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Review Article

Factors Influencing Extravasation of Newborn Intravenous Infusions: A Review

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Abstract

Newborns, with their low immune system, lack of self-care ability, and inability to express discomfort through language, face challenges during the treatment of diseases, especially during intravenous infusion treatments where extravasation can occur. The inability of nurses to immediately detect extravasation often leads to severe consequences, including disability and even death. This increases the pain and treatment costs for children and places a heavy burden on healthcare professionals, hospitals, and society. Neonatal infusion extravasation is widespread during intravenous infusion and is influenced by various factors. Therefore, this article aims to review the research progress on relevant influencing factors that cause neonatal infusion extravasation.

Introduction

Intravenous infusion is widely used in the treatment of newborns, but it is susceptible to various factors that can lead to extravasation of the infusion. This can range from local skin redness and swelling to severe skin tissue necrosis and damage to nerves and joints, ultimately leading to skin dysfunction.[1,2] Newborns, especially premature infants, have weak resistance, small venous lumens, and they cannot cooperate during puncture, easily leading to puncture failure and infusion leakage. Moreover, the skin sensitivity of newborns is low, and the pain caused by infusion extravasation cannot be expressed promptly. Additionally, there is no accompanying care in the neonatal ward, and extravasation can only be detected by nurses. These consequences are more severe in children than in adults.[3,4] Research has shown that the incidence of neonatal infusion extravasation is 18.18–75%.[5] Therefore, studying and summarizing the relevant factors that affect neonatal infusion extravasation are of great significance for preventing infusion extravasation in clinical nursing.

Many factors can cause infusion extravasation. This review elaborates on the mechanisms of infusion extravasation, including self-factors, external factors, and disease-related factors that contribute to neonatal infusion extravasation. The mechanism of infusion extravasation is as follows (Fig. 1).

Chemical stimulation of the blood vessels using drugs

Blood composition changes as well as the direct stimulation of drugs leads to the release of inflammatory mediators and an increase in the permeability of the damaged inner wall of blood vessels, resulting in inflammatory reactions.

When the pH of the drug falls below five or exceeds nine, the solution becomes excessively acidic or alkaline, respectively. Mixing the drug with a diluent in an intravenous solution can alter its pH. An overly acidic or alkaline pH can stimulate the blood vessel wall, damage cell proteins, cause cell death, and promote extravasation of the infusion fluid.[6,7] Intravenous injection of hypertonic drugs disrupts the osmotic pressure balance inside and outside the cells, increasing plasma osmotic pressure. This can lead to the dehydration of vascular endothelial cells, resulting in hypoxia, hyperemia, and edema. The damaged cell transmission mechanism can cause vasoconstriction, spasm, platelet aggregation, and prostaglandins E1 and E2 release. These events lead to increased vein wall permeability, inflammatory changes due to leukocyte infiltration, and his-

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Abbreviations: DIC, disseminated intravascular coagulation; MAS, meconium aspiration syndrome.
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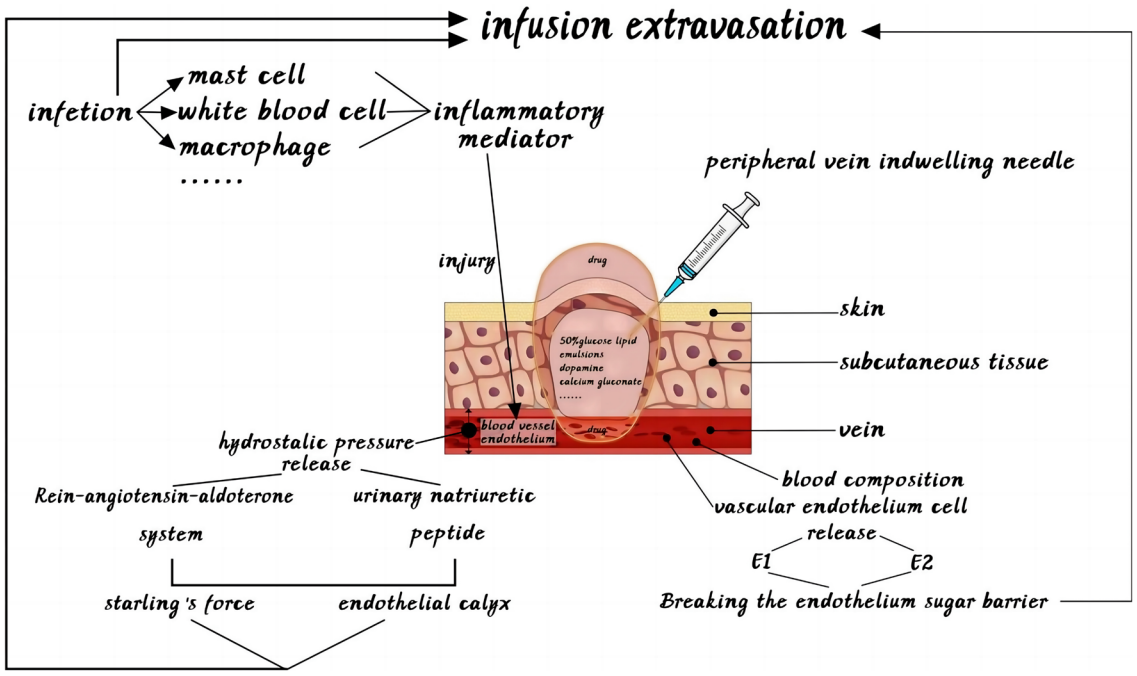

Fig. 1. The mechanism of infusion extravasation.

tamine release, ultimately causing the veins to contract and harden.[8] Exosmosis of the drug solution chemically stimulates vein vessels, leading to inflammation and thrombus formation. E-selectin and Intercellular adhesion molecule-1 facilitate the adherence of granulocytes to endothelial cells, causing further inflammatory damage to local tissues and breaking the endothelial glycocalyx barrier, ultimately leading to exosmotic infusion. Additionally, the progress of infusion exosmosis may cause local tissue edema.[8–10]

Continuous infusion of drugs to change the blood volume

Water, electrolytes, glucose, and nutrients can freely pass through the vascular endothelium via capillaries. This exchange depends on the balance between hydrostatic pressures, determined by factors like the volume of blood vessels, the tension of the endothelium, and pressure from residual proteins and colloids in the blood vessels. During intravenous infusion, the fluid crossing the complete vascular barrier in the intravascular and extravascular spaces is reabsorbed by the lymphatic system to maintain balance and prevent edema.[11] When fluid is continuously infused, changes in blood vessel volume trigger the activation of the renin-angiotensin-aldosterone system and the release of urinary natriuretic peptide. This disrupts the balance between Starling's force and endothelial calyx injury, leading to water and sodium retention. Consequently, fluid from the blood vessel is transferred to the stroma, causing leakage into the third space.[12]

Increased venous and hydrostatic pressures

Transfusion exosmosis is affected by blood vessel cavity pressure, infusion speed, infusion pump pressure, and liquid osmotic pressure. The vein lumen of newborn infants is small and fragile. Consequently, it becomes difficult to bear excessive infusion speed and increased venous pressure.[3] Research has shown that a high infusion rate at the tip of a small intravenous infusion catheter, increased venous pressure at the catheter's distal end, and fragile veins in newborns contribute to a higher incidence of intravenous infusion extravasation. When normal skin is gradually stretched beyond its critical point, the force (stress) required to increase the given length (strain) increases exponentially. Infusion extravasation can occur when the expansion of the subcutaneous space greatly exceeds the tensile capacity of the overlying skin.[13] If an infusion pump is used and the pump alarms, the infusion system becomes closed, resulting in the pressure in the infusion pipe exceeding the alarm setting range. Infusion extravasation occurs when the pipeline pressure increases beyond a certain threshold.[14] The osmotic pressure concentration of the isotonic solution is similar to that of blood. The concentration of solute in the venous solution can alter the osmotic pressure of the drug due to the mixture of drugs or diluents. When the osmotic pressure of a solution is too high or too low, cell death can occur, leading to transfusion exosmosis. When vasoactive drugs cause the contraction of small veins or arterioles, it reduces blood flow, leading to tissue necrosis and potentially causing infusion extravasation.[15]

Infection

Research has found that inflammatory mediators may play an important role in vascular endothelial injury by stimulating the body to produce relevant immune responses and to generate immune complexes that may damage the vascular wall.[16] During the occurrence and development of infections in children, endotoxins can be released by the activity of bacteria owing to the role of toxins and bacteria in their bodies. Inflammatory cells such as mast cells, white blood cells, and macrophages aggregate in the body and release inflammatory mediators. The permeability of vascular endothelial cells in children will also increase with the release of inflammatory mediators; When endothelial cells and platelets interact, endothelial cell damage, pathological changes in platelet activity can occur, and the vascular endothelial barrier is damaged, resulting in increased vascular permeability, tissue edema, and the

occurrence of infusion extravasation.[17–21]

The integrity of the vascular endothelial barrier is paramount for maintaining the balance of blood circulation and the proper functioning of various organs in the body. The sugar calyx, a crucial component of this barrier, exhibits a villous structure. It is a generic term for the polysaccharide-protein complexes that cover the lumen membranes of vascular endothelial cells. As a vascular endothelial barrier, the sugar calyx is pivotal in maintaining vascular system homeostasis, regulating vascular permeability and inflammatory reactions, transmitting mechanical shear forces, and inhibiting intravascular coagulation.[22,23] In physiological conditions, the sugar calyx forms a protective, spongy layer on the surface of endothelial cells. At the same time, plasma-soluble components fill the "pores" of the sugar calyx, contributing to the surface layer of endothelial cells. The skeletal structure of this surface layer is closely associated with vascular permeability and primarily regulates fluid balance inside and outside the blood vessel. Under physiological conditions, when blood pressure and blood volume increase, the sheer force of blood on the vascular wall stimulates vascular endothelial cells to release nitric oxide, resulting in microvascular relaxation. When a child is in a pathological state, and an infection triggers inflammation, the vascular endothelial glycocalyx is the earliest site invaded by inflammation, affecting blood vessels. In response to inflammation activation, inflammatory cells release enzymes and reactive substances, increasing plasma-free glycocalyx component heparan sulfate levels. This increase activates Toll-like receptor-4 on the surface of macrophages, releasing nuclear factors- κB pathway.

Consequently, proinflammatory cytokines such as nuclear factors and interleukin-6 are released, exacerbating endothelial glycocalyx damage and leading to a rapid loss of function.[23,24] When the sugar calyx is damaged, its layer becomes thinner, and its components are compromised. This damage is reflected in the elevated levels of important markers of sugar calyx degradation in circulating blood, such as free poly-ligand glycan-1 and heparan sulfate.[24–27] The consequences of sugar calyx damage include increased vascular permeability, vasodilation, abnormal coagulation function, microvascular thrombosis, and other pathological conditions. As inflammatory cells escape into the surrounding tissue, blood seeps into the gaps, leading to edema and hypotension, which further exacerbates tissue ischemia and hypoxia, ultimately increasing the risk of infusion extravasation.[28]

Self-factors of neonatal transfusion extravasation

Extravasation in infants is caused by various factors, including neonatal body function, skin condition, vascular condition, and sensitivity. Premature infants face additional challenges due to poor sucking ability, gastrointestinal intolerance, and disease susceptibility, making oral feeding difficult and rendering independent nutrient intake insufficient to meet their energy needs. Consequently, intravenous administration of nutrition becomes crucial for these neonatal patients. They often require 24-hour infusion of high osmotic nutritional solutions and medications, such as fat emulsion, amino acids, water-soluble vitamins, 50% glucose, 10% sodium chloride, 10% potassium chloride, dopamine, and dobutamine,[29–32] to address their illnesses and nutritional requirements. Neonatal skin exhibits distinct characteristics compared to children and adults, primarily due to differences in physiology and development. Their skin is delicate, with immature endothelial cell development in the vascular wall, making it less resistant to local stimulation.

Moreover, premature infants have thin blood vessels with reduced visibility, less subcutaneous tissue, and even more delicate and sparse skin.[33–34] Additionally, neonates have fetal fat distributed throughout their body, resulting in pale or bluish skin appearance with poor filling and orientation. This characteristic makes it easy for the puncture needle to dislodge after fixation, and shift during feeding or breastfeeding, increasing the risk of extravasation in neonates.[5,35]

External influencing factors of neonatal transfusion extravasation

In addition to its inherent factors, neonatal transfusion extravasation can also be influenced by external factors, including nurses, drugs, infusion tools, and administration sites.

Nurse factors and extravasation of intravenous fluids in neonates

Extravasation during neonatal infusion can be influenced by nurses' proficiency in using peripheral intravenous catheters, mastery of intravenous infusion knowledge, accumulated clinical experience, and psychological qualities. Lack of familiarity with new peripheral intravenous catheters, inadequate knowledge of drug properties and usage, improper vein selection when using special drugs, and a lack of assessment and handling methods for extravasation can all contribute to the risk of neonatal extravasation during puncture operations.[36] Due to their limited clinical experience, some clinical nurses may struggle to identify the direction of blood vessels during infusion, have uncertainties about local anatomical structures, and lack skills in controlling puncture depth, resulting in mechanical damage to blood vessels from repeated punctures.[37] This issue may also be influenced by factors such as a weak sense of responsibility, inadequate inspection of infusion sites, and insufficient inspection frequency.[38–40] In addition, the delicate and complex nature of neonatal ward work, coupled with environmental factors such as instrument alarms and infant crying, can significantly impact nurses' emotional stability and psychological qualities, potentially affecting the success rate of punctures leading to neonatal extravasation.[41,42]

Drug factors and extravasation of neonatal infusion

Pharmaceutical factors, such as osmotic pressure, vascular irritability, pH, drug cytotoxicity, and treatment-related factors, such as drug infusion rate, temperature, and duration, are all relevant factors influencing the extravasation of intravenous fluids in newborns. Common drugs that may cause extravasation in newborns include 50% glucose, lipid emulsions, dopamine, epinephrine, norepinephrine, amiodarone, and calcium gluconate. High osmotic pressure fluids like 50% glucose and lipid emulsions can lead to dehydration, tissue cell shrinkage, and necrosis due to their osmotic pressure, leading to sterile inflammation. Additionally, drugs can cause local platelet aggregation, thrombosis, and prostaglandin release, resulting in increased vascular permeability, infiltration of white blood cells into the venous intima, and release of large amounts of histamine, causing venous constriction and hardness and leading to venous injury in newborns.[43] Vasoactive drugs such as dopamine, adrenaline, and noradrenaline can cause peripheral blood vessel constriction and spasms, leading to tissue ischemia and hypoxia, increased permeability of the vessel wall, and infiltration of the drug into the tissue spaces, resulting in tissue damage and even necrosis after administration.[15,44,45] Amiodarone, an antiarrhythmic drug with a pH value

Table 1. External influencing factors of neonatal transfusion extravasation

Influence factor	Specific influencing factors
Nurse factors	Mastery of knowledge related to intravenous infusion; Clinical experience; Master anatomical structure; Proficient in using Peripheral Intravenous Catheter; Responsibility; Own emotions Psychological quality.
Drug factors	Drug osmotic pressure; Drug stimulation to blood vessels; Drug pH; Drug cytotoxicity; Speed, temperature, duration of drug infusion.
Infusion tools infusion sites	Peripheral Intravenous Catheter; Disposable infusion steel needle; Retention time of Peripheral Intravenous Catheter; Upper and lower limb infusion sites; Selection of puncture vein.

of 2.5–4.0, can stimulate the local blood vessels beyond their buffering capacity when continuously infused through a vein, leading to phlebitis and extravasation of the infusion.[6,7] Intravenous administration of calcium gluconate, often used to prevent neonatal metabolic bone disease, can stimulate blood vessels and surrounding tissues, causing inflammatory changes and deposition of calcium phosphate leading to tissue hardening and even necrosis.

Additionally, calcium supplements can cause lysosomal rupture, which releases hydrolytic enzymes, leading to autolysis, congestion, bleeding, and inflammation of the surrounding tissues.[46] Studies by Payen and others have shown that the infusion rate is also an essential factor in infusion extravasation.[47] It is important to avoid long-term repeated infusion of irritant liquids into the same area and to limit continuous infusion of irritant solutions to less than 2 hours.[48,49] Furthermore, maintaining an appropriate drug infusion temperature is vital, as excessively low temperatures can cause local blood to spasm, thus increasing vascular permeability and the risk of drug extravasation.[42,50] The recommended temperature for drug solutions is around 15°C.[42]

Selection of infusion tools and infusion sites and extravasation in neonatal infusion

Extravasation in neonatal infusion varies depending on the type of infusion tool and the site of infusion. Research has indicated that the rate of medication extravasation is lower with peripheral intravenous catheters than with disposable infusion steel needles.[51,52] The probability of drug extravasation with a disposable steel infusion needle is twice as high as that with a peripheral intravenous catheter. Peripheral intravenous catheters cause less irritation to blood vessels. They can remain in place for 3–4 days after a single puncture, reducing the need for repeated punctures, protecting the veins, and alleviating patient discomfort. However, some studies have shown that the longer a peripheral intravenous catheter remains in place, the higher the risk of intravenous medication extravasation.[53,54] Park *et al*. found that infants and young children have a higher incidence of extravasation in the lower limbs than in the upper limbs.[55,56] Moreover, important veins and their branches are more sensitive to irritating drugs, and the infusion of such drugs is more likely to cause venous inflammation and extravasation (Table 1).

Factors influencing diseases and extravasation of newborn infusion

Research indicates that certain neonatal diseases can lead to lesions in blood vessels or subcutaneous tissues, increasing the likelihood of extravasation of intravenous fluids. Common neonatal diseases prone to intravenous fluid extravasation include acute respiratory distress syndrome, meconium aspiration pneumonia, neonatal asphyxia, and pulmonary hypertension.

Acute respiratory distress syndrome and extravasation of intravenous fluids in neonates

When a newborn develops acute respiratory distress syndrome, an inflammatory response is triggered by a bacterial infection or trauma to the lungs. Early acute lung injury is caused by an uncontrolled inflammatory response, which, while helpful in clearing pathogenic microorganisms, can also damage epithelial cells and the endothelium, leading to increased permeability. After an alveolar injury, a systemic inflammatory response can occur when exogenous bacterial products or endogenous molecules produced by cell damage bind to receptors on epithelial cells and macrophages, activating the immune system and exacerbating the systemic inflammatory response. This results in increased levels of thrombin, tumor necrosis factor-alpha, vascular endothelial growth factor, and leukocyte-related signaling molecules. Neutrophil migration can disrupt cell-to-cell connections, leading to cell apoptosis and shedding, ultimately causing epithelial cell damage, increasing permeability, and a higher risk of fluid extravasation.[57–59]

Extravasation of fluids caused by aspiration pneumonia due to meconium aspiration syndrome (MAS)

Meconium aspiration syndrome (MAS) occurs when a newborn inhales meconium-stained amniotic fluid during labor and delivery. This inhalation causes airway blockage, mechanical obstruction, and chemical inflammation in the lungs and respiratory tract. Meconium, which contains substances such as bile acids, large stool particles, and bilirubin, is thick and can block narrow air passages in the lungs. Consequently, it leads to hypercapnia, hypoxemia, vasoconstriction, increased peripheral vascular resistance, and difficulty obtaining intravenous access.[60,61] Additionally, MAS may also lead to fluid extravasation during fluid administration.

Neonatal asphyxia and extravasation of neonatal infusions

Neonatal asphyxia is a condition caused by various prenatal, intrapartum, or postnatal factors resulting in newborns being born without breathing and unable to establish regular and effective autonomous respiration or respiratory suppression. The primary pathological and physiological characteristics of this condition include hypoxemia, hypercapnia, and acidosis. In the early stage of asphyxia, to ensure the blood supply to vital organs such as the brain, heart, and adrenal glands, the body redistributes blood, reducing the blood supply to the lungs, intestines, muscles, skin, and other nonessential organs, which is the classic "diving reflex".[62] After the diving reflex occurs, the body prioritizes blood supply to essential organs like the heart and brain. The constriction of blood vessels in non-essential organs causes changes in the body's hemodynamics, increasing peripheral vascular resistance and causing intense peripheral vasoconstriction. As a result, fluid extravasation may occur due to failed vascular puncture. Under normal circumstances, endothelial cells in blood vessels release various active substances, such as nitric oxide and prostaglandins, to regulate vasodilation and vasoconstric-

Table 2. Factors influencing diseases and extravasation of newborn infusion

Factors influencing diseases	Specific influencing factors
Acute respiratory distress syndrome	Inflammation; Destroy epithelial cells; Destroy vascular endothelium; Thrombin; Tumor necrosis factor-α; Leukocyte related signal molecule.
Meconium aspiration pneumonia	Inflammation; Hypercapnia; Hypoxemia; Vasoconstriction; Stenosis of vascular lumen; Increased peripheral vascular resistance.
Neonatal Asphyxia	Phreatic reflex; Changes in body hemodynamics; nitric oxide; prostaglandin; DIC; Thrombus haemorrhage.
Pulmonary arterial hypertension	Increased pulmonary vascular resistance; Hypoxemia; Endothelin-1; Leukotriene; Thromboxane; Increased vascular pressure, vasoconstriction.
Necrotizing enterocolitis	Toxin-activated immune cytokine; Changes in vascular permeability; tissue damage; Changes in microvascular internal environment; Blood platelet; Leukocyte.
Epidermolysis bullosa	Skin structural protein defect; Skin and mucous membrane lysis.

DIC, disseminated intravascular coagulation.

tion. However, when neonatal hypoxia-ischemia occurs, these active substances decrease, exacerbating vasoconstriction. Simultaneously, endothelial cells in the blood vessels release tissue factors, platelet activation factors, and other substances that damage the endothelium and activate the coagulation system, leading to disseminated intravascular coagulation.[63] In a state of high coagulation or hemolysis, blood clots or bleeding may occur at the puncture site, which is also one of the reasons for fluid extravasation.

Pulmonary arterial hypertension and extravasation of fluids in neonates

Pulmonary arterial hypertension in newborns arises from various factors that obstruct the neonatal circulatory system, leading to heightened pulmonary vascular resistance and severe hypoxemia.[64] Failure to achieve a normal cardiopulmonary transition after birth can result in an upsurge of vasoconstrictive substances, such as endothelin-1, leukotrienes, and thromboxane, circulating in the body. This, in turn, causes peripheral vasoconstriction and sustained elevation of vascular pressure. As a result, the success rate of a single puncture is low, and the risk of extravasation during fluid infusion increases.

Other diseases in newborns and extravasation of intravenous fluids in newborns

Necrotizing enterocolitis and epidermolysis bullosa are two factors that can affect fluid extravasation in newborns. In cases where necrotizing enterocolitis in newborns is complicated by sepsis, the toxins produced by microorganisms can cause changes in vascular permeability and tissue damage by activating immune cells to produce cytokines.[65] This, in turn, can lead to the aggregation of platelets and white blood cells in microvessels, ultimately affecting fluid extravasation in newborns. Epidermolysis bullosa is characterized by skin and mucosal detachment caused by congenital deficiencies in the structural proteins of the skin.[66] Even minor friction can cause blistering and separation of the epidermis and dermis. Children with this condition have fragile skin, making them susceptible to skin damage from external forces, such as punctures or fixation, which can result in fluid extravasation in newborns (Table 2).

Future directions

In the future, our research should focus on understanding the unique needs and responses of neonatal patients to intravenous therapy. This could involve investigating pain perception in neonates, assessing their ability to communicate discomfort nonverbally, and finding ways to improve their overall comfort during treatment. The potential of new medical devices, such as smart catheters or wearable sensors, needs to be explored, which can continuously monitor the intravenous sites and provide real-time feedback to healthcare providers when signs of extravasation are detected. Moreover, comparative studies of different intravenous devices, catheters, and materials to assess their risk of extravasation in neonates should be conducted. This could aid in developing evidence-based guidelines for the selection of the most appropriate devices for neonatal intravenous therapy.

Conclusion

The incidence of intravenous infusion extravasation in newborns is high. This occurrence not only increases the patient's pain but also leads to medical disputes and higher medical costs. Therefore, a comprehensive study of factors related to extravasation in newborns can help propose appropriate prevention measures. Furthermore, the long-term consequences of extravasation in neonatal patients, including potential effects on neurodevelopmental outcomes, growth, and quality of life should be investigated. Doing so might reduce the incidence of extravasation and adverse nursing events, achieve precise nursing, and ultimately satisfy patients, families, doctors, and nurses.

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Conflict of interest

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Author contributions

Wrote the manuscript (FH), contributed to study design (ZPH), ac-

quisition of the data (FZL and JPH), critical revision of the manuscript (ZPH and LXH), and supervision (JJW and QL). All authors read and approved the final version of the manuscript.

Reference

[1] Kostogloudis N, Demiri E, Tsimponis A, Dionyssiou D, Ioannidis S, Chatziioannidis I, *et al*. Severe Extravasation Injuries in Neonates: A Report of 34 Cases. Pediatr Dermatol 2015;32(6):830–835. doi:10.1111/pde.12664, PMID:26337780.

[2] Bosque EM. Development of an alarm algorithm, with nanotechnology multimodal sensor, to predict impending infusion failure and improve safety of peripheral intravenous catheters in Neonates. Adv Neonatal Care 2020;20(3):233–243. doi:10.1097/ANC.0000000000000690, PMID:31815770.

[3] van Rens MFPT, Hugill K, Mahmah MA, Bayoumi M, Francia ALV, Garcia KLP, *et al*. Evaluation of unmodifiable and potentially modifiable factors affecting peripheral intravenous device-related complications in neonates: a retrospective observational study. BMJ Open 2021;11(9):e047788. doi:10.1136/bmjopen-2020-047788, PMID:34497079.

[4] García HJ, Torres-Yáñez HL. Survival and complication rate of central venous catheters in newborns. Rev Med Inst Mex Seguro Soc 2015;53(Suppl 3):S300–S309. PMID:26509306.

[5] van Rens M, Hugill K, Francia AL, Abdelwahab AH, Garcia KL. Treatment of a neonatal peripheral intravenous infiltration/extravasation (PIVIE) injury with hyaluronidase: a case report. Br J Nurs 2022;31(8):S31–S36. doi:10.12968/bjon.2022.31.8.S31, PMID:35439074.

[6] Liu L, Mai Y, Liang Y, Zhou X, Chen K. Experimental study on the effect of chrysin on skin injury induced by amiodarone extravasation in rats. Microvasc Res 2022;139:104257. doi:10.1016/j.mvr.2021.104257, PMID:34534572.

[7] Ledingham D, Cordato D. Focal myositis and contracture secondary to amiodarone extravasation from a peripheral cannula. BMJ Case Rep 2019;12(1):bcr-2018-227725. doi:10.1136/bcr-2018-227725, PMID:30661048.

[8] Stolz A, Efendy R, Apte Y, Craswell A, Lin F, Ramanan M. Safety and efficacy of peripheral versus centrally administered vasopressor infusion: A single-centre retrospective observational study. Aust Crit Care 2022;35(5):506–511. doi:10.1016/j.aucc.2021.08.005, PMID:34600834.

[9] Uslusoy E, Mete S. Predisposing factors to phlebitis in patients with peripheral intravenous catheters: a descriptive study. J Am Acad Nurse Pract 2008;20(4):172–180. doi:10.1111/j.1745-7599.2008.00305.x, PMID:18387013.

[10] de Lima Jacinto AK, Avelar AF, Pedreira ML. Predisposing factors for infiltration in children submitted to peripheral venous catheterization. J Infus Nurs 2011;34(6):391–398. doi:10.1097/NAN.0b013e3182306491, PMID:22101633.

[11] El-Nawawy A, Moustafa AA, Antonios MAM, Atta MM. Clinical outcomes associated with fluid overload in critically Ill pediatric patients. J Trop Pediatr 2020;66(2):152–162. doi:10.1093/tropej/fmz045, PMID:31280298.

[12] Leow EH, Wong JJ, Mok YH, Hornik CP, Ng YH, Lee JH. Fluid overload in children with pediatric acute respiratory distress syndrome: A retrospective cohort study. Pediatr Pulmonol 2022;57(1):300–307. doi:10.1002/ppul.25720, PMID:34633156.

[13] Kvistedal YA, Nielsen PM. Estimating material parameters of human skin in vivo. Biomech Model Mechanobiol 2009;8(1):1–8. doi:10.1007/s10237-007-0112-z, PMID:18040732.

[14] Gibson LE, Knudsen AS, Arney D, Deng H, Sims NM, Peterfreund RA. Lag times to steady state drug delivery by continuous intravenous infusion: direct comparison of peristaltic and syringe pump performance identifies contributions from infusion system dead volume and pump startup characteristics. J Clin Monit Comput 2022;36(5):1489–1498. doi:10.1007/s10877-021-00790-1, PMID:34878612.

[15] Marques CG, Mwemerashyaka L, Martin K, Tang O, Uwamahoro C, Ndebwanimana V, *et al*. Utilisation of peripheral vasopressor medications and extravasation events among critically ill patients in Rwanda: A prospective cohort study. Afr J Emerg Med 2022;12(2):154–159. doi:10.1016/j.afjem.2022.03.006, PMID:35505668.

[16] Spiel AO, Mayr FB, Leitner JM, Firbas C, Sieghart W, Jilma B. Simvastatin and rosuvastatin mobilize Endothelial Progenitor Cells but do not prevent their acute decrease during systemic inflammation. Thromb Res 2008;123(1):108–113. doi:10.1016/j.thromres.2008.03.007, PMID:18433844.

[17] Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med 2015;372(17):1629–1638. doi:10.1056/NEJMoa1415236, PMID:25776936.

[18] Sakr Y, Moreira CL, Rhodes A, Ferguson ND, Kleinpell R, Pickkers P, *et al*. The impact of hospital and ICU organizational factors on outcome in critically ill patients: results from the Extended Prevalence of Infection in Intensive Care study. Crit Care Med 2015;43(3):519–526. doi:10.1097/CCM.0000000000000754, PMID:25479111.

[19] Gao M, Yu T, Liu D, Shi Y, Yang P, Zhang J, *et al*. Sepsis plasma-derived exosomal miR-1-3p induces endothelial cell dysfunction by targeting SERP1. Clin Sci (Lond) 2021;135(2):347–365. doi:10.1042/CS20200573, PMID:33416075.

[20] Halbertsma FJ, Vaneker M, Pickkers P, Neeleman C, Scheffer GJ, Hoeven van der JG. A single recruitment maneuver in ventilated critically ill children can translocate pulmonary cytokines into the circulation. J Crit Care 2010;25(1):10–15. doi:10.1016/j.jcrc.2009.01.006, PMID:19327947.

[21] Xia X, Zhang L, Chi J, Li H, Liu X, Hu T, *et al*. Helicobacter pylori Infection Impairs Endothelial Function Through an Exosome-Mediated Mechanism. J Am Heart Assoc 2020;9(6):e014120. doi:10.1161/JAHA.119.014120, PMID:32174233.

[22] Milusev A, Despont A, Shaw J, Rieben R, Sorvillo N. Inflammatory stimuli induce shedding of heparan sulfate from arterial but not venous porcine endothelial cells leading to differential proinflammatory and procoagulant responses. Sci Rep 2023;13(1):4483. doi:10.1038/s41598-023-31396-z, PMID:36934164.

[23] Dolmatova EV, Wang K, Mandavilli R, Griendling KK. The effects of sepsis on endothelium and clinical implications. Cardiovasc Res 2021;117(1):60–73. doi:10.1093/cvr/cvaa070, PMID:32215570.

[24] Ostrowski SR, Gaïni S, Pedersen C, Johansson PI. Sympathoadrenal activation and endothelial damage in patients with varying degrees of acute infectious disease: an observational study. J Crit Care 2015;30(1):90–96. doi:10.1016/j.jcrc.2014.10.006, PMID:25457118.

[25] Wu F, Peng Z, Park PW, Kozar RA. Loss of Syndecan-1 Abrogates the Pulmonary Protective Phenotype Induced by Plasma After Hemorrhagic Shock. Shock 2017;48(3):340–345. doi:10.1097/SHK.0000000000000832, PMID:28107214.

[26] Nikmanesh M, Cancel LM, Shi ZD, Tarbell JM. Heparan sulfate proteoglycan, integrin, and syndecan-4 are mechanosensors mediating cyclic strain-modulated endothelial gene expression in mouse embryonic stem cell-derived endothelial cells. Biotechnol Bioeng 2019;116(10):2730–2741. doi:10.1002/bit.27104, PMID:31282995.

[27] Yuan L, Cheng S, Sol WMPJ, van der Velden AIM, Vink H, Rabelink TJ, *et al*. Heparan sulfate mimetic fucoidan restores the endothelial glycocalyx and protects against dysfunction induced by serum of COVID-19 patients in the intensive care unit. ERJ Open Res 2022;8(2):00652–2021. doi:10.1183/23120541.00652-2021, PMID:35509442.

[28] Brewster LM, Garcia VP, Levy MV, Stockelman KA, Goulding A, DeSouza NM, *et al*. Endothelin-1-induced endothelial microvesicles impair endothelial cell function. J Appl Physiol (1985) 2020;128(6):1497–1505. doi:10.1152/japplphysiol.00816.2019, PMID:32324474.

[29] Patregnani JT, Sochet AA, Klugman D. Short-term peripheral vasoactive infusions in pediatrics: where is the Harm? Pediatr Crit Care Med 2017;18(8):e378–e381. doi:10.1097/PCC.0000000000001230, PMID:28617763.

[30] Lu YX, Wu Y, Liang PF, Wu RC, Tian LY, Mo HY. Efficacy of combination of localized closure, ethacridine lactate dressing, and phototherapy in treatment of severe extravasation injuries: A case series. World J Clin Cases 2021;9(18):4599–4606. doi:10.12998/wjcc.v9.i18.4599, PMID:34222426.

[31] Correani A, Giretti I, Antognoli L, Monachesi C, Cogo P, D'Ascenzo R, *et al*. Hypertriglyceridemia and Intravenous Lipid Titration During Routine Parenteral Nutrition in Small Preterm Infants. J Pediatr Gastroenterol Nutr 2019;69(5):619–625. doi:10.1097/MPG.0000000000002459, PMID:31436699.

[32] Meneghin F, Manzalini M, Acunzo M, Daniele I, Bastrenta P, Castoldi F, *et*

al. Management of asymptomatic hypoglycemia with 40% oral dextrose gel in near term at-risk infants to reduce intensive care need and promote breastfeeding. Ital J Pediatr 2021;47(1):201. doi:10.1186/s13052-021-01149-7, PMID:34627324.
[33] Dunk AM, Carville K. The international clinical practice guideline for prevention and treatment of pressure ulcers/injuries. J Adv Nurs 2016;72(2):243–244. doi:10.1111/jan.12614, PMID:25558893.
[34] Vance DA, Demel S, Kirksey K, Moynihan M, Hollis K. A Delphi study for the development of an infant skin breakdown risk assessment tool. Adv Neonatal Care 2015;15(2):150–157. doi:10.1097/ANC.0000000000000104, PMID:25000102.
[35] Danski MT, Mingorance P, Johann DA, Vayego SA, Lind J. Incidence of local complications and risk factors associated with peripheral intravenous catheter in neonates. Rev Esc Enferm USP 2016;50(1):22–28. doi:10.1590/S0080-623420160000100003, PMID:27007416.
[36] Liu C, Chen L, Kong D, Lyu F, Luan L, Yang L. Incidence, risk factors and medical cost of peripheral intravenous catheter-related complications in hospitalised adult patients. J Vasc Access 2022;23(1):57–66. doi:10.1177/1129729820978124, PMID:33302797.
[37] Taşdelen Y, Çağlar S. Effect of intravenous infiltration management program on peripheral intravenous catheter success and infiltration in hospitalized infants. J Nurs Care Qual 2021;36(3):E44–E49. doi:10.1097/NCQ.0000000000000511, PMID:32826695.
[38] Lee SU, Jung JY, Ham EM, Wang SW, Park JW, Hwang S, *et al*. Factors associated with difficult intravenous access in the pediatric emergency department. J Vasc Access 2020;21(2):180–185. doi:10.1177/1129729819865709, PMID:31379251.
[39] Lv DN, Xu HZ, Zheng LL, Chen LL, Ling Y, Ye AQ. Extravasation of chemotherapeutic drug from an implantable intravenous infusion port in a child: A case report. World J Clin Cases 2021;9(26):7840–7844. doi:10.12998/wjcc.v9.i26.7840, PMID:34621835.
[40] Boyar V, Galiczewski C. Reducing peripheral intravenous catheter extravasation in neonates: a quality improvement project. J Wound Ostomy Continence Nurs 2021;48(1):31–38. doi:10.1097/WON.0000000000000728, PMID:33427807.
[41] Karaoğlan N, Sarı HY, Devrim İ. Complications of peripheral intravenous catheters and risk factors for infiltration and phlebitis in children. Br J Nurs 2022;31(8):S14–S23. doi:10.12968/bjon.2022.31.8.S14, PMID:35439080.
[42] Chan KM, Chau JPC, Choi KC, Fung GPG, Lui WW, Chan MSY, *et al*. Clinical practice guideline on the prevention and management of neonatal extravasation injury: a before-and-after study design. BMC Pediatr 2020;20(1):445. doi:10.1186/s12887-020-02346-9, PMID:32967637.
[43] Zdolsek JH, Bergek C, Lindahl TL, Hahn RG. Colloid osmotic pressure and extravasation of plasma proteins following infusion of Ringer's acetate and hydroxyethyl starch 130/0.4. Acta Anaesthesiol Scand 2015;59(10):1303–1310. doi:10.1111/aas.12558, PMID:26079310.
[44] Milcheski DA, Mota WM, Lobato RC, Monteiro Júnior AA, Gemperli R. Surgical treatment of extravasation injuries: experience of the Hospital das Clínicas, Faculty of Medicine, University of São Paulo. Rev Col Bras Cir 2018;45(4):e1912. doi:10.1590/0100-6991e-20181912, PMID:30141825.
[45] Cardenas-Garcia J, Schaub KF, Belchikov YG, Narasimhan M, Koenig SJ, Mayo PH. Safety of peripheral intravenous administration of vasoactive medication. J Hosp Med 2015;10(9):581–585. doi:10.1002/jhm.2394, PMID:26014852.
[46] Girard P, Plancq MC, Tourneux P, Deroussen F, Gouron R, Klein C. Extravasation of calcium solution in the child: Value of negative-pressure wound therapy. Arch Pediatr 2019;26(7):407–410. doi:10.1016/j.arcped.2019.09.011, PMID:31630900.
[47] Payen JF, Vuillez JP, Geoffray B, Lafond JL, Comet M, Stieglitz P, *et al*. Effects of preoperative intentional hemodilution on the extravasation rate of albumin and fluid. Crit Care Med 1997;25(2):243–248. doi:10.1097/00003246-199702000-00008, PMID:9034258.
[48] Pohl CE, Harvey H, Foley J, Lee E, Xu R, O'Brien NF, *et al*. Peripheral IV administration of hypertonic saline: single-center retrospective PICU study. Pediatr Crit Care Med 2022;23(4):277–285. doi:10.1097/PCC.0000000000002903, PMID:35180199.
[49] Hoff R, Vervisch K, De Coen K, Smets K. Continuous infusion vs. intermittent flushing of peripheral cannulas in neonates using a needleless connector: a prospective cohort study. J Perinat Med 2019;47(4):464–469. doi:10.1515/jpm-2018-0285, PMID:30730844.
[50] Shen J, Wang Q, Zhang Y, Wang X, Shi P. Combination of warming blanket and prewarmed intravenous infusion is effective for rewarming in infants with postoperative hypothermia in China. Paediatr Anaesth 2015;25(11):1139–1143. doi:10.1111/pan.12733, PMID:26265109.
[51] Park SM, Jeong IS, Kim KL, Park KJ, Jung MJ, Jun SS. The effect of intravenous infiltration management program for hospitalized children. J Pediatr Nurs 2016;31(2):172–178. doi:10.1016/j.pedn.2015.10.013, PMID:26608556.
[52] Jeong IS, Park SM, Park KJ. Effect of observation window at peripheral intravenous catheter site on early recognition of infiltration among hospitalized children. J Korean Acad Nurs 2016;46(4):534–541. doi:10.4040/jkan.2016.46.4.534, PMID:27615043.
[53] Guo JL, Yan XY, Zhao QL, Gao CN, Wei CH, Wei Z, *et al*. Time to occurrence of phlebitis after continuous infusion of total nutrient admixture through peripheral veins: an experimental animal study. J Inflamm Res 2022;15:205–215. doi:10.2147/JIR.S346186, PMID:35046695.
[54] Monasor-Ortolá D, Cortés-Castell E, Martínez-Pascual C, Esteve-Ríos A, Rizo-Baeza MM. Factors influencing the success of peripheral venous access in neonates. J Pediatr Nurs 2019;47:e30–e35. doi:10.1016/j.pedn.2019.04.017, PMID:31031059.
[55] Park SM, Jeong IS, Jun SS. Identification of risk factors for intravenous infiltration among hospitalized children: a retrospective study. PLoS One 2016;11(6):e0158045. doi:10.1371/journal.pone.0158045, PMID:27351488.
[56] Odom B, Lowe L, Yates C. Peripheral infiltration and extravasation injury methodology: a retrospective study. J Infus Nurs 2018;41(4):247–252. doi:10.1097/NAN.0000000000000287, PMID:29958261.
[57] Ginzberg HH, Shannon PT, Suzuki T, Hong O, Vachon E, Moraes T, *et al*. Leukocyte elastase induces epithelial apoptosis: role of mitochondial permeability changes and Akt. Am J Physiol Gastrointest Liver Physiol 2004;287(1):G286–G298. doi:10.1152/ajpgi.00350.2003, PMID:15194561.
[58] Imai Y, Kuba K, Neely GG, Yaghubian-Malhami R, Perkmann T, van Loo G, *et al*. Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. Cell 2008;133(2):235–249. doi:10.1016/j.cell.2008.02.043, PMID:18423196.
[59] Park J, Pabon M, Choi AMK, Siempos II, Fredenburgh LE, Baron RM, *et al*. Plasma surfactant protein-D as a diagnostic biomarker for acute respiratory distress syndrome: validation in US and Korean cohorts. BMC Pulm Med 2017;17(1):204. doi:10.1186/s12890-017-0532-1, PMID:29246207.
[60] Ding S, Xu Y, Wang H, Yue H, Pan Z, Sun B, *et al*. Outcome of neonatal hypoxemic respiratory failure: a livebirth population-based retrospective survey. BMC Pediatr 2022;22(1):552. doi:10.1186/s12887-022-03603-9, PMID:36115974.
[61] Haliti A, Mustafa L, Bexheti S, Islami D, Bozalija A, Shabani R, *et al*. In vitro action of meconium on bronochomotor tonus of newborns with meconium aspiration syndrome. Open Access Maced J Med Sci 2018;6(6):992–996. doi:10.3889/oamjms.2018.244, PMID:29983790.
[62] Aridas JD, McDonald CA, Paton MC, Yawno T, Sutherland AE, Nitsos I, *et al*. Cord blood mononuclear cells prevent neuronal apoptosis in response to perinatal asphyxia in the newborn lamb. J Physiol 2016;594(5):1421–1435. doi:10.1113/JP271104, PMID:26527561.
[63] Sweetman DU, Onwuneme C, Watson WR, Murphy JF, Molloy EJ. Perinatal asphyxia and erythropoietin and vegf: serial serum and cerebrospinal fluid responses. Neonatology 2017;111(3):253–259. doi:10.1159/000448702, PMID:27902983.
[64] Menon RT, Shrestha AK, Reynolds CL, Barrios R, Shivanna B. Long-term pulmonary and cardiovascular morbidities of neonatal hyperoxia exposure in mice. Int J Biochem Cell Biol 2018;94:119–124. doi:10.1016/j.biocel.2017.12.001, PMID:29223466.
[65] Ducey J, Owen A, Coombs R, Cohen M. Vasculitis as part of the fetal response to acute chorioamnionitis likely plays a role in the development of necrotizing enterocolitis and spontaneous intestinal perforation in premature neonates. Eur J Pediatr Surg 2015;25(3):284–291. doi:10.1055/s-0034-1373849, PMID:24819242.
[66] Filoni A, Bonamonte D, Cicco G, Panza R, Bisceglie V, Laforgia N. Nutritional impairment of neonates with epidermolysis bullosa: a retrospective study. Ital J Dermatol Venerol 2022;157(4):330–334. doi:10.23736/S2784-8671.22.07259-0, PMID:35389041.