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Review Article

Topical use of antithrombotics: Review of literature

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ABSTRACT

While antithrombotics are usually administered intravenously, subcutaneously or orally, there are a number of publications reporting topical application of anticoagulation therapy. This paper aims to review the available literature regarding clinical conditions, the details of the topical antithrombotic treatment, as well as positive or adverse effects in an attempt to ascertain the safety and efficacy of this form of treatment. Published literature was searched to identify publications reporting the use of antithrombotic treatments administered via topical application between 1st January1990 and 1st January 2013. There were 43 studies reported in 10 different clinical conditions. Majority of the studies were randomized controlled trials (51.2%), prospective studies (18.6%) or case reports (11.6%). The clinical conditions in which topical antithrombotics were administered included: microangiopathy, acute haemorrhoids, periodontitis, dermatitis, burns, ocular conditions and surgery, blunt force impact, scars, as well as clinical conditions associated with superficial venous thrombosis (SVT). The most commonly used topical antithrombotic was heparin (79.1% of studies). The respective dosage of different antithrombotics varied depending on specific clinical conditions. While most studies reported mean improvements or resolution of symptoms/condition in patients, the patient outcomes were variable. This review demonstrates that topical antithrombotic treatment is used according to a wide variety of protocols, with a subsequent variability in patient outcomes. Specific guidelines for the use of topical antithrombotics should be developed to standardize this form of treatment and ensure the best possible outcomes for patients.

Contents

Abbreviations: SVT, superficial venous thrombosis; LMWH, low molecular weight heparin; EPL, essential phospholipids; LDF, laser-Doppler flowmetry; PO_2, oxygen partial pressure; PCO_2, carbon dioxide partial pressure; SCORAD, SCORing Atopic Dermatitis; IU, international units; DHEP, diclofenac epolamine and heparin; RCT, randomised controlled trial.

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Introduction

The overarching role of antithrombotic therapies is for the prophylactic and therapeutic treatment of confirmed thrombosis or the risk of thrombosis within a blood vessel. Used for the treatment and prevention of a number of clinical conditions such as atrial fibrillation and cardiovascular diseases, their administration has been associated with the reduced risk of thromboembolic complications such as stroke [1–7].

The advancement of technology and the relentless investigation of antithrombotics have resulted in identification of features unique to each agent that enable nuanced and more specific treatment. This comprehensive understanding of antithrombotic agents resulting from years of research supports their administration in clinical conditions, allowing patients to obtain maximum benefits with minimal risks.

This takes into account the clinical indications, as well as monitoring, management and the potential adverse events associated with administration; either intravenously for heparin, subcutaneously for Low Molecular Weight Heparin (LMWH) or orally for warfarin [8].

However, there is a growing trend of administering antithrombotic treatments to extravascular spaces despite there being little evidence detailing the efficacy or safety of this method of application [9–11].

As such, the purpose of this paper was to review the available literature regarding the use of antithrombotic agents via topical administration in humans and attempt to determine the safety and effectiveness of such treatment.

Methods

The MEDLINE/Pubmed and Embase databases were utilized in order to identify publications reporting the use of antithrombotic treatments administered via topical application between 1st January1990 and 1st January 2013. The following search strategy was employed using "topical" and: antithrombotic/s, anticoagulant/s, heparin; warfarin; low molecular weight heparin; tissue plasminogen activator; urokinase; streptokinase; activated protein C.

The literature search did not discriminate between the study designs, and included case reports, trials, cohort studies, retrospective studies and cross over studies examining outcomes from antithrombotics applied via topical means in humans of any age. The search was limited to "humans" and the "English language". Review articles were included in the search strategy to enable cross-referencing between original studies identified and references in published reviews and were subsequently excluded from further analysis.

Results

The database interrogation identified 43 articles that were eligible to be included in this review. The number of studies according to the antithrombotic agent included: Heparin (34 studies, 79.1%), LMWH (2 studies, 4.7%), tissue plasminogen activator (2 studies, 4.7%), streptokinase (2 studies, 4.7%) and activated protein C (2 studies, 4.7%). Identified manuscripts were categorized into the following topical antithrombotic treatments: Microangiopathy (7 studies, 16.3%), Acute haemorrhoids (1 study, 2.3%), Dermatitis (2 studies, 4.7%), Clinical conditions associated with superficial venous thrombosis (SVT) (6 studies, 14.0%), Burns (2 studies, 4.7%), Ocular conditions and surgery (4 studies, 9.3%), Ulcers (5 studies, 11.6%), Blunt force impact (8 studies, 18.6%), Scars including surgical (6 studies, 14.0%) and Other (5 studies, 11.6%).

Topical Antithrombotic Treatment in Healthy Volunteers

A randomized, placebo controlled, double blind study investigating the topical administration of essaven gel, comprising 10 mg aescinate, 10 mg essential phospholipids (EPL) and 10 IU/g heparin, found it to have a positive effect on the microcirculation of healthy individuals[12].

Patients had their skin flux (rate of circulation at the deeper capillary levels) measured using laser-Doppler flowmetry (LDF). LDF flux value was the average of continuous measurement in 2 minutes.

Patients on essaven gel treatment demonstrated higher flux increase as compared to control and placebo groups. This indicated that essaven gel treatment affected microcirculation at deeper capillary levels, with oxygen partial pressure (PO_2) increase and carbon dioxide partial pressure (PCO_2) decrease also pointing to changes in the thin-superficial capillary layer.

It is unclear exactly how large a role heparin plays in the achievement of these results. However, it does indicate that topical treatment of essaven gel, which includes heparin, can improve or positively alter the microcirculation in normal skin at both deep and superficial capillary layers.

Essaven Gel Treatments for Microangiopathy

A total of 7 studies (16.7%) were identified in the setting of microangiopathy [13–19]. Despite variations in the indication for use of essaven gel in this setting, the outcomes of the studies were similar, with no reported adverse effects and patients displaying mean improvements in the measures of outcomes of all studies.

The following types of microangiopathy were identified: Diabetic microangiopathy without ulcers [15], diabetic microangiopathy with ulcers [14,17], venous hypertensive microangiopathy with ulcers [16,19], venous hypertensive microangiopathy due to chronic venous insufficiency and ulcers [18] and venous hypertensive microangiopathy with varicose veins [13].

All studies utilized a double blind, placebo controlled study, with essaven gel, containing 10 mg aescinate, 10 mg EPL and 10 IU/g heparin, administered through a gentle superficial massage using two fingers for 5 minutes. The only variation in the protocol for use was specific to the frequency, with two studies requiring three daily applications of essaven gel for four weeks [15,16], one study for two weeks [14], with the remaining four studies administering a single acute application of the gel [13,17–19].

The primary outcome measures for these studies were skin flux using laser-Doppler flowmetry and PO_2 /PCO_2 standards obtained with a Kontron analyser with a Combi sensor for simultaneous measurement. Basal value measurements were taken before treatment application to allow for comparisons with measurements taken during treatment.

All seven studies showed that patients on topical antithrombotic treatment experienced positive outcomes, with significant decrease in flux values indicating increased nutritional support and oxygen levels, corroborated by corresponding increases in PO_2 and decreases in PCO_2 as compared to control and placebo groups.

However, it is not clear how much of these beneficial outcomes were a result of heparin's effects as it was utilized in conjunction with other