the needle was removed, and compression is applied with a sterile gauze for a 1-2 minutes.

Variables

Patient demographics, reservoir characteristics, number of punctures, complications, and times to first infusion and times to device removal were determined from a prospectively maintained surgical database and patient notes. Operative times were obtained from anaesthetic charts and electronic records and was based on knife-to-skin to closure times.

Analysis

Normality of data was determined using a QQ plot confirming data to be non-parametric. Number of punctures between revised and non-revised catheters was compared with a Mann-Whitney test. For reservoir survival analysis, the defined endpoint criterium was the point at which the device was removed or changed. Reservoir survival was assessed using Kaplan-Meier curves and Logrank (Cox-Mantel) test. All statistical tests were performed on GraphPad Prism 8.4.2c. A p-value of less than 0.05 was considered significant.

RESULTS

Demographics

Table 1 summarises the patient demographics and the days each reservoir was in-situ (up to last follow-up). A total of 17 patients (8 male and 9 female), had reservoirs inserted for drug delivery. The median age at surgery was 4 years 4 months (range 1 year 8 months - 15 years). A total of 26 VADs were inserted, of which 17 were primary and 9 were revisional. Each VAD was in-situ for a median time of 273 days (interquartile range (IQR) 108.3 – 1213 days).

Procedural data

Eleven patients had a Rickham (Codman®, Integra Life Sciences, Princeton), five had an Ommaya (Integra Life Sciences, Princeton) and two had Burrhole Port reservoirs (Meithke, Paediatric Burrhole Port, Potsdam). The median operative time (knife-to-skin to closure) was 37 minutes (range 32 – 51 minutes).

Time to first infusion

For those with VADs in-situ, median time to first infusion was 14 days (range of 7 days to 21 days). Of the 9 cases who had delayed infusions (two weeks or more), 3 were due to post-operative swelling and difficulty palpating the reservoir, with the remaining cases being due to non-medical, logistical reasons. Two patients (patients 3 and 4) had a period of 5 weeks without any drug delivery, due to early infection requiring removal of the device.

Complications

Of the 26 VADs inserted, 12 had a complication, of which 9 resulted in revision of the device. The 12 complications include: CSF infection (n=6), significant surgical site swelling preventing infusion (n=3), leakage/wound breakdown (n=2) and catheter obstruction (n=1). Post-operative MRI scans confirmed no malpositioned catheters.

Of those infected, 1 had an early infection, within 1 month of surgery (surgery related) and 5 were delayed (puncture related), developing at a mean of 777.6 days.

Per patient, the rate of infection and significant complication was 23.5% and 29.4% respectively. However, complications were clustered to the same 5 patients, with of 12 of the 17 patients had no complication over the period of the study.

Revisions

There was a total of 9 revisions (in 5 patients). The reasons for revision included CSF infection (with confirmed organisms), including one with a hair embedded in the reservoir membrane (figure 2A), leakage of fluid around the reservoir (figure 2B showing fractured reservoir) and catheter obstruction.

The most frequently encountered organisms were skin commensals, *Propionibacterium* and *Staphylococcus* species. All infections were treated by removal of the device and antibiotics according to sensitivities. There were no episodes of recurrence of infection.

Reservoir survival

The median survival of revisional reservoirs (n=9) was significantly lower (301 days) compared to primary (n=17) reservoirs (2317 days) (p=0.019) (figure 3).

Revision rate per puncture

The overall revision rate per reservoir insertion was 34.6%, and for every 129 reservoir punctures, a revision was needed. However, as the Kaplan-Meir curve demonstrates, the survival of a reservoir was worse in cases with a prior history of revision.

There was no significant difference in the median number of reservoir punctures between cases requiring revision (n=9) and cases not revised (n=17). The median number of punctures for non-revised VADs (n=17) versus revised VADs (n=9) was 12.0 punctures (IQR 7.5-82.0) and 29.0 punctures (IQR of 6-87.5) respectively (p=0.70).

DISCUSSION

Intracerebroventricular drug delivery

The ICV route is an established and well-tolerated method of drug delivery [6,10]. Many drugs for neurological disease require direct administration in CSF as they are unable to cross the blood brain barrier (BBB). ICV therapy overcomes the issue of the BBB and enables targeted drug delivery. As such, this technique has been used to treat a multitude of diseases including neoplastic meningitis, leukaemia, lymphoma, pain, infection, and progressive multifocal leukoencephalopathy (PML), [11-18].

There is an increasing repertoire of neuro-metabolic disorders of childhood where, ICV drug delivery might be beneficial and so increasingly paediatric neurosurgeons will be called upon to place VAD`s. Studies have demonstrated that the volume of distribution and bioavailability of intrathecally administered drugs is better following intraventricular administration compared with lumbar puncture [11]. Furthermore, repeated lumbar puncture is not tolerable nor feasible in the long-term [11].

A major concern regarding the use of VAD is infection; both surgery related infection and infection secondary to repeated reservoir puncture [19]. Patients with CLN1 receiving cerliponase alfa may require years of treatment [3]. The survival of reservoirs implanted for infusion medications, requiring multiple punctures, is not well established [10]. Therefore, experiences of VAD maintenance and longevity, in this population, are important to report.

Reservoir survival

The main finding of this study is that these devices have good longevity and tolerate multiple punctures. Those who require at least one revision of their VAD are significantly more likely to have further complications. The median survival of primarily inserted reservoirs was minimum of 2317 days (to the point of follow-up), significantly higher than revisional reservoirs with a median survival of 301 days (p=0.019). Recurrent infection was a cause of repeated failure in one patient this study. Small ventricular size, intraventricular adhesions or abnormal CSF characteristics (e.g. cell count, protein level) might be additional reasons to explain the trend for recurrent VAD related complications in some patients.

Complications per puncture

In total, for every 129 reservoir punctures, a revision was needed. However, as the Kaplan-Meir curve demonstrates, the survival of a reservoir was worse in cases with a prior history of revision. This is important when counselling families about this treatment. Cohen-Pfeffer *et al.*'s recent systematic review of ICV safety found that infection rate per puncture was often not being reported, despite being a vital metric associated with risk [6]. Whilst puncture frequency is a reported risk factor for development of infection, we found no significant difference in the number of reservoir punctures between cases requiring revision and cases not revised.

Complications per patient

Per patient, the rate of significant complication requiring revision was 29.4% and the rate of infection per patient was 23.5%. In previous studies, rates of complications and infections in ICV devices were as high as 33.0% and 27.0% respectively [6].

Observed Complications

Types of observed complications included infection, significant surgical site swelling preventing infusion, leakage/wound breakdown, and catheter obstruction. Most complications had a clear cause, including a fractured reservoir, a CSF leak (preceding infection), or a hair embedded into the device, allowing a tract from the scalp to the catheter and subsequent infection.

Infections

At this unit, practitioners adhere to recommended evidence based protocols to minimise infection, including preoperative bacteriostatic hair washing, pre-operative hair clipping, use of CHG with 70% isopropyl alcohol skin preparation, placement of the reservoir away from the incision, implantation and access in sterile conditions, the use of antibiotic impregnated catheters and intraoperative antibiotic prophylaxis [10,20,21]. Despite these precautions,

infection was the most common complication occurring in this cohort. In previous studies, the most common infectious organisms were *Staphylococcus epidermis* and *Staphylococcus aureus* [6,20]. In our study, *Propionibacterium*, another common scalp commensal was observed, in addition to *Staphylococcus* species and *Streptococcus.* Families should be counselled appropriately for the risk of infection, its implication for device removal and therefore a period without drug delivery.

Multiple revisions

Those who required revision were more likely to have further complications. Of note, two patients in our cohort needed more than three revisions.

The first patient suffered from multiple repeat infections with the same organism, *Propionibacterium acnes*, a known skin commensal. Despite a 10-day course of intravenous antibiotics and alternating the insertion site, the infection persisted. This may have been either have been due to the patient having a scalp microbiome with a high proportion of *Propionibacterium acnes* or that the infection had been incompletely treated. The time between removal and reinsertion of a device in this patient was 5 weeks. In view of this patients with repeat infections might be considered for deferred reinsertion (after two weeks for example) or delayed lumbar puncture to confirm CSF sterility

The second patient with multiple revisions had an initial CSF leak, which, despite changing the reservoir, resulted in bacterial growth in the CSF on culture. Subsequently this patient's ventricular catheter blocked.

Strengths and limitations

We present a homogenous group of patients and conditions, where in the most part, the same two surgeons inserting the devices in a standardised format, and the same specialist nurse practitioners accessing the device, with a set protocol for drug delivery. The exception was that four devices that were inserted at other centres. However treatment punctures were delivered at this this single centre.

Future Implications

Intrathecal treatment is an expanding route for long term targeted drug delivery, for rare metabolic or neurodegenerative diseases, and may develop further for delivery of gene therapy vectors [3,22,23]. Therefore, presentation of the long-term experiences in this niche population will help counsel families and optimise protocols for VAD drug delivery.

Whilst the overall initial rate of complication is low, this rate increases rapidly after one complication. Individuals with a complication may require closer monitoring, potentially longer periods without a device, to prevent infection. Furthermore, this data can be used to guide family counselling prior to commencing therapy and implanting of a VAD.

Development of pumps, such as those used for spasticity and pain management, may further reduce infection, and need to assess the device.

CONCLUSION

Given current interest in intrathecal drug delivery for rare metabolic disorders the need for VADs is likely to increase. This audit of medium to long term outcomes associated with these devices confirms a high accuracy of placement, low operative risk and sustained durability. Infection and mechanical damage due to repeated puncture remain the principal complications. The results of this study will inform the consenting process for future patients and have potential implications for the development of new VAD technology.

LEGEND

- **Figure 1**. Key steps of reservoir insertion. **A:** Position, prepared skin and drape, **B:** Neuronavigation trajectory for ventricular catheter, **C:** Neuronavigated placement of ventricular catheter and **D:** Connection and final position of reservoir device (prior to skin closure).

- **Figure 2.** Two cases requiring revision, **A:** with an infected reservoir and a hair embedded in the reservoir casing and **B**: a fractured reservoir after multiple punctures.

- **Figure 3.** Survival analysis of primary vs. revisional reservoirs (p=0.019)

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