COMPLICATIONS DURING INTENSIVE CHELATION THERAPY BY PORT-A-CATH DEVICES IN HIGH-RISK β THALASSEMIA PATIENTS

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SUMMARY

Implantable central venous access devices (ICVAS) have been used for a long time in patients with malignant disease, HIV or cystic fibrosis. In thalassemia, information on the use of ICVAS is limited. Thalassemic patients may be predisposed to infectious complications by splenectomy, diabetes mellitus, and possibly by iron overload.

We report a retrospective multicenter experience in assessing the rate of complications during long term intensive chelation therapy with desferrioxamine (DFO) by ICVAS and portable infusors. A total of 113 Port-A-Cath were implanted in 96 high-risk homozygous β-thalassemia patients; (mean age 19.7 ± 4.4 years). Indications for intravenous (i.v.) therapy were severe iron overload for all patients and intolerance to subcutaneous therapy with DFO (15%) or cardiac disease (23%). The total functional duration of the devices was of 129.652 catheter days, with a mean functional duration of the first device of 1.181 ± 996 days. Complications occurred in 63 devices in 53 patients.

Catheter-related infections occurred in 28 patients (0.29 per 1,000 catheter patient days). Symptomatic venous thrombosis occurred in 9 patients (0.11 per 1,000 catheter patients days).

Fifteen patients had other non-infective complications; 3 patients had the device removed for subjective discomfort. The planned therapy has been completed in 50% of the patients; on the average the planned treatment schedule has been run up to 71%. In this large series of patients, complication rates seem to be lower than previously reported in thalassemia and in other diseases.

This could be due to the catheter care being performed by a trained hospital staff. However, the high probability of not completing the chelation program must be taken into account.

Key words: Thalassemia, chelation therapy, central venous access devices

RIASSUNTO

I cateteri venosi centrali (ICVAS) sono utilizzati da molto tempo nei pazienti oncologici, in quelli con HIV o con fibrosi cistica. Nel campo della talassemia, i dati relativi all’utilizzo di tali dispositivi sono scarsci. Fattori quali la splenectomia, il diabete mellito e l’accumulo di ferro, possono rappresentare una predisposizione alle infezioni. Riportiamo l’esperienza di uno studio retrospettivo multicentrico che ha valutato l’incidenza di complicanze durante un periodo di terapia chelante intensiva con desferrioxamina (DFO) tramite ICVAS ed infusori portatili. Sono stati impiantati complessivamente, 113 Port a Cath in 96 pazienti con β talassemia omozigote, ad alto rischio (età media 19.7 ± 4.4 anni). Le complicanze durante la terapia chelante sono state di tipo infettivo e non infettivo. La durata funzionale totale dei cateteri è stata di 129.652 giorni/catetere, con una durata media del primo dispositivo di 1.181 ± 996 giorni. Le complicanze sono avvenute in 63 cateteri su 53 pazienti.

Le infezioni cateteri-correlate sono state di tipo infettivo e non infettivo. I cateteri venosi centrali sono stati utilizzati in 96 pazienti con talassemia, in quelli con HIV o con fibrosi cistica. Nella talassemia, i dati relativi all’utilizzo di tali dispositivi sono scarsci. Fattori quali la splenectomia, il diabete mellito e l’accumulo di ferro, possono rappresentare una predisposizione alle infezioni. Riportiamo l’esperienza di uno studio retrospettivo multicentrico che ha valutato l’incidenza di complicanze durante un periodo di terapia chelante intensiva con desferrioxamina (DFO) tramite ICVAS ed infusori portatili. Sono stati impiantati complessivamente, 113 Port a Cath in 96 pazienti con β talassemia omozigote, ad alto rischio (età media 19.7 ± 4.4 anni). Le complicanze durante la terapia chelante sono state di tipo infettivo e non infettivo. La durata funzionale totale dei cateteri è stata di 129.652 giorni/catetere, con una durata media del primo dispositivo di 1.181 ± 996 giorni. Le complicanze sono avvenute in 63 cateteri su 53 pazienti.

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Parole chiave: Talassemia, terapia chelante, catetere venoso centrale

Background

Long-term studies of desferrioxamine (DFO) therapy in multiply-transfused patients with beta-thalassemia major have clearly shown to be effective in removing excess iron and preventing the organ damage associated with chronic iron overload614.

The improvement in survival and quality of life in thalassemia achieved by regular chelation, made available since the mid Seventies has been extensively documented18,15.
Standard chelation therapy consists of life-long overnight subcutaneous infusion of desferrioxamine by an electric pump\textsuperscript{(20)}.

Unfortunately, compliance with this treatment is often poor\textsuperscript{(3)}, especially during adolescence, and consequently many young adults are severely iron overloaded and at risk of endocrine organ damage and early cardiac death\textsuperscript{(23)}.

The oral chelator deferiprone has not proved to be equally effective, may require a long time to deplete iron stores, and in many patients fail to produce a negative iron balance\textsuperscript{(8)}.

Therefore, several protocols of intensive i.v. chelation therapy by implantable central venous access devices (ICVAS) have been developed to reverse high degrees of iron overload in a relatively short period of time\textsuperscript{(7, 12)}.

Intravenous DFO is able to produce a rapid decrease in hepatic iron content and can reverse functional complications such as liver fibrosis\textsuperscript{(2)}, arrhythmia and echocardiography abnormalities\textsuperscript{(14, 17)}.

In addition, patients allergic to subcutaneous desferrioxamine may successfully be desensitized by i.v. DFO\textsuperscript{(16)}. ICVAS have been used for a long time in patients with malignant diseases, HIV and cystic fibrosis and numerous reports on complications have been published\textsuperscript{(13)}.

In a cohort of 17 thalassemic patients the principal ICVAS complications were infection (1.15 per 1,000 days of catheter use) and thromboembolism (0.48 per 1,000 days of catheter use)\textsuperscript{(10)}.

Thalassemic patients may be predisposed to infectious complications because of splenectomy, diabetes mellitus, and possibly iron overload, and thrombosis is also more common\textsuperscript{(4)}.

In the following, we wish to report on our experience with ICVAS in the largest group of thalassemic patients described so far receiving intensive i.v. chelation with DFO.

Materials and methods

We performed a retrospective multicenter study on the use of ICVAS for intensive chelation therapy. Treatment indications where severe iron overload, intolerance of subcutaneous desferrioxamine and/or cardiopathy. Follow-up observations lasted until the end of chelation therapy, death, or removal of the ICVAS system. Demographic data, operative summaries, duration of devices, complications related and percentage of planned chelation program completed were collected.

Modalities of catheter implantation and kind of anemia were reviewed. In all centers, careful attention has been paid to aseptic techniques in the preparation of DFO and catheter handling by trained personnel. Data collection was performed by questionnaires sent to the participating centers. The data obtained were analyzed descriptively according to the following definitions:

- **Local infection**: signs of local skin infection over the infusion device such as erythema, swelling, tenderness, indurations, purulence, inflammation, with or without positive culture, in absence of evidence of systemic infection.
- **Systemic infection**: documented sepsis or inflammatory response to infection with or without fever and signs of remote organ dysfunction.
- **Thrombosis**: clinically relevant occlusion of large veins confirmed by Doppler ultrasonography or phlebography.
- **Catheter occlusion**: all catheter thromboses that did not respond to fibrinolysis and led to replacement of the system.

Significance of difference between subgroups was calculated by Student-t-test. Kaplan-Meier curve was plotted to estimate the risk of catheter removal for complications in our cohort of patients.

Organisms were identified by standard microbiological methods.

Results

Eight centers participated in the study.

113 Port-a-Cath\textsuperscript{®} catheters (Pharmacia Inc., San Paul, MN) have been implanted in 96 subjects (90 β thalassemia homozygous and 5 β thal/sickle cell anemia and 1 sickle cell anemia) between February 1989 and August 2005. The age of patients ranged between 5.0 and 31.2 years (mean 19.7 ± 4.4 years), 48 were male, 48 splenectomized and 19 diabetics. All patients were regularly transfused.

Indications for i.v. therapy were severe iron overload for all patients and cardiac disease (23%) or intolerance to subcutaneous therapy with DFO (15%). ICVAS were implanted surgically under local or general anesthesia by percutaneous cannulation of the subclavian vein (65), or by venous cut down on the jugular vein (48); catheter tip location was verified to be in the right atrium or superior vein cava in all patients by chest x-ray and/or fluoroscopy. The port was placed in a subcutaneous pocket on the anterior chest wall. No perioperative complications were noted.
Drug delivery was performed by elastomeric infusors (CADD-I®, Pharmacia Deltec Inc) in 94 patients and disposable balloon pump (Intermate LY®, Baxter Healthcare Ltd and WALKMED 300®, Logomed) in two patients. Mean dosage of desferrioxamine infused was 18.5 ± 8.3 g (range 5.8-55.0) corresponding to 55.2 ± 16.1 mg/kg/d (range 25.0-88.0), diluted in a mean of 105.6 ± 26.5 ml of distilled water (range 50-200) for a mean period of 6.4 ± 1.1 days a week (range 4-14).

Care and maintenance of the device were performed in the hospital by the same operators who took care regularly of the patient. The number of the operators varied from 1 to 3. In one center, the reservoir was not prepared under sterile condition and in 2 cases, only sterile gloves were used. Six centers used sterile gauze covered with pre-cut medication (Surgifix®); in the others the needle was covered with a transparent dressing (Tegaderm®). In all centers iodine solution was used in combination with chlorhexidine (2 centers) or benzalconium (2 centers). Careful flushing was done after each blood sampling.

Complications occurred in 64 (57%) of devices in 53 (55%) of patients (fig. 1).

A total of 55 catheters (49%) were removed because of complications (fig. 2).

Catheter-related infection (tab. 1) sepsis, 4 fevers, 23 local infections) occurred in 29 (30%) of patients (0.29 per 1.000 catheter patients days). Symptomatic venous thrombosis occurred in 9 (9%) patients (0.11 per 1.000 catheter patients days). A further 17% of patients experienced other non-infective complications (6 catheter occlusions, 3 catheter traumatic rupture, 3 catheter dislocations, 4 discomfort).

The organisms involved in 10/11 episodes of sepsis were Staphylococcus aureus\(^{21}\), coagulase negative Staphylococcus\(^{21}\), Pseudomonas aeruginosa\(^{21}\) and in the 4/4 episodes of fever Staphylococcus aureus\(^{21}\) and Pseudomonas aeruginosa\(^{21}\) respectively.

In the 21/23 local infections the organisms involved were Staphylococcus aureus\(^{20}\), coagulase negative Staphylococcus\(^{20}\), Pseudomonas aeruginosa\(^{20}\) Pseudomonas specie\(^{20}\), Klebsiella pneumoniae\(^{22}\).

Nine (9%) ICVAS were removed because of subjective discomfort\(^{20}\), catheters for ruptured\(^{20}\) or malposition\(^{20}\).

Due to complications, 11 patients experienced a double ICVAS insertion and 3 patients a triple.

The total functional duration of the entire series was 129,652 catheter days.

<table>
<thead>
<tr>
<th>Type of complication</th>
<th>Nature of complication</th>
<th>Number of episodes</th>
<th>Cause of removal</th>
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<td>19</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus aureus</td>
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<tr>
<td></td>
<td>Coagulase negative Staphylococcus</td>
<td>(9)</td>
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<tr>
<td></td>
<td>Klebsiella pneumoniae</td>
<td>(2)</td>
<td></td>
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<tr>
<td></td>
<td>Pseudomonas aeruginosa</td>
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<tr>
<td></td>
<td>Pseudomonas specie</td>
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<td></td>
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<td>Pseudomonas aeruginosa</td>
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<tr>
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<td>Pseudomonas aeruginosa</td>
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<td></td>
<td>n.d.</td>
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<td>Total</td>
<td>Prevalence of infections</td>
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<td>0.29/1000 catheter days</td>
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<td>Prevalence of total adverse events</td>
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<td>0.95/1000 catheter days</td>
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Tab. 1: Type of central venous catheter-related complications in thalassemia patients during intensive chelation therapy with desferrioxamine (n=113 catheters in n=96 patients)
The mean functional duration of the first device was 1.181 ± 669 days (range 31-3,863).

The median length of time from implantation to the diagnosis of a line-associated infection was 472 ± 415 days (range 46-1704). Thrombosis occurred after a median time of 652 ± 618 days (range 30-2,058).

The incidence of catheter-related adverse events was 0.49 per 1,000 catheter days.

Fifty-three patients completed the chelation therapy programme in a mean period of 2.4 ± 0.9 years (range 0.5-4.2). One device was in regular use and functioning well at the time of review. There were no catheter-related deaths.

The basal and final mean ferritin values were 5,914 ± 3,094 ng/mL (range 900-14,000) and 2,747 ± 2,015 ng/mL (range 229-11,900) respectively.

On August 31st 2005, 72 (75%) patients were still alive; 24 (25%) of them presented clinical cardiopathy. Mean ferritin value on August 2005 was 2,961 ± 2,487 ng/mL.

Discussion

This study reports the incidence and type of complications of ICVAS observed in the largest cohort of thalassemic patients published so far.

Comparing our data with the experience in thalassemic patients reported by Davis et al[10] the etiology of complications was similar, but with a lower rate of infections as well as that of thrombosis.

This may be attributed to meticulous hospital care, continuous staff education regarding aseptic techniques; the training of expert infusion-therapy teams, effective sterile barrier precautions, and the systematic use of topical disinfection, in line with previously reported methods and recommendations regarding the prevention of catheter-related complications[9].

While severe systemic infections as well as major thrombotic events did not occur within the first two years and increased thereafter, a steady incidence was seen for local infections, irrespective of the duration of catheter life. The duration of catheter insertion did not predict complications leading to removal. Hence, a reasonable approach may be to leave the catheter in situ safely, until completion of the treatment program or until the development of complications.

Although the decision of using ICVAS may appear to be a trivial, technical matter, this is far from being so. In thalassemia major, patients in need of a central venous access device represent a high risk group failing conventional chelation therapy, often with severe iron overload, heart disease or inability to continue subcutaneous DFO treatment because of severe local reaction. In such patients a technology allowing continued effective DFO chelation by i.v. access is often life-saving and of most importance.

Neither should the limited functional duration of roughly 2 years be regarded as a serious impediment to the effective use of ICVAS devices.

Intensified continuous i.v. DFO treatment often results in a rapid initial effect followed by a prolonged phase of gradual improvement[12,17,19,10].

Some of the rapid initial improvement may be attributed to an effective elimination of NTBI and prevention of peroxidative damage associated with a toxic labile iron pool[21,15]. Once the steady chronic phase of disease regression is set in motion, improved compliance with the chelating program will often continue even with the resumption of conventional subcutaneous DFO treatment[19].

The present study was not designed to document the effectiveness of chelating therapy utilizing ICVAS devices. However, it does offer useful information regarding the duration and potential complications of this technology when a decision is to be made regarding therapeutic options in high-risk patients failing conventional chelation treatment and requiring combination therapy with desferroxamine and oral iron chelator.

Bibliografía


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