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Risks of long-term port use in enzyme replacement therapy for lysosomal storage disorders

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A R T I C L E   I N F O

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A B S T R A C T

Totally implantable vascular access devices (TIVADs) are commonly used in conjunction with enzyme replacement therapy (ERT) for lysosomal storage disorders (LSDs). This case series describes potential complications associated with long-term TIVAD use, such as compromise of skin integrity, infection, or port failures. Best practices and skilled specialists are essential for minimizing complications from long-term TIVAD use for ERT.

1. Introduction

A totally implantable vascular access device (TIVAD) is an implanted reservoir with a self-sealing silicone septum attached to a silicone catheter that is tunneled under the skin with its tip positioned in a large central vein. Local anesthetic creams, such as lidocaine/prilocaine (EMLA\textsuperscript{®}) or tetracaine (Ametop\textsuperscript{®}), are applied to reduce pain and minimize trauma during Huber needle accessing.

TIVADs were designed for temporary use, but currently, these devices have been utilized for enzyme replacement therapy (ERT) in lysosomal storage disorders (LSDs), including mucopolysaccharidosis (MPS) disorders, which are lifelong diseases requiring ongoing treatment. Complications of insertion, such as bleeding or bruising, or line dislodgment, break, or blockage, and complications related to long-term usage, such as infection and venous thrombosis, must be considered [1–4]. Additional serious, rare complications, including pneumothorax, hemothorax, pericardial effusion, or cardiac arrhythmias are also possible [3].

The purpose of this case series is to discuss the potential risks when considering long-term port use for ERT administration.

2. Materials and methods

Individual cases representative of the spectrum of TIVAD-associated complications in patients with LSDs were selected for presentation, based on an informal discussion with clinicians from multiple centers. A group of 64 pediatric patients from Birmingham Children’s hospital with inherited metabolic disorders, including LSDs and general metabolic disorders was included for a general (acute and chronic) assessment of TIVAD complication rate in rare diseases. An additional 33 pediatric patients from Birmingham Children’s hospital, exclusively with LSDs were assessed over the period of January 2007 to December 2014 to determine complications arising from chronic TIVAD use.

TIVADs were inserted into the internal jugular or innominate veins via an ultrasound-guided percutaneous approach [5] with the port implanted on the chest wall (e.g., below and lateral to the nipple). The tip of the line would be positioned in the high right atrium or superior vena cava/right atrium junction.

3. Results

A summary of 8 selected cases are presented in Table 1.

Patient #1 had a TIVAD inserted in 2011 for weekly hospital-based ERT for alpha mannosidosis. After 3 years of treatment, along with use of lidocaine/prilocaine cream, the skin was thinned and discolored, and a small bruise developed over the TIVAD site. No further changes were seen in skin integrity. In 2016, the patient was admitted...
Table 1  
Demographics and clinical characteristics of patients with port use complications.

| Case | Disorder | Age (years) | Sex (M/F) | Time with TIVAD | Complication | Resolution |
|------|----------|-------------|-----------|-----------------|--------------|------------|
| 1    | Alpha mannosidosis | 18 | M | 3 years | Skin thinning and discoloration; small bruise over TIVAD site | N | Change from lidocaine/prilocaine cream to ethyl chloride spray |
| 2    | MPS II   | 19 | M | 2 years, 8 months | Skin atrophy; bruise around TIVAD site; small scab over port | Reinserted | Change from lidocaine/prilocaine cream to ethyl chloride spray. |
| 3    | MPS VI   | 20 | M | 8 months | Skin burn from overuse of tetracaine cream | Reinserted | Change from tetracaine to lidocaine/prilocaine cream. |
| 4    | MPS I    | N/A | N/A | 2 years | Infective endocarditis | Y | Valve replacement; after port removal, used warfarin treatment; after port removal, used warfarin treatment. |
| 5    | MPS II   | 20 | M | 8 years | Thrombus | Y | Successful placement of pacemaker after third complex procedure; continue with fourth TIVAD; however, distorted vasculature revealed. |
| 6    | MPS II   | 26 | F | 2 years; 6 months; 5 years; | Port failure; subsequent difficulties placing pacemaker | Y | Final general infection port was considered infection site. |
| 7    | MPS I    | 27 | F | 27 at time of death | Multiple port failures (fourth port in use); collateral vessel interference with angiography | Y | Removed. |
| 8    | MPS VI   | 27 | F | 5 years | Fatal, generalized infection. Port was considered infection. | Y | Removed. |

MPS, mucopolysaccharidosis; N/A, not available; TIVAD, totally implantable vascular access device.

4. Discussion and conclusions

TIVADs are widely used in cancer and cystic fibrosis, and are considered safe and effective [6,7]. The most common TIVAD-related complications in patients with cystic fibrosis include occlusion,
infection, leakage, pain or discomfort, venous thrombosis, stenosis, and port extrusion [7,8]. In patients with cancer, common TIVAD complications include infection, sepsis, thrombosis, skin dehiscence, and pain [6,9,10]. While some overlap exists, the complication profile for TIVAD use for LSDs is unique.

Due to the characteristics of proteins infused and the clinical nature of LSDs themselves, patients with LSD might experience a higher rate of infusion-related reactions than patients treated for other conditions [11]. In a recent review of TIVAD use in patients with inherited metabolic disorders, the main complications were infection and allergic reaction [11]. Patients with LSD may have abnormal vasculature as part of the disease; this may contribute to higher complication rates in these patients [12–15]. An issue among LSD patients is skin integrity (thinning skin, dimpling, bruising) over the TIVAD sites. Skin erosion at the implantation site is usually a rare complication of long-term TIVAD use, with an estimated incidence of 1.67% in patients with average catheter duration of 335 days [16]. We observed a higher rate of skin complications (10.9%), which while easier to manage than some complications, is supportive of skin involvement in LSDs [17].

Because ERT is considered a lifelong therapy, we encourage the use of peripheral intravenous access; thus, it is important to develop nursing and physician access skills to further this objective. Newer topical vascular imaging techniques and percutaneous ultrasound vascular access tools may facilitate placement in very difficult patients [18]. In a pediatric cohort, use of the ultrasound-guided percutaneous technique meant that venous occlusion of the great veins (internal jugular, innominate, or superior vena cava) was exceptionally uncommon at < 3% [19]. Additionally, use of distraction techniques during the procedure can greatly reduce the pain and distress for children and adolescents [20].

To decrease the risk of complications in patients with LSD who are using TIVADs for long-term ERT, we recommend following best practices, such as ultrasound guidance to place central venous catheters [3–5,21], experienced surgical team and personnel [1,5], hand hygiene and barrier precautions, and regular examination for thrombus via ultrasound [3,22] and of skin integrity over TIVAD sites. The major long-term risk for patients with a potentially lifelong requirement for venous access is occlusion of the great veins and thus consideration should be made from the start to avoid this occurring by using specialist teams of surgeons with an interest in vascular access [23] and the ultrasound-guided percutaneous approach [19,22]. With these measures and careful placement, monitoring, and confirmation of the need for TIVAD, specialists will be equipped to strive for optimal outcomes with ERT with minimal complications from long-term TIVAD use.

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Conflicts of interest

C. J. Hendriksz is the director of FYMCA Medical Ltd. and has received consulting fees from BioMarin, Chiesi, Actelion, Shire, Sanofi Genzyme, Inventiva, Evivera, and Amicus.

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G. S. Arul reports no conflicts of interest.

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