S P E C I A L P A P E R

Extravasations of Vesicant / Non- Vesicant Drugs and Evidence – Based Management

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Abstract

The intravenous applications that have been used widely can lead to some complications such as extravasation, ecchymosis, hematoma and phlebitis. The extravasation is one of these complications. Extravasation leads to some undesirable happenings such as prolonged times of hospitalization of the patients, unnecessary diagnostic procedures and even unnecessary treatments, stress effects on the relatives of patients, extra workload for health staff and the economic loss as well as to threatening the lives of patients.It is important for the health professionals, who are responsible for managing of intravenous applications, to know the drugs that cause tissue injury and take the necessary measures to prevent extravasation. Therefore, this article defines the pathogenesis of extravasation, types, symptoms, and evidence-based management.

Keywords: Vesicant/non-vesicant drugs, Extravasation, Evidence-Based Management

Introduction

Intra-venous (IV) initiatives is one of the most common practices in hospitals (Hadaway, 2007). It is reported that in the US, 20 millions of almost 40 millions of hospitalized patients each year have received intravenous treatment (Jones, Coe, 2004). In general, any study has not been noticed yet to represent Turkey in this field. However according to a multicenter study of intensive care units in Turkey, it was observed that while the rate of catheter utilization was being noticed at 61% in the units (as per data of 2002-2005) in Turkey, this rate varied between 49-56 % in the US hospitals (as per data of NNIS -National Nasocomial Infection Surveillance- 1992-2004) thus it was determined that our country had a very high utilization rate (Aygün et al. 2004; Yarbro, Wujcik,, Gobel, 2011).

Intra-venous initiatives that are widely used can lead to some complications such as extravasation, ecchymosis, hematoma, and phlebitis (Uzun, 1991; Sauerland, Engelking, Wickham, Corbi, 2006; Yarbro, Wujcik, Gobel, 2010). Extravasation as one of these complications can be described as an inflammation as a result of when intravenous fluid or drug undergoes perivascular or subcutan tissue even tissue damage that can lead to ulceration and necrosis, loss of function in extremity or even amputation in extremity that can go up to contain all the layers of skin and subcutaneous tissue (Leslie, Ambler, 1995). Extravasation induces prolonged duration of the patient's hospital stay, unnecessary diagnostic procedures and treatment, stress in the life of the patients' relatives, extra work load on the health personnel and economic loss accordingly (Karadağ, 1999; Sauerland, Engelking, Wickham, Corbi, 2006).

It is difficult to determine the incidence of extravasation since insufficient documentation in this matter. However, depending on some studies

carried out, it is reported that vesicant chemotherapy extravasation is observed in children by 11% and in adults by 22%. (Ener,2004; Özbaş, 2007; Hadaway, 2007; Yarbro, Wujcik,, Gobel, 2011). Vesicant chemotherapy extravasation is exposed in peripheral IV infusions by 0.1-6% and in port infusion by 0,3 - 4.7%. In addition, negative results caused by extravasation can be prevented. So it is important for the health professionals who are responsible for managing of IV applications to know the drugs that can cause tissue and be capable to early diagnose of extravasation and take the measures accordingly. Therefore, this article defines the pathogenesis of extravasation, types, symptoms and management (Sauerland, Engelking, Wickham, Corbi, 2006).

Pathogenesis of Extravasation

Extravasation occurs as a result of vesicant, non-vesicant and irritant drugs leaked out of blood vessels (Table 1,2). The reason and mechanism of damage that have been formed due to vesicant, non-vesicant and irritant drugs is not fully understood. The severity of tissue damage concerns the drug linking on DNA (Leslie,Ambler, 1995; Schulmeister, Camp-Sorrel, 2000; Sauerland, Engelking, Wickham, Corbi, 2006; Schulmeister, 2007; Yarbro, Wujcik, Gobel, 2010). Antineoplastic agents have direct toxic effect on the cell. As an example; depending on a leading theory, it is widely accepted that the drug spreads the toxic agent to the surrounding healthy cells by means of necrotic cells during a period lasting up to weeks even months in doxorubicin extravasation (Schulmeister, 2007; Yarbro, Wujcik,, Gobel, 2011).The reasons of tissue damage that may occur depending on vesicant, non-vesicant and irritant drugs extravasation are given as follows;

Agents bound to DNA

Anthracyclines (Doxorubicin, Dounurobicin, İdarubicin and Mitoxantron), antitumor antibiotics (Mitomycin) and some alkalizing agents (Mechlorathamine and platinum analogs) are bound to nucleic acid in DNA thus lead to the formation of toxic topoisomeraz II and break out the fibers in DNA (Yarbro, Wujcik, Gobel, 2010). The resulting free radicals make complex cellular structure by inhibiting RNA and protein synthesis then cause the formation of apoptosis. For example; free radicals forming in doxorubicin extravasation create serious damage to small blood vessels by breaking the structure of damaged cell, cell membranes and vascular structure therefore those free radicals cause inflammation of the cells and the formation of necrosis in tissue thus lead to cell apoptosis (Sauerland, Engelking, Wickham, Corbi, 2006; Schulmeister, 2007).

Antineoplastic Agents unbound to DNA

Agents that are not bound to DNA cause less tissue damage compared to the agents bound to DNA. The drug group including vinca alkaloids containing microtubule toxins (Vincristin, vinblastin, and vinorelbin), microtubule inhibitors and taxans (paclitaxel, docataxel) improves the stability of microtubules. Intracellular microtubule toxins and topoisomerase inhibitors prevent mitotic cell division so inhibit the connection with DNA thus lead to cell apoptosis. Topoisomerase enzyme inhibitors (Etaposid, irrinotecan, topotecan) make DNA spirals initiative easier so primarily restructure DNA again then divide the cell. At the end, by preventing DNA copying and replication, it leads to cell death (Steele, 2001; Schulmeister, 2007).

Non-antineoplastic vesicant agents

Extravasation formed due to non-antineoplastic agents can lead to the results i.e. Tissue necrosis, debridement flap or skin graft reconstruction depending on the dugs' vesicant features. Hyper osmotic solutions lead to compartment syndrome due to vesicant features, concentrated electrolyte solutions lead to prolongation of muscle depolarization and finally ischemia, intracellular agents affecting pH (sodium bicarbonate) or various agents causing ischemia by forming severe vasoconstriction lead to the formation of necrosis in extravasated tissue(Schulmeister, 2007; Yarbro, Wujcik, Gobel, 2010).
Drugs w and w/o vesicant potential are given in the following Table 1 and 2; (Polovich, White, Kelleher, 2005; Schulmeister, 2007).

Table 1.Antineoplastic Agents with Vesicant Potential

Non-vesicant agents	Irritant agents	Vesicant agents
İnterleukin-2	Carmustine	Cisplatin
Asparaginase	Cisplatin	Dactinomycin
Bleomycin	Dacarbazin	Daunorubicin
Cladribine	Daunorubicin	Doxorubicin
Fludarabin	Daunorubicin liposomal	Epirubicin
Gemcitabine	Etoposide	Idarabucin
Gemtuzumab ozogamicin	Irrinotecan	Mechlorethamine
Ifosfamide	Mitoxantrone	Melphelan
Methotrexate	Oxaliplatin	Mitomycin
Pentostatin	Topetecan	Paclitaxel
Rituximab		Vinblastine
Thiotepa		Vincristine
Transtuzumab		Vindesine
		Vinorelbin

Table 2. Non-antineoplastic Agents W/O Vesicant Potential

Electrolyte Solutions	Vasocompressive agents	Hyperosmolar agents	Others
Calcium Chloride 5.5%	Dopamine	Central venous nutrition	Penicillin
Calcium Glokonate 10%	Dobutamine	>10% glucose	Radiographic contrast material
Potassium chloride 7.45%	Epinephrine	15% mannitol	vancomycin
sodium bicarbonate 4.2 or 8.4%	Norepinephrine	Fentoin	
sodium chloride 10%	vasopressin		

Risk Factors Affecting the Formation of Extravasation

The potential for tissue damage is affected by the factors such as the drug concentration, high vesicant potential of drug and the unfiltered amount, tissue exposure and extravasated zone, repeated use of drugs having the vesicant characteristic (Luke, 2005; Schulmeister, 2007; Yarbro, Wujcik, Gobel, 2010). For example; excess quantity extravasation management of an agent bond to DNA in high dose is rather difficult. In addition, nerves, blood vessels, antecubital region that is rich in terms of tendons and the chest wall in patients exposed to port application and the thoracic structures are the parts under risk. The risk factors affecting the formation of extravasation or making this formation easier are given as follows;

In terms of patient*:* In newborns, children, adults, seniors (patients with fragile veins), those who are less sensitive to pain, the patients exposed to repeated times of catheter and those with problem in vascular thrombosis of the veins, those having difficulty in communication (those with hearing problems etc), unconscious, sedated or confused patients, Patients treated with an infusion in mastectomy side or in the field of lymph edema, patients who experience intense anxiety or fear, patients who are unable to lodge complaints from the point of view of cultural aspects (Polovich, White, Kelleher, 2005; Schulmeister, 2007).

In terms of history of disease: Cancer patients, people with diabetes, cardiovascular patients. (Polovich, White, Kelleher, 2005; Schulmeister, 2007).

Issues related to Peripheral IV Catheter: thickness of the *I*V catheter tip, IV catheter length ,IV access area (antecubital fossa, on hand, on foot, wrist.), Using the butterfly infusion set. (Polovich, White, Kelleher, 2005; Schulmeister, 2007).

***Issues related to Central venous catheters*:** Placement of catheter in the region instable to motion, bending or dislocation of the catheter, injection needle on the port not fully accessed or have never accessed, excessive back pressure around the needle, washing done with injector with small needle, fibrin deposition or thrombosis at the catheter (Polovich, White, Kelleher, 2005; Schulmeister, 2007; Yarbro, Wujcik,, Gobel, 2011).

Clinical issues: Intensive work conditions, knowledge lack of staff, inexperienced staff, and insufficient information on the drug management (Polovich, White, Kelleher, 2005; Schulmeister, 2007).

Types of Extravasation

National Extravasation Information Service (NEIS) examined the types of extravasation by separating into three types (Jones, Coe, 2004).

Pre-extravasation syndrome: It leads to flexibility and local hyper-sensibility in various degrees.

Type I: stiffness and swelling that around buller and infusion area;

Type II: soft tissue damage at infusion area;

Extravasation is examined in 4 types according to the process of change created by the drug in tissue (Schulmeister, 2007);

a. ***When it is formed with vesicant agents***, blistering of the skin and tissue damage, the formation of pain and tissue necrosis can develop.
b. When it is formed in terms of **e*xfoliate flaking off, the inflammation occurs.*** Tissue death is less common.
c. ***In the case of irritant formation,*** inflammation, a sense of tension, pain, swelling, bruising in the zone and rarely damage in tissues
d. ***In case of inflammation,*** pain and redness occur in the area.

Symptom and Results in Extravasation

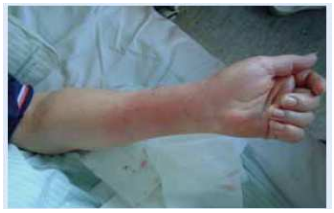
The symptoms of extravasation can occur during or after infusion in two-three days. The widespread stiffness, pain, and burning, stinging, tissue damage occur at extravasation area. All symptoms of cellular injury such as inflammation and pain felt by touch occur 3-5 days after extravasation (Clifton, 2006; Hamilton, 2006; Yarbro, Wujcik,, Gobel, 2011). In case of the results e.g. resistance that occurs in applying the IV drug, bleeding from cannula, slower infusion, swelling at the point of cannula, burning and pain around the cannula burns are the findings reminding the extravasation. (Fig1). In addition, the volume of the fluid unfiltered in the subcutaneous tissue, exposure to extravasated fluid for a long time, osmolarity and PH value of the liquid etc can result in the formation of scar. As a result of extravasation of isotonic liquids such as dextrose 5%, the bullous and necrosis can

occur (Jones, Coe, 2004; Clifton, 2006). Additionally, there is always risk to develop compartment syndrome in various extravasations. Developed compartment syndrome can affect the local circulation and cellular function in tissue. In the area of extravasation, irreversible ulceration and necrosis can occur (Clifton, 2006).

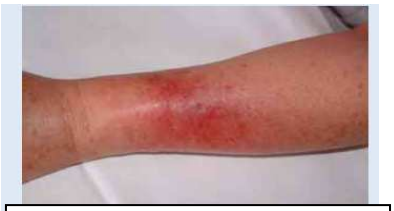
Necroses that can occur extend to fascia, tendon, and periostiuma. The necrosis that cannot be noticed at early stage can lead to significant organ insufficiency even to extremity amputation (Yeşilbalkan, 2005; Keskin, 2006). An urgent treatment has to be planned and the measures have to be taken (Wickham, Engelking, Sauerland, Corbi, 2006).

The extravasation process of Doxorubicin that leads to tissue damage by bounding to DNA takes part by days as follows; (Fig 1).

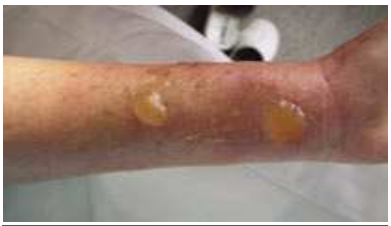
Fig 1.Doxurobicin Extravasataion Process (Wickham, Engelking, Sauerland, Corbi, 2006).



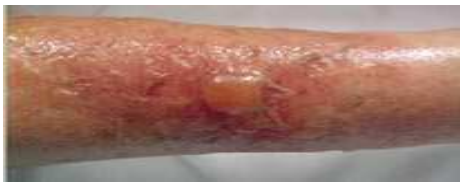
1st day: reddness at extravasation area



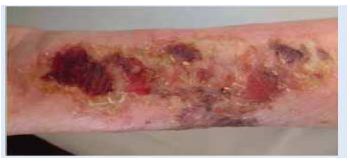
4th day: The development of redness and swelling



8th day: bullouse develops

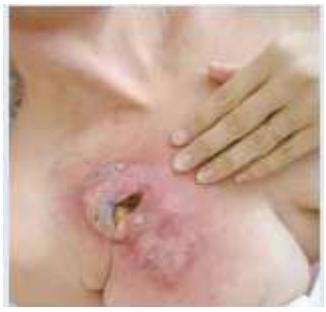


10th day: bullouse continues to develop and the skin peels off at damaged parts.



12th day: loss of sensation in the arm of the patient and deep tissue necrosis develops.

surgical debridement applies to remove the necrotic tissue



doxurobicin extravasation on a port placed in subclavicular zone

In scope of intravenous attempts of vesicant or non-vesicant drugs, the reactions such as fever reaction at vascular structure against the drug, vascular irritation, phlebitis development on the vessel wall and development of venous shock etc can occur. The fever reaction has shown itself by itching along the vessel; in case the vessel patency is taken under control, bleeding starts (Hamilton, 2006; Yarbro, Wujcik,, Gobel, 2011). IV Ondansetron is a common symptom in scope of Epirubicin and Doxurobicin application. In case of vascular irritation, pain and stiffness occur throughout the vascular. It is a common symptom during the application of Vinorelbin and Dacarbazin. When the PH value of drugs leads to irritation at vascular wall, phlebitis develops on vascular wall. It is a common reaction in scope of the applications of 5-FU, Doxorubicin, Epirubicin and Etoposide. Additionally, in case the drug is given cold or too fast, spasm develops at venous muscular wall thus vascular venous shock occurs. It is necessary to distinguish the extravasation formation from such reactions then the necessary attempts should be started. (Hamilton, 2006).

Evidence – Based Management Extravasation Management

The patients particularly newborns have to be taken under treatment urgently when extravasation develops in IV zone. Extravasation that is one of avoidable complications of intravenous applications can be reduced significantly in case it is determined within the first 24 hour and the treatment is applied accordingly (Yeşilbalkan, 2005; Wickham, Engelkin, Sauerland, Corbi, 2006).The nurses have great responsibility for ensuring the benefits of the fluid applications to the patient, the effective maintenance of the application and preventing the onset of complications. The nurse should observe IV attempt zone in terms of damage, pain and sensitivity. Particularly, upper part of the hand and intravenous zone taking part in antecubital area should be monitored in terms of nerves, tendons, blood vessels. The chest wall or thoracic structures should permanently tracked in terms of significant signs of damage, pain and signs of organ failure that can cause a variety of surgical interventions (MacCara,1983; Wickham, Engelkin, Sauerland, Corbi, 2006; Yarbro, Wujcik,, Gobel, 2011).

The nurses should keep the records of the pextravsation subjects including the patient's identification information and the details of the process such as the location of extravasated zone, diagnoses of the zone, time, the drugs and the order of administration, the estimated amount of extravasated drug, photo of the lesion, if possible, venous intervention site, number of catheter and the date of application, patient complaints, extravasation treatment plan and treatment outcomes (MacCara, 1983;Karadağ, 1999; Schulmeister, Camp-Sorrel,2000;Ener,2004; Hayden, Goodman, 2005). In case extravasation is detected as developed within 24 hour in the patient, the following steps have to be taken respectively (Table 3).

In Table 4, the steps taken and appropriate antidotes that have been used are explained in details with the purpose to extravasation of irritant and vesicant antineoplastic agents (Wickham, Engelkin, Sauerland, Corbi, 2006; Yarbro, Wujcik,, Gobel, 2011).

Hot or cold application methods are determined according to cytotoxic agents as specified in table 4. The hot application disrupts DNA helix and increases the absorption and distribution of the drug y performing vasodilatation; thus reduces the density of local drug in tissue. The hot application is done for 4 times a day at 20 minutes sessions during 24-48 hour (Sauerland, Engelking, Wickham, Corbi, 2006). The local hot application is done after the extravasation of Vinca alkaloids that increase the formation of ulcers. The cold application limits the field of extravasation causing the vasoconstriction (Jones, Coe, 2004; Sauerland, Engelking, Wickham, Corbi, 2006; Yarbro, Wujcik,, Gobel, 2011). The local cold application is done to reduce swelling after İV extravasation and determine the limits of tissue damage reducing the metabolic needs of damaged tissue. The cold application particularly done in scope of doxorubicin extravasation forms vaso-construction due to its cold effect thus reduces the effect of local spread of the drug, makes the drug intake slower by the cell and prevents peripheral damage. The cold application is done for 4 times a day at 20 minutes sessions during 24-48 hour (Wickham, Engelkin, Sauerland, Corbi, 2006; Sauerland, Engelking, Wickham, Corbi, 2006). In fact, local hot or cold application to be done after extravasation should be discussed in newborns and non- evidence-based researches. In fact, because of the structure of the epidermis the temperature of the zone should be controlled in scope of local hot and cold applications. In the literature there is no enough research that identifies the effect of hot and cold applications

(Wickham, Engelkin, Sauerland, Corbi, 2006; Sauerland, Engelking, Wickham, Corbi, 2006).

Table 3. The Steps To Be Taken Respectively When Extravasation Develops

Steps	Causes
Infusion is stopped	To prevent liquid extravasation to subcutaneous tissue;
Keeping brannule in place, serum set is separated.	To prevent liquid extravasation to subcutaneous tissue and prepare IV way to draw back the drug from subcutaneous tissue.
Extravasation zone is marked with pen.	To determine the Extravasated zone
Drug is applied with injector (10-20 cc)	To reduce the damage in subcutaneous tissue (many researchers recommend to draw back the Extravasated fluid from the zone)
Brannul removed	To observe the way IV and make the patient comfortable
Extremity is raised	To prevent edema formation in subcutaneous tissue
Drug- specific hot or cold application is launched and if appropriate antidote is available, it is applied.	To improve the extravasated zone and prevent the formation of ulcers and necrosis
Regular and continuous records are kept to include hot / cold application and any attempts.	To monitor the effects of attempts on the zone and keep the other health staff informed about currently taken steps.

Table 4. Applications Performed In Scope Of Extravasation Of Irritant And Vesicant Antineoplastic Drugs

Drugs	Classification	Hot / Cold Application Type And length	Proposed Subcutaneous Antidotes
Cisplatin	Irritant (<20 ml, 0.5mg/ml) Vesicant (>20 ml, 0.5 mg / ml)	Cold	sodium Thiosulphade 0.16M
Dactinomycin	Vesicant	Cold	N/A
Daunorobicin	Vesicant	Cold	Topical DMSO 99% Dexrazoxane
Docetaxel	Irritant	Cold	Normal saline (dilution effect) Hyaluronidase Topical DMSO %99
Doxorubicin	Vesicant	cold	Topical DMSO %99 Dexrazoxane G-CSF or GM-CSF
Epirubicin	Vesicant	Cold	Topical DMSO %99
Idarubicin	Vesicant	Cold	Topical DMSO %99
Mechlorethamine	Vesicant	N/A	Sodium thiosulphade 0.16M
Mitomycin	Vesicant	cold	Topical DMSO %99
Mitoxantron	Vesicant, Irritant	cold	Topical DMSO %99
Oxaliplatin	Vesicant, Irritant	Hot	Sodium thiosulphade 0.16M
Paclitaxel	Vesicant, Irritant	Cold	Normal saline (dilution effect) Topical DMSO %99
Streptozocin	Vesicant	Cold	N/A
Vinblastine	Vesicant	Hot	Hyaluronidase
Vincristine	Vesicant	Hot	Hyaluronidase
Vinorelbine	Vesicant	Hot	Hyaluronidase

DMSO: Dimethyl sulfoxide; G-CSF: granulocyte colony Stimulating factor, GM-CSF: granulocyte macrophage Colony Stimulating factor

Drugs Used in the Administration of Extravasation and Evidence-Based Applications

The mechanisms of action of antidotes used in the administration of extravasation and the information regarding to the evidence-based applications are given in Table 5 (Wickham, Engelkin, Sauerland, Corbi, 2006; Sauerland, Engelking, Wickham, Corbi, 2006).

Is it Possible to Avoid from Extravasation?

According to the definition in the literature, the protection from extravasation is identified as the limitation of tissue damage (Yarbro, Wujcik,, Gobel, 2011). It is possible to avoid from most of vesicant extravasation occurrences. It is very important for nurses who are managing all chemotherapy treatment or who take part continuously in intravenous chemotherapy treatment and responsible for the chemotherapy treatment to protect the patient from extravasation (Hadaway, 2007). The protection from extravasation should include simple and understandable chemotherapy education, patient-centered information related to the specific drugs, and critical appraisal skills. The nurses should keep on providing safe patient care, preventing the development of damage and providing continuity by using extravasation directive (Hayden, Goodman, 2005). It is necessary to distinguish the risk factors that may lead to the development of extravasation, use suitable venous catheters and control the risk factors permanently. In case of extravasation happening, the administration of occurrence and the measures to be taken to prevent the development should be properly managed (Hadaway, 2007; Yarbro, Wujcik,, Gobel, 2011).

To reduce the risk of progression in patients developed extravasation, the nurses and doctors should use implant systems reducing the vesicant damage or prefer using the central venous catheters complying with the use of vesicant drugs (Hadaway, 2007).Using appropriate venous access equipment will enable the vesicant and irritant drugs to be conveyed safely by keeping the peripheral access ready constantly thus it reduces the patient's anxiety related to frequently vein access (Hamilton, 2006; Hadaway, 2007).

In the patients with central venous catheter, before giving the vacant drug, it should be controlled whether the blood comes back; if not, the placement of central venous catheter should be controlled in accompany with fluoroscopy or x - ray. The nurses primarily have to check the septum in the patients with port then control whether the blood comes back or not by flushing (Keskin, 2006; Yarbro, Wujcik,, Gobel, 2011).

Intravenous catheters, central venous catheters and ports should be placed in the manner of easily visible and the applied serum sets should be fixed functionally and finally easy observation should be provided. Especially, the drugs having strong vesicant effects should be marked with dark stickers. The nurses should observe IV zone and surrounding during the vesicant infusions lasting more than 60 minutes. Before starting the vesicant treatment, the nurses should control whether the intravenous blood comes back again and if it is placed properly, intravenous treatment is commenced (Schulmeister, 2000; Hadaway, 2007). Particularly after the nurse had started the vesicant treatment, intravenous zone should be observed in terms of erythema, redness, swelling once 5-10 minutes. Any local pain and intravenous sensory change in the area should be carefully observed (Polovich, White, Kelleher 2005). When the extravasation develops, the nurse should observe the zone of IV catheter in terms of good current (arterial, venous and lymphatic), sensory disability, loss of function and the necessity of surgical repair. It is possible that the loss of tissue and organ can develop in hand, wrist and antecubital areas following the extravasation process such parts of the body should not be used as much as possible (Hadaway,2004; Luke, 2005). For IV zone, muscular forearm can be chosen. Initially, the direct selection of the proximal veins is not suitable. One or more vein attempts in chosen zone IV increases the risk of extravasation. (Hadaway,2004; Luke, 2005). In addition, there are conflicting opinions about the sequence of vesicant drugs. According to one of these opinions, the vesicant drugs should be given before the non-irritant drugs. However any other opinion suggests the vesicant drugs can be given in the manner of "sandwich method" sequentially together with non-vesicant drugs. There is no sufficient proof for both views. The important point here is that the nurses should have information regarding to the vesicant drug administration very well (Sauerland, Engelking, Wickham, Corbi, 2006; Yarbro, Wujcik,, Gobel, 2011). The frequency of observation on the zone under chemotherapy treatment varies depending on the giving method of chemotherapeutic agent whether bolus or infusion. If the chemotherapeutic agent was given in manner of bolus or in case of

extravasated position, 2-5 ml blood can be drawn back. In case of vesicant drugs given in continuous drops, the catheter position should always be observed and should a sensitivity is noticed in the zone IV, a saline solution of 5-10 ml is given and the zone will be observed accordingly. In addition, the nurse should carefully observe the patients who are chemotherapy treated with permanent central venous catheters in terms of intra-thoracic extravasation findings (fever not bringing down, plevratic pain, cough, swelling of the upper limbs or neck …) (Sauerland, Engelking, Wickham, Corbi,2006; Bozkurt, Uzel, Akman et. al. 2003). IV pump alarms signaling that intravenous set is clogged should be taken into consideration by the nurses for early detection of extravasation. In such a case, the rate of infusion should be reduced and the infusion are has to be observed. (Sauerland, Engelking, Wickham, Corbi,2006).

The nurse should have the control on the pain that has developed in extravasated zone. If it is necessary, the nurse can use nonopids with the previous approval of the doctor. However it is required to observe the patient in terms of any possible adverse effects when nonopiodis are used in pain control (Yarbro, Wujcik, Gobel, 2010).

The detailed chapters including the risk factors that may lead to extravasation should take part in concerning documentation about chemotherapy. These sections will provide the nurses with great benefits to determine the population of the patients under risk and keep strict tracking (Polovich, White, Kelleher, 2005; Clifton, 2006)

Table 5. Antidotes Used In The Administration Of Extravasation, Effects And The Evidence-Based Studies

Antidotes	Effect	Evidence-Based Practices
- Saline Flash	- Reported that it stimulates the formation of local edema local by providing the dilution of the drug in Extravasated area and enables the drug to enter into circulation easier.	- *Davies et.al* suggested that the clinical results of subcutaneous Hyaluronidase and application of saline -in flash in two preterm infants provided healing benefits (particularly when it is applied within first 6 hours). - Harris and Moss washed up the Extravasated zones of 56 babies with normal saline solution and determined that no tissue damage occurred in any patient. (Wickham, Engelkin, Sauerland, Corbi, 2006; Sauerland, Engelking, Wickham, Corbi, 2006).
- Hyaluronidase (Vitrase, Amphdase)	-It is a protein structured enzyme. -Reported that it has effect on reduction the length of necrosis length by increasing the drug absorption in subcutaneous tissue and connective tissue permeability after extravasation. -Particularly used in extravasation of 10% Dextrose, calcium salts, potassium salts, sodium bicarbonate, aminophylline, radiocontrast ingredients, hypertonic saline, naficylin, blood, parenteral nutrition, and other drugs.	- *Davies et.al* suggested that the clinical results of subcutaneous Hyaluronidase and application of saline -in flash in two preterm infants provided healing benefits (particularly when it is applied within first 6 hours) (Wickham, Engelkin, Sauerland, Corbi, 2006; Sauerland, Engelking, Wickham, Corbi, 2006).
- Sodium Thiosulphate (0.16M)	- Recommended by Oncology Nursing Society to use as antidote in mechlorethamine or concentrated Cisplatin (> 20 cc or 0.5 mg/ml) extravasation.	- N/A (Wickham, Engelkin, Sauerland, Corbi, 2006)

	- 2ml sodium sulphade, each 1 mg mechlorethamine hydrochloride (or each 100 mg cisplatin) extravasation is recommended to apply subcutaneous for a short time.	
- Dimethyl sulfoxide (DMSO 70 and 90% Solution)	- It is pointed out that DMSO potentially cleans out thoroughly the free radicals and reduces the pain due to effect of vasodilatation. It has anti inflammatory characteristic thus shows the effect by ensuring the stability of the cell membrane.	- It is reported that the effectiveness of DMSO application in antracylin and mitomycin extravasation is less in animal experiments however no sufficient information regarding to its use is obtained in human experiments. -127 persons who have developed extravasation due to Doxurobicin, Epirubicin, Mitomycin, Mitoxantron, Cisplatin, Carboplatin, 5-FU and phosphamide were applied DMSO for seven days thus ulcer development decreased in that area. - 20 patients, who developed antrcycline cyclin extravasation, were applied DMSO for 16 hours during 14 days and finally no ulcer formation observed in that area (Wickham, Engelkin, Sauerland, Corbi, 2006).
- Dextrazone	- It is used to be protected from the increased cardio toxic effects of anthracyclines. - Protective mechanism on the heart is not fully known however it is pointed out that it prevents the formation of free radicals by strengthening intracellular structure.	- The experimental data of Dextrazone on humans is limited however it was observed that doxorubicin, daunorobicin and idarobucin limited the area of extravasation in a study conducted on mice (Wickham, Engelkin, Sauerland, Corbi, 2006).
- Topical Corticosteroids	- Used because of the anti-inflammatory effect in extravasation area. - Its use is controversial because the development of inflammatory cell in damaged tissue at extravasated area is less. -It can be used in ulcers developed as a result of vinca alkaloids or antracycline extravasation. -Dexamethasone can be used for 10-14 days to suppress the inflammatory process following the oxaliplatine extravasation.	-No sufficient work is available (Wickham, Engelkin, Sauerland, Corbi, 2006).
- Growth factors (Sargromastin, Neupogen..)	-It is considered that it prevents necrosis development in extravasated area.	- No sufficient work is available (Wickham, Engelkin, Sauerland, Corbi, 2006).
- Topical Nitroglycerin	- It leads to local vasodilation in extravasated area. - It was reported that it reduced the formation of extravasation and phlebitis.	- In a randomized controlled study conducted on adult patients, it was reported that it reduced the formation of extravasation and phlebitis.

	- In preterm infants, there is risk to increase the absorption of topical nitroglycerin through stratum corneum that has not developed sufficiently. - The health staff has to be informed that topical application of nitroglycerin has potential adverse effects and in case of any adverse effect, the controls need to be done more frequent.	- In a descriptive case study, two preterm infants that developed peripheral tissue ischemia as a result of dopamine extravasation were applied topical nitroglycerinso a significant decrease was reported in extravasation following the treatment. (Sauerland, Engelking, Wickham, Corbi, 2006).
- Phentolamin mesylate (Regitine)	- Potent alpha is an adrenergic blocker. - It makes local vasoconstriction by inhibiting alpha effects of Katekolamins and protects the extravasated area from skin necrosis. - It is used in extravasation of vasoactive agents such as Dopamine and norepinephrine. -when it is applied in extravasated area, coldness and pallor is observed with edema.	- N/A (Wickham, Engelkin, Sauerland, Corbi, 2006; Sauerland, Engelking, Wickham, Corbi, 2006).

Education of Patient and Family

The education of the patients and caregivers especially for those who take vesicant drug treatment in the clinics and the outpatient emphasize a vital importance. Both patient and caregiver should be trained about potential harmful effects in scope of verbal training techniques and written educational materials. The nurse is responsible for arranging the training programs by evaluating the patient's language or communication barriers and anxiety so the nurse should keep the patient informed at some certain intervals (Yarbro, Wujcik, Gobel, 2011).

The patient's initial training should be given before the administration of drugs affecting the central nervous system and the patient has to be questioned at some certain intervals to determine if he/she understands the given trainings properly (Özbaş, 2007; Yarbro, Wujcik, Gobel, 2010).

The patient and the caregiver should be kept informed about the importance to observe the effects at intravenous area in scope of local pain, swelling, temperature rise, changes in the skin during the intravenous process. It is also important to inform the patient about the measures to be taken e.g. elevation of the arm, hot or cold application type depending on the type of chemotherapeutic drug used, application time in case of extravasated fluid (Yarbro, Wujcik, Gobel, 2011).

Conclusion

Extravasation injuries are a potentially serious consequence of all intravenous therapy. The best "treatment" of extravasation is *prevention*. While there is no real treatment *per se*, there are some techniques that can be applied in case of extravasation, though their efficacy is modest. If there is tissue necrosis, surgical reconstruction may be helpful.

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