

Upper limb extravasation of cytotoxic drugs: results of the saline washout technique in children

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Abstract

Purpose Extravasation of cytotoxic vesicant drugs is a surgical emergency (within six hours) since this incident can lead to severe skin and soft-tissue damage. Outcomes after the saline washout procedure have been extensively described in adults, but rarely in children. The aim of this study was to evaluate the outcome of early saline washout procedure for upper limb cytotoxic drug extravasation in children.

Methods All consecutive children with vesicant drug extravasation were retrospectively reviewed. The saline washout procedure was performed. Cosmetic aspect, residual pain and range of movement were analyzed as well as time to surgery and chemotherapy resumption at last follow-up.

Results Between 2014 and 2018, 13 cytotoxic vesicant drug extravasations occurred (mean age 8 years (sem 5)), including 11 treated by the saline washout procedure. At mean follow-up of 11 months (sem 7), the patients had no or low pain and ranges of movement were fully conserved. Two patients (one within the six hours' delay) had soft-tissue necrosis leading to extensive reconstructive surgery.

Conclusion The saline washout procedure is safe and easy and significantly reduces the incidence of extensive skin damage. Early referral to a specialized department is essential. However, the key parameter remains prevention by educating medical staff and nurses about these injuries and by training

them for early and urgent management.

Level of Evidence: IV

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Keywords: cytotoxic solutes; extravasation; chemotherapy; saline washout procedure; children; upper limb; vesicant agent

Introduction

Extravasation injury is defined as an inadvertent administration of intravenous medications into the soft-tissue rather than the intended vascularization.^{1,2} These incidents might occur after a chemotherapy diffusion, after perfusion of antibiotics, radiopaque contrast agent or parenteral nutrition.^{3,4} Ineffective management can cause devastating damage such as severe soft-tissues necrosis, depending on the type of perfused drugs. Two types of agents exist: vesicant and irritant agents. Vesicants have the potential to cause blistering, skin slough and ulceration with variable subcutaneous tissues injuries when the drug is accidentally disseminated.^{5,6} Conversely, irritants are drugs that do not destroy tissues if they disseminate.

While the incidence of cytotoxic vesicant drug extravasation is low (0.1% to 6.5%), the natural course is unpredictable and initial clinical symptoms are non-specific and difficult to identify.^{7,8} Nonetheless, these incidents must be detected early (within six hours) because medical management and surgical treatment are urgent.⁸⁻¹² Among these incidents, the literature reported a low rate (0.25%) of extravasations evolving towards severe necrosis and extensive soft-tissue destruction requiring further reconstruction surgeries. The severity of the damage depends on the volume, concentration and toxicity of the substance.^{9,10} Upper limbs should be carefully managed because of the presence of important functional structures (tendons, muscles and nerves) that could be permanently damaged.^{2,3,11} As a matter of fact, an upper limb is frequently involved (dorsal hand, wrist and forearm).

Numerous strategies have been reported in adults.^{8,11-17} Two types of treatment predominate: conservative management (local topic application, antidotes) and saline washout.^{11,15,16} However, there is a lack of evidence

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regarding the superiority of one technique above the other in recent literature.¹⁷⁻²⁰ Furthermore, conservative management is not always possible in extravasation injuries since many of them have proper cytotoxic effects incompatible with local perfusion.^{11,21} As reported by Gault et al, local washout has proved to significantly reduce the risk of soft-tissue necrosis and also the need for revision surgeries in adults, unless the patients were referred early (less than six hours) to a team qualified for the procedure.^{11,17}

The aim of this study was to evaluate the results of early surgical management by the saline washout procedure in children with upper limb cytotoxic extravasation.

Materials and methods

Patients and initial assessment

Between 2014 and 2018, 13 consecutive children treated for an upper limb cytotoxic extravasation by a qualified paediatric orthopaedic surgery team were retrospectively reviewed. All the extravasations occurred after intravenous administration (peripheral and central venous perfusion) of a vesicant agent (chemotherapy, antibiotics, antiviral drug) and were considered as a trigger to decide the saline washout procedure. The list of at-risk vesicant agents was distributed in the paediatric departments (Table 1). Pre-operative and perioperative data was collected from the patient's medical records (initial symptoms, type of drug, delay to surgery) and all the patients were examined at latest follow-up by one of the senior paediatric surgeons who specialized in upper limb surgery. Our institutional review board approved this retrospective study.

Table 1 List of vesicant and irritant agents available on the written protocol. The list is exhaustive and was established according to the data from the literature

Vesicant drugs	Irritant drugs
Actinomycin	Alemtuzumab
Acyclovir	Bleomycin
Amsacrin	Carmustin
Carboplatine	Cetuximab
Chlormethine	Cidofovir
Cisplatin	Cladribin
Dactinomycin	Cyclophosphamide
Daunorubicin	Cytarabin
Doxorubicin	Dacarbazine
Elliptinium	Docetaxel
Epirubicin	Gemcitabine
Etoposid	Ifosfamide
Fluorouracil	Oxaliplatin
Idarubicin	Pentostatin
Melphalan	Rituximab
Mitomycin	Thiotepa
Mitoxantron	
Paclitaxel	
Pirarubicin	
Plicamycin	
Vinblastin	
Vincristin	
Vinorebin	

Initial management

A standardized procedure has been used for the management of all the cases based on an institutional written protocol, following international guidelines.^{20,22}

First, the nurse stops the administration of the solute, then starts to elevate the upper limb, administers an intravenous painkiller on another perfusion site and applies cool or hot (depending on the drug) compresses soaked with a 5% glucose solution. The estimated volume of cytotoxic drug that diffused is recorded in the medical file. Then, the nurse contacts the paediatric orthopaedic surgeon (standby duty list of hand surgeons). The following details must be provided to the surgeon: time of injury, distal vascularization, area and site of injury, local examination and details of the drug/fluid. Thereafter, the surgeon rapidly examines clinical symptoms and gives an indication for surgical intervention if necessary.

Operative technique

The washout saline procedure used for the study corresponds to the emergency approach described by Gault et al, performed within six hours following the diffusion, if possible.^{11,23} A 0.9% saline solution was administered in subcutaneous tissues with a syringe under sterile conditions around the affected area. The infiltrated volume was deliberately high (200 ml to 500 ml) and depended on the affected anatomical area for a maximal dilutive effect. Multiple small skin stab incisions (minimum of four) were performed afterwards, to allow placement of a blunt cannula with a diameter of 2 mm (Fig. 1). Then, the cannula was introduced in order to create multiple subcutaneous tunnels. A lipoaspiration was carefully performed with the cannula through all the incisions to aspirate saline solution diluted with the cytotoxic drug. This procedure was repeated a couple of times to obtain maximal dilution of the cytotoxic solute. The saline was evacuated through the small incisions, which were not sutured in order to maintain the evacuation of the saline. Local analgesics were not used since the product could have poured from the small incisions and might have hidden symptoms of skin necrosis. Scars were covered with pads soaked with a 5% glucose solution for better absorption.

Outcomes evaluation

Initial follow-up consisted of daily visits to ensure that the patient healed well and that no skin necrosis developed. Then, the patients were seen during outpatient clinic visits between six and 12 months after the procedure. At last follow-up, the following data were recorded: residual pain assessed by the visual analogue scale (VAS),²⁴ aesthetic aspect of the scars and goniometric measurement of upper limb ranges of movement.²⁴ Concerning the VAS,

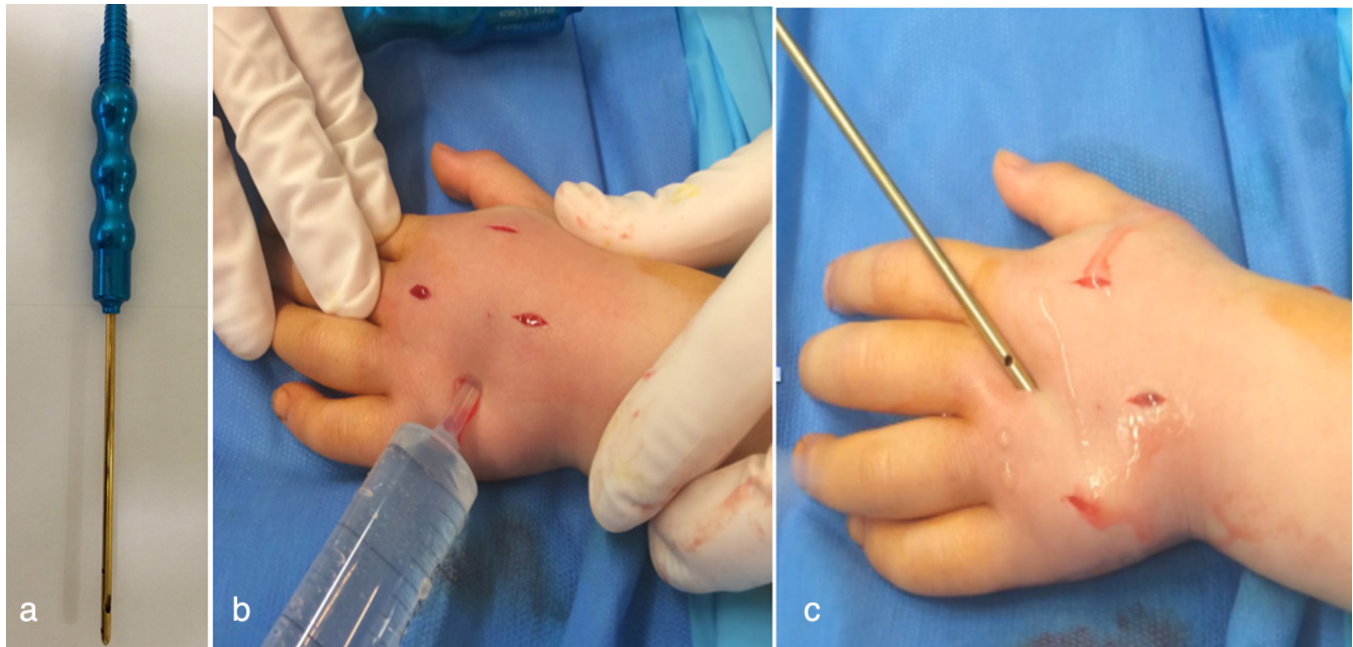


Fig. 1 Saline washout technique: **a)** the 2-mm blunt cannula; **b)** saline solution introduction through the small skin incision; **c)** washout procedure with the lipoaspiration cannula.

it was considered that there was no pain, low, moderate, high or unbearable pain if the VAS was respectively scored as < 2, 3 to 4, 5 to 6, 7 to 8 and > 8. Cosmetic aspect was subjectively evaluated by the patient and/or the parents. The surgeon asked the parents and the patient if they considered the appearance of the scar as normal or as a low, moderate or important scar. Further data were also recorded: delay to surgical intervention, delay to restart the chemotherapy and postoperative complications.

Statistical analysis

All statistical analyses were performed using the Stata 13.0 software package (Stata Corp., College Station, Texas). Numerical data were expressed as means (SEM). No comparative analysis was possible as the study is descriptive.

Results

Initial assessment and operative intervention

Among the 13 patients, saline washout was performed for 11 children and extravasation was located as followed: anterior forearm (seven), dorsal hand (five) and thorax with a central-venous system (one) (Table 2).

Initial clinical symptoms were oedema (seven), erythema (three), blister (two) and paraesthesia (one). Mean age at surgery was eight years (SEM 5; 4 to 15) and mean time to surgery was 6.2 hours (SEM 2; 2 to 12). The mean volume of cytotoxic drug that accidentally diffused in upper-limb soft tissues was 33 ml (SEM 8; 20 to 55).

The delay to further medication (chemotherapy or antiviral) was 6.5 days (SEM 5; 2 to 25). Regarding the one patient with trunk extravasation on a port-a-cath, the central catheter was removed under the same anaesthesia as the saline washout procedure and chemotherapy was later administered on a peripheral catheter.

Outcomes evaluation

Mean follow-up was 11 months (SEM 7; 2 to 21). Ten patients had no pain at last follow-up and three patients had low pain essentially located at the forearm. No patient used painkillers. Surgery did not leave any significant scar except for in two patients (Fig. 2). There was no limitation of upper limb range of movement in any patient.

Complications

Severe tissue necrosis required surgery in two patients. First, a 15-years old girl treated for a Hodgkin lymphoma by Vincristine on a peripheral forearm line. The saline washout procedure was carried out four hours after the extravasation, the volume of which was estimated at 55 ml. Two days postoperatively, she developed external signs of skin infection (fever, inflammatory aspect and C-reactive protein > 10 mg/L). After collecting blood cultures, a probabilistic intravenous antibiotherapy (80 mg/kg per day of Clavulanic Acid – Amoxicillin) was initiated. The infection did not progress well, since the patient developed necrotizing fasciitis, and surgical debridement was necessary 48 hours after the saline washout.

Table 2 Demographic data

Patient	Disease	Age at surgery (yrs)	Follow-up (mths)	Localization	Initial symptoms	Injection product	Volume of injection (ml)	Time to surgery (hrs)	Delay to ongoing chemotherapy (days)	Complications
1	Lymphoblastic leukemia (T)	7	6	Thorax (portacath)	Erythema	Vincristin	25	3	3	
2	Lymphoma	8	10	Anterior forearm	Erythema	Cisplatin	35 (0.7 mg/ml)	7	6	
3	Hodgkin lymphoma	7	7	Anterior forearm	Erythema	Vincristin	30	4	6	
4	Lymphoma	4	7	Dorsal hand	Oedema	Cisplatin	20 (0.5 mg/ml)	7	4	
5	Myeloid leukemia	12	8	Dorsal hand	Erythema	Adriamycin	25	3	5	
6	Myeloid leukemia	13	5	Anterior forearm	Oedema-paresthesia	Adriamycin	25	2	5	
7	Hodgkin lymphoma	14	2	Anterior forearm	Oedema	Doxorubicin	55	4	11	
8	Lymphoblastic leukemia (B)	15	12	Anterior forearm	Blisters-oedema	Vincristin	45	-	25	
9	Burkitt lymphoma	9	15	Dorsal hand	Erythema	Cisplatin	30 (0.6mg/ml)	10	2	
10	Lymphoma	12	21	Dorsal hand	Blisters	Oxaliplatin	35	12	2	
11	Lymphoblastic leukemia (T)	8	12	Dorsal hand	Oedema-erythema	Acyclovir	25	7	4	
12	Hodgkin lymphoma	15	20	Anterior forearm	Oedema-erythema	Vincristin	55	4	10	Necrotizing fasciitis
13	Hodgkin lymphoma	14	4	Anterior forearm	Oedema	Doxorubicin	40	-	3	Skin necrosis



Fig. 2 A good outcome in a four-year-old boy treated for a lymphoma. Dorsal right hand diffusion of Cisplatin. Seven months later, there was no visible scar.

procedure. After there was no sign of residual infection (no inflammatory syndrome, no fever, good local evolution), a secondary skin graft was performed causing unattractive scars. However, upper limb range of movement was preserved (Fig. 3). The second patient was a 14-year-old boy also treated for a Hodgkin lymphoma by Doxorubicin, perfused on a peripheral forearm line. At that time, the written extravasation protocol was not yet established and hand surgeons were not contacted within six hours (> 12 hours in this case). A conservative treatment was decided on (cold compresses soaked with a 5% glucose solute) without the antidote administration (dexrazoxane) that has proper cytotoxicity if locally administrated.^{8,18,20,25} The boy had severe forearm skin necrosis requiring reconstructive surgery with a free latissimus dorsi flap. Even if the elbow flexion-extension range of movement was fully preserved, the cosmetic sequela was major.



Fig. 3 Illustration of a 15-year-old girl with poor result at ten months. Vincristine disseminated in the left forearm. A necrotizing fasciitis occurred 48 hours after the saline washout procedure, requiring surgical debridement and skin graft. It should be noted that in this case, initial washout management was performed on time but the volume of diffused drug was the highest volume reported in the present study.

Discussion

Extravasation injury might cause serious and permanent damage such as skin necrosis, skin infections with abscess and necrotizing fasciitis and sequelae such as un-aesthetic skin and muscular contractures and/or digit amputation.^{2,3,14}

Initial assessment

Reliable criteria for decision-making must be defined in order to decide if a patient requires surgery or not, even

though initial symptoms are poor and non-specific and the evolution is unpredictable.^{7,18,22} Local adverse effects of antineoplastic drugs are variable.^{5,6,12,26} Vesicant agents induce necrosis and secondary infections, the severity of which is mostly influenced by the tissue–drug concentration (volume and speed of drug perfusion) and the localization of the injury.^{9,10,12}

Surgical management

The treatment of extravasation injuries remains controversial, but all have the same objective: to remove the toxic agent from the affected tissues.^{13,14,18,25} The washout technique initially described by Gault et al is rather quick, with few complications and consists of a mechanical process combining the dilution and aspiration of the cytotoxic drug.^{11,13,16,23} Several technical modifications have been added (cannula size, solute infiltrated) without changing the initial concept of the mechanical dilution.^{12,13} While the washout procedure is the reference method in most studies, some vesicant agents have specific antidotes that can be used to treat these injuries.^{15,17,19,27,28} However, the lack of agreement between animal studies and human clinical findings, antidotes inherent toxicity if locally administered, should make their use cautious.^{1,18,29,30} On the other hand, other authors have suggested complete excision of all abnormal tissues that could leave either cosmetic damage or functional sequelae.^{1,18,29,30}

Prevention

Prevention remains crucial for the management of cytotoxic extravasation, following international guidelines.^{20,22,28,31} As a matter of fact, medical staff and paediatric nurses, especially in haematology, must be trained for cytotoxic intravenous administration and for early detection and management of extravasation injuries as previously described.^{12,20,22} Simple recommendations must also be developed in paediatric haematology, such as the use of a central venous system, avoiding perfusion next to a joint, the use of a small plastic gauge cannula and verification of blood return prior to vesicant administration. Finally, one risk factor has been well-identified and crucial to avoid sequela: the delay of management, either conservative or surgical.^{12,19} Therefore, in our institution, a standby duty list was available for the concerned department and the written protocol was essential in making the different teams aware of the risk, helping to reduce the delay of management.^{22,30,32}

Limitations

The current study has several limitations. First, it is a descriptive and retrospective study based on a small group of patients. Despite the low sample size, the study shows good effectiveness on children. Second, a control group has

not been established to assess the reliability of this method. Indeed, there is no evidence in the literature about the superiority of conservative management compared with the washout technique, especially in children with extravasation of cytotoxic drugs such as chemotherapy.^{17,22,31} A randomized control study comparing various procedures (antidote administration and conservative treatment) is required. Furthermore, cytotoxicity of chemotherapy drugs has been essentially reviewed for the study (except one case of antiviral drug), in order to provide a more consistent and homogenous work.³³ Finally, the incidence of extravasation injuries was not reported since it is impossible to report all diffusion incidents occurring in a single institution.

In conclusion, upper limb extravasation of cytotoxic solutes remains a surgical emergency that can lead to serious sequelae. The saline washout procedure is a safe and easy procedure that reduces the incidence of skin necrosis. Early referral to a specialized department is essential. However, the key parameter remains prevention by educating medical staff and nurses following international guidelines.

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COMPLIANCE WITH ETHICAL STANDARDS

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No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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ETHICAL STATEMENT

Ethical approval: All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was not required for this retrospective work.

ICMJE CONFLICT OF INTEREST STATEMENT

BI reports they are a consultant for Implanet, ZimmerBiomet and Medtronic, outside the submitted work.

The other authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

VM: Data collection and analysis, Manuscript writing.

ALS: Data analysis, Manuscript writing and revision.

AP: Data collection, Manuscript revision.

CM: Data analysis, Manuscript revision.

BI: Study design, Manuscript revision.

PJ: Study design, Manuscript revision.

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