A Proof of Principle Study Investigating the Influence of Diclofenac on Perfusion Changes During Cutaneous Negative Pressure Wound Therapy

Published: 25-04-2019
Last updated: 12-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON48444

Source
ToetsingOnline

Brief title
The DicloFlow study

Condition

- Other condition

Synonym
Wounds

Health condition

Wonden die behandeld kunnen worden met negatieve druk therapie

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Er is geen financiering voor dit onderzoek door externe partijen buiten de afdeling om.

Intervention

Keyword: Diclofenac, Negative pressure wound therapy

Outcome measures

Primary outcome

8.1.1 Main study parameter/endpoint

The main study parameter of this experiment will be the mean LDF flux of the last 5 minutes of the 20-minute -200 mm Hg NPWT period of the thee study arms.

Secondary outcome

8.1.2 Secondary study parameters/endpoints (if applicable)

The Single Fibre Reflectance Spectroscopy (SFRS) device will provide us with signals that can be used to calculate measures of blood content (*), micro-vessel saturation (StO2) and mean microvessel diameter (Dvessel). Because there is only one probe available this probe will be placed beneath the NPWT foam only. It takes 30 seconds to record 10 SFRS recordings. 10 measurements will be made every minute for the 20 minute -200 mm Hg NPWT period. Using both the blood content (*) and the oxygen saturation of the blood (StO2), oxygenated blood content of the tissue under investigation with SFRS can be calculated.

8.1.3 Other study parameters (if applicable)

Sex, age, length, weight and BMI of every participant will be recorded before the experiment. Room temperature will be measured during every measurement session. If a measurement period deviates from normal because of disturbance such as leaks, or if the volunteer wants to quit, this will be recorded and reported appropriately. Any adverse event during or after the experiment will be reported as well.

Study description

Background summary

Negative Pressure Wound Therapy (NPWT) is a common treatment for acute, chronic, and recently also postoperative surgical wounds.2-6 In the first NPWT basic research paper, augmented blood flow is put forward as one of its mechanisms of action.5 Although a multitude of studies currently reports that NPWT improves blood flow5,7-22, the underlying mechanism remains elusive. Moreover, an increasing amount of studies that report a negative effect of NPWT on perfusion and oxygenation has been published in recent years.23-31 This has resulted in a debate whether NPWT is truly able to increase perfusion immediately after initiation of therapy23-31, and some investigators currently advise clinicians to use NPWT cautiously on tissues at risk of ischemia.27,30 Because adequate perfusion is of such vital importance in wound healing32,33, elucidation of this controversy seems warranted.

The Pressure-induced Vasodilation Phenomenon

Outside of the field of NPWT, several researchers have demonstrated that tissue blood flow increases during moderate amounts of mechanical deformation in healthy individuals, for example during tissue compression.34-36 This phenomenon is commonly referred to as *pressure-induced vasodilation* (PIV, where pressure stands for the exertion of a compressive mechanical force).37,38 PIV has been shown to act as a protective mechanism against the ulcerations from mechanical stress.37,38 Several investigators have elucidated the physiology behind PIV: mechanical deformation as a result from cutaneous pressure exertion leads to activation of the mechanosensor acid-sensing ion channel 3 (ASIC3), an ion channel located in sensory nerve endings (i), which triggers the release of the neuropeptide calcitonin gene-related peptide (CGRP) (ii), a potent vasodilator39, thus resulting in vasodilation and ultimately, an increase in perfusion.38 CGRP is able to induce vasodilation in both the

microcirculation (through release of nitric oxide by the endothelium), or independently through direct action on vascular smooth muscle cells (e.g. resistance arteries), depending on the vascular bed involved.39 CGRP is stated to be the most potent vasodilator currently known to exist in the human body39, having a potency 10-100 times higher than the most potent prostaglandins or other vasodilators such as acetylcholine and substance P39, and has also been shown to increase angiogenesis and wound healing.39-41 Administration of ASIC3- or CGRP-blockers, as well as ASIC3 knock-out (KO), was shown to eliminate PIV in response to mechanical deformation in mice, and ASIC3-blockers have been confirmed to prevent PIV from occurring in humans as well.38 Additionally, ASIC3-KO was associated with elimination of reactive pressure-induced hyperemia after compression of skin, and abolishment of ASIC3-mediated CGRP release resulted in earlier onset and increased severity of pressure-induced necrosis.38,42 Other researchers have demonstrated that ASIC3 is activated not only by compression but also by stretch43, implicating that PIV is not only involved in tissue subject to compression but also in tissues subject to stretch. Moreover, the main tissues involved in this protective mechanism, afferent sensory nerves and vasculature, can be found virtually everywhere in the human body outside of the central nervous system, and PIV already has been demonstrated to exist in muscular tissue as well.44 The same applies to ASIC3, which is present in many of these sensory afferent nerves, and CGRP, which is also present in many sensory afferent nerves, especially those innervating resistance arteries.39,45 This implies that PIV is a relevant part of mechanobiology everywhere outside of the central nervous system.

PIV involvement in NPWT?

NPWT has been shown to result in both mechanical deformation of tissue25,26,46,47 as well as increased blood flow.8,9,48,49 Although these findings may seem contradictory, they can be explained by involvement of PIV. Therefore we propose that perfusion increases during NPWT are mediated (at least in part) by the same physiology involved in PIV (see Figure 1).Thus, in the articles denouncing the ability of NPWT to quickly increase perfusion because of concerns regarding negative effects of mechanical deformation on blood flow23-27,29,30,47, the link has not been made to the release of vasodilatory PIV mediators during NPWT, which simply has not been previously investigated in the context of blood flow during NPWT. Yet, NPWT already has been shown to result in an increase of the PIV mediators CGRP and NO, contributorily suggesting involvement of PIV (although these authors did not link CGRP to the vasodilation seen during NPWT in their papers).50-52

Figure 1. Proposed NPWT-vasodilation pathway. NPWT, Negative-pressure wound therapy; ASIC3, acid-sensing ion channel 3; CGRP, calcitonin gene-related peptide.

Impairment of PIV

The research group of Fromy et al have demonstrated that several drugs, such as Diclofenac and Amiloride (ASIC3 antagonists45) eliminate PIV.38,53,54 Although NSAIDs such as Diclofenac also inhibit the cyclooxygenase-mediated production of vasodilatory arachidonic acid metabolites such as prostacyclin (PGI2)55, abolishment of PIV was attributed to their ASIC3-antagonism45 because COX-inhibition with the NSAID indomethacin did not completely eliminate PIV, while ASIC3-antagonists did.56 Because many patients receive both Diclofenac and NPWT during their treatment, this may have substantial implications for pain management during NPWT.57

Measurement techniques of perfusion
One of the criticisms brought forth against LDF as a measurement technique in NPWT perfusion research has been that *the diameter of the underlying vessels is not factored into the calculation of the laser Doppler device, which records an effect of increased velocity only*27, *which is erroneously interpreted as increased perfusion*.27 For this reason, this study will not only perform perfusion measurements using LDF, but also with single fiber reflectance spectroscopy (SFRS). SFRS is a validated optic technique frequently used for providing tissue oxygenation levels and total hemoglobin.58-60 Moreover, because blood in tissue is strong absorber of certain light frequencies, and concentrated in blood vessels, this results in a measurable difference in absorption of light between vessels with a different vessel diameter. Based on this principle, Van Veen et al developed an approach where SFRS can be used to calculate a mean vessel diameter, thus allowing for the monitoring of dynamic processes such as vasodilation of the tissue under investigation.61,62 Although widely used in other fields, SFRS has not been used before in NPWT perfusion research, and will provide us with the additional parameters, allowing us to study these parameters in relation to each other, the LDF measurements, as well as between study groups. The combination of LDF with SFRS will provide us with a thorough assessment of the vascular tissue response to the NPWT.

Cutaneous NPWT application has been shown to result in an increase of LDF-measured blood flow in healthy volunteers.7 Additionally, the experiment of Fromy et al illustrating elimination of PIV with Diclofenac has been performed in healthy volunteers as well. Moreover, patients need to be without neurovascular disease in order for PIV to take place.38 This implies that young healthy volunteers are the ideal study population for this study.

*
Stepwise summary of background and study rationale

1. Increased perfusion is one of the main mechanisms of action suggested for Negative Pressure Wound Therapy (NPWT).
2. Acid-sensing ion channel 3 (ASIC3), a mechanosensor located in sensory nerves, initiates a vasodilatory pathway during mechanical deformation of tissue, often referred as *pressure-induced vasodilation* (PIV).
3. Because NPWT results in mechanical deformation, this suggests that the increased perfusion during NPWT may be explained by involvement of PIV.
4. Because Diclofenac is an ASIC3-antagonist that eliminates PIV, this implies that Diclofenac may eliminate the increase of perfusion normally seen during cutaneous NPWT.
5. Diclofenac can therefore be used as proof of principle for the hypothesis that increased perfusion during NPWT is due to ASIC3-mediated PIV.

By potentially revealing the underlying physiology behind the blood flow changes seen during NPWT, this study will contribute to the scientific knowledge regarding the mechanisms of action of NPWT This may provide windows of opportunity for improvement of clinical NPWT treatment.

This study is not a study to investigate clinical application of Diclofenac. Diclofenac is only used as a challenge agent to induct a physiological blockade of the normal physiology we hypothesize to lead to increased blood flow during NPWT. Diclofenac formulations will only be provided once to every participant. This study should therefore not to be seen as a clinical drug trial.

Study objective

The primary objective of this study is to investigate the effects of a Diclofenac challenge on perfusion changes during NPWT as a proof of principle for the involvement of ASIC3*mediated PIV physiology in the blood flow changes seen during NPWT.

Secondary Objectives

Secondary objectives of this study are:

* To investigate potential differences between an orally and topically administered Diclofenac challenge
* To investigate the relationship between LDF and SFRS-measured outcomes

Study design

Study design

In order to achieve the maximum power while limiting the amount of participants necessary, this will be a prospective cross-over study with repeated measurements where healthy volunteers their dominant forearm will be randomized

to a random order of three arms consisting of NPWT on the forearm with either:

* No challenge agent
* Topical Diclofenac challenge
* Oral Diclofenac challenge

Participants will receive ± 4 gram of gel in this study to their forearm during the topical challenge, which equals around 40 mg Diclofenac, around the approximate location where the probe holder will be placed. During the oral challenge, participants will receive 100 mg Diclofenac.

This study design will facilitate investigation whether ASIC3-mediated PIV is indeed involved during the blood flow changes seen during NPWT. This will also facilitate investigation of the influence of Diclofenac, as well as any potential differences between topically and orally administered Diclofenac.

This study is investigator-initiated and will be performed in the Academic Medical Center only.

Intervention

Three sessions with Negative Pressure Wound Therapy, once with oral Diclofenac, and once with Diclofenac gel.

Study burden and risks

5. TREATMENT OF SUBJECTS

5.1 Treatment

Healthy volunteers their dominant forearm will be randomized to a random order of three arms:

* No challenge agent
* Topical Diclofenac challenge
* Oral Diclofenac challenge

Participants will receive ± 4 gram of gel in this study to their forearm during the topical Diclofenac challenge, which equals around 40 mg Diclofenac, around the approximate location where the probe holder will be placed. During the oral Diclofenac challenge, participants will receive 100 mg Diclofenac.

According to the summary of product characteristics, the maximum plasma concentration is reached 1-4 hours after oral administration. Topical administration of 2.5 gram of Diclofenac 5% gel 1 hour before measurement was able to completely abolish PIV in humans in the experiment of Fromy et al.38

The gel and medication will therefore be supplied to the participant sixty minutes prior to the measurements, during which the patient will be sitting comfortably in a chair in order to have an acclimatisation period of 50 minutes in order to adjust to the conditions in the room where the measurements will be performed. During the last ten minutes, the gel will be removed gently and NPWT and measurement probes will be applied. The summary of product characteristics of the gel that we will use (Diclofenac HTP 1%, gel (Healthypharm B.V., Etten-Leur, The Netherlands) mentions that the amount of gel needed to treat an area of 4 to 8 dm2 is 2-4 gram. Therefore we will apply ± 4 gram of gel in this study to the patients their forearm, around the approximate location where the probe holder will be placed. Subsequently, the dominant forearm of the participant will be subjected to 5 minutes of cutaneous NPWT with -25 mm Hg of subatmospheric pressure, during which perfusion will be measured to attain a baseline measurement. The -25 mm Hg of subatmospheric pressure is to ensure the equipment is held in place correctly onto the skin.7 After 5 minutes, the amount of subatmospheric pressure will be increased to -200 mm Hg subatmospheric pressure. After 20 minutes of -200 mm Hg NPWT, the NPWT device will be turned off and the equipment removed. During the measurement sessions and acclimatisation periods, participants will be instructed to relax, breathe as normal, and will be assured to be free from distractions. Participants will be instructed to not move their upper extremities in order to stabilize the probes during the measurements. If a measurement session is hampered by leaks from the NPWT, the measurement will be attempted again at a later point in time during another week, at approximately the same time of day. During each measurement session, all participants will receive 20 minutes of cutaneous NPWT with -200 mm Hg with a foam pad of 7 x 12 x 2 cm.

5.2 Use of co-intervention

Participants will be instructed to abstain from eating or drinking in the 2 hours before and during the experiment. Participants will be instructed to abstain from smoking, caffeine, alcohol, and use of other pharmaceuticals during participation in the experiment. Participants will only receive one dose of 100 mg of oral Diclofenac during the complete duration of the study. The study population will consist of healthy volunteers between 18 and 35 of age free from a history of gastro-intestinal complaints. Co-medication such as proton pump inhibitors aimed at preventing gastro-intestinal adverse events is therefore not considered to be indicated in this experiment.

5.3 Escape medication

Not applicable.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

NPWT:
NPWT is considered to result in increased wound healing as a result of the mechanical stimulation of the tissue and removal of wound fluid.80 The mechanical stimulation is thought to result in augmentation of perfusion and granulation tissue proliferation. Moreover, the foil of the NPWT provides a wound with a sealed-off environment where the wound can remain moist.

Diclofenac:
Diclofenac is a phenyl acetic acid that inhibits cyclooxygenase activity, which can result in a reduction of the synthesis of prostaglandins and other inflammatory mediators.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

NPWT:
There are no known risks of cutaneous NPWT, other than a possible allergic skin reaction to polyurethane foam or the foil that will be used in this experiment. Several studies have demonstrated cutaneous NPWT application to volunteers in an experimental setting to be safe and did not report any adverse events related to their study7,27,29-31,46, one of which performed in the Leiden University Medical Center.7 This study will not convey any benefits to its participants other than providing an interesting experience and the knowledge they will contribute to increased scientific knowledge and ultimately maybe even more effective and safer health care.

Diclofenac:

A Cochrane review (350 studies, around 35000 participants) from 2015, investigating the peri-operative incidence of adverse events with single-dose analgesics when compared with placebo, indicated that single-dose NSAIDs do not seem to convey additional risks, suggesting that the risk of taking a single-dose of an NSAID (such as Diclofenac) is comparable to normal daily life.70 Moreover, a Cochrane review investigating the incidence of adverse events specifically with single-dose Diclofenac, concluded that adverse event rates were low in these single-dose studies, with no difference between diclofenac and placebo (moderate quality evidence).1

Although these reviews concern populations that underwent surgery, the observation that Diclofenac did not appear to convey risks to these patients suggests a single-dose of oral Diclofenac is safe for volunteers as well. Studies that investigated Diclofenac in a population of healthy volunteers have not reported any noticeable adverse events during their experiments.75-79

c. Can the primary or secondary mechanism be induced in animals and/or in

ex-vivo human cell material?

In animals, yes.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

NPWT:
NPWT is able to increase perfusion all over the body.

Diclofenac:
Diclofenac is thought to act all over the body. Please be referred to the summary of product characteristics for details.

e. Analysis of potential effect

Participants will receive a single-dose of oral Diclofenac, and a single-dose of topical Diclofenac. Because our study design incorporates a *wash-out* period of >3 days, plasma concentrations will be lower than during regular clinical treatment with Diclofenac.
It is considered highly unlikely that the administration of Diclofenac will result in harmful effects in this study, as substantiated by the review of Moore1, and the Summary of Product Characteristics document.

f. Pharmacokinetic considerations

Diclofenac:
Resorption: Fast and complete.
F: 50%
Tmax: 1-4 hours.
Metabolism: Mainly through hydroxylation, followed by binding with glucuronic acid
Elimination: As metabolites, 60% in urine, rest in feces.
T* 1-2 hour

g. Study population

Healthy volunteers.

h. Interaction with other products

The interaction of Diclofenac with NPWT is the subject of this study. This interaction is not considered harmful in healthy volunteers.

i. Predictability of effect

Not applicable.

j. Can effects be managed?

If any adverse events will be detected during the conduct of the study, NPWT will be removed immediately.

In case of any unexpected emergencies, participants will be brought to the medical support when deemed necessary, for example at the emergency department.

13.2 Synthesis

In order to reduce the risk of this study as much as possible, we have chosen to select a study population of healthy volunteers. Moreover, candidates with an elevated risk will be excluded according to our exclusion criteria. Additionally, we do not dose the Diclofenac above the maximum dose according the Summary of Product Characteristics document.

Diclofenac is available over-the-counter and is one of the most frequently prescribed pharmaceuticals. This suggests that the information regarding safety is relatively reliable.

If this study shows Diclofenac impairs blood flow increases during NPWT, this is relevant information to healthcare providers caring for thousands of patients receiving both NPWT and Diclofenac concomitantly. This could have substantial clinical impact. Thus, this study is evidently warranted, supported by a design aimed to limit any risk as much as possible.

The risks of this study are deemed very limited and thus acceptable for subjects. Yet, this will be their decision because every participant will receive appropriate information regarding the study during recruitment. Only after informed consent has been obtained will any candidate be included into this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Between 18-35 years of age
* Informed consent
* Male

Exclusion criteria

* Nicotine abuse
* Gastro-intestinal complaints
* Diclofenac allergy
* Cardiovascular disease
* Neuropathy
* Skin disease of the forearm
* Use of drugs outside of those relating to the study

Study design

Design

Study phase:	4
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-04-2019
Enrollment:	18
Type:	Actual

Ethics review

Approved WMO

Date:	25-04-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL67853.018.18