The Art and Science of Infusion Nursing

ABSTRACT
This study presents a systematic review for evaluating effective pharmacological actions for the treatment of phlebitis stemming from infusion therapy. The studies reviewed were categorized according to the type of therapeutic approach proposed by the author and by the level of evidence presented. The review found that topical nitroglycerin and notoginsen were more effective in the reduction of the inflammatory process when compared with other proposed alternatives. Nevertheless, the development of research related to possible alternatives for the treatment of phlebitis is important.

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Phlebitis is defined as an inflammatory process of the vascular endothelial wall, called the tunica intima. It is characterized by local redness and heat, edema, and the formation of fibrous cords that are palpable along the venous passageway. In terms of origin, it can be classified as mechanical, chemical, bacterial, or postinfusional and can present variable and progressive degrees of intensity.

Considered an intravenous therapy complication, phlebitis is common in hospitalized patients. Various studies report phlebitis incidence between 20% and 80% in patients who are receiving peripheral intravenous therapy. If it is not treated early, it can prolong hospital stays.

The pathophysiology of phlebitis involves a classic inflammatory process that develops rapidly. The inflammatory process is initiated upon the sensitization of the vascular endothelium, due to friction caused by the vascular apparatus against the vascular endothelium, hyperosmolarity of the administered solution, or bacterial toxins. This leads to the release of serotonin, bradykinin, and histamine, which are inflammatory agents that can cause vasodilation, thus increasing vascular permeability and promoting extravasation of proteins and blood plasma toward the interstitial space, which will characterize the edema. Along with the increase in platelet aggregation stimulated by histamine, there is a thrombotic formation along the vein wall that extends all the way to the lumen of the vascular apparatus, characterized by localized erythema and a palpable vascular cord of up to 3.5 cm. Leukocytes begin to migrate to the site where the inflammation has taken hold, augmenting the local edema. The vascular cord, which was palpable earlier, now becomes visible (7.5-15 cm), and localized heat becomes perceptible upon palpation. Exudates can be present at the site of the vein puncture. Pyrogens, resulting from leukocytic apoptosis, now stimulate the hypothalamus to increase the body temperature. In this phase, phlebitis is characterized by a vascular strain that is palpable to
the extent of more than 15 cm along the vascular passage, is enriched, thick, and sensitive, and shows classic signs of inflammation: pain, heat, erythema, and edema.4,9

PURPOSE AND PROBLEM

Regardless of the type of phlebitis involved, some complications are always prevalent, such as the formation of the palpable vascular strain that may result in vascular sclerosis, which is frequently irreversible. This prevents the vessel where the phlebitis occurred from being used again for infusion or taking simple lab specimens.

There are countless studies in the scientific literature of nursing, both domestic and foreign, that point to the main risk factors for the occurrence of phlebitis and propose guidelines for its prevention.4,10,11

Nursing entails not only professional competence for the prevention and diagnosis of phlebitis but also knowledge of possible therapeutic forms for adequate actions that will prevent phlebitis from evolving toward irreversible complications. The purpose of this review is to identify evidence in scientific literature relating to the effectiveness of pharmacological actions for the treatment of phlebitis stemming from infusion therapy.

RESEARCH DESIGN AND METHODOLOGY

Search Strategy

The literature search strategy involved a systematic review based on the question “What are the actions used for the treatment of phlebitis?” A publications search was performed in the following indexed databases: Cochrane Library, MEDLINE, EMBASE, and CINAHL. Keywords included phlebitis, treatment, saline solution, heparin solution, heparinoid substances, nitroglycerin, glyceryl trinitrate, cold compress, warm compress, and notoginseny. Pertinent keywords were also searched in Portuguese and Spanish in the BDENF and LILACS databases. An inverse search was also done through a referenced bibliography included in the found documents.

The following cross-searches were also performed, using the keywords phlebitis and treatment, phlebitis and saline solution, phlebitis and heparin solution, phlebitis and heparinoid substances, phlebitis and nitroglycerin, phlebitis and cold compress, phlebitis and warm compress, and phlebitis and notoginseny.

Selection Criteria

Selection criteria included human studies that touched on some pharmacological or nonpharmacological therapeutic action for phlebitis stemming from peripheral intravenous therapy. There were no restrictions as to the design of the study or the language.

Data Collection and Analysis

Data were collected in November 2007. The documents were located by means of bibliographic subject search, online access to available subject groupings, particular subject groupings of researchers in the area, and contact with the authors of publications through e-mail.

The studies were analyzed critically in their entirety. To systematize the procedure and guarantee adequate qualitative analysis of studies, a data collection instrument, based on a guide12 for the analysis of studies relating to therapy and prevention, was created. Data referring to a particular periodical, author, and study were assessed.

The first and second authors of this review read the selected studies, each filling out a data collection instrument. Then the authors compared the instruments in order to validate the procedure and to verify the concordance index. Any discrepancies were resolved by means of discussion between the authors.

The study was categorized according to the type of therapeutic action proposed by the author and by the level of evidence, according to Melnyk and Fineout-Overholt13:

- **Level 1**: systematic reviews or meta-analysis of all relevant randomized controlled trials
- **Level 2**: evidence derived from at least 1 clearly outlined randomized controlled trial
- **Level 3**: well-outlined controlled trial without randomization
- **Level 4**: cohort studies or well-outlined case-control
- **Level 5**: systematic review of descriptive and qualitative studies
- **Level 6**: evidence derived from a single descriptive or qualitative study
- **Level 7**: opinion of authorities or reports from committees of specialists

Studies repeated in 1 or more databases were considered only once.

The authors identified 77 studies, of which 72 did not comply with the established criteria of inclusion, since they reported prophylactic interventions to avoid phlebitis occurrence or they referred to the peripheral phlebitis of lower limbs without relation to intravenous therapy. The remaining 5 studies dealt with the topical pharmacological treatment of phlebitis cases tied to peripheral intravenous therapy. As for the methodological design used in the studies, the majority (80%) were randomized controlled trials, while 20% were quasi-experimental.

RESULTS

Various therapeutic methods were used, depending on whether there were any indications of products with
different pharmaceutical forms (Table 1). Therapeutic methods included nitroglycerin (NTG) in the form of transdermal patch and gel; creams containing heparin or polysulfate of mucopolysaccharide, also known as heparinoid substances (ie, Hirudoid®, Sankyo Pharma GmbH, Pfaffenhofen, Germany); pyroxicam in gel form; notoginseny cream; and diclofenac in gel and oral form.14–18

The size of the sample involved in the randomized controlled trials (n = 4) varied between 22 and 100 patients. The studies compared the therapeutic effectiveness deriving from the use of a 5-mg glycercyl trinitrate patch with cream of heparin, glycercyl trinitrate in gel form with heparinoid substances (Hirudoid®), pyroxicam in gel form with polysulfate of mucopolysaccharide (Hirudoid®), and a nonsteroidal anti-inflammatory drug diclofenac sodium in gel form (Solarze®, SkyPharma, London, England) or oral form.14–17 Solarze® received FDA approval in 2000 for the treatment of actinic keratosis.

In the quasi-experimental approach (n = 1), notoginseny cream, a topical Chinese medicine developed and produced by the pharmacological department of the Second Affiliated Hospital of Sun Yat-sen University, was compared with polysulfate of mucopolysaccharide (Hirudoid®), using 65 patients.18

Regarding the level of evidence13 found in publications, 80% were classified as level 214–17 and 20% were classified as level 3.18 No description with a therapeutic purpose was found for the saline solution, although it was used in a preventive context. There was no study by any Brazilian authority that dealt with interventions for the treatment of phlebitis.

Notoginseny proved to be more effective than polysulfate of mucopolysaccharide (Hirudoid®) for the treatment of chemical phlebitis deriving from the peripheral intravenous administration of antibiotics, amino acids, and lipidic emulsions. The study compared both treatments, taking variables such as the cure of phlebitis and the timeframe for the regression of signs and symptoms into consideration. Notoginseny cream was as effective as Hirudoid® for the treatment of chemical phlebitis cases deriving from chemotherapy infusion.18

A Spanish study, in a randomized controlled trial involving 22 patients, compared the effectiveness of a transdermal patch of NTG in a dose of 5 mg (Transiderm Nitro®, Ciba Laboratories, Horsham, England) with the effectiveness of heparinoid cream for the treatment of postinfusion phlebitis. NTG proved to be superior to heparinoid cream in 100% of the phlebitis cases. However, the size of the sample did not permit any statistical tests.15

A double-blind, randomized controlled trial of 100 patients with infusional phlebitis compared NTG in gel form to heparinoid substances. NTG proved superior in terms of pain regression time in hours (NTG: 50.2 ± 39.7, heparinoids: 72.0 ± 39.9); regression time of erythema by one-half (NTG: 28.0 ± 24.2, heparinoids: 54.6 ± 34.5); and time of reduction of palpable venous strand by one-half (NTG: 58.3 ± 38.4, heparinoids: 84.5 ± 41.5). The edema regression time was also shortened with NTG, although that difference is not statistically significant (NTG: 31.2 ± 20.3, heparinoids: 33.0 ± 25.7). The authors concluded that using NTG in gel form, which is absorbed faster, is more effective than using the heparinoid substances.16

No statistically significant difference was found between the 2 groups when a comparison was made between the use of heparinoid substances and topical inflammatory substances in the form of gel. Both treatments were effective.16

In a randomized controlled trial, using 120 patients divided into G-control (n = 40), without treatment; G-topical (n = 40), with the application of diclofenac in the form of gel, every 8 hours for a span of 48 hours; and G-oral (n = 40), use of diclofenac, 75 mg, orally, every 12 hours, for a span of 48 hours, the following variables were observed: pain, edema, and erythema. The first assessment occurred at the diagnostic moment and the second assessment occurred 48 hours later. Comparing groups with regard to the reduction of the signs and symptoms of phlebitis after 48 hours, the G-topical and G-oral groups revealed 60% of phlebitis reduction, versus 20% in the G-control. However, the group that received the oral diclofenac displayed diverse collateral effects not found in the group that received the topical form. Collateral effects included headache (P = .2), epigastric pain (P = .0009), nausea (P = .01), and local pruritis (P = .2).17

**DISCUSSION**

In some studies, topical anti-inflammatories were recommended as a simple, safe, and effective alternative for the treatment of phlebitis cases deriving from infusional therapy in comparison with systemic anti-inflammatories. This is due to the collateral effects systemic anti-inflammatories produce, such as headache, epigastric pain, nausea, and local pruritis.14 When compared with polysulfate of mucopolysaccharide, a medication that is generally used as a control for clinical studies on the treatment of phlebitis, the topical anti-inflammatories were found to be as effective.17

The heparinoid substances, such as polysulfate of mucopolysaccharide, present specific pharmacological properties for percutaneous application and are ultimately intended to reduce the localized inflammation. Polysulfate of mucopolysaccharide has an anticoagulant action in working on thromboplastin and thrombin, inhibiting or delaying the formation of thrombi and their subsequent growth. On the other hand, upon activating plasmin and plasminogen, polysulfate of mucopolysaccharide stimulates fibrinolysis.
### TABLE 1

Distribution of Scientific Studies According to Methodological Detail, Intervention, Result Attained, Conclusion, and Recommendation

<table>
<thead>
<tr>
<th>Article Selected</th>
<th>Methodological Detail</th>
<th>Intervention</th>
<th>Result</th>
<th>Conclusion/Recommendation</th>
</tr>
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<tbody>
<tr>
<td>Berqvist et al16</td>
<td>RCT. n = 88 patients, divided into 2 groups: A and B.</td>
<td>Group A received Hirudoid® daily, Group B received pyroxicam in gel form daily, at the site of phlebitis.</td>
<td>Variables were degree of phlebitis, area of phlebitis, and intensity of pain. There was no statistically significant difference when the groups were compared.</td>
<td>Both treatments proved to be effective in terms of reduction of signs and symptoms of phlebitis.</td>
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<tr>
<td>Almenar et al15</td>
<td>RCT. n = 100 patients, divided into 2 groups: A = 50 patients and B = 50 patients.</td>
<td>Group A received 2 cm of NTG in gel form, on phlebitis, once a day. Group B received heparinoid substances 3 times a day.</td>
<td>Variables were time of regression of pain, of erythema, edema, and fibrous cord. NTG was significantly superior to the heparinoid for erythema, pain, and fibrous cord. There was no difference for edema.</td>
<td>Adopt NTG as the treatment of first choice in superficial phlebitis cases to the detriment of the heparinoids.</td>
</tr>
<tr>
<td>Becheruci et al17</td>
<td>RCT. n = 120 patients, divided into 3 groups: G-control = 40 patients, G-topical = 40 patients, and G-oral = 40 patients.</td>
<td>G-control did not receive any treatment. G-topical = diclofenac in gel form, every 8 h for a span of 48 h. G-oral = diclofenac 75 mg, oral, every 12 h, for a period of 48 h.</td>
<td>The following were evaluated: pain, edema, and erythema. Response to treatment was considered to be a reduction of phlebitis by at least 30%. Both G-topical and G-oral attained a phlebitis reduction score of 60%, versus 20% for G-control. However, G-oral presented collateral effects: headache, epigastric pain, nausea, and local pruritis.</td>
<td>Both treatments were effective; however, the use of oral diclofenac was not advisable because of the collateral effects.</td>
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<tr>
<td>Gouping et al18</td>
<td>Quasi-experimental study. n = 65 patients, divided into 2 groups: A = 34 patients and B = 31 patients.</td>
<td>Group A = application of 14 g of notoginseny cream. Group B = 14 g of Hirudoid® (mucopolysaccharide-polysulfuric acid). The treatments were applied at the site where the phlebitis had developed, from 0800 until 2000, with an interval of 4 h each time.</td>
<td>The time for the regression of phlebitis signs and symptoms was significantly shorter in patients of Group A, treated with notoginseny. The notoginseny was more effective than the Hirudoid® when it came to curing the phlebitis cases deriving from the infusion of antibiotics, amino acids, lipidic emulsions, and mannitol. There was no statistically significant difference with relation to phlebitis cases deriving from the infusion of chemotherapy and for the reduction of the edema variable.</td>
<td>The authors concluded that notoginseny can constitute effective treatment for phlebitis cases induced by peripheral infusions. Authors suggest an in-depth search of the pharmacological constituents of notoginseny and a subsequent clinical test with a larger number of patients.</td>
</tr>
<tr>
<td>Trillo and Esteban14</td>
<td>Randomized clinical test. n = 22 patients, divided into 2 groups: A = 11 patients and B = 11 patients.</td>
<td>Group A received transdermal patch of NTG, 5 mg. Group B received heparinoid cream.</td>
<td>NTG produced a statistically significant result in 48 h, whereas heparinoid cream produced a result in 36 to 72 h.</td>
<td>Since it acts as a local vasodilator, NTG alleviates the signs and symptoms deriving from postinfusion phlebitis.</td>
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**Abbreviations:** RCT, randomized clinical trial; NTG, nitroglycerin.
It also activates the local and general blood flow, which gives it anti-inflammatory and antiexsudative characteristics. Although it is an effective topical anti-inflammatory for the treatment of phlebitis, its efficacy lessens when compared with notoginseny and NTG, except when evaluated in terms of edema regression time effectiveness, for which both notoginseny and NTG are effective.\textsuperscript{14,16}

Notoginseny cream is commonly used in Chinese medicine and is generally associated with medicinal plants. It is found in the root of the ginseng plant. Notoginseny is indicated for the purpose of staunching hemorrhages, and the Chinese consider it to be an agent capable of supplying nutrients to the blood. When applied clinically for the treatment of phlebitis cases, it has proven to be effective in the reduction of pain, fibrous cord, erythema, and edema.\textsuperscript{18}

NTG is a vasodilator substance commonly used as a facilitator for the vascular puncture procedure. The drug has a high absorption power when in contact with the skin, promoting an increased concentration at the site of application, which consequently induces vasodilation and a greater local blood flow, facilitating the visual display of the vascular network and better conditions for puncture. When NTG is applied to the skin, its vasodilator effect, which lasts for between 3 and 6 hours, can be observed within 10 minutes.\textsuperscript{15,19}

Studies have suggested that infusion phlebitis is initiated by vasoconstriction at the infusion site, brought about by irritation of tunica intima.\textsuperscript{20} Thus, induction of local vasodilation by applying NTG has proven to be effective for prevention of phlebitis, as well as for treating the first degrees of phlebitis.\textsuperscript{11,15,19,21}

Generally used in a dosage of 5 mg, in the form of a transdermal patch, NTG has also been recommended for the treatment of angina pectoris. There are recommendations to refrain from using the patch, however, for other therapeutic purposes; this is to reduce headaches, which are a collateral effect of NTG.\textsuperscript{11,19}

Other studies confirm the vasodilator effects of NTG. Lohmann et al\textsuperscript{22} reported an increase of 50\% in vessel width within 15 minutes after the application of NTG, in the pharmaceutical form of a cream, on the upper limbs of patients subjected to vascular puncture. Because of NTG’s vasodilator effect, some Australian hospitals allow nurses to apply it in cream form or through infiltration upon evidence of the first stages of infusional phlebitis. Although infiltrations do not have an inflammatory component, maintaining vessel dilation consequently decreases intravascular osmotic pressure, avoiding fluids that pass into surrounding tissues and limiting the dislocation of the intravenous cannula.\textsuperscript{19} The vasodilator effect of NTG is identified when used in the pharmaceutical form of a gel, a cream, or a transdermal patch; it is not effective for the treatment of phlebitis when used as spray.\textsuperscript{16,19,21}

Several pharmacological interventions have been used to treat infusion phlebitis. Although not all drugs may be commercially available in different countries, knowledge of them is relevant for nursing practice and for clinical research development.

Study results suggest that the use of topical notoginseny cream and NTG is more effective in the treatment of phlebitis in comparison with the use of creams or ointments containing polysulfate of mucopolysaccharide, also known as heparinoid substances. In turn, vehicles containing heparinoid substances were considered as effective as topical anti-inflammatories, which only underscores the efficacy of notoginseny and NTG. However, no result permits us to conclude that either treatment is more effective in the cure or regression of phlebitis.

Although the sample consisted mostly of a randomized controlled trial, notoginseny and NTG were evaluated in studies that reported various clinical outcomes and considered different types of phlebitis, which were not well defined in some studies. Thus, the evaluation of the efficacy of these products in terms of the type of phlebitis was impaired.

The studies used presented some limitations regarding the definition of variables and the reading of the clinical outcomes. The profile of the patients studied makes it impossible to analyze and determine whether the sample was pertinent in terms of evaluating the efficacy of the products. Variables were not explicitly explained, the site of the study was mentioned only in 1 publication, and no study offered a calculation of the size of the sample.

Except for notoginseny cream, the FDA has approved substances referred to in this review for the treatment of diseases other than phlebitis. Therefore, it is important to conduct clinical studies evaluating the efficacy of possible alternatives to the treatment of phlebitis.

REFERENCES