Vitamin c to Improve Tissue healing by Administration of Multiple INtravenous dosages

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PrimaryImproved woundhealing in 30 days in patients with an open revascularisation of the lower extremities after treatment with 4 dosages of 2 grams ascorbic acid on 4 consecutive days. (First dosage 1 hour preoperative)SecondaryWith preoperative...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Vitamin related disorders
Study type	Interventional

Summary

ID

NL-OMON41803

Source
ToetsingOnline

Brief title
VITAMIN

Condition

- Vitamin related disorders
- Vascular therapeutic procedures
- Vascular disorders NEC

Synonym
wound healing

Research involving
Human

Sponsors and support

Primary sponsor: Meander Medisch Centrum

Source(s) of monetary or material Support: Ziekenhuisbudget.

Intervention

Keyword: Ascorbic acid, Tissue healing, Vascular surgery, Wound healing

Outcome measures

Primary outcome

Reduction in woundsurface (%) of the surgical wound 30 days after surgery by intravenous suppletion of ascorbic acid in vascular surgery, with correction for the ascorbic acid level.

Secondary outcome

1. Relation between the ascorbicacid bloodlevel and the reduction in wound surface area of the primary surgical wound 4 weeks post-surgery.

2. Reduction in wound surface area of a secondary wound (pre-surgical existing) 4 weeks post-surgery (corrected for baseline ascorbicacid level)

3. Decreasing the incidence of woundinfections of the surgical wound within 30 days post-surgery(corrected for baseline ascorbicacid level)

4. Reduction of hospital stay (corrected for baseline ascorbicacid level)

5. Reduction of the number of readmissions within 30 days postsurgery(corrected for baseline ascorbicacid level)

6. Reduction of the number of 'all cause complications' within 30 days postsurgery(corrected for baseline ascorbicacid level)

7. Reduction of mortality within 30 days post-surgery (corrected for baseline ascorbicacid level)

8. Reduction of the time till median wound surface area healing in case the wounds in both groups are fully closed within 30 days post-surgery.

(corrected for baseline ascorbicacid level)

Study description

Background summary

Vascular Surgical patients are eligible for revascularization surgery to improve blood flow in the corresponding tissue. Case reports from the Meander Medical Centre show that the healing process of surgical wounds from such procedures is sometimes far from optimal. This gives the patient a prolonged situation with risk of infections, frequent hospital visits and possibly re-surgery. Ascorbic acid supplementation in the case reports gave remarkably fast and good results in the healing process. Literature can theoretically confirm this.

Ascorbic acid is involved in several processes in the body, including tissue repair. Following tissue damage it has a function in the migration of neutrophils during the inflammatory phase and a function in the formation of cross-links between collagen during the proliferative phase. In trauma patients it is also found that ascorbic acid levels at admission were significantly lower than in a healthy population. This suggests possible depletion as a result of tissue damage.

A RCT from 1974 with 20 surgical patients already demonstrated that ascorbic acid in a oral dose of 500mg twice daily versus placebo after one month, resulted in a significant reduction of the wound surface of ulcers in paraplegic patients. Such an effect was attempted to reproduce in a study among nursing home patients where twice daily 500mg ascorbic acid was administered orally and compared to 10mg orally twice daily with as endpoint the reduction of wound surface area per week for 12 weeks. There was no difference. A pilot study in the Meander Medical Centre in vascular surgery patients showed that 36% the ascorbicacid levels were below the desired level (target 25 mmol/L). In another study, ascorbic acid levels were compared in patients with an ulcer on the leg versus patients without an ulcer. This showed that the prevalence of low to very low levels was significantly higher in the ulcer group. It is unclear whether this effect is causal.

Several animal studies have investigated the effects of ascorbic acid. Three groups of rats which were treated with placebo versus ascorbic acid 100mg/kg/day intramuscular versus ascorbic acid 200mg/kg/day intramuscular were compared with eachother on the basis of healing of a gastrointestinal anastomosis after bowel resection. This showed a positive correlation between the anastomotic strength and dosage of ascorbic acid. A significant difference in wound healing was also found in a different rat study. The effect of

ascorbic acid (100mg/kg orally) versus control on the healing of end-to-end anastomoses was examined after a gastrointestinal resection. The effect was significant in favor of the ascorbic acid group. A similar effect was found when comparing rats, divided into four groups. Here, a control group was compared with an intramuscular vitamin A group, an ascorbic acid 100 mg/kg/day orally, and a group of ascorbic acid orally, vitamin A intramuscular group. This study showed reduced adhesion, inflamation and fibrosis in favor of the vitamin A + ascorbic acid group.

A surgical procedure creates oxidative stress. The effect of this on the ascorbicacid level was examined and showed a decrease during surgery. In addition, the population of vascular surgery patients contains a large number of smokers. Smoking also works oxidative. They are therefore required approximately 30% higher doses of ascorbic acid to achieve the same level as non-smokers. All these effects may explain reduced wound healing in vascular surgery patients.

This double-blind placebo-controlled randomized study examines the effect of once daily intravenous supplementation with ascorbic acid for four days starting one hour before surgery. As primary endpoint the percentage of wound healing four weeks after surgery has been chosesn. Secondary the percentage of wound healing of any ulcers on the lower extremities 4 weeks after surgery, the number of wound infections within 30 days from the day of surgery, the number and type of complications within 30 days from the day of surgery, the duration of hospital stay from the day of surgery, the number of readmissions within 30 days from the day of surgery and the number of deaths within 30 days from the day of surgery is being investigated.

When studying wound healing the time to complete wound healing is often used as a primary endpoint. The time till complete wound healing is probably unrealistic and not feasible within the available time of this study. From literature, the degree of wound healing is after 4 weeks, however, seems to be a clear prognostic factor for the probability of complete wound healing.

During this study deficient as well as non-deficient patiënts are included. Being deficient or not depends on the target bloodlevel of ascorbic acid. The current target is based on the occurence of Scorbutus (scurvy) and lies around the 2-35 µmol/L (Meander MC 25 µmol/L). It is questionable whether this target value is also the lower limit for all of the other processes in which ascorbic acid plays a role. There currently is no target value for the improvement of woundhealing. Also, as mentioned before, there is oxidative stress during surgical intervention. This can lead to a decrease in ascorbic acid level during the surgical procedure in patients who where not defined as deficient. It is of importance to know whether this phenomenon also occurs in our population, and it also provides information whether the proposed suppletion scheme is sufficient to prevent such a fall in ascorbic acid level.
Due to the extra information delivered by the non-deficient group, combined

with the minimal risks of ascorbic acid administration, the choice has been made to include patients indepent of their baseline ascorbic acid level.

The investigation of the effect of ascorbic acid in this category of patients is of interest. If there actually exists an effect, then this can lead to an inexpensive, simple and safe intervention in a vulnerable group of patients.

Study objective

Primary
Improved woundhealing in 30 days in patients with an open revascularisation of the lower extremities after treatment with 4 dosages of 2 grams ascorbic acid on 4 consecutive days. (First dosage 1 hour preoperative)

Secondary
With preoperative existent ulcers of the lower extremities: Improved woundhealing of the ulcers of the lower extremities in 30 days.

Reduction of the postoperative complications within 30 days postoperative (woundinfections, readmissions, all cause complications, death).

Reduction of postoperative hospital duration.

Study design

Doubleblind placebo controlled randomised monocentre study.

Intervention

Interventiongroup receives 4 administrations of 2000mg ascorbic acid (20ml) intravenously in 4 consecutive days.
Controlgroup receives 4 administrations of NaCl 0.9% (20ml) intravenously in 4 consecutive days.
First dosage in both situaties is given 1 hour preoperative.

Study burden and risks

Patients are not affected by the administration of the study drug because they already have a venflon because of the surgery. In addition, they experience minimal discomfort of the six blood samples throughout the study which all coincide with the regular blood tests. There is no additional work in the form of questionnaires, nor are there additional policlinical visits. All of the measurements take place during the regular policlinical visits.

The likelihood that patients will experience side effects of the administered amounts of ascorbic acid is small. The dosage used is registered and may result

in some cases nausea and diarrhea. With prolonged use, the risk of side effects is greater. Within the framework of this study, however, with only 4 dosages, the expected risk of side effects is minimal. Moreover, the literature suggests that the therapeutic index of intravenous ascorbic acid is very large and the incidence of adverse events is limited to mild symptoms that also occur sporadically.

The risk of unknown side effects is almost non existent because the used drug has been registered for a long period of time.

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

Planned open arterial revascularisation surgery on 1 or 2 legs.;Age >= 18 yrs.;Vascular

disease fontaine IIb or higher.

Exclusion criteria

Age < 18yrs.
Hyperoxaluria.
Patients on dialysis.
Paroxismal nocturnal haemoglobinuria.
G6P deficiency.
Recurrent kidney stones.
Hemochromatosis.
Hemosiderosis.
Usage of deferoxamine (in the past).
Immunological disease.
Pregancy.
Bilateral surgery, other than the revascularisation.
Intolerance for study medication.
Mentally incompetent patients.
Previous participation in this study.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-03-2016
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ascorbic acid
Generic name:	ascorbic acid
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-11-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-11-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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
EudraCT	EUCTR2014-005612-41-NL
CCMO	NL52012.100.15
Other	volgt