

Nitroglycerin in Dermatology

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Abstract. Nitroglycerin has traditionally been used in medicine for over 130 years for its potent dilator effect on both venous and arterial blood vessels. Cardiovascular ischemic diseases are among the classic indications. However, the possibility to incorporate nitroglycerin in different galenic forms renders it new therapeutic potential through topical application, both in surgery and in dermatology (Raynaud syndrome, chondrodermatitis, pernio erythema, alopecia areata, ulcers of different etiologies). Nitroglycerin is used for topical treatment as 0.5%, 1% or 2% ointment, lower concentrations limiting the probability of systemic adverse effects occurrence.

Keywords: nitroglycerin, dermatology, vasodilation, analgesia

1. Introduction

Nitroglycerin is a chemical substance with explosive properties, initially synthesized in 1847 by the chemist Ascanio Sobrero and exploited for three decades in the ammunition industry [1]. It is obtained by esterification of cooled glycerin (to minimize unwanted effects of this strongly exothermic reaction) with concentrated nitric acid in the presence of sulfuric acid (Figure 1).

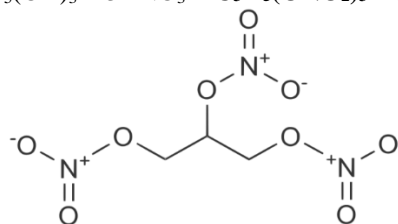
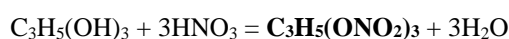


Figure 1. Nitroglycerin (trinitroglycerin, glycerin trinitrate, 1,2,3-trinitroxypropane) – chemical structure

Since 1878 nitroglycerin has been used in medicine in a diluted, non-explosive form, for its potent vasodilator effect on both arteries and veins. It is included by the World Health Organisation in the list of essential drugs, that comprises the most effective and safe medicines.

Cardiovascular ischemic morbid conditions (acute coronary syndrome, acute myocardial infarction, angina pectoris) are the main target of nitroglycerin therapy [2, 3]. Topical nitroglycerin is indicated in dermatology (Raynaud syndrome, chondrodermatitis, ulcers, post-filler injection necrosis, alopecia areata, pernio erythema), surgery (anal fissures, hemorrhoids), orthopedics (tendinopathy), for treating several conditions with vasoconstriction as a common pathogenic mechanism [4- 6].

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The chemical structure of glyceril trinitrate renders nitroglycerin the possibility to be incorporated in different pharmaceutical forms with either systemic effects (pills, solutions, sprays, patches) or local effects (creams). Absorption and duration of action onset are correlated with the pharmaceutical form, from 5 minutes in the case of sublingual pills to the delay effect of patches, which gives nitroglycerin superior bioavailability and multiple indications [7].

After absorption, nitroglycerin (NTG) is degraded to nitric oxide under the action of the mitochondrial aldehyde-dehydrogenase (MAD). Nitric oxide (NO), the active metabolite, activates guanylate cyclase (GC) which induces an increase in the concentration of cyclic guanosine monophosphate (GMP) in smooth muscles and in other tissues. These events lead to dephosphorylation of myosin light chains which, in turn, induces smooth muscle relaxation and vasodilation (Figure 2). Even though this effect is predominant on venous blood vessels, it is also noted in a dose-dependent manner on arterial blood vessels as well [8, 9].

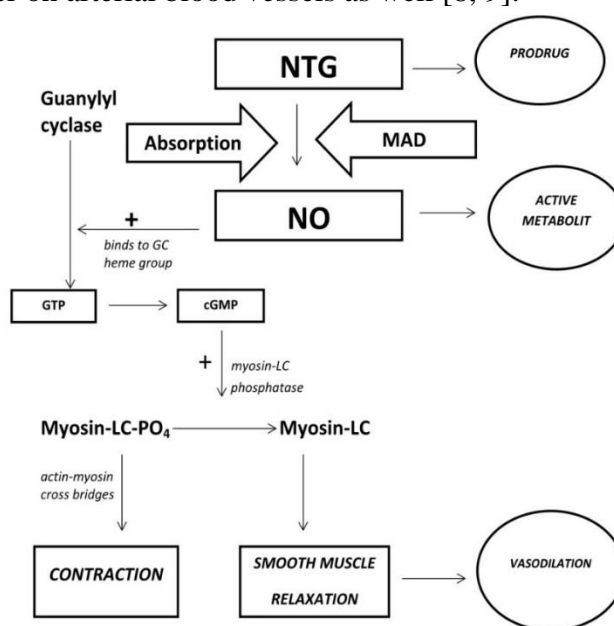


Figure 2. Nitroglycerin- biochemical mechanism of action

Experimental part

Nitroglycerin indications in dermatology are based on its vasodilator effect through topical application. Concentrations of 0.2%, to 2% are utilized, according to the dimensions and location of the affected area, in order to minimize systemic absorption and to prevent adverse effects. Thus, concentrations of 0.5 and 1% are preferred for topical administration on the skin and 0.2% to 0.4% for rectal mucous membrane application, with proven efficacy and safety [10]. Adverse effects to topical nitroglycerin were only reported in a small number of cases, consisting mainly of local irritation. Rarely, headache appearing 2 hours after topical administration was reported.

Topical nitroglycerin is indicated in several dermatologic disorders with vasoconstriction as a common pathogenic mechanism, but with variable clinical manifestations, such as Raynaud syndrome, chondrodermatitis nodularis helices, cutaneous ulcers, pernio erythema, alopecia areata, tissular necrosis after dermal filler injections [11, 12].

Our paper aims to review the main etiopathogenic and clinical aspects of several disorders that may benefit from topical nitroglycerin therapy and to analyze the mechanism responsible for its therapeutic effect. The clinical images are part of the archive of the Dermatology Clinic of the Clinical University Hospital of the Railways system in Iasi. The study was conducted in accordance with the bioethical norms of the European Union legislation.

3. Results and discussions

Raynaud syndrome is a common vascular condition, with a prevalence of 5-10% in the general population, characterized by recurrent digital arterial vasospasm, that manifests with episodes of colour changes from pale to cyanosis and hyperemia, paresthesia, burning sensation and throbbing pain (Figure 3). It may evolve to ischemia with digital ulcers, gangrene or other potentially invalidating complications that may require surgical treatment.

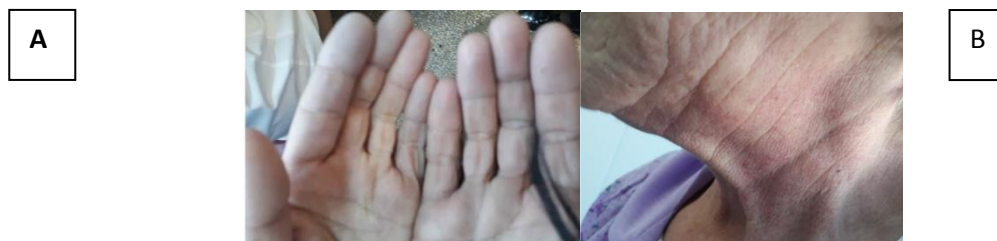


Figure 3. A. Raynaud syndrome - acral cyanosis and edema of the fingers; B. Scleroderma - indurated, sclerous plaque

Raynaud syndrome is classified into primary, also called Raynaud disease and secondary, also known as Raynaud phenomenon, associated to connective tissue autoimmune diseases, mainly scleroderma, mixed connective tissue disease or lupus erythematosus. While primary Raynaud syndrome is related to functional vascular alterations alone, in secondary Raynaud syndrome structural microvascular damage also occurs. Pathogenic mechanisms include an unbalance between vasodilatory and vasoconstrictor mediators, with increased levels of angiotensin II and decreased levels of nitric oxide, neural abnormalities with overactivity of α_2 -adrenoreceptors and increased levels of neuropeptide Y that contribute to vasoconstriction, as well as intravascular abnormalities with increased production of platelet thromboxane A_2 , a potent vasoconstrictor, as well as oxidative stress [11, 13, 14].

Classic therapy includes systemic vasodilator drugs with moderate effects on symptoms such as pain [15]. Association with topical nitroglycerin proved efficacious by increasing local temperature with an average of 3°C after 3 h of topical application (patch or ointment with 2% nitroglycerin, reapplied every 6 h), with constant maintenance of temperature for up to 12 h. The main reported adverse effect was headache 2 hours after patch application [16].

Nitroglycerin targets both vasoconstriction and remodeling of the altered vascular endothelium in scleroderma, by increasing vascular elasticity. It acts in a similar way to 5-phosphodiesterase inhibitors by increasing GMP which induces vasodilation and smooth muscle relaxation. The active metabolite, nitric oxide, increases the local oxygen influx, thus improving symptoms in Raynaud syndrome.

Chondrodermatitis nodularis helices is a benign dermatologic condition affecting the skin of the helix and antehelix, predominantly in male patients (M/F-10/1). It manifests as nodular, indurated, extremely painful lesions due to dermal and chondral ischemia generated by thinning of perichondral arteriols (Figure 4), leading to altered quality of sleep [17, 18].



Figure 4. Nodular, indurated lesions on the helix and antehelix - chondrodermatitis nodularis helices

Therapeutic options with proven efficacy include minimally invasive methods such as intralesional cortisone or collagen injections, cryotherapy, or invasive methods such as electrodesiccation or surgical removal, with potential irreversible esthetic impairment [19]. Topical nitroglycerin, a non-invasive, safe and efficient method, is indicated due to both its vasodilator and analgic effect. Nitroglycerin 2% ointment is recommended twice daily for three to four weeks until complete resolution. In case headache occurs the concentration is reduced to 1% [20].

Nitroglycerin beneficial effects are due to its ability to induce relaxation of arteriolar muscle fibers leading to a restored local blood flow and a decrease in local edema. Nitroglycerin also has an analgic effect by central and peripheral nervous system pain modulation, leading to an improved quality of life and avoidance of invasive treatment methods.

Trophic ulcers are defined as deep dermal-hypodermal losses of substance, affecting mainly the lower extremities, in an area altered by disease, vascular or neural impairment, caused by an external factor and with no tendency to heal spontaneously [3, 8]. They manifest as deep crateriform ulcers with variable shapes, sizes and colour (Figure 5).



Figure 5. *Venous ulcer*

According to etiopathogeny, trophic ulcers are classified into two main categories: vascular and non-vascular. The vast majority (95%) are due to vascular impairment, either venous (venous insufficiency, venous thrombosis) in 70% of the cases, or arterial (chronic obliterant arteriopathy, obliterant thrombangeitis, acute arterial occlusion) in 30% of the cases. 15-20% of the trophic ulcers due to vascular causes are the result of mixed arterial and venous impairment. The non-vascular trophic ulcers account for the rest of 5% and may have several causes: infectious, neuropathic, hematologic, traumatic [21].

Venous ulcer is the most severe complication of venous insufficiency, with a prevalence of 1.69% in patients aged over 65 years. Raffetto et al. considered venous ulcers the consequence of high venous pressure on dermal microvasculature (22). Therapy of venous ulcers includes: chronic systemic treatment with vasodilators, antithrombotic drugs, venotrophic medication, local treatment (debridement, cleaning, wound dressings), surgical intervention in selected cases, avoidance of prolonged standing, treatment of high blood pressure, cessation of smoking, compression therapy [23].

Topical nitroglycerin stimulates vasodilation which decreases venous pressure and restores local blood flow leading to adequate tissue oxygenation required for tissue regeneration. According to ulcer size concentrations of 1% or 2% may be used.

In diabetic patients trophic ulcers have specific features in regard to etiopathogeny and evolution. Diabetic neuropathy favors trauma and ulcerations in the lower legs, both by posture anomalies with increased pressure on the feet and by decreased sensitivity to pain, temperature and pressure, increasing the risk of injury [24]. Clinical manifestations include xerosis, fissures and ulcers (Figure 6).

Ischemia leads to a delay in wound healing by decreased blood flow and reduced tissular oxygenation [25]. Topical nitroglycerin therapeutic effects are due to increasing GMP and nitric oxide resulting in local vasodilation and increased oxygen which accelerates the elimination of catabolites and reduces pain, pruritus and inflammation.



Figure 6. Interdigital ulcer in a diabetic patient

Alopecia areata is considered a T-cell mediated autoimmune disease characterized by recurrent non-scarring hair loss that may affect all hair-bearing areas. It manifests with smooth, slightly erythematous or normal coloured, round to oval alopecic patches that may contain several pathognomonic exclamation point hairs (Figure 7). Most patients are asymptomatic. However some may experience discomfort or a burning sensation [26].



Figure 7. Alopecia areata with exclamation point hairs at the periphery of the alopecic patch

Pathophysiology of alopecia areata is not yet completely understood. Autoimmunity in genetically predisposed individuals, cytokines inhibiting hair growth such as interleukin 1 and tumor necrosis factor, viral etiology and changes in the local innervation and vasculature with decreased levels of calcitonin gene-related peptide were hypothesized.

Treatment options include potent topical corticosteroids, minoxidil solution, topical dithranol, topical nitroglycerin, intralesional corticosteroids [27]. Topical nitroglycerin may counteract the effect of decreased levels of calcitonin gene-related peptide. Also, by inducing vasodilation, it favors the afflux of nutritional substances, as well as the absorption of therapeutic substances concomitantly administered.

Tissue necrosis related to dermal filler injection is a rare, but potentially serious adverse reaction due to vascular compromise through mainly two mechanisms: either direct intravascular injection of the filler with vascular occlusion, or compression of the adjacent vasculature by the injected material, when its volume exceeds the pressure of the arteriole perfusing the area. Symptoms of arterial occlusion include immediate or early white discoloration of the skin and severe pain. Venous impairment manifests with delayed dull pain and dark discoloration. Treatment includes massage of the affected area, warm compresses, hyperbaric oxygen in cases of impending massive skin necrosis. Injection of hyaluronidase may be attempted if a hyaluronic acid dermal filler was used. Nitroglycerin 2% paste is recommended in order to promote vasodilation and to facilitate blood flow to the affected area (28).

4. Conclusions

Nitroglycerin is a substance with multiple therapeutic indications, superior bioavailability and optimal safety profile. The possibility to incorporate nitroglycerin in pharmaceutical forms suitable for topical administration renders it new indications in dermatology, surgery and orthopedics. In dermatology, nitroglycerin may be used as monotherapy or in combination with other therapies for its vasodilator, anti-inflammatory and antalgic properties.



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