Vitamin C and ultrasound in the treatment of pressure ulcers

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Vitamin C and ultrasound in the treatment of pressure ulcers

Vitamin C and ultrasound in the treatment of pressure ulcers

PROEFSCHRIFT

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Chapter 1

Pressure ulcers, vitamin C and ultrasound

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Introduction

The lion's share of this thesis is devoted to the implementation of a randomised clinical trial of ascorbic acid supplementation and ultrasound in the treatment of pressure ulcers. This chapter provides a general background.

Pressure ulcers

Definition, grading and areas at risk

A pressure ulcer is an area of cellular necrosis arising from excessive (in magnitude and time) compressive or shear forces acting on a tissue.¹ More briefly, it is any lesion caused by unrelieved pressure.² To start with the exceptional, there are reports of pressure ulcers caused by the weight of bedclothes, a hand lying on the abdomen, the resting of one cutaneous surface against another.³ Pressure ulcers are also known as decubitus ulcers. The word 'decubitus' stems from *decumbere* (Latin: to lie down)⁴, but it is clear that prolonged pressure may occur in any body position. Another synonym is 'bedsore', but this too is misleading, because many bedsores are really 'chair' or 'operating-table' sores. We shall use the term 'pressure ulcer' throughout this thesis. Internationally, there are several similar grading systems to classify pressure ulcers with respect to the degree of tissue damage or severity.^{2,5,6} Straightforward and easy to remember is the way of grading as described in table 1 (adapted from reference 2 and 5). The Dutch grading system is unique in defining grade II as 'blister formation'only, which is rarely seen,^{7,8} whereas grade III is a combination of the international grades II and III.² Replacement of the aberrant Dutch system by one of its internationally accepted counterparts seems timely. To make the system complete, blister formation could be classified under grade II. Necrosis under intact skin and sinus tract could be classified as grade V.

Table 1. Grading system for pressure ulcers (adapted from references 2,5)

Grade I	nonblanchable redness of intact skin
Grade II	(epi)dermal skin loss only or blister formation
Grade III	involvement of subcutaneous tissue, not extending beyond the underlying fascia
grade IV	muscle, tendon, bone or joint involvement
grade V	necrosis under intact skin, sinus tract

Pressure ulcers are usually - but not exclusively - found over bony prominences. Four body areas frequently affected are: the sacrum, the heels, the greater trochanters of the femur, and the ischial tuberosities.⁹

Occurrence

Many decubitologists appear not to be aware of the difference between prevalence and incidence.^{2,9,10} The comparison of prevalence rates with risks and of various incidences with each other without specification of their time referents causes much confusion.² Incidence is properly defined as the appearance of events of a particular kind in a population of candidates over time.¹¹ Prevalence,

somewhat simpler, is defined as the proportion of a population that is in a particular state.¹¹ For diseases with a protracted course low incidences may result in high prevalences. Because the large majority of new pressure ulcers seem to occur during the first two weeks after hospitalisation,^{12,13} focusing on the two-week cumulative incidence to express an individual's risk might be more useful than on cumulative incidence also based on longer periods with hardly any new cases emerging after the first two weeks. Counting occurrences as an aim per se sheds light on the magnitude of the problem, and may be useful for planning purposes. Good insight into the occurrence of pressure ulcers is hampered by two opposing factors. On the one hand, it is still known as the emblem of bad nursing,¹⁴ possibly resulting in underestimation. On the other hand, investigators might be tempted to overestimate occurrence because research into a prevalent (and expensive) medical problem is more likely to bring funds and prestige. To be able to influence incidence and prevalence (prevention and therapy) both must be studied as functions of their determinants.

Etiology

Although some authors complain that the etiology has been insufficiently elucidated,¹⁵⁻¹⁷ it is generally believed that three main forces are implicated in pressure ulcer formation. They are (axial) pressure^{3,18}, shearing forces^{19,21}, and frictional forces.²² The last two could be viewed as forces acting on tissue tangentially, but friction is usually connected with repetitiveness,^{8,22} whereas shear forces are classically linked to raising the head of the bed with the patient tending to slide downward.¹⁹ It has been said that shear forces cause deep pressure ulcers, whereas friction usually causes more superficial ulcers.⁸ Moisture is sometimes mentioned as a separate cause of pressure ulcers. These factors, usually in interaction with each other, may obstruct local blood flow. It is known that the presence of shearing forces or friction reduces the amount of (axial) pressure necessary to produce blood flow obstruction.^{20,21} It is also known that intermediate amounts of moisture increase friction, potentially producing larger shearing forces.⁸ In addition, moisture can cause maceration of the skin. Given that the pressure exceeds a certain threshold value and is of sufficient duration, ulceration will ensue. The level of the threshold pressure is still not completely clear. Some sources maintain that because small venules collapse at a pressure exceeding only 11 mmHg (1.5 kPa), such pressures may obstruct blood flow. Others believe that the disruption of blood flow, whether capillary or venous, is not the whole story. They stress the importance of disruption of lymph flow, the accumulation of metabolic waste products, interstitial fluid flow and cell to cell contact.^{1,23} Table 2, which is not intended to be complete, summarises findings of several studies on the damaging effects of experimental pressure.

It is important to recognise that many factors can modify the (baseline) threshold pressure. Note that all investigators listed in table 2 used animals. We are not aware of similar data in humans and this is understandable because even among animals we seldom find volunteers for these experiments. We do not know how general anaesthesia and a perhaps slightly reduced muscle tone have influenced the results of these experiments. Research in which blood flow changes under the influence of external pressures are studied exists, but has typically used healthy volunteers, not debilitated patients or paraplegics.

Table 2. Summary of studies into the effects of experimental pressure on the formation of pressure ulcers

(1st) author (year, reference)	animal (organ)	pressure applied through	first damage* at mmHg†: hours	level of observation	modifying factors/first damage at (mmHg:hours)
Groth (1942, 24)	102 rabbits (gluteal region)	rounded metal indenter	24;14	microscopic	
		rounded metal indenter	24;16	macroscopic	
Husain (1953, 3)	141 rats (leg)	cuff	100;2	microscopic	3 days after femoral artery ligation (50;1) 3 days after ischial nerve division (100;1) 2 days after spinal cord transection (100;1) scurvy (50;1)
	45 guinea pigs (leg)	cuff	200;2	microscopic	
Kosiak (1959, 18)	14 dogs (hamstring area) (trochanter m. femoris & ischial tuberosity)	inverted syringe	60;1	microscopic	
		inverted syringe	500;2	macroscopic	
Kosiak (1961, 25)	12 normal rats (hamstrings)	inverted syringe	70;2	microscopic	alternating pressures at 5 min intervals (70;3)‡
	8 paraplegic rats (hamstrings)	inverted syringe	70;2	microscopic	alternating pressures at 5 min intervals (70;2)‡
Lindan (1961, 26)	rabbits (ears) (N=?)	plastic clips	60;13	macroscopic	
Dinsdale (1974, 22)	22 normal swine (posterior superior iliac spine)	metal square	290;3x1.5§	macroscopic	friction 45;3x1.5§
	10 paraplegic swine (post. sup. iliac spine)	metal square	520;3	macroscopic	friction 200;3
Daniel (1981, 27)	30 normal swine (trochanter m. femoris)	plexiglas indenter	100;10	macroscopic & microscopic	
Daniel (1985, 28)	normal swine (N=?) (trochanter m. femoris)	plexiglas indenter	200;18	macroscopic	
	30 chronic paraplegic swine (trochanter m. femoris)	plexiglas indenter	100;14	macroscopic	

* the lowest product of pressure and time was taken as the threshold of first damage.

† 1 mmHg = 0.13 kPa.

‡ alternating pressures showed consistently less change compared with constant pressure.

§ 1 hour rest period in between pressure periods.

|| standardised, but not exactly described. Six times every 15 minutes.

There seems to be no hard evidence that (applied) pressures under 24 mmHg (3.1 kPa) can induce pressure ulcers. If we restrict our observations to studies in

swine, whose skin is comparable with that of humans, at least 100 mmHg seems required to induce pressure ulcers, unless friction is applied. Maximum interface pressures observed with various supporting systems in one study are listed in table 3.^{29,30}

Table 3. Maximum interface pressures measured by Redfern et al. on ten different support systems²⁹

	Maximum pressure (mmHg)*
Low-air-loss bed	26
Feather pillows	36
Water bed	58
Polyether foam mattress	68
Ripple mattress	122
Operating table	140
Sprung mattress	164
Orthopaedic operating table with pelvic rest	260
Lino-covered floor	260

* 1 mmHg = 0.13 kPa.

As will be explained below, these absolute values must be interpreted with caution because they depend much on the pressure measurement device used. It should also be borne in mind that applied pressures are not necessarily equal to interface pressures. The measurement of the pressure that is transmitted to the deeper tissue layers is even more problematic. However, the pressure in deeper layers seems to be increased in areas where a firm protuberance, such as the greater femoric trochanter or the ischial tuberosity, is present.³¹ Lack of oxygen and nutrition ultimately leads to tissue necrosis. As early as 1946 investigators noticed that progressive damage occurs after occlusion is released and blood flow re-established (in the myocardium).³² More recently, this phenomenon has been called 'reperfusion injury' in which free radicals play an important role.³³ This has led to research into the preventive effects of free radical scavengers, such as superoxide dismutase and allopurinol.³⁴⁻³⁶

Prevention

Prevalence of pressure ulcers in skilled care and nursing homes in the U.S. is said to be approximately 23 per cent. At the same time, the U.S. Department of Health and Human Services has stated that "most [pressure ulcers] can be prevented".² When one reads these two statements, several things may be suboptimal: the care facilities, the counting, the statement that most can be prevented, or combinations of the three. Many findings from (animal) research have been translated into preventive measures. Two hourly repositioning is perhaps the most famous, taken seriously by many decubitologists. However, there are dissenters: "Sheep skins are not necessary, just as the unrealistic nursing order: Turn the patient every 2 hours. No scientific evidence exists for these notions."³⁷

There is a multitude of pressure relief products intended to divide the pressure more evenly across the body surface. It has been calculated that if pressure were evenly distributed over one fifth of the human skin area it would amount to only 16 mmHg at any spot compared to pressures as high as 100 mmHg on the sacrum and under the ischial tuberosities.^{26,38} The human body has no problems in handling pressures as high as 12,800 mmHg, as long as they are evenly distributed, such as in deep sea diving. Point pressures as low as 50 mmHg can cause damage, however.³ Producers of pressure relief products often use interface pressures, i.e., the pressure between the patient and their product, to indicate that the device will keep the pressure lower than (the magic) intracapillary pressure of 32 mmHg. But interface pressure readings are much affected by the size, shape and positioning of the measurement devices. This makes the data from different products and investigators difficult to compare. In addition, as Krouskop has pointed out, "32 mmHg is an average value for the capillary pressure in the finger tips of young healthy male volunteers [...] capillary pressures as low as 12 mmHg have been reported in geriatric patients."³⁹ Barbenel reports that there is no evidence of a critical closing pressure.¹⁶ The instruction not to elevate the head of the bed for longer periods of time is a measure that relates to the shearing forces acting under such circumstances. The patient tends to slide downwards, and kinking of blood vessels penetrating a fascia may occur.¹⁹ Caregivers are also advised not to pull the patient across the sheets, but instead to lift the patient completely. The latter reflects the importance given to reducing frictional forces.

A number of scales and instruments to predict pressure ulcer formation in individual patients have been developed. Such instruments, if valid, allow one to direct (scarce) preventive measures specifically to patients at high risk of ulcer formation. The Norton scale was developed in 1962 and has been modified by some, who now have their own scales.^{12,40-43} Braden and associates put some effort in actually testing the predictive power of their scale.^{42,43} Other techniques used are, for example, thermography¹⁴ and a pressure-time-temperature method that uses the pattern in the recovery of skin temperature to predict who is at high risk.⁴⁴

Treatment

Most experts agree that if a pressure ulcer develops, preventive measures should be continued, if not intensified. Treatment may be divided in general measures such as pressure relief and optimal nutrition, and topical measures. A recent development in the topical treatment of pressure ulcers is the use of recombinant human growth factors.^{45,46} Surgery is another option. If people have multiple ulcers it may be difficult to position them in such a way as to avoid any pressure on existing ulcers. In the elderly nursing home patients, even increasing the nutritional intake - advocated by many - may not be as easy as it seems. There is a multitude of topical treatments, relatively few of which have been adequately tested on effectiveness.

Reviewing the literature on all treatments of pressure ulcers is beyond the scope of this thesis. We know of many proposed treatments, most of which have never been rigorously studied in clinical trials.⁴⁷ The randomised trial that we have carried out tests the effects of two treatments on which clinical research was

scarce. We will discuss the design, the problems and the results of this trial in the chapters that follow.

Ascorbic acid, vitamin C

For many people, ascorbic acid is synonymous with vitamin C. What is a vitamin? A recent monograph defined a vitamin as: "(1) an organic compound distinct from fats, carbohydrates and proteins; (2) a natural component of foods where it is usually present in minute amounts; (3) essential, also usually in minute amounts, for normal physiological function; (4) causing a specific deficiency syndrome by its absence or under-utilization, and finally (5) not being synthesized by the host in amounts adequate to meet normal physiological needs."⁴⁸ As many animals can synthesise ascorbic acid, the latter is not a vitamin for them. However, man, the guinea pig and several other species have lost the ability to synthesise ascorbic acid from D-glucose or D-galactose. They lack the enzyme L-gulonolactone oxidase, which catalyses the final step in the biosynthesis of ascorbic acid. So, for these species vitamin C is an essential dietary requirement, guinea pigs dying after 25-30 days on a vitamin C free diet. The specific syndrome caused by vitamin C deficiency is known as scurvy [scurbutus in Latin], a lethal disease when untreated. In a healthy man, it may take up to 4-6 months on a vitamin C free diet to produce frank scurvy. Striking features of scurvy are the reappearance of (long) healed wounds and fractures and the disturbed healing of fresh wounds.

Vitamin C is the generic descriptor for all compounds (Combs⁴⁸ lists nine) exhibiting qualitatively the biological activity of ascorbic acid.⁴⁸ L-xylo-ascorbic acid ($C_6H_8O_6$) is the naturally occurring vitamin. It is reversibly oxidised to L-dehydroascorbic acid that has about 80 per cent of the anti-scorbutic biopotency of ascorbic acid.^{48,49} In man, several enzymes are dependent on ascorbic acid for maximal function.⁵⁰ Ascorbic acid acts as co-factor of these enzymes, of which proline and lysine hydroxylase and a procollagen dioxygenase are of direct relevance to the topic of wound healing.⁵⁰

Some highlights in the relation between vitamin C and wound healing

The history of vitamin C and wound healing is closely linked to that of the clinical trial. In 1747, the Scottish naval physician, Lind, carried out what is probably the first controlled clinical trial in history on 12 sailors suffering from scurvy. He showed that the daily intake of two oranges and a lemon cured scurvy whereas the intake of cyder, elixir vitriol, vinegar, sea water or purgatives did not.⁵¹ The effect was so clear cut - within a week the two sailors who took the fruit were fit for duty and able to assist in nursing their fellow-patients - that Lind did not have to rely on multiple regression analysis or large numbers of sailors.

In 1926, Wolbach and Howe observed, in scorbutic guinea pigs, that the supplementation of the diet with the 'antiscorbutic substance' (in this case, orange juice) resulted in "no difference between treated and untreated guinea pigs in the promptness and volume of fibroblastic proliferation, though striking contrasts were present in collagen formation and in growth of capillaries." They "advance the theory that the failure of cells to produce intercellular substance in scorbutus is due to the absence of an agent common to all supporting tissues which is responsible for the setting or jelling of a liquid product."⁵²

Early in the 1930s vitamin C was identified as the agent Wolbach and Howe were hinting at.^{53,54} Today, it is known that vitamin C is necessary for the formation of stable collagen, a fibrous protein found in all multicellular animals. The synthesis of collagen proceeds in steps. First, polypeptide chains are formed on membrane-bound ribosomes. These are injected into the lumen of the endoplasmic reticulum as so-called pro- α -chains. Here some parts of the chain, proline and lysine residues, react with water molecules. Vitamin C is necessary in these hydroxylation reactions, which are catalysed by the enzymes proline and lysine hydroxylase respectively. The pro- α -chains then form triple-stranded helical molecules known as procollagen. Procollagen is excreted from the cell and turned into collagen by removal of some extra amino acids located at both terminals of the molecule, the propeptides. Normal collagens are continuously degraded by extracellular enzymes, the so-called collagenases. In scurvy, the defective pro- α -chains that are synthesised, fail to form a triple helix and are immediately degraded. The hydroxylation of the lysine residues is thought to be necessary for the extensive cross-linking of collagen molecules in the extracellular space.⁵⁵ A role for vitamin C has also been suggested in the synthesis of proteoglycans⁴⁸, which, together with glycosaminoglycans, form the gel-like tissue ground substance. In this substance fibrous proteins, such as collagen, are embedded.⁵⁵

Experimental scurvy in humans

Studies in which scurvy was experimentally induced in healthy volunteers have shown that imperfect healing of wounds does not occur in the early stages of depletion.⁵⁶ In one study (one volunteer, who was the first author) it took between three and six months before wound healing became clinically and histologically impaired.⁵⁷ In a few other studies of the effects of depletion it could not be excluded that the diet contained a few milligrams of vitamin C.^{58,59} However, it is clear from these studies also, that, apparently very small daily amounts of vitamin C prevent the occurrence of clinically disturbed wound healing and scurvy. In a more recent study, six prisoner volunteers received a vitamin C free diet for 100 days. Unfortunately for science, two prisoners were lost to follow-up because they escaped after 55 days. On the 100th day surgical incisions on the thighs were made in the remaining four men. They were then supplemented with daily amounts of 4, 8, 16, and 32 mg of vitamin C. The authors report that "Wound healing proceeded to completion" and "Punch biopsies taken from the wound margins after 1 and 2 weeks did not show convincing histologic differences in the rate of healing."⁶⁰ This study does not strictly exclude the possibility that a megadose would have caused more rapid or better healing.

The most informative study with respect to vitamin C depletion and wound healing was performed between 1944 and 1946, in England, and is known as the Sheffield study (N=20), in which "scurvy developed in all those volunteers completely deprived of vitamin C (N=10) but could be quickly relieved by a daily dose of 10 mg".⁵⁶ Much attention was given to wound healing experiments. It was not sooner than after six months after the start of deprivation that wound healing became clearly disturbed. In three volunteers who stayed on a daily dose of 10 mg for almost nine months, wound healing proceeded normally "judged by the appearance of the excision scar on inspection".⁵⁶ One month after saturation with vitamin C breaking strength experiments on excised wounds showed that "normal

capacity for wound healing was not restored (...) in those who had undergone prolonged deprivation".⁵⁶

In conclusion, these experiments seem to indicate that in healthy volunteers small amounts of vitamin C are sufficient for normal wound healing. These studies do not unequivocally exclude the possibility that vitamin C in high dosages enhances wound healing or breaking strength. Furthermore, the studies were not designed to elucidate what the requirements with regard to wound healing are in debilitated people or specific categories of patients.

Higher dosages in guinea pigs

We have just seen that a daily vitamin C intake of 10 mg protects humans from scurvy. The corresponding amount, the minimal requirement, in guinea pigs is about 0.5 mg.⁶¹ These requirements put into perspective the amounts used in the studies that we shall discuss below.

Guinea pig wound tissue shows wide variations of vitamin C concentration in line with high or low intake of the vitamin.⁶² It was also shown that the wound rupture levels of wounds having a high vitamin C content are much higher than those of wounds with a low vitamin C content.⁶² Abt and associates broadly confirmed these results in a later study.⁶³ It was also observed that, in contrast to intact muscle at some distance from the wound, wound tissue showed a large increase in vitamin C during the healing period.^{63,64} Bourne observed in experiments in guinea pigs that tensile strength of wounds of animals that had received 30 mg of vitamin C daily was not increased over that in animals that had obtained a daily dose of 2 mg.⁶¹ However, tensile strengths in animals receiving 1 mg or less was much lower than in those that received 2 mg. Results by Yew, who measured the time required for scabs to fall off also indicated that intakes over 2 mg do not speed up healing.⁶⁵ Abt et al. found that the wound rupture levels were higher after daily intakes of 6, 30 or 90 mg as compared to intakes of 0 mg. However, the differences between the daily intakes of 6, 30 and 90 were neither large nor statistically significant.⁶³ In conclusion, these data show that, at least in guinea pigs, the minimal daily amount required (0.5 mg, oral administration) does not produce maximum tensile strength. However, they also indicate that daily intakes of about 4 to 12 times the minimal requirement do make sense.^{61,63}

Higher dosages in humans

No systematic studies have been performed to see whether wound healing is enhanced by supplementing healthy people not deficient in vitamin C. However, three placebo-controlled trials of the effect of ascorbic acid supplementation (100-200 mg daily) on the incidence of bleeding gums, carried out in R.A.F. personnel during the World War II, provided no evidence that supplementation is useful.⁶⁶ There are some indications that the utilisation of vitamin C might be increased under physically and mentally stressful circumstances. However the significance of these findings is unclear.⁶⁷

Higher dosages in pressure ulcers

Rajan and Burr found that pressure ulcers in paraplegics contained higher concentrations of vitamin C after three-day supplementation with one gramme of vitamin C compared to placebo.⁶⁸ This confirms the observations made in guinea pigs.^{62,63} However, the direct inducement for our own research was a controlled

trial published in 1974. Taylor et al. found a great enhancement of the wound healing rate in ten surgical patients with pressure ulcers compared to ten patients receiving a placebo.⁶⁹ In 1982, in their book on vitamin C, Basu and Schorah summarise the role of vitamin C in wound healing as follows: "... with the possible exception of certain types of wound such as the bed sore, research in both animals and humans indicates that large doses of vitamin C do not encourage more rapid tissue healing than the smaller intakes to prevent hypovitaminosis C (60 mg/day)."⁷⁰

Additional inducement

Vitamin C is the molly-coddle of orthomolecular medicine, a term coined by Linus Pauling in 1968.⁷¹ In his book, *How to live longer and feel better*, Pauling, referring to the study by Taylor et al.⁶⁹, states: "The investigators point out that their results have high statistical significance in showing the acceleration of healing of pressure sores by 1 g per day of vitamin C. A larger intake should even be more effective."

We argue that before accepting Pauling's claim it might be useful to find out whether the results by Taylor et al. could be reproduced. The study that we designed and carried out to do this is described in the chapters three to five of this thesis.

Ultrasound

Sound is our perception of a train of periodic compressions and rarefactions of an elastic medium, such as air, water or living tissue. It is transmitted in the form of waves.⁷² Waves can be reflected, and the reflections received and translated into a visual image. This is done in diagnostic ultrasound. However, in our work we used ultrasound for a therapeutic purpose. Our interest was to transmit sound energy into the tissues, hoping that this would affect wound healing in a beneficial way.

One of the characteristics of sound is its frequency (in cycles per second (c/s) or Hertz (Hz)). Sound with a frequency above the human upper limit of auditory sensation - 15,000 to 20,000 Hz - is called ultrasound.

For detailed information on ultrasound physics we refer the reader to handbooks.⁷²⁻⁷⁵

The ultrasound that we have employed in our research had a frequency of just over three million Hertz or 3 MHz. High-frequency sound (> 1 MHz) tends to travel in flat wavefronts. Ultrasound is produced with the help of the piezoelectric effect (also known as the reverse Curie effect), discovered about a century ago. When an alternating voltage is applied to the two faces of a crystal the crystal expands and contracts in synchrony with the electrical potential applied.⁷² Before turning to the alleged healing properties of ultrasound we should mention in passing that in the early days damaging effects of ultrasound were studied in unicellular organisms, small fish and frogs.⁷⁶ Ultrasound has also been employed in experimental embryology to induce abnormal embryonic development in insects.⁷⁷ Much research focusing on mechanisms of action of ultrasound has been carried out in plant tissues. In agriculture, people have tried to enhance germination and growth of seeds.⁷⁸

In 1949, at the First International Ultrasonics Congress, (uncontrolled) statistics on over 100,000 patients were presented. Excellent or good results were claimed in over 70 percent of cases of venous ulcers.⁷² From the 1950s onwards the use of ultrasound in medicine spread rapidly, therapeutic ultrasound being used mainly by physiotherapists. During our research in Dutch nursing homes in 1991 and 1992 we gained the impression that the use of ultrasound in the treatment of pressure ulcers was on the decline, sometimes being replaced by other modalities of questionable efficacy, such as laser therapy. For our project this had the advantage that few patients had been treated with ultrasound before participating in our trial. On the other hand, we sometimes feared that if our findings were to indicate the inefficacy of ultrasound in the treatment of pressure ulcers, physiotherapists might simply say that they had stopped using it anyway. Positive findings that come too late may sometimes also be considered as irrelevant if a new, but not necessarily effective, technique has replaced the one that was studied over a period of some years.⁷⁹

Mechanism of action

Let us turn to the mechanisms by which ultrasound might produce its effects on living tissues. It is not our purpose to review the extensive literature on this subject here, but merely to convey some concepts that might clarify to the non-biologist why ultrasound could have an effect at all. With respect to wound healing, several mechanisms that might explain the possibly beneficial effects of ultrasound have been proposed. Usually, thermal effects and nonthermal effects are distinguished. To separate the consequences of these two, investigators have for example carried out experiments with ultrasound on tissues cooled in ice water arguing that any effects found could only be due to nonthermal mechanisms. Furthermore, by performing experiments under different atmospheric pressures it may be possible to rule out nonthermal effects, such as cavitation (see below), which are unlikely to act under high pressure. If sound energy is absorbed by a medium, this energy is converted into heat. Lehmann et al. observed that living tissues are heated up by ultrasound.^{80,81} We know that biochemical reactions, rates of fluid flow, and particle diffusion are temperature dependent.⁷⁴ So, in theory, a whole range of consequences could be expected on the basis of thermal effects alone. Nyborg calculated that ultrasound with characteristics very close to the ones we used (3 - 3.5 MHz and a (time averaged) intensity of 0.1 W/cm²) causes an initial rise of the local tissue temperature of 0.7 degrees Celsius per minute.⁷⁴ This rise is not constant as the blood flow and conduction are influenced by temperature. Hykes et al. wrote that "thermal effects dominate at low megahertz frequencies (1-10 MHz), which tend to mask other nonthermal effects."⁷³

Other mechanisms of action are not related to raising the temperatures. One could distinguish between cavitation and torques.^{74,75} Cavitation involves the formation in tissue fluids of micron-sized bubbles. The bubbles may start to pulsate in the ultrasonic field and may cause fluid movements. These fluid movements are known as microstreaming. If local pressures become too high, the micro-bubbles can violently collapse causing free radical formation and tissue damage. This type of cavitation is called 'unstable (or transient) cavitation' and should be avoided by keeping local peak intensities low. According to Hykes et al. "there is general consensus that cavitation is a threshold effect, but the

intensity levels necessary for the production of cavitation in tissue are a matter of debate.⁷³

Microstreaming can also occur without cavitation as a result of local torques. Such torques may occur if objects with densities different from that of the surrounding medium are in an ultrasonic field.⁷³

Microstreaming is capable of changing diffusion rates and cell membrane permeability e.g. to calcium ions.⁷⁵ There are reports of increased protein, and more specifically, collagen synthesis by fibroblasts⁸² and increased release of histamine and serotonin by mast cells⁸³ and macrophages.⁸⁴ In conclusion, most authors seem to believe that the biologic membrane is the site of interaction.⁸⁵

An undesirable effect of ultrasound is standing wave formation, which may occur if a reflected sound wave interacts with an incident wave. If the conditions are suitable, dangerously high local pressures may be produced. This can easily be avoided by continuous movement of the ultrasound transducer during treatment.⁷⁵

A distinction is often made between therapeutic ultrasound applied in a continuous and a pulsed mode. In contrast to the continuous mode, in the pulsed mode there are pauses in which no energy is emitted. For example, the duration of a sound pulse in our devices was 2 milliseconds (ms). This was followed by a period of 8 ms in which no ultrasound was emitted. This cycle, the pulse repetition period, was then repeated 100 times per second. The rationale for the use of the pulsed mode is that during the 'silent' periods, heat can be carried off by blood flow and conduction. One could argue that in areas with sluggish blood flow, as areas of pressure ulcers are likely to be, one should be especially careful to avoid potentially dangerous rises in temperature.⁷⁵

Clinical trials have a very limited potential to cast light on the validity of the mechanisms explained above. Their utility lies in answering a much simpler question, viz.: is the wound healing process enhanced to such an extent that we should consider the use of ultrasound in the treatment of, in this case, pressure ulcers? Our research project was designed to answer this question. In the choice of treatment parameters we have been quite pragmatic. We wanted to attain absorption by fibroblasts located superficially in the wound. That is why we chose a fairly high frequency (3 MHz) instead of 1 MHz. We wanted to avoid too much heat production and chose therefore a pulsed instead of continuous mode. Last but not least, replication of the trial by McDiarmid, where the same choices were made, was important to us.⁸⁶ Leaving aside our trial, theirs is the only published randomised trial of ultrasound in the treatment of pressure ulcers. They were unable to find an overall beneficial effect. However, they reported that ultrasound was superior to sham in a subgroup of infected wounds. For a summary of controlled clinical research on the healing of venous ulcers the reader is referred to chapter 6.

This thesis is organised as follows. **Chapter 2** is the report of a survey. In that survey, we presented a well-defined case of a patient with a pressure ulcer to members of three health-care specialties. We asked their opinion on the efficacy of thirty treatments for pressure ulcer in this kind of patient. In **chapter 3** we describe the rationale behind our own trial and its design. **Chapter 4** should be interesting to those who do not like our findings. It deals with things that, almost, went wrong. In **chapter 5** we present the results of the vitamin C part of the trial.

In **chapter 6** the ultrasound part of the trial is **presented**. Finally, **chapter 7** contains a summary of this thesis.

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Chapter 2

Health-care professionals' views of the effectiveness of pressure ulcer treatments

A survey among nursing-home physicians, dermatologists and nursing staff in the Netherlands*

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Abstract

In a survey, 237 nursing home physicians, 113 dermatologists, and 164 supervisory nurses in nursing homes rated 30 treatments for stage III pressure ulcers by scoring their effectiveness.

On average, there seems to be a fair degree of consensus between these groups of health-care workers about the effectiveness of most treatments. The most notable exceptions are ultraviolet light, ultrasound, and laser therapy, and myocutaneous flap operations. Here, the dermatologists disagree with both nursing-home physicians and nurses.

However, within all specialties there is disagreement about the efficacy of ultraviolet light, ultrasound, and laser therapy, and the topical application of zinc oxide, betadine iodine, sodium hypochlorite and a few others.

Introduction

In Britain, a consensus report on the prevention and treatment of pressure ulcers is likely to be published this year.¹ In the Netherlands, such a report was published in 1985 (on prevention)^{2,3} and 1986 (on treatment)^{4,5}. These reports may suggest that matters have been settled. However, as Skrabanek has pointed out, "the very need for consensus stems from a lack of consensus".⁶

In a survey among members of three relevant medical specialties involved in the care of patients with pressure ulcers in the Netherlands, we investigated the extent to which they agreed about the effectiveness of different treatments, many of which are mentioned in the Dutch consensus report^{4,5}. An English summary of that report is given in Appendix 1.

Another background of this survey was the preparation for a repeat of the only controlled clinical trial of ascorbic acid supplementation for patients with pressure ulcers.⁷ We wanted to assess the prior opinions of specialists in this field with regard to this hypothesis in order to judge whether they would change their opinion in the light of new evidence. In addition, we were looking for a 'free rider' in the trial, i.e. another intervention that we could investigate in the same trial using a factorial design.⁸ Because we surmised that the ascorbic acid hypothesis would have low credibility among specialists we preferred to choose a free rider that would be more controversial while, at the same time, lacking adequate support from controlled trials. In that case the results of this part of the trial would be informative to the medical community regardless of the outcome. One can compare this strategy to that which experienced clinicians use in selecting diagnostic tests. There, test results are most informative where the pretest odds of disease are close to 50:50.

In the survey, apart from the Dutch participants, we included all authors of articles on clinical research on pressure ulcers listed in the Science Citation Index from January 1985 to April 1990 in this survey. We expected them to have greater knowledge of the relevant literature thus serving as a kind of 'gold standard'. Unfortunately, the response in this group was very low (<40%), hardly forming a sound basis for generalization. Therefore, we decided not to include the results from this group in the paper.

Participants and methods

We selected 30 treatments as items for the survey. These were chosen partly because of their widespread use and partly because their efficacy has been tested in clinical trials.

From the address books of nursing-home physicians, dermatologists, and supervisory nursing-staff in nursing homes (in short: nurses) in the Netherlands random samples containing 282, 183, and 225 subjects respectively were drawn. These numbers represent approximately 50% of all members of these specialties in the Netherlands. The samples of the nursing home physicians and the nurses were drawn in such a way that each nursing home was represented by one member of each specialty. This was not the case for the dermatologists.

In the spring of 1990 they received a postal questionnaire seeking their opinion about the effectiveness of different pressure ulcer treatments, presented in alphabetical order. We confronted them with a well defined clinical case which

was thought to be representative of a large category of patients. The following text clarified our survey: 'Of course, in practice interventions are very often combined. However, we ask you to rate them separately. The question which we ask you to answer 30 times is the following: how effective do you rate this intervention, if performed according to the accepted standards, in the treatment of the pressure ulcer in the following patient?' (see table 1).

Table 1.

It concerns a 76-year-old female nursing-home patient. Her right buttock shows a 3-day-old pressure ulcer. It has the following characteristics: stage IIIa (ulcer reaching into the subcutaneous fat, no necrotic tissue, and on palpation no signs of deep tissue involvement); surface area: 12 cm ² ; little or no granulation tissue; no scab formation; the skin surrounding the ulcer is red. General information: the medical reason for her admission is a paralysis of the left side of her body (hemiplegia); body-weight:	73 kg; length: 1.62 m (5.3 ft); she has been bed-ridden for the last week due to influenza; otherwise healthy with good appetite; no loss of sensibility on the right side of her body; no peripheral vascular problems; no incontinence; no diabetes mellitus; no intake of soporific medication; body temperature: 38.8°C; mobility: she uses a wheelchair for distances >100 m (90 yd); serum albumin concentration: 42 g/l; hemoglobin: 8.4 mmol/l.
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Participants could express their opinion as a score between 0 and 10, where 0 meant harmful, and 1-10 ranged from 'not at all effective' to 'very effective'. In addition, 'no opinion' could be indicated. In the analysis (separate for each specialty), we calculated for all interventions the percentage of responders who indicated 'no opinion', who considered the treatment harmful, and the distribution of perceived effectiveness. The mean values in table 2 are based only on the people who responded with a score from 1 to 10. By comparing the means one gets an idea of the agreement between specialties, whereas the distributions show the extent to which agreement exists within each specialty.

Results

After two reminders the response among nursing home physicians, dermatologists, and nurses was 237 (84%), 113 (62%), and 164 (73)%, respectively. Table 2 shows the scores for each specialty. We report these scores under five headings namely measures involving body support, nutritional measures, application of physical energy, topical wound care, and miscellaneous other measures. There seems to be a high degree of consensus both among and within the three specialties that the *measures involving body support* are effective treatments. For example, in all specialties, over 90% considered positioning of patients every 2 hours to be effective (or even very effective; score >7). Also, a fair degree of consensus was found for air-fluidised beds and water mattresses with mean scores of approximately 7. The effectiveness of flotation pads appeared more controversial.

Table 2. Opinion of three medical specialties in the Netherlands about the effectiveness of 30 treatments for the patient with a grade IIIa pressure ulcer described in table 1

Specialty Respondents	nursing home physicians (n=237)						dermatologists (n=113)						nursing home nurses (n=164)					
	Distribution%						Distribution%						Distribution%					
	a	≤4	5-6	≥7	b	c	a	≤4	5-6	≥7	b	c	a	≤4	5-6	≥7	b	c
Measures involving body support																		
Positioning every 2 h*	8.3	1	2	97	0	0	8.2	1	4	95	0	0	8.3	0	3	95	0	2
Air-fluidised bed†	7.1	5	7	71	0	18	7.6	3	7	76	1	14	7.0	6	8	61	0	25
Water mattress†	7.0	6	14	73	0	8	6.6	12	14	63	1	10	7.0	6	11	76	0	7
Low-air-loss bed†	6.7	8	4	44	0	44	6.9	6	8	46	0	40	6.5	6	10	33	0	51
Rotation pad†	6.2	13	19	60	1	7	5.3	17	23	28	6	27	6.0	18	15	58	1	7
Nutritional measures																		
Protein-enriched diet	5.2	31	22	42	1	4	5.0	35	17	44	0	5	5.2	30	20	42	2	6
Multivitamin supplementation	2.3	72	14	3	2	8	2.5	69	8	7	5	11	3.0	44	11	9	3	33
Vitamin C 1000 mg/day orally	2.1	69	8	5	2	17	2.0	65	7	3	6	19	2.3	49	8	4	3	36
Zinc sulphate 660 mg/day orally	1.7	45	1	2	8	43	2.2	56	12	1	4	28	2.1	32	1	4	6	57
Application of physical energy																		
Ultraviolet light therapy‡	4.0	43	22	22	7	7	2.3	54	8	4	19	15	4.4	33	15	27	5	20
Ultrasound therapy†	4.0	44	20	22	4	10	2.6	59	11	6	9	15	4.3	35	3	25	11	24
Laser therapy	2.1	28	2	3	9	58	1.5	41	3	0	16	40	3.1	20	4	7	6	63
Electrical nerve stimulation	2.0	48	4	3	5	39	2.0	53	8	2	5	32	2.6	40	9	6	2	44
Topical wound care																		
Zinc oxide topically*	5.3	29	16	46	3	6	5.0	29	34	30	2	6	5.6	17	19	41	3	20
Betadine iodine*	5.3	31	22	45	6	3	4.7	30	35	28	4	4	4.7	33	25	29	7	6
Duoderm™†	5.1	31	18	43	2	7	5.3	26	15	44	9	6	5.4	27	18	46	3	6
Silversulphadiazine	4.4	32	17	25	7	20	5.4	21	33	41	2	3	3.9	27	8	16	7	43
Dakin's solution (Na hypochlorite)†	4.0	30	9	18	9	35	4.2	34	15	20	7	24	3.9	24	12	14	4	46
Opsite™†	3.7	44	18	15	4	18	3.8	41	19	16	9	15	3.8	41	20	19	5	16
Dextranomer (Debrisen™)	3.1	52	14	11	10	14	4.1	43	27	21	4	6	3.8	39	13	19	8	22
Collagenases	2.2	59	7	4	11	19	2.8	60	9	10	3	17	3.0	30	7	6	8	49
Ketanserin topically	1.7	32	1	2	7	58	2.5	38	8	5	3	47	2.0	16	1	1	9	74
Growth factors (autologous)	1.5	28	1	0	4	67	2.3	29	6	4	5	57	2.0	20	1	1	4	74
Vitamin C topically	1.3	64	0	0	9	26	1.3	65	0	0	12	23	1.7	49	2	2	6	41
Insulin topically	1.1	41	0	0	15	45	1.4	46	0	0	11	43	1.5	22	2	0	15	62
Miscellaneous treatments																		
Patient education*	6.9	11	11	77	0	0	6.8	13	9	70	1	7	7.0	8	14	74	0	4
Myocutaneous flap operation	4.5	29	5	28	16	22	6.1	17	8	46	11	18	4.5	21	9	19	7	44
Metronidazole	2.5	52	8	8	8	25	2.6	57	7	7	3	20	2.5	30	3	4	5	59
Complamin iontophoresis‡	2.5	49	6	7	4	35	2.0	51	5	3	6	36	2.8	32	6	5	6	53
Hyperbaric oxygen therapy	1.7	45	2	2	5	47	2.3	51	8	3	2	37	2.5	25	7	3	6	59

a mean score
b harmful
c no opinion
* intervention judged as useful for grade IIIa in the Dutch consensus report^{4,5}
† intervention judged as potentially useful in individual cases of grade IIIa in the Dutch consensus report^{4,5}
‡ intervention judged as not useful in grade IIIa in the Dutch consensus report^{4,5}
1- 4 not or hardly effective
5- 6 not very effective
7-10 effective or very effective

In the area of *nutritional measures*, on average, the three specialties agreed to a large extent. However, a protein-enriched diet (in this patient with a normal serum albumin) turned out to be a source of disagreement with some 40% of respondents rating it with a 7 or higher and some 30% with a 4 or lower in all specialties. The other measures under this heading were not given much credit.

The different *applications of physical energy* were not rated very positively, i.e. no mean scores over 4.4 in any of the groups. Fairly common therapies such as ultraviolet light and ultrasound therapy were given low credit by all three specialties, especially by the dermatologists. Also, the dermatologists agreed among each other that these therapies are ineffective, while in the other specialties opposing beliefs were more prevalent.

Surprisingly, the *topical wound care measures* were not judged to be effective by most respondents. However, in all specialties there was much disagreement on zinc oxide, betadine iodine, Duoderm™, silversulphadiazine, sodium hypochlorite, and Opsite™. A high percentage of respondents indicating no opinion suggests that many did not know what to think of therapies such as the use of autologous growth factors and the topical application of ketanserin or insulin. It may also indicate that many had never heard of them.

In the category of *miscellaneous treatments* there was striking consensus that patient education was effective. Whether myocutaneous flap operations are effective in patients with the kind of pressure ulcer described, appeared to be a matter of dispute in all specialties.

Discussion

The data apply strictly to the opinions of the specialties. Of course, these opinions should not be taken as proof of true efficacy. Also, the opinions apply to patients with pressure ulcers such as the one described in table 1. In our opinion, presenting a well-defined clinical case representative of a large but specific category of patients is the only way to collect this kind of data in an unambiguous way. Thus, instead of limiting it, the generalized applicability is enhanced. On the other hand, the small non-response somewhat limits the generality of the results. We are not aware of similar studies in other countries.

In the Dutch consensus report^{4,5} specific mention is made of 14 of the 30 therapies in table 2. Ironically, in seven of them a large degree of within-specialty-disagreement can be seen. On the measures involving body support (except, perhaps, flotation pads), patient education and treatment with complamin iontophoresis a good deal of consensus exists between and within the specialties. The dissent is not surprising. Why should there be agreement if unequivocal evidence is lacking?

Of course, there may be useful evidence which clinical decision makers (usually physicians) are unaware of. That is to say, some of the disagreements may be unnecessary. A potentially useful way to confront clinical decision makers with the evidence from clinical trials might be the publication of review articles.

Where useful evidence is lacking, a survey such as the one presented here could be helpful in selecting therapies for formal testing in a new clinical trial. The analogy with diagnostic strategies was explained in the introduction of this article. We selected ultrasound therapy (little evidence and a great deal of disagreement) as a treatment in a randomised trial, in which, for other reasons, the effect of vitamin C will also be tested. This trial started in January 1991. Data collection will be complete at the end of 1992.

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Appendix 1

Summary of the Netherlands Consensus Report on the treatment of pressure ulcers.^{4,5}

The report notes that relatively little evidence from controlled clinical research on the effectiveness of several treatments exists. Available evidence together with measures that seem logical and not harmful have been summarised in the report. In addition, a description of grades of severity is given. Basically, four grades are distinguished: (I) local redness (not removable by pressure); (II) formation of a blister; (III) superficial lesion, and (IV) deep lesion. Grades III and IV are both subdivided into grades 'a' and 'b' to indicate lack or presence of necrosis, respectively.

With regard to treatment three levels of usefulness are distinguished: useful, potentially useful in individual cases (not advised for general use), and not useful. The continuation of preventive measures (frequent positioning, patient instruction and establishing an individualised nursing plan) is considered useful in every treatment. Detailed description of the consensus on cleaning and covering of ulcers is beyond the scope of this article. However, table 2 shows how the report judges 14 treatments that were mentioned specifically when dealing with grade IIIa ulcers.

Irrespective of grade, the report designates a number of topical treatments as 'not useful' e.g. preparations likely to induce allergic reactions, mercurychrome, complamin iontophoresis, and irradiation with ultraviolet light.

As regards treatment evaluation, much is expected from meticulous registration of risk assessments, grading, and prescribed therapies.

Chapter 3

Design of a randomised clinical trial of ascorbic acid supplementation and ultrasound in the treatment of pressure ulcers*

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Abstract

In a randomised clinical trial we investigated the effects of ascorbic acid supplementation and ultrasound in the treatment of pressure ulcers. In this article we discuss the choice of the interventions, the choice of the patients (and their pressure ulcers), and the choice of the effect measurements. In addition, the techniques used to increase the likelihood of between-group similarity are discussed. We distinguish between similarity at baseline (by means of selection and stratified randomisation), similarity of co-interventions (by means of standardisation and blinding), and similarity of effect measurement (by means of standardisation and blinding).

Introduction

This article describes the design of a multicentre blinded randomised clinical trial of ascorbic acid (AA) and ultrasound therapy (UST) in the treatment of pressure ulcers.

Compromises with regard to the study methods generally occur at two stages. First, the investigator, who is aware of the ethical, financial and time constraints, usually does an exercise in self-censorship when writing the study protocol. One aims at doing the feasible. Further compromises during the conduct of the trial, e.g. loss to follow-up, usually cannot be avoided. Here, we focus on the design of our trial. The problems encountered during its execution are described elsewhere.¹

The design is presented under seven headings. We start with a discussion on the choice of (1) the interventions, (2) the patients, and (3) effect measurements respectively. The next three headings discuss various techniques used to maximise between-group similarity at (4) baseline, (5) at the level of the cointerventions, and (6) at the level of the effect measurements. A separate section (7) deals with data analysis.

Choice of the interventions: ascorbic acid (AA)

Reviews on food supplements frequently cite a placebo-controlled trial published in 1974 by Taylor et al.² They found that the oral administration, twice a day during one month, of 500 mg AA accelerated the healing of pressure ulcers considerably, viz. 84% vs 43% mean reduction in pressure ulcer area in the index and reference groups respectively. Unfortunately, the trial was small ($N=2 \times 10$) and has, to our knowledge, never been replicated. If the results are valid, they may be explained by an enhanced collagen formation and secretion by fibroblasts.^{3,4} Evidence that AA supplementation in non-scorbutic people does not appear to affect the healing of incisional wounds can be found in several other studies.⁵⁻⁷ A closer look at the trial by Taylor et al. shows that the patients had fairly low leukocyte (actually buffy layer) AA concentrations at baseline (median: $20 \mu\text{g}/10^8$ cells in both groups; 75% of values between 11 and $40 \mu\text{g}/10^8$ cells and 14 and $31 \mu\text{g}/10^8$ cells in the placebo and AA group respectively; lower limit of normal in their laboratory: $18 \mu\text{g}/10^8$ cells). Although suggestive, these values do not prove poor tissue reserves of the vitamin, because interpretation of buffy layer AA levels is problematic if the relative numbers of cells constituting the buffy layer - polymorphonuclear leukocytes, lymphocytes and platelets - are unknown.⁸ Evidence of a beneficial effect of AA in the prevention of pressure ulcers, although from less rigorous research, is presented in two other studies.^{9,10}

We conducted a therapeutic trial, mainly to replicate the trial of Taylor et al. From a therapeutic viewpoint, findings consistent with those of Taylor et al. even if the effect were slightly less impressive, could result in firmer establishment of an effective, inexpensive, and easy to administer treatment in the management of pressure ulcer patients. From a scientific viewpoint, a negative result, in our larger trial, would undermine the idea that pressure ulcers represent the exceptional category of wounds where AA supplementation would be useful.¹¹ Such a result might end the debate on the usefulness of AA supplementation in the enhancement of wound healing.

Taylor and co-workers employed pure placebos (0 mg AA) in their reference group. However, we chose to contrast a 1000 mg daily AA supplementation with a dose capable of alleviating frank deficiency. In that case, a positive result could not be countered by the argument that the mere alleviation of deficiency might have produced the same results as a 'kilodose' supplementation. Thus, the trial should provide a valid answer to the following clinical question: 'Should we simply supply our pressure ulcer patients with about 70 mg AA per day (diet included) in order to optimise the healing of their pressure ulcers or should we supplement them with 1000 mg per day?' Seventy milligrams is the recommended daily allowance (RDA) in the Netherlands.¹² Taking into account that the nutritional AA intake of many Dutch institutionalised elderly people appears to be less than the RDA (between 41 and 84 mg/day for elderly people who eat three meals a day),^{13,14} it seemed wise to add 10 mg of AA to our placebos. Therefore, patients received effervescent tablets (Roche Ltd., Basel) containing either 10 or 500 mg AA. These were dissolved in water and given to the patients twice daily (morning and early evening). We opted for twice daily supplementation because the proportion of AA absorbed from two doses of 500 mg appears to be larger than that absorbed from a single 1000 mg dose.¹⁵ We feared that further subdivision of the daily dosis, while enhancing the proportion absorbed from each tablet, might result in lower compliance with a net decrease in AA bioavailability. Table 1 shows the tablet characteristics.

Table 1. Effervescent tablet characteristics

	Control	Index
Ascorbic acid	10 mg	500 mg
Citric acid	1290 mg	800 mg
Sodium bicarbonate	800 mg	800 mg
Sodium carbonate	80 mg	80 mg
Maltisorb	1640 mg	1640 mg
Aspartame	20 mg	20 mg
Sodium cyclamate	30 mg	30 mg
Polyethylene glycol 6000	100 mg	100 mg
Orange flavour	20 mg	20 mg
Tangerine flavour	10 mg	10 mg
Hardness	70 Newton	62 Newton
Friability	1.1%	1.9%
Disintegration time	1 min 45 s	1 min 45 s

Patients received the tablets until seven days after wound closure or after 12 weeks had passed, whichever occurred first. The reason to extend the period of tablet supply by seven days will be explained below.

Choice of the interventions: ultrasound therapy (UST)

There are many therapies in the treatment of pressure ulcers for which convincing evidence of their efficacy is lacking. Therefore, we found it attractive to investigate

a second intervention in the same trial, using a factorial design. We used a survey to aid us in the selection of a second intervention worth studying. It appeared to us that few clinicians believed AA to be an effective therapy in the treatment of pressure ulcers. The survey confirmed this suspicion.¹⁶ We decided that the second intervention - a so-called 'free rider' - had to be more controversial, i.e. among clinicians, opinions on its efficacy had to differ substantially more than was the case for the AA hypothesis. The survey revealed that among other things this was the case for ultrasound therapy. We chose UST as the free rider mainly because of the disagreement on its efficacy and partly because our department was becoming increasingly interested in the efficacy of physiotherapeutic interventions in general. The UST arm of the trial would be informative for a large part of the medical community regardless of the outcome. A negative outcome would potentially influence the believers' opinions, whereas a positive outcome might change the sceptics' minds. After a literature search we found that the clinicians' disagreement seemed justified. Results from laboratory research indicated that UST enhances protein synthesis (e.g. collagen) by fibroblasts *in vitro*.^{9, 17} Although these reports have been encouraging, the only randomised clinical trial (N=40 (21+19)) on UST for pressure ulcers that we are aware of has shown ambiguous results.¹⁸

Exact description of the UST parameters used in trials, although important, is often neglected. It is unwise to rely on front panel calibrations of the UST machines.^{19,20} One of the two devices (Phyaction 796, Uniphy, Eindhoven) was gauged before the start of the trial by the Department of Biophysics at the University of Limburg, assuming the other to be similar since it consisted of similar software and hardware. After completion of the data collection, 22 months later, both machines were gauged by the biophysicists. Table 2 shows the features of UST in the trial.

As a first line quality control during the trial, the manufacturer checked the power output of both devices about every three months by means of a beam pressure balance immersed in water.

Treatment duration was determined by defining a treatment area slightly larger than the actual wound surface area. This was done by drawing a contour that ran parallel to the wound edge at a distance of approximately 0.75 cm on pieces of overhead transparency with a grid (1x1 cm) using a fine-tipped transparency marker. The sum of the fully enclosed squares, and the sum of the partially enclosed squares divided by two, were added to obtain a 'treatment area' in square centimetres. We extended the wound radius by 0.75 cm because many physiotherapists we talked to, believed that the wound edge played an important part in the healing of (superficial) wounds. We thought that direct treatment of the wound surface was likely to be most effective and we decided to do both.

In addition, circular movement of the transducer across the wound results in insonating the central wound area more often than the areas at the periphery. By extension of the wound radius we insonated the wound margins more, thereby complying with the physiotherapists' views. Treatment duration (in minutes) was read from a table derived on the basis of the following formula: treatment area estimate divided by effective radiating area (at the face of the transducer) times 3 minutes. The minimum treatment duration was 3 minutes and 45 seconds.

Table 2. Ultrasound therapy characteristics

frequency (MHz)	3.28*
pulse duration (ms)	2
pulse repetition frequency (Hz)	100
SATA intensity† (W/cm ²)	0.10
BNR	<4
ERA (cm ²)	4‡

- * The small transducers had frequencies of 3.42 and 3.29 MHz respectively.
- † Measurements at 3 monthly intervals showed that the SATA intensities ranged between the following values (W/cm²): device 1 (large transducer) 0.08-0.10; device 2 (large transducer) 0.08-0.12. The small transducers had SATA intensities of 0.10 at all checks.
- ‡ The small transducers had an ERA of 1 cm².

List of abbreviations and formulas.

- SATA intensity: Spatial Average Temporal Average intensity
- ERA: Effective Radiating Area (at the face of the transducer)
- BNR: Beam Non-uniformity Ratio (SPTA/SATA)
- Ptot: total acoustic power

- SPTA intensity: Spatial Peak Temporal Average intensity
- SATP intensity: Spatial Average Temporal Peak intensity

$SATP = 5 \times SATA$ $P_{tot} = SATA \times ERA$ $SPTA = SATA \times BNR$

Wounds with a treatment area over 5 cm² were treated longer. For example, a wound with a treatment area of 10 cm² was treated for seven and a half minutes. All patients were treated once daily, 5 times per week, not during the weekends. Full compliance over 12 weeks resulted in 60 treatments. We used neutral Sonocol™ coupling gel (Franckline Products, Maurik). The transducers were moved in a circular fashion at all times in order to average out intensity differences in the near field. Transducers were cleaned with cold tap water and soap and put in a 2% lyorthol solution for at least 5 minutes after each treatment. Before using them on another patient any remaining lyorthol was washed off with tap water.

After the UST protocol was designed, it was approved by a sample of Dutch education centres for physiotherapy. Sham UST had an identical protocol, except that no energy was delivered.

Choice of the patients

We graded pressure ulcers according to the system commonly used in the Netherlands, where grade II means blister formation only.²¹ Ulcers were thus labelled grade III if the continuity of the skin was broken. Ulcers were labelled grade IV if a tissue beyond the deep fascia (i.e. muscle, tendon, joint capsule or bone) was also involved. This means that, according to most international standards,²² our group of grade III patients is a mixture of grade II (partial thickness skin loss) and grade III (full thickness skin loss) patients.

We tried to enrol patients with a grade III (partial or full thickness skin loss) or IV pressure ulcer. The reason was that we expected beneficial effects, if present, to occur in those pressure ulcer grades where a clear need for the formation of new collagen exists. A follow-up duration of 12 weeks, which seems sufficient to detect potential beneficial effects,^{2,18} meant that we could not rely on the participation of hospital patients because of the risk of early discharge and consequent loss to follow-up. Therefore, nursing home patients were asked to participate. Five hospital patients did participate, but we knew that arrangements had been made for them to go to the neighbouring nursing home where they could be followed up.

Patients with clear signs of venous insufficiency with leg ulceration were excluded. A patient with a grade III or IV pressure ulcer was still excluded if (1) poor compliance was expected, (2) a contraindication for either AA supplementation or UST existed, or (3) if he or she had any characteristic known to affect collagen formation. Translating these three considerations into fairly unambiguous criteria led to the following exclusion criteria:

- Difficulties with swallowing or frequent vomiting. (Patients known to be choosy were offered a sip of the low dose solution. If they liked it, they could be enrolled).
- Idiopathic haemochromatosis, thalassaemia major, and sideroblastic anaemia because these have been considered contraindications for AA supplementation.²³
- Any patients receiving medication or therapy likely to interfere with collagen formation (actinomycin D, colchicine, penicillamine, systemic glucocorticosteroids, 5-fluorouracil, vinblastin or radiotherapy in the ulcer area).²⁴
- The presence of clinical conditions with a probable effect on collagen formation (Cushing's syndrome, Cushing's disease, pregnancy).
- A high probability to drop out within the 12-week follow-up period (terminally ill patients, patients for whom surgical treatment of the ulcer - other than surgical debridement - had been planned).
- Documented osteomyelitis in the treatment area.
- Supplemental AA in excess of 50 mg per day.

Patients with grade III ulcers could only participate if deepithelialisation had existed for at least 7 days without interruption. If a patient had multiple ulcers, we used two hierarchical criteria to choose one ulcer for inclusion in the trial. First, we preferred ulcers located on the trunk. Second, we chose the most serious one. Stratified analyses with ulcer site or grade as stratifying variables assume statistical independence of data in different strata. This assumption would not be met if the same patient supplied ulcers to several strata. A pragmatic reason for selecting only one ulcer per patient was the reduction of inconvenience of daily UST, regular photography and volume measurements for patients and personnel.

Choice of the effect measurements

To estimate the proportion of wounds healed completely after a given period of follow-up (wound survival analysis) we noted the date of randomisation and date of complete closure for each patient. To end follow-up we required that each

wound remained closed for seven consecutive days during which AA supplementation was continued, but UST stopped. On inadvertent reopening of the wound within this seven-day period UST was recommenced. If no reopening occurred the date of first wound closure was used in the analysis. To estimate the healing rates we measured surface areas from colour slides (with a maximum of 8 per patient) and calculated their changes over time. Appendix 1 shows how photography was done.

The distance between a vertically placed slide projector, hanging from the ceiling, and a table was fixed in such a way that each wound was magnified 6.2 times. This factor of magnification just allowed projection of the largest wound on an A4-sized sheet of paper. Two co-workers projected the slides and drew wound contours. Each co-worker then digitised her own set of wound contours. The mean of each pair of surface area estimates was calculated for the final analyses. They were blinded with regard to the treatment allocations and they worked independently from each other. In the surface area calculations, the difference between the focusing distance (78 cm) and the grey calibration card distance (75 cm) was accounted for (appendix 1).

It was our opinion that volume measurement performed in a subgroup, where a flat representation of wounds could underestimate their severity, would be a useful adjunct to the surface estimations. Appendix 2 shows how this was done. The decision whether to perform a volume measurement was taken on clinical grounds, i.e. without unequivocal criteria. A pragmatic criterion used was whether volume measurement was feasible without the Tegaderm™ plaster touching the wound surface for this might influence the healing process adversely. Finally, we constructed a clinimetric index consisting of seven items, of which four were visual (Appendix 3). The index was constructed after discussions with nursing home physicians and dermatologists. We thought that the addition of an index was useful because wounds that show identical treatment effects with regard to surface areas or volumes might react differently on other clinically relevant aspects.

The visual items were also scored by a panel of four experts at a later stage using the slides. This panel also gave each slide a report mark between 1 and 10, i.e. from very bad to excellent. We calculated that scoring the 490 slides would take about five hours. In order to avoid inadvertent changes in scoring behaviour over this time period, during the whole session, each panel member could consult a few typical photographs of pressure ulcers (mild, average, very serious) on which we had indicated the corresponding scores. In addition, we made separate slide carrouseles, each containing the slides of eight patients, two of each treatment group. Within each carrousel the slide order was random.

The panel also gave scores for overall clinical change (between -100% and +100%) within each patient's series, always comparing follow-up slides in random order to the baseline slide. Members of the panel were blinded with regard to both treatment allocation and week of follow-up. Table 3 shows the outcome variables we constructed.

Table 3. Outcome variables in the trial

1. Survival analysis
a) Crude survival analysis, where survival indicates the proportion of wounds surviving, i.e. not healed, at any point of time during follow-up.
b) Multivariate survival analysis (Cox regression) to adjust for confounding.
2. Change of surface area
a) Absolute healing rates: (1) mean linear regression coefficient, expressing healing rate as the number of square centimetres per week. (2) mean healing rate adjusted for the wound circumference in centimetres per week.
b) Relative healing rates: $((\text{surface area}(t) - \text{surface area}(0)) / t) / \text{surface area}(0) \times 100\%$, where (t) is the number of the week the last measurement was taken and (0) indicates the baseline value.
3. Change of volume
a) Absolute rates: mean linear regression coefficient for each group, expressing healing rate as the number of millilitres per week.
b) Relative rates: $((\text{volume}(t) - \text{volume}(0)) / t) / \text{volume}(0) \times 100\%$, where (t) represents the number of the week the last measurement was taken and (0) the baseline value.
4. Overall clinical change (range -100% to +100%)
Mean change per week as scored by the panel using the slides.
5. Change on visual items of clinimetric index and report marks
Mean linear regression coefficient for each group, indicating the mean change on a particular item per week as scored by the panel using the slides.

Between-group similarity at baseline

Prognostic similarity at baseline is important for drawing causal conclusions with regard to differences in therapeutic effects found. We used four techniques to increase the likelihood of prognostic similarity of the study groups at baseline: (a) selection of patients, (b) selection of wounds, (c) prognostic stratification, and (d) treatment allocation via random permuted blocks.

Selecting a homogeneous study population is useful both for the validity and the (clinical) applicability of the results. However, if the admission criteria are too restrictive, an insufficient number of patients will be enrolled. This too may have repercussions on the internal validity because randomisation of small numbers of patients is less likely to result in prognostic similarity of the groups contrasted. Considerations for the selection of patients and ulcers have been described in the section on 'choice of patients'. We shall now discuss point (c) and (d).

(c) Prognostic stratification.

Simple randomisation of limited numbers of patients may result in unequal distributions of prognostic indicators over the treatment groups. It may be advantageous, in this respect, to reduce one's dependence on the luck of the draw by prestratifying on a few important indicators before random allocation. Under the assumption that the distinction between grade III and grade IV ulcers (Dutch standard) is most important prognostically, we stratified on this variable as

adequately as possible. We also stratified on participating centre according to the type of patients, care and co-interventions. Randomisation was then carried out separately in each stratum.

(d) Allocation via random permuted blocks.

We used randomisation as a last powerful tool for increasing the likelihood of prognostic similarity of the groups contrasted. Simple randomisation of a limited number of patients carries the risk of producing study groups of very different sizes,²⁵ making data-analysis less efficient. To increase the likelihood of equally sized groups, we used random permuted blocks, which were created by a computer program. A block contained four allocations. After four random allocations (patients), using this block, each of the treatment groups received one patient. This kind of randomisation also takes account of seasonal variations in nutrient contents of food items and differences in food preparation between centres. Inconsistencies in treatment procedures or topical wound care that could occur over time are likely to be evenly spread over the treatment groups in this way as well. Batch analysis of blood samples stored for a prolonged period (up to 24 months), which might have undergone slight chemical change, is another reason to opt for blocked randomisation.

In a medium-sized trial such as this, there is a fair chance that imbalances at baseline occur despite the four techniques mentioned above. Measurement of potential prognostic indicators at baseline enables one to check and, to some extent, adjust for imbalances of these variables in the study groups.

Between-group similarity of co-interventions

Co-interventions influencing patients' prognoses must be balanced over the groups contrasted. Causal interpretation of the study is hampered if they are not. We used two techniques to increase the likelihood of similarity of co-interventions: (1) standardisation of basic treatments and (2) blinding.

(1) Standardisation of basic treatments.

We tried to standardise basic treatments (Appendix 4). We could not standardise meals; to do so would have been too difficult. Assuming a consistent method of basic food preparation within each centre (all centres had a central kitchen) and knowing that the randomisation in blocks would allocate patients from each centre to all study groups fairly equally, we hoped that important imbalances would not occur. In addition, we asked staff and visitors to choose from a list of drinks and snacks low in ascorbic acid (< 10 mg/100 g) whenever they wanted to give a patient something extra. We interviewed staff at regular intervals to discover the extra intake of food items we considered of potential impact on patients' prognoses (products enriched with proteins, vitamins or minerals). Note that, in this trial, only imbalances in co-interventions with an impact on wound healing are a threat to causal interpretation of the outcome.

(2) Blinding

Most investigators prefer a particular outcome of their study. We are no exception to this rule. There are subtle ways in which the results can be adjusted to one's preferences. Blinding is a tool to prevent these biases. Table 4 shows possible

biases resulting from incomplete blinding in a trial on the healing of pressure ulcers. Note that blinding is intended not only to prevent biased effect measurement and analysis, but also to increase similarity of co-interventions.

Table 4. Possible biases resulting from incomplete blinding in a trial on the healing of pressure ulcers

Co-Interventions

1. selective meticulousness in applying UST.
2. selective meticulousness in topical wound care or body support.
3. selective advice and encouragement: (1) investigator to patient and staff and (2) staff to patients.

Measurement

1. selective cleansing of pressure ulcers prior to photography.
2. selective manipulation of lens-to-object distance or perpendicularity of lens to wound plane.
3. selective stretching of (deeper) wounds at photography.
4. selective assessment of the moment of complete epithelialisation leading to a biased decision to terminate follow-up.
5. biased surface estimations (especially with respect to vaguely demarcated ulcers).
6. biased clinimetric assessment, 'live' and on the slides.
7. biased decision whether or not to perform volume measurement.
8. biased volume measurement.
9. biased recording of potential confounders and adverse effects.
10. selective judgment in terminating follow-up for ethical reasons.

Analysis

1. manipulation of cut-off points for ordinal or interval data.
 2. fitting a model to the desired outcome instead of reasoning from biological considerations.
-

In our trial blinding the investigators and staff was both more difficult and more important than blinding of patients. Patients were generally very old people (median age 81, 25th and 75th percentile were 77 and 86 respectively) in a bad condition who may have found it difficult to understand what was happening even after they or their guardian had given informed consent. Furthermore, given their high degree of dependence, even an awareness of treatment allocation cannot have easily led to any effective co-intervention. Table 4 shows that the reverse is true for investigators and staff. At any rate, investigators, staff and patients were blinded.

The main investigator (GtR) and a trained nurse performed more than 75 percent of the treatments and all effect measurements, except those where the panel of experts scored the slides. GtR and the nurse also performed the standardised topical wound care after UST most of the time. The topical wound care closely matched the Dutch consensus protocol on this issue and is described in appendix 4. The rest of the USTs (in weeks 7, 9, and 11 of the twelve-week period of follow-up) was performed by participating physiotherapists, who sometimes left the topical wound care for nursing staff. All were requested to keep to the written wound care protocol available at the wards. To simplify the trial's organisation eligible patients (incident or prevalent) were enrolled only during the first week of a 12-week period. The maximum duration of follow-up was 12 weeks per patient.

As regarding ascorbic acid we realised blind conditions as follows. A test batch of both types of effervescent tablets was sent to us by the manufacturer. A panel consisting of four members of our department tried to distinguish between the two kinds of tablets using four of their senses (vision, touch, smell, taste). We considered the first batch unsatisfactory as the tablets could be told apart on colour by all four and on taste by three of the panel members. The tablets of the second test batch sent to us were indistinguishable using these methods. After two years the tablet AA content was analysed by the Department of Clinical Pharmacy of the University Hospital Maastricht.

UST with the characteristics mentioned earlier cannot be distinguished from the sham UST, unless a few drops of water are put on an activated probe. Immersion of a probe in a tray filled with water also does the job. We asked participating physiotherapists not to do this, after explaining to them the importance of blind conditions. Instead of a switch button with two positions, the ultrasound device had 20 codes randomly divided over the two treatment options, active or sham. Obviously, inadvertent unblinding of one treatment code left the quality of the other codes hidden.

After two and 12 weeks the investigator, nurse, and physiotherapist who were most involved were interviewed to detect breaking of the code. They were asked to guess the interventions that each patient had received and how certain they felt of their guess on a scale of 0 to 100 percent. Assuming that the effects of both therapies, if present, would not show within two weeks this timing seemed right to detect unblinding not connected with a treatment effect.

Between-group similarity of the effect measurements

Table 4 sums up several sources of measurement bias that might occur if blind conditions are compromised. Strict standardisation of measurements, in addition to reducing random error, may help to ensure unbiased outcome assessment when blind conditions are suboptimal.

The appendices 1 to 3 give a detailed account of how the effect measurements were carried out.

A subtle form of confounding is an unbalanced proportion of outcome assessments per evaluator over the groups.²⁶ This occurs only if at the same time systematic differences exist between the assessments made by the evaluators, here, the investigator and the research nurse. We tried to avoid this by alternately allocating blocks of four patients to each of the two investigators, at the same time balancing grade III and grade IV patients over the evaluators.

Table 5 shows which variables were measured over the 12-week period of follow-up. To improve readability, follow-up assessments after 1, 4, 8 and 10 weeks are not shown. They were similar to week 2, except for blood sampling. All blood determinations, except those for haemoglobin, glycosylated haemoglobin, and erythrocyte sedimentation rates, were done in one batch after storage at -76 degrees Celsius for up to 24 months. Figure 1 shows the general outline of the study.

Table 5. Assessment scheme (alphabetically)

Variables	Week of follow-up			
	0	2	6	12
<u>adverse reactions</u>		x	x	x
age	x			
age of ulcer at randomisation	x			
albumin (serum)	x	x	x	x
ascorbic acid (plasma/serum)	x	x	x	x
bed/chair riddenness	x	x	x	x
blindness to treatment allocation		x		x
body temperature	x	x	x	x
body weight	x			x
cardiovascular disease*	x			
centre	x			
<u>clinimetric index</u>	x	x	x	x
co-intervention	x	x	x	x
compliance*		x	x	x
creatinin (serum)	x	x	x	x
erythrocyte sedimentation rate (1 hour)	x	x	x	x
fracture (major)	x	x	x	x
glycosylated haemoglobin (HbA _{1c})	x		x	x
grade of ulcer	x			
haemoglobin	x		x	
height	x			x
incontinence (urinary & faecal)*	x	x	x	x
infection (requiring systemic antibiotics)	x	x	x	x
<u>localisation of pressure ulcer</u>	x			
mid-arm circumference	x			x
mobility*	x	x	x	x
nutritional status* (clinical guess)	x	x	x	x
oedema*	x	x	x	x
oral contraceptive (use of)	x			
paralysis	x			
<u>photography</u> (surface area)	x	x	x	x
pressure ulcer history	x			
pressure ulcers (other present & grade)	x	x	x	x
previous treatments*	x			
sedatives/pain killers (effect on mobility)*	x	x	x	x
sensory deficits*	x		x	
sex	x			
skinfolts (biceps/triceps/suprailiacal/subscapular)	x			x
smoking	x		x	
trial termination (reasons for)		x	x	x
urea (serum)	x	x	x	x
vasoactive medication (use of)	x		x	
vitamin/mineral preparations (use of)*	x	x	x	x
<u>volume measurement</u> (subgroup)	x	x	x	x
zinc (serum)	x	x	x	x

Items underlined represent outcome phenomena.

* Asterisks indicate that a variable is measured imprecisely.

Assessments after 1, 4, 8 and 10 weeks are not shown. These are similar to week 2, but no blood samples were collected.

Figure 1. General outline of the study design

Data analysis

Data collection started on January 28, 1991 and was completed on December 22, 1992.

Before we started with the analysis, a separate protocol for analysis had been written. The protocol dealt with five main issues. First, we remained ignorant of treatment allocation until all decisions about outcome variables chosen and patients to be excluded from per protocol analyses (see further) were taken. Second, we would present the outcome of an intention-to-treat analysis and an analysis restricted to a group of patients in which everything went the way we had planned it. We used the term 'per protocol analysis' for this latter analysis. Third, we distinguished between exclusions (one patient was randomised who appeared later to be ineligible) and drop-outs (no effect measurements after at least a

baseline measurement). Missing values on effect measurements were substituted by values calculated by extrapolation, using the trend of the group that received sham UST and the 10 mg tablets, say the double placebo group. In cases for whom less than five measurements were available, we prefer using the trend of the double placebo group for extrapolation because it is the best estimate of the natural course (placebo effects included) in these patients. In patients for whom at least five measurements were present, their own personal trend was extrapolated. Two other much used options (removal from the analysis and substitution of the trend of their own treatment group) would be calculated for those readers who do not like the option we prefer. Fourth, the plethora of prognostic variables would be grouped into clinically cogent clusters. The cluster variables would be used for control of confounding.²⁷ Fifth, we would present the results using precision curves to enable the reader to judge the probability of our data or more extreme ones for a range of hypotheses including the null hypothesis.²⁸ Further details are discussed elsewhere.^{29,30}

Ethical improvements

The trial was approved by the Medical Ethics Committee of both the Maastricht University Hospital and the National Hospital Federation in the Netherlands (NZR). Only patients, who gave their written informed consent were enrolled. In many instances written informed consent was obtained from a close family member or a guardian.

Acknowledgments

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Appendix 1. Photography

The wound areas were photographed on Fuji™ chrome 100 film with a 35 mm camera (Nikon™ F601). All films had an identical emulsion number. Each wound was photographed twice on each occasion from a point perpendicular to the (main) plane of the wound. Perpendicularity was estimated as adequately as possible without instruments. Shadowless illumination was obtained by two flash lamps mounted on the right and left sides of the camera (Nikon™ AS21 in combination with a Nikon™ AS14 controller fed by 4 rechargeable batteries). To minimise geometric distortion a 105 mm focal length lens was used (Nikon™ AF105). Focusing was done at full aperture on a standard grey card (Kodak™, 9 square cm) at a right angle to the lens with a code for patient and time of photography. This grey card was mounted on a steel rod fixed to the camera. The focusing distance was 78 cm. After focusing on the grey card, the rod (which was marked at 78 and 75 cm from the site at which the grey card was attached) was pulled to the 75 cm mark to avoid the rod from touching the patient during photography. Thus, the factor of magnification was identical for all slides. The equipment was supported by a tripod on a mobile dolly. Subsequent focusing on the wound edge was done by adjustment of the lens-to-object distance by moving the dolly. All exposures were done at f/11 aperture.

Appendix 2. Volume measurement

Volume measurement was carried out before UST in order to avoid remains of coupling gel reducing the readings. We then followed the method as described by Berg et al.³¹ Tegaderm™ transparent dressing was applied tightly over the ulcer and the surrounding skin. The ulcer was then filled with sterile physiological saline by injection through the film. Another needle was placed at the highest point of the ulcer to allow air to escape. If necessary, air bubbles hidden under an ulcer margin were gently massaged out of the ulcer. We did every measurement twice, also scoring the quality of the measurement on a three-point scale (1=low, 2=moderate, 3=high).

Appendix 3. Clinimetric index*

Colour of the surrounding skin

- 0= blue
- 1= pale
- 2= red inflamed
- 3= pink

Necrosis

- 0= mainly black
- 1= mainly yellow, partly black
- 2= yellow only
- 3= none

Deepest tissue involved

- 0= bone
- 1= muscle
- 2= subcutaneous fat
- 3= skin

Disc palpable

- 0= severe
- 1= moderate
- 2= slight
- 3= none

Granulation tissue

- 0= absent
- 1= little
- 2= moderate
- 3= much

Time interval to complete wound closure

- 0= more than nine months
- 1= six to nine months
- 2= three to six months
- 3= within three months

Pain (ask the patient: how much pain do you experience from this wound?)

- 0= much
- 1= moderate
- 2= little
- 3= none

* Initially stratified by evaluator to avoid confounding by an uneven distribution of the number of assessments per evaluator over the groups contrasted

Appendix 4. Standardised wound care protocol

Basic treatment for all patients: water mattress (Semperit™ 130x70 cm), Jobst Hydro Float™ flotation pad (Ireland) (unless the patient was completely bedridden or the pad interfered with special chair adaptations). Personnel was encouraged to reposition immobile patients at least once every three hours. Personnel was also asked to lift patients who spent most of the time passively sitting in a (wheel)chair. This latter advice, we think, was seldom heeded.

Once or twice daily topical wound care: basically consisting of: gentle cleansing or rinsing with sterile saline (0.9%) or chlorhexidine 0.1% on gauze or in a syringe. Surgical debridement and Elase™ when indicated.
Covering: Unitulle™ or Jelonet™ paraffin gauze covered by hydrophilic gauze and fixated with Fixomull™ or Leucopor™. Use of topical antibiotics was left to the treating physician, but discouraged by us.

Chapter 4

Problems encountered in the conduct of a randomised clinical trial of ascorbic acid supplementation and ultrasound in the treatment of pressure ulcers

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Abstract

We conducted a blinded randomised clinical trial of ascorbic acid supplementation and ultrasound in the treatment of pressure ulcers. We encountered a number of problems in the execution of the trial, and these are described here together with their potential impact on the validity of our findings. The expression 'polished data' is well known in research circles. Basically, it refers to the process of making data look more decisive than they really are. Investigators may decide to focus on their success in 'proving' the hypothesis at the expense of reporting on protocol deviations and errors that occurred during the execution of their project. The aim of this paper is to optimise the reader's ability to judge the validity of our findings.

Introduction

This article describes the problems we encountered in the execution of a randomised clinical trial of ascorbic acid (AA) supplementation and ultrasound therapy (UST) in the treatment of pressure ulcers. The design and the rationale of the study are explained in chapter 3.¹

The, partly unavoidable, problems in the execution of therapeutic trials on pressure ulcers have not always been described in great detail. Hence, the results of some of the older papers are difficult to interpret. In addition, investigators who design a new trial are likely to make mistakes that could have been avoided, if previous research articles had been more explicit.

This paper, then, should both enable the reader to assess the validity of the results of our trial, described in chapters 5 and 6,^{2,3} and enlighten other investigators who might want to carry out similar trials in the future.

The distinction between problems caused by choices in the design phase of a trial and those unexpectedly encountered during its execution is arbitrary to some extent. Compromises with regard to the study methods generally come in at two stages. First, an investigator who is aware of the ethical, financial and time constraints, usually aims at doing what seems feasible, rather than what might seem ideal. Second, further compromises during the conduct of the trial usually cannot be avoided.

The problems are discussed under seven headings, viz., those related to (1) interventions, (2) patients, (3) effect measurements, (4) between-group similarity at baseline, (5) between-group similarity of co-interventions and (6) similarity of effect measurements. A last section (7) deals with problems in the analysis.

Problems related to the interventions: ascorbic acid (AA)

In the second participating centre, while checking the storage of our tablets, we discovered that tablets of two trial patients, who were on the same ward, had been mixed. This discovery was made 10 weeks after randomisation. We knew the tablets had probably been mixed because we noticed some slightly pink, instead of only white, tablets in the open container where the tablets were kept. Staff was reinstructed to keep tablets stored in the coded dispensers until used by the corresponding patient. At that time, none of the investigators knew that AA turns slightly pink when oxidised. In addition, we only supplied staff with 20 coded tablet dispensers at the start of a 12-week period and were not involved in dispensing the tablets to patients. Cautious questioning of staff did not suggest that their knowledge of chemistry was better than that of the investigators. However, these two patients had probably shared about equally the total daily trial medication of 1020 mg (2x[verum+ 'placebo']) during the first 10 weeks, blurring the therapeutic contrast.

We knew, through this event, that a slight colour difference could arise between the 10 and the 500 mg versions. Only once during the remainder of the data collection phase did staff remark on such a difference. After the incident we stressed correct storage even more. The colour difference was hardly noticeable if the tablets were kept in the dispensers until usage. The analysis of data collected to detect breaking of blind conditions (after 2 and 12 weeks) does not support the assumption that the colour difference was a threat to blind conditions.²

Chemical analysis using high performance liquid chromatography (HPLC) of a sample of tablets by the Department of Clinical Pharmacy of the Maastricht University Hospital reassuringly showed that, two years after delivery, the 10 and the 500 mg tablets contained on average 10.4 mg (range 10.1 - 10.7) and 504 mg (range 502 - 508) vitamin C respectively.

Strictly speaking there were two therapeutic contrasts in the AA arm of the trial. The 490 mg weight difference between the two kinds of tablets was compensated by addition of extra citric acid to the tablets containing 10 mg AA (see also table 1 on page 34. Therapeutic effects of citric acid on ulcer healing seem very unlikely. Two to five hours are required to reach maximum plasma AA levels after oral ingestion in healthy volunteers.^{11,12} However, a sharp increase is seen over the first 90 minutes.¹³ Thus, every 15 minutes difference in time of blood sampling may cause a large difference in the plasma AA concentration measured. Unfortunately, we did not standardise the timing of blood sampling, rendering them suitable only for rough compliance estimations. It would have been better to collect all follow-up AA samples before breakfast and the intake of the first daily tablet. However, it is doubtful whether laboratory personnel, who usually carried out the venipunctures, could have complied with such a request to change their routine, all the more because laboratories were not paid for their participation.

Problems related to the interventions: ultrasound therapy (UST)

UST durations including topical wound care turned out to take more time than anticipated. With the exception of the physiotherapy department in one nursing home, this precluded full involvement of nursing home physiotherapists in executing USTs. Therefore, about 75 percent of treatments were given by the main investigator and the research nurse, who received training from a consultant physiotherapist. Although very time consuming, and at times rather dull, it had the advantage of an increased compliance with the topical wound care protocol. This problem of time investment should have been assessed better in a more extensive pilot phase.

Treatment duration was flexible, because it was coupled to surface area estimations. The larger the surface area, the longer the treatment duration.¹ Slowness in the recognition of change has probably led to small dosing errors, since the reassessment of a wound surface area was prompted by the subjective impression of those giving treatment that some change had occurred over the past 24 hours (72 hours over the weekends). The, perhaps ideal, situation in which a camera, linked to a computer (with appropriate software) estimates the wound surface area each day and produces the correct treatment duration could not be realised. Our method, which is described elsewhere,¹ resulted in the relative overtreatment of smaller wounds compared with larger wounds. This was caused by extending each wound radius by approximately 0.75 cm when drawing the treatment area, which has relatively more influence on wounds with small radiuses.

UST was guided by three main principles. First, using a thin layer of coupling gel, we tried to establish close contact between transducers and wounds. Second, we tried to establish contact between transducers and wounds at a right angle to ensure maximal absorption of sound energy. Third, transducers were moved in a circular fashion to average out intensity fluctuations in the near field. The latter

principle could be adhered to without problems. However, the first two were sometimes compromised to a slight extent. In four cases the narrow opening of deep wounds prevented close transducer-to-wound contact at a right angle, even with a small (1 square cm) transducer. These wounds were filled with coupling gel and treated as adequately as possible. Smaller, pen-like transducers with the metal treating surfaces at an (adjustable) angle with the rest of the rod would have been helpful, but were not available. Exclusion of these patients would have circumvented this problem of suboptimal UST dosing.

On several occasions we had technical problems with the two UST devices that we had at our disposal. Usually, loose contacts due to strong vibrations during transport in and between nursing homes appeared to be the cause. Because at no time both devices broke down simultaneously, compliance was not affected by these problems. However, on August 17, 1992 the manufacturer, during one of the checks, discovered that the output of one of the devices was reduced to 25 percent of the normal value. This affected the compliance of five patients (three on sham UST and two on UST) to an extent ranging from 2 to 20%. An intention-to-treat analysis disregarding degrees of compliance does not account for these problems and some dilution of the results may occur. However, in a per protocol analysis, which is restricted to a subgroup where the trial went the way it was planned (no UST prior to randomisation, compliance > 80%, no major co-interventions and precise outcome measurements) all patients with a compliance lower than 80 percent were excluded. In the compliance calculations we assumed that the defect had occurred right after the previous check, 110 days earlier. We advise future investigators to install a test position on their devices, which should be active but not included as a treatment code. It may be used to get a rough impression whether the device is working properly without breaking any treatment code.

We had problems with gauging the UST devices. We preferred an appraisal of the machines independent of the manufacturer. But it appeared that the equipment at the Department of Biophysics of the university was more suitable for gauging diagnostic than for therapeutic ultrasound machines. For example, intensity measurements at 5 mm from the transducer face were impossible. This became clear when both devices were gauged after completion of data collection. We decided to report the ultrasound parameters specified by the manufacturer. We advise other investigators, not completely familiar with the physics connected to UST, to facilitate the mutual consultation of gauger and manufacturer, to ensure correct gauging by an independent institute.

Problems related to the interventions: a factorial design

Various sources comment on the use of factorial designs.⁴⁻⁷ A potential problem of factorial trials is that an uneven distribution of compliance over one therapeutic contrast, given that the efficacy of that intervention depends on compliance, affects a valid comparison of the other therapeutic contrast and vice versa.

Another consideration in deciding whether a factorial design should be used is that if patients drop out because of inconvenience of one of the interventions, this might cause their drop out in the other arm of the trial as well.

If these problems can be avoided, a factorial design is, of course, a very economical way of conducting clinical research.

Problems related to the choice of patients

Terminal illness was an exclusion criterion. However, as visiting investigators, we had difficulty in predicting which patients were unlikely to survive 12 weeks. The attending physician may also err on these prognoses.⁶ The desire to increase the number of patients in the trial should be carefully weighed against the likelihood of including too many patients who become drop-outs due to (from an investigator's viewpoint) premature death. Our trial counted 8 deaths (9%) with a median duration of follow-up after randomisation of 10 days.

Patients with clear signs of venous insufficiency with leg ulceration were excluded. But, of course, arterial disease as a cause of ulceration is also prevalent at this age and harder to assess. However, in all cases we sought a positive history of pressure or shear forces acting on the wound area before including them in the trial as a pressure ulcer.

Problems related to the choice of effect measurements

Deciding exactly when a wound is healed may sometimes be difficult. Unawareness of treatment allocation is therefore important. In most instances we decided that a wound was healed when the gauze was completely clean when removed after one day. We found this criterion useful. Only in a very few instances, in which callous skin covered the wound without true epithelialisation, could it have led to a false decision of wound closure. Except in one patient we always removed this callous skin in order for epithelialisation to take place. When we could remove a completely clean gauze on Mondays, the preceding Saturday was recorded as the date of healing. When physiotherapists thought a wound had healed, they phoned us, and we visited the patient within 24 hours. In all instances, we made the final decision about the termination of treatment and follow-up.

A subtle form of imprecision is the representation of a multiplanar wound on a slide. Some underestimation of the wound surface could not be avoided by taking a picture from one angle only, as we did. Randomisation hopefully resulted in the same amount of error in all treatment groups, but this cannot be guaranteed. Photography in more than one plane, or restriction to small wounds could perhaps eliminate this problem in future trials. Perpendicularity of photography will not always have been perfect, although the angle must be rather big to have a substantial impact on surface estimation. In our study this does not appear to be a serious source of imprecision.

Although the problems in connection with maintaining blind conditions had been few, we argued that the two main investigators were not the right persons to carry out unbiased surface area estimations. A detailed account of the procedure to estimate the surface areas is given in appendix 1. Briefly, we had to deal with a high proportion of disagreement on surface areas among the two blinded surface area assessors. In the end, 80 percent of the slides were redrawn in a session where the two co-workers in cooperation with the main investigator (GtR) decided on the wound edges together.

Out of a total number of 370 volume measurements, 29 (8%) were judged as having low quality, indicating that major leaking had occurred. The quality of the remainder was judged as moderate (26%) or high (66%).

Between-group similarity at baseline

Flawless selection of patients and ulcers, prestratification on ulcer grade and finally blocked randomisation within each stratum should, in theory, result in prognostic similarity between the groups at baseline. However, a couple of problems arose.

In the Dutch grading system, determining whether an ulcer is grade III or grade IV reduces to the question whether muscle is involved. This sometimes turned out to be more problematic than anticipated. Ulcers of seven patients were coded grade IV at baseline and in the analysis, although muscle involvement was not evident. In these cases, however, the wounds had measurable volumes (median ulcer volume 2 ml, range: 0.2 - 4 ml). In two cases we changed the initial decision on ulcer grade before the analysis started. One grade III ulcer clearly turned out to involve muscle after debridement. One sacral ulcer initially graded as IV appeared quite shallow and was recoded into grade III. These decisions were made before the treatment code was broken. These classification problems potentially reduced the efficiency of the analysis somewhat.

For each centre, we had planned to allocate equal proportions of grade III and IV patients to all treatment groups. This was considered useful to control for differences in patient care between centres. However, in some centres only a few patients could be enrolled (median: 5; range: 1 - 12). Especially the number of grade IV patients was low in most centres (median: 1; range 0 - 4). Thus, prestratification on centre was unsuccessful, because many random permuted blocks (size=4) were incompletely used within single centres. We tried to counter this problem by retrospectively assigning to each patient a score for the quality of patient care with respect to its influence on ulcer healing. This score (either bad or good) was used in the multivariate analyses. One could argue that we should have prestratified on ward level, or even on nurse level. However, low patient numbers make such approaches unfeasible. With hindsight, an individual score for each patient's quality of care seems a good way to control for potential confounding. But we should have assigned the scores during their actual period of follow-up, instead of doing this retrospectively.

A few problems with the randomisation occurred. It should be noted, however, that these problems did not cause biased allocation since blindness and unpredictability of each allocation remained intact. As we shall explain below, we changed the UST codes twice during the trial. However, we overlooked that in reshuffling the codes we had no longer a guarantee of a balanced distribution of patients over the UST group and the sham UST group respectively. However, the largest part of the imbalance was caused by the randomisation in blocks of size 4, with too many centres providing less than four patients. With two centres to go, it became clear that an efficient distribution of patients over the treatment groups should probably not be left to chance completely. Two members of the steering committee, in possession of the treatment codes, provided the main investigator with an alternative list of codes intended to repair the overall balance while randomising the last 12 patients. Although we tried to measure many potential confounders and effect modifiers, we found six factors with a potential effect on wound healing in the literature, on which we do not have any information. These are degree of chronic stress⁹,

(frequency of changes in) environmental temperature⁹, concentrations of local (growth) factors (e.g. histamine), mechanical stress on the wound, blood viscosity¹⁰ and hypovolaemia. With regard to these factors we completely depend on the luck of the draw, i.e. on randomisation.

Between-group similarity: co-interventions

Ideally, once prognostic similarity between the groups has been established at baseline, all patients should be exposed either to the experimental interventions or the reference intervention under identical circumstances. Strict standardisation of every part of treatment could, in theory, result in identical circumstances for each patient. In practice, however, one is glad to reach identical circumstances *on average*, the likelihood of which increases in line with numbers of patients. Proper blinding is an extra safeguard against bias in cases where standardisation is compromised. Problems with blind conditions have been discussed. We now focus on the problems that arose with standardisation.

Patients were provided with identical waterbeds within 24 hours after randomisation. However, eight patients lay on different mattresses at some time during the trial. Reasons were that staff thought that providing patient care (especially repositioning) would be too difficult on a waterbed (N=3), mild hypothermia (N=1) and patients preferring their previous mattress (N=4), usually an inflatable system. Of these eight patients five were in the high dose AA group and three in the low dose group. In the ultrasound part of the trial, six of these eight were in the ultrasound group and two in the sham group.

Unless the ulcer was below the knee, patients sat on a flotation pad during the trial. However, in ten patients this was not the case because they had specially adapted wheelchairs or a strong preference for their previous cushion. An unexpected problem was that, after about one year, our flotation pads appeared to weigh less than indicated in the instructions (and that there were large differences in weight between the cushions (range: 5.8 - 9.2 kg). We do not know whether these differences existed at the start or were caused by usage.

Standardisation of local wound care was reasonably successful because the investigators performed about 75 percent of wound care (following UST) themselves. However, during the weekends protocol deviations could not always be avoided.

Between-group similarity: effect measurements

Breaking the UST codes is fairly easy. Simply applying the transducer to one's own skin does not reveal any differences between the treatment codes with our UST characteristics.¹ However, the immersion of an activated probe in water or the application of a few drops of water (not gel) on it quickly shows which treatment is behind which code. Participating physiotherapists were asked not to do such things after explaining to them the importance of blind conditions. On one occasion a physiotherapist could not suppress his curiosity and broke one (out of 20) treatment codes 4 days before the end of follow-up of this particular patient. Interference of UST devices on an apparently active code with transistor radios caused breaking of a code twice. On both occasions the random division of the two treatment modes (active or sham) over the 20 codes was changed at

the next change of centre. Of course, the investigators were kept blinded at all times. These and a couple of other vicissitudes, involving the emission of a high frequency sound, made properly blind conditions with regard to UST doubtful in one patient after two weeks and in seven patients after 12 weeks. Future investigators are strongly advised to make sure that their UST equipment cannot jam radios or other audio signals.

The principles of strict standardisation and proper blinding are important in ensuring precise and unbiased measurements. Bedside scoring of the clinimetric index may have been affected by knowledge of UST allocation. Therefore, the blinded panel's scores were used in the analysis of the outcome measures. Bedside scores at baseline, always blinded, were only used in control of confounding.^{2,3}

Analysis

Table 1 shows how we dealt with missing values. Our approach is that missing values, which, no doubt, should be avoided, can be carefully estimated using other information that actually was obtained. Note that other ways of dealing with missing values, usually listwise or pairwise deletion, have their own drawbacks.

Table 1. Missing values on independent variables at baseline, their frequency, and the methods of estimating them

Variable	Frequency	Method of estimation*
plasma ascorbic acid†	5	linear regression with independent variables: age, sex, estimated ascorbic acid intake, age of ulcer, creatinin, infection, intake of extra vitamins, urea, zinc, albumin, skinfolds, nutritional status (clinical guess), body mass index.
ESR‡	1	linear regression with independent variables: albumin, ESR(2), ESR(6), infection, temperature, wound surface area.
prognostic guess	22	retrospectively from baseline slides.§
HbA,	1	substitution of HbA,(6).
haemoglobin	1	substitution of haemoglobin(6).
height	1	linear regression with independent variables: age, sex, weight.
subscapular skinfold	6	linear regression with independent variables: age, body mass index, sex, skinfolds (iliacal, biceps, triceps).
weight	1	linear regression with independent variables: age, height, mid-arm circumference, nutritional status (clinical guess), sex, skinfolds).
zinc	3	in two cases where follow-up had ended before next blood sampling, the grand mean was used. In one case the mean of his own zinc values in week 2, 6, and 12 was used as baseline value.

* Baseline values were used unless indicated otherwise. Numbers (in brackets) refer to the week of follow-up. If regression was used, continuous baseline variables were split into tertiles. Missing values were then estimated using linear regression with two dummy variables for each continuous variable.

† 10 plasma ascorbic acid concentrations were below detection limit (<1mg/L). These were substituted by the value 0.9.

‡ ESR = erythrocyte sedimentation rate after one hour.

§ The idea of an overall prognostic guess by the main investigator for each patient developed during the trial, after 22 patients had already been randomised.

Eleven patients (eight deaths and three withdrawals) became drop-outs. We had complete follow-up up to week six of two of them. For these two we extrapolated their own trend on outcome variables. For the other nine cases (seven deaths (after 2, 2, 5, 8, 13, 14, and 18 days respectively) and two withdrawals (after 6 and 7 days respectively)) the trend of the group receiving sham UST and the 10 mg tablets, say the double placebo group trend, was used to extrapolate their own trend, beginning at the point of the last available value. Another analysis was carried out in which we used the trend of their own group for extrapolation instead of that of the double placebo group. Missing values are a nuisance. It seems justified to calculate the outcomes under several reasonable assumptions (sensitivity analysis) to see how stable the outcomes are.⁶

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Appendix 1. The procedure followed to obtain one value for each wound surface area

1. The best slide was chosen from each pair of slides. In most cases the slides in a pair were of identical quality.
2. Two co-workers (a nutritionist and a dietitian) received brief 'contour training' on a small subset (N=5) by GtR.
3. Slides for each patient were put together in sets. Within these sets, slides were presented in random order, for which the co-workers were blinded. This was done to prevent a possible tendency to think that wounds would become smaller during follow-up from influencing the tracings. Such a tendency would not have resulted in biased estimates because the co-workers were blind for treatment allocation. However, the data could have been biologically less cogent, possibly indicating spuriously high healing rates in all treatment groups. Each co-worker drew all slide projections and digitised the resulting contours (N=490).
4. Disagreement was defined as a difference $> 10\%$ of the smallest measurement, agreement if otherwise. Disagreement was taken as an indication that the wound contours had to be reviewed together with the investigator to reach a consensus.
5. The proportion of disagreements was calculated as 68%. This proportion was so high that we reconsidered our criterion for disagreement. Especially, digitising 490 contours proved to be very tiring and time consuming. We relaxed the criterion somewhat and decided to replace manual digitising by automatic scanning of the contours drawn.
6. Disagreement was redefined for small wounds ($\leq 1 \text{ cm}^2$) as a difference $> 20\%$ of the mean of two measurements; agreement if otherwise. For large wounds ($> 1 \text{ cm}^2$) disagreement was redefined as a difference $> 10\%$ of the mean of two measurements; agreement if otherwise.
7. All contours were scanned with 300 dots per inch (DPI) using a Scanjet scanner (Hewlett Packard) and converted to bit image files using Scanning Gallery 5 software. A specially developed computer program (A.C.L. van Montfort) calculated wound surface areas from the files. The proportion of disagreements was calculated under the new criteria as 53%.
8. The main investigator and two co-workers redrew all slides disagreed upon. Furthermore, we redrew a patient's complete set of slides if at least one slide was part of the consensus round because it appeared that the investigator viewed a good number of the wounds quite differently than the co-workers. We thought that it would be better that his reinterpretations should also be made for other slides in a patient's set to avoid inconsistencies. The slight risk that the investigator might be able to guess treatment allocation adequately from some of the slides was judged to be small, given that the

patient codes on the slides were masked and the time period that had passed since data collection (between 7 and 29 months). All in all, 80% of slides were redrawn.

9. The main investigator reviewed all slides which belonged to series without any disagreements to check whether drawings of the co-workers had been valid. Result: all drawings were valid. Very clear wound edges were found in this subset.
10. Contours of wounds that were redrawn (one contour per slide) were scanned, processed and the result used in the analysis. Scan results from contour pairs in series with agreement according to the definition given under point six were averaged. The average was used in the analysis.

Chapter 5

A randomised clinical trial of ascorbic acid supplementation in the treatment of pressure ulcers*

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Abstract

Objective - To assess the effects of ascorbic acid supplementation, 500 mg twice daily in the treatment of pressure ulcers as an adjunct to standardised treatment.

Design - A multi-centre blinded randomised trial. The control group received 10 mg of ascorbic acid twice daily.

Setting - Patients from 11 nursing homes and one hospital participated.

Main outcome measures - Wound survival, healing rates of wound surfaces, and clinimetric changes over 12 weeks.

Results - 88 patients were randomised. Intention-to-treat analysis showed that the wound closure probability per unit time (i.e. the closure rate) was not higher in the intervention group than in the control group (Cox hazard ratio of 0.78 (90% precision interval(PI): 0.44 to 1.39)). Mean absolute healing rates were 0.21 and 0.27 cm² per week in the intervention and the control group respectively (PI of the adjusted difference: -0.17 to 0.13). Relative healing rates and healing velocities did not show favourable results of ascorbic acid supplementation either. A panel scored slides of the ulcers with a report mark between 1 (bad) and 10 (excellent). The improvement was 0.45 and 0.72 points per week in the intervention and control group respectively (PI of the adjusted difference: -0.50 to 0.20). With another clinimetric index we could not show any differences either.

Conclusion - These data do not support the idea that ascorbic acid supplementation (500 vs 10 mg twice daily) speeds up the healing of pressure ulcers.

Introduction

Historically, ascorbic acid (AA, the reduced form of vitamin C) is connected with scurvy. Scurvy is a deficiency disease characterised by defective wound healing and other symptoms. Studies in which experimental scurvy was induced in humans have shown that a daily intake of approximately 10-20 mg of vitamin C prevents and cures the disease. Although we are not aware of controlled studies in which dosages over 70 mg were tested, most authors believe that in incisional or punch biopsy wounds optimal wound healing is attained at intakes of 10-20 mg per day and that higher intakes do not enhance wound healing further.¹⁻³ Several authors make a possible exception for the healing of chronic wounds and pressure ulcers.⁴⁻⁶ The one clinical study always cited in this respect was published twenty years ago by Taylor et al.⁷ They conducted a double-blind placebo-controlled trial (N=2x10) in which the twice daily supplementation with 500 mg AA almost doubled the healing rate of pressure ulcers. We repeated this trial. But we replaced the pure placebo by a daily dose of 20 mg to avoid deficiencies in the control group. We argued that, from a therapeutic viewpoint, findings consistent with those of Taylor et al. could result in firmer establishment of an effective, inexpensive, and easy to administer treatment in the management of pressure ulcer patients. From a scientific viewpoint, a negative result, in our larger trial, would undermine the idea that pressure ulcers represent the exceptional category of wounds where AA supplementation would be efficacious. Such a result might end the debate on its usefulness in wound healing.

Patients and methods

An elaborate description of the study design can be found elsewhere.⁸ We recruited patients with pressure ulcers grade II, III, or IV from 11 nursing homes and one hospital, located in the south of the Netherlands. If a patient had multiple ulcers, we used two hierarchical criteria to choose one ulcer for inclusion in the trial. First, we preferred ulcers located on the trunk. Second, we chose the most serious one. Exclusion criteria were difficulties with swallowing or frequent vomiting, osteomyelitis in the ulcer area, idiopathic haemochromatosis, thalassaemia major, sideroblastic anaemia, Cushing's syndrome or disease, pregnancy, radiotherapy in the ulcer area, and the use of antineoplastic agents or systemic glucocorticosteroids. A high probability to drop out within the 12-week follow-up period (terminally ill patients, patients for whom surgical treatment of the ulcer - other than debridement - had been planned) also led to exclusion. Furthermore, we excluded patients if they were already taking vitamin C supplements in excess of 50 mg per day. Patients with grade II ulcers could only participate if deepithelialisation had persisted for at least seven days without interruption. Patients with leg ulcers had to have a positive history of pressure on that site to be eligible. The trial was approved by the ethics committee of the University Hospital of Maastricht and written informed consent was obtained from each patient or his or her guardian before enrolment.

The trial had a full factorial design and ultrasound was the second intervention under study. Patients were randomly allocated to one of two treatment groups after stratification (muscle involvement (yes /no), nursing home, and ultrasound

treatment (real/sham)). Randomisation was carried out in random permuted blocks (size = 4) prepared in advance with the help of a computer program. At baseline, and after two, six and 12 weeks venous blood samples were collected. Serum samples for the determination of albumin and zinc were frozen at minus 76 degrees Celsius. They were analysed in one batch after data collection had been completed. Plasma samples for vitamin C determinations were stabilised with 5% metaphosphoric acid, usually within one hour, and stored with the serum samples. Plasma vitamin C was assayed fluorometrically.⁹ Twice daily (in the morning and early evening), patients in the intervention group received effervescent tablets (Roche, Basel) containing 500 mg AA. The control group received indistinguishable (colour, taste, smell, disintegration time, friability) tablets containing 10 mg AA. All patients lay on water beds (Semperit, Austria). Staff were instructed to reposition patients once every three hours. Flotation pads (Jobst, Ireland) were provided if patients sat up and their chairs permitted installation. Local wound care consisted of once (exceptionally twice) daily gentle cleansing or rinsing with sterile saline (0.9%) or chlorhexidine (0.1%) on gauze or in a syringe. We performed surgical debridement and used Elase™ when indicated. Ulcers were covered by Unitulle™ or Jelonet™ paraffin gauze, followed by hydrophilic gauze and fixated with Fixomull™ or Leucopor™. Use of topical antibiotics was left to the treating physician, but discouraged by us. The investigators, nursing staff (and physiotherapists) and patients were blinded as to treatment allocation. The main investigator (GtR) and a research nurse performed most (weeks 1 to 6 and then all even weeks to 12, except during weekends) of the topical wound care themselves. Success of blinding was checked after 2 and 12 weeks.

Effect measurements

GtR and the nurse took colour slides perpendicularly to the (main) plane of the wounds at baseline and after 1, 2, 4, 6, 8, 10 and 12 weeks. If possible, we measured ulcer volumes using the method described by Berg et al.¹⁰ Slides were projected (in random order per patient and magnified 6.2 times) and the wound contours drawn by trained co-workers unaware of treatment allocation and follow-up week. Wound contours were scanned (Hewlett Packard Scanjet) and surface areas calculated with a computer program. In addition to absolute (cm²/week) and relative (percent change) healing rates, this program enabled us to calculate healing velocities (in cm per week) indicating at which rate the wound edges are growing toward the centre. These velocities take into account that wounds with a large contour might have more healing potential than smaller ones because they have a greater number of dividing epithelial cells along their edge.

Two nursing home physicians and two senior staff nurses in nursing homes, with an interest in pressure ulcers but unaware of treatment allocation, scored all slides separately on four visual items (colour of the surrounding skin, necrotic tissue, granulation tissue, deepest tissue involved; each on a four-point scale) and then gave an overall report mark between 1 and 10 (1=bad, 10=excellent) for each ulcer. For this purpose, we prepared slide carousels carrying the slides of eight patients (four from each treatment group). In each carrousel the slide order was random. Signs with regard to follow-up week were masked. In addition, panel members scored the overall clinical change (between -100% and +100%),

comparing each follow-up slide with the corresponding baseline slide. In that session, the slide order for each patient was again random, except for the baseline slides, and signs on follow-up week were masked.

Statistical analysis

We carried out an intention-to-treat as well as a per protocol analysis. We defined the latter as an analysis restricted to those patients in whom no major co-interventions occurred and whose effect measurements were relatively unproblematic. Furthermore, control group patients with a vitamin C level higher than 10 mg/L in any of their plasma samples were excluded from the per protocol analysis.

Co-variables

At baseline, for each patient some 60 co-variables, allegedly related to wound healing prognosis were measured as adequately as possible. This plethora of co-variables prevented the standard use of multivariate analysis. Therefore, we grouped together baseline variables into eight clinically cogent clusters, and used these to control confounding.¹¹ Appendix 1 shows the eight clusters and their most important component variables. The partitioning code was broken only after all cluster variables and outcome variables were defined and cut-off points for independent variables chosen. We estimated missing values on independent variables using information on relevant baseline data from cases that had complete information on those variables. To do this, we used linear regression in which continuous variables were trichotomised in order to avoid unnecessary assumptions of linearity. For instance, to estimate a missing value on height (one case), information on sex, weight and age (the latter two in tertiles) was used.

Outcome variables

We used the Kaplan-Meier method to calculate wound survival times and Cox proportional hazards analysis to calculate the ratio of the wound closure probabilities per unit time. Absolute mean surface reductions (cm²/week) were calculated by fitting a straight line through the surface area values for each patient. We calculated the relative changes in surface area (percent/week) by subtracting a patient's baseline value from his last value. This difference was then divided by baseline value and time interval. The potential to epithelialise is related, at least in superficial wounds, to the length of the wound edge (i.e. the number of dividing epithelial cells). Therefore, we also calculated mean healing velocities (cm/week), indicating how rapidly the edge moves toward the centre of the wound. Mean changes per week in report marks were calculated by fitting a straight line through the report marks for each patient. Mean overall clinical changes per week were calculated by taking the mean of the panel's judgments for each patient.

The influence of loss to follow-up on the study outcome was tested in a sensitivity analysis in which a patient's trend was extrapolated either using the control group trend or the trend of the group the patient had been allocated to. Deletion was a third option. We prefer using the control group trend for extrapolation because it is the best estimate of the natural course (placebo effects included) in these patients. We present results from that analysis in the tables.

We report differences with their 90 percent precision intervals (also called confidence intervals), allowing easy one-tailed testing of the null hypothesis at a P-value of 5 percent. Readers can choose any desired precision interval for two important outcome variables using the P-value curve in figure 3.

Results

Altogether, eighty-eight patients were randomised in 1991 and 1992. In about half of the patients the number of incorrect guesses on treatment allocation by nurses, investigators (and physiotherapists) slightly exceeded the number of correct ones with no differences in the degree of certainty of the guesses between the groups. In the remaining patients nurses, investigators (and physiotherapists) did not have any idea about treatment allocation. This indicates that blinding was successful. On average, plasma vitamin C concentrations (samples taken 0.5 to 1.5 h after breakfast) in the intervention group rose by 11.3 mg/L (inner 50 percentile range (ipr_{50}), i.e. the range of values between the 25th and the 75th percentile: 8.1 to 15.3) in the first two weeks, reaching levels of about 14.9 mg/L (ipr_{50} : 11.7 to 17.4). In five patients the rise was less than 5 mg/L. On average, in the control group, plasma vitamin C concentrations rose by 0.9 mg/L (ipr_{50} : -0.1 to 2.1) in the first two weeks, reaching levels of 4.8 mg/L (ipr_{50} : 2.0 to 8.8) and in 6 patients the rise was more than 3 mg/L.

There were three deaths and one withdrawal in the intervention and five deaths and two withdrawals in the control group respectively. Seven patients died and two withdrew before effect measurements at six weeks. One patient died and one withdrew after six weeks of follow-up. For the latter two cases we estimated missing outcome variable values by extrapolating their own trend instead of using the group trend substitution mentioned earlier. No side effects were reported.

Results: intention-to-treat analysis

Table 1 shows the extent of baseline similarity of the treatment groups at the level of the cluster variables and table 1a of some important separate variables. Figure 1 shows the wound survival times by means of Kaplan-Meier curves. The two curves do not reveal significant differences between the groups. A Cox proportional hazards analysis in which wound survival ratio was adjusted for differences at baseline yielded a hazard ratio of 0.78 (PI from 0.44 to 1.39), indicating no larger wound closure probability per unit time in the intervention group. Table 2 shows the crude and the adjusted results for the other outcome variables. Figure 3 provides extra data for absolute surface reduction and clinimetric change. There are no indications that the intervention group fared better than the control group. The results of two analyses in which we dealt with missing values on outcome variables differently (sensitivity analysis) were almost identical to the ones presented here.

Table 1 Percentage of patients across levels of the prognostic cluster variables for each treatment group. Each cluster variable is constructed of separate baseline variables (see appendix 1)

	intervention (n=43)	control (n=45)
wound status		
bad	34.9	33.3
normal	58.1	48.9
good	7.0	17.8
nutritional status		
bad	69.8	71.1
normal	30.2	28.9
vitamin C		
≤ 2 mg/L	25.6	26.7
2- 4 mg/L	37.2	24.4
> 4 mg/L	37.2	48.9
mobility		
bad	39.5	42.2
normal	60.5	57.8
subcutaneous cushioning		
bad	16.3	22.2
normal	83.7	77.8
care level		
bad	37.2	33.3
normal	62.8	66.7
concomitant diseases		
bad	20.9	20.0
normal	79.1	80.0
overall pressure ulcer status		
bad	65.1	77.8
normal	34.9	22.2

Table 1a Distribution of a selection of separate baseline variables for each treatment group. For continuous variables the median and (in parentheses the 25th and 75th percentile) is given

	intervention (n=43)	control (n=45)
age of ulcer at randomisation (days)	97 (30-219)	83 (40-178)
grade II & III (%)	86.0	77.8
ulcers located on the trunk	55.8	62.2
report mark (1=bad;10=excellent)	6.0 (5.5-7.0)	6.5 (5.5-7.0)
wound surface area (cm ²) (%)		
0.01- 1.00	37.2	40.0
1.01- 5.00	48.8	35.6
5.01-10.00	14.0	13.3
> 10	0.0	11.1
wound volume* (ml) (%)		
0.01- 1.00	50.0	38.5
1.01- 5.00	50.0	30.8
5.01-10.00	0.0	15.4
> 10	0.0	15.4
body mass index (kg/m ²)	21.5 (17.0-24.3)	20.7 (18.5-24.1)
serum albumin (g/L)	32.5 (29.9-33.7)	30.3 (27.9-32.8)
serum zinc (μmol/L)	12 (10-13)	12 (11-13)
hemiplegia (%)	18.6	17.8
diabetes mellitus (%)	25.6	20.0
time in bed (h/24h)	16.0 (14.0-24.0)	17.0 (14.8-23.1)
exposure to faeces (min/24h)	26 (13-120)	26 (8-62)
exposure to urine (min/24h)	180 (0-480)	120 (0-510)

* Available for 12 and 13 patients in the intervention and control group respectively.

Figure 1. Kaplan-Meier wound survival curves for all 88 patients (intention-to-treat analysis). The solid line and the broken line represent the survival curves for the intervention and control group respectively. P-value = 0.84 (log rank test, one-tailed).

Table 2. Results of intention-to-treat analysis of outcome variables of surface, volume, and clinimetric changes

	intervention (n=43)	control (n=45)	intervention minus control	adjusted difference (PI)*
mean surface reduction (cm ² /week)	0.21	0.27	- 0.06	- 0.02 (- 0.17;0.13)
mean surface reduction (percent/week)	13.88	22.85	- 8.97	- 3.13 (-13.66;7.39)
mean healing velocity (cm/week)	0.12	0.19	- 0.08	- 0.05 (- 0.13;0.03)
mean volume reduction† (ml/week)	0.00	0.20	- 0.20	- 0.66 (- 1.32;0.00)
mean volume reduction† (percent/week)	- 3.39	16.71	-20.10	-35.33 (-74.58;3.91)
overall clinical assessments from slides				
mean change in report mark per week‡	0.45	0.72	- 0.27	- 0.15 (- 0.50;0.20)
mean clinical change (percent/week)§	17.89	26.08	- 8.19	- 3.46 (-14.00;7.09)

* PI = 90 percent precision interval; other intervals can be read from figure 3.

† Volume measurements were available for 12 and 13 patients in the intervention and control group respectively.

‡ Improvements (changes) were scored on a scale from 1 (bad) to 10 (excellent).

§ Improvements (changes) were scored on a scale from -100 to +100 percent.

Results: per protocol analysis

We restricted the per protocol analyses to 67 patients. Three patients were excluded only from analyses pertaining to wound surface areas. We decided on exclusions before the partitioning code was broken. One patient was later found to be ineligible, six controls had plasma vitamin C levels > 10 mg/L in at least one of their samples, compliance was estimated < 80% (tablet count) in five patients with only a baseline plasma sample available, eight received a potentially powerful co-intervention during the trial, e.g. specially adapted wheelchairs in cases of sacral ulcers, and in five effect measurements were considered

unreliable, usually due to the wound surface areas depending considerably on the degree of traction applied to the wound edge during photography. One patient was excluded for more than one reason. This analysis including only patients who had no major protocol deviations broadly confirms the results of the intention-to-treat analysis. This is shown in figure 2 and table 3.

Figure 2. Kaplan-Meier wound survival curves for 67 patients (per protocol analysis). The solid line and the broken line represent the survival curves for the intervention and control group respectively. P-value = 0.82 (log rank test, one-tailed).

The Kaplan-Meier curves are not significantly different between the groups. The Cox hazard ratio was 0.86 (PI from 0.42 to 1.78). Again, the results of two analyses in which we dealt with missing values on outcome variables differently were almost identical to the ones presented here.

Table 3. Results of per protocol analysis* of outcome variables of surface, volume, and clinimetric changes

	intervention (n=35)	control (n=28)	intervention minus control	adjusted difference (PI)†
mean surface reduction (cm ² /week)	0.23	0.27	- 0.03	0.00 (- 0.21; 0.21)
mean surface reduction (percent/week)	15.32	26.21	-10.89	- 3.15 (- 18.08; 11.79)
mean healing velocity (cm/week)	0.12	0.22	- 0.10	- 0.06 (- 0.17; 0.05)
mean volume reduction‡ (ml/week)	0.05	0.11	- 0.05	- 0.74 (- 1.28; - 0.02)
mean volume reduction‡ (percent/week)	1.82	6.90	- 5.08	-42.63 (-121.44; 36.17)
overall clinical assessments from slides§				
mean change in report mark per week	0.45	0.87	- 0.42	- 0.27 (- 0.73; 0.18)
mean clinical change (percent/week)¶	18.69	29.50	-10.81	- 5.39 (- 18.99; 8.20)

* This analysis was restricted to those patients in whom no major co-interventions (except our standardised treatment consisting of 3 hourly repositioning, waterbed, flotation pad and protocolled topical wound care) occurred and whose effect measurements were relatively unproblematic. In addition, control group patients with a vitamin C level higher than 10 mg/L in any of their plasma samples were excluded from this analysis. Decisions on exclusions were made before the partitioning code was broken.

† PI = 90 per cent precision interval.

‡ Volume measurements were available for 5 and 8 patients in the intervention and control group respectively.

§ These measurements pertain to 38 and 29 patients in the intervention and control group respectively.

|| Improvements (changes) were scored on a scale from 1 (bad) to 10 (excellent).

¶ Improvements (changes) were scored on a scale from -100 to +100 percent.

Figure 3. P-value curve from the intention-to-treat analysis. The x-axis (bottom) represents the surface reduction (cm²/week) as well as (top) the change in report marks on a scale between 1 and 10. The sigmas below the figure indicate the localisation of treatment differences (intervention minus control) one and two standard deviations (to both sides) from our estimate and facilitate the construction of 68% and 95% precision intervals respectively. The point estimate (P=0.5) of the adjusted difference in surface reduction is -0.02 cm²/week and for the adjusted change in report mark it is -0.15. For example, for the hypothesis of a true difference of +0.07 cm²/week (or +0.06 report mark points), the figure shows that the probability to find the measured or a larger difference is 85%. In this figure, P-values higher than 50% should be subtracted from 100%, which leads to a value of 15% in this example.

Results: multivariate subgroup analyses

We carried out three additional analyses to explore the possibility that the effects of AA supplementation differed over special subgroups. We focused on baseline surface area (≤ 1 vs 1-10 cm²), mobility (no spontaneous body movements and movements that are destructive with regard to the ulcer vs at least some (non-destructive) spontaneous body movements), and plasma vitamin C level (≤ 2 vs 2-4 vs >4 mg/L). In these analyses the influence of other variables was adjusted for by means of the cluster variables. Table 4 shows that the effect of AA supplementation does not significantly differ in the various subgroups.

Table 4. Results of multivariate subgroup analyses of mean surface reduction (cm²/week)

	number of patients		adjusted difference (PI)*
	intervention	control	intervention minus control
Baseline surface area (cm²)			
≤ 1	16	18	-0.10 (-0.31;0.11)
1.01 - 10	27	22	0.00 (-0.17;0.17)
Spontaneous body movements			
at least some (non-destructive)	7	16	0.06 (-0.27;0.39)
none or destructive	36	29	-0.09 (-0.27;0.09)
Baseline plasma vitamin C concentration (mg/L)			
≤ 2	11	12	-0.16 (-0.47;0.16)
2-4	16	11	0.02 (-0.27;0.30)
> 4	16	22	0.03 (-0.21;0.28)

Discussion

A useful interpretation of our findings presupposes the internal validity of the trial. Therefore, we shall briefly comment on that first. Table 1a shows that the control group had a greater proportion of patients with very large ulcers, which might be a prognostic disadvantage. Baseline similarity on the level of the cluster variables was good for five out of eight clusters, leaving some room for confounding. However, when we used the clusters in a multivariate analysis to correct for potential confounding, the adjusted differences were close to the crude ones. Increases in plasma vitamin C levels in the intervention group were striking, in contrast to the control group, indicating good compliance. We tried to establish similar circumstances, apart from the intervention, in both treatment groups by standardising body support measures and topical wound care and strict blinding. Because the main investigator and the nurse assistant personally carried out topical wound care most of the time, standardisation was much enhanced. Measurement bias was eliminated by working under blinded conditions. We assessed the impact of loss to follow-up by doing the analyses under three different assumptions, i.e. a sensitivity analysis. The results of these were almost identical. Thus, we think that our trial is internally valid.

Let us turn to external validity. Our findings differ considerably from those of Taylor et al.⁷ that indicated a clear beneficial effect of a high dosis of AA. The patients in Taylor et al.'s trial had low vitamin C levels, which were not corrected in the control group who received pure placebos. Yet, even in their control group the mean healing rate was 1.45 cm² per week over a one month period, which is more than five times as much as in our control group. We recruited patients from a nursing home population, whereas their trial was performed on a hospital ward. Nine out of 20 patients in their trial had a fractured femoral neck and only one patient had a significant paralysis. Our population consisted of typical nursing home patients, many with dementia, cerebrovascular disease and hemiplegia. The average ulcer size at baseline in their patients was about 16 cm², whereas in our trial it was 1.4 cm². We were, however, unable to show a favourable effect of AA supplementation in larger ulcers separately (table 4).

There is a considerable chance of important prognostic incomparability in their small trial (N=2x10) in which only buffy layer vitamin C and surface area were measured at baseline. Finally, small trials similar to the one by Taylor et al. may easily have become the victim of publication bias if no positive effects were found. Considering our result more reliable, we believe that their trial gave a false positive finding, but further research must give a more definitive answer.

The extensive literature on vitamin C and wound healing shows clearly that scurvy delays wound healing in humans, but 10 to 20 mg AA per day corrects the disturbance. Further supplementation does not seem to speed up healing. Our data indicate that pressure ulcers are no exception to this rule.

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Appendix 1. Approximate definition of the cluster variables using baseline variables.

Wound status (3 levels)

bad: muscle involvement and an estimated time needed for closure of more than 12 weeks or ulcer has been present for more than 180 days.

good: no muscle involvement and a median panel report mark ≥ 7 (1=bad, 10=excellent) and ulcer has been present for 30 days or less.

normal: otherwise.

Nutritional status (2 levels)

bad: severely undernourished (clinical impression) or serum albumin < 30 g/L or upper arm fat area < 10 th percentile (adjusted for sex and age) or upper arm muscle area < 10 th percentile (adjusted for sex and age).

normal: otherwise.

vitamin C in plasma (3 levels)

bad: ≤ 2 mg/L; intermediate: 2-4 mg/L; good: > 4 mg/L.

Mobility (2 levels)

bad: patient moves destructively with regard to ulcer (judgment nurse) or is paralysed.

normal: otherwise.

Subcutaneous cushioning (2 levels)

bad: ulcer on the trunk and the sum of 4 skinfolds < 3 cm, or ulcer on the trunk and weight over 70 kg and sum of 4 skinfolds > 6 cm.

normal: otherwise.

Care level (2 levels)

bad: insufficient general or topical wound care, especially during weekends, (investigators' judgment) or a sacral or ischial ulcer is combined with a daily faecal exposure of at least 2 hours.

normal: otherwise.

Concomitant diseases (2 levels)

bad: a positive cardiovascular history and paralysis.

normal: otherwise.

Overall pressure ulcer status (2 levels)

bad: more than one grade II or grade III ulcer or any number of grade IV ulcers or has suffered from pressure ulcers before.

normal: otherwise.

Chapter 6

A randomised clinical trial of ultrasound in the treatment of pressure ulcers*

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Abstract

Objective - To assess the effects of ultrasound therapy in the treatment of pressure ulcers as an adjunct to standardised treatment.

Design - A multi-centre placebo-controlled randomised trial.

Setting - Patients from 11 nursing homes and one hospital participated.

Main outcome measures - Wound survival, healing rates of wound surfaces, and clinimetric changes over 12 weeks.

Results - 88 patients were randomised. Intention-to-treat analysis showed that the wound closure probability per unit time (i.e. the closure rate) was almost equal in the two treatment groups (Cox hazard ratio of 1.08 (90% precision interval(PI): 0.56 to 2.06). Mean absolute healing rates were 0.18 and 0.31 cm² per week in the ultrasound and the sham group respectively (PI of the adjusted difference: -0.27 to 0.03). Relative healing rates and healing velocities did not show favourable results of ultrasound either. A panel scored slides of the ulcers with a report mark between 1 (bad) and 10 (excellent). The improvement was 0.71 and 0.46 points per week in the ultrasound and sham group respectively (PI of the adjusted difference: -0.14 to 0.57). With another clinimetric index we could not show a significant difference either.

Conclusion - These data do not support the idea that ultrasound speeds up the healing of pressure ulcers.

Introduction

In 1960, Paul et al. treated 23 pressure ulcers with ultrasound therapy (UST). They concluded that: "From our clinical observations it would appear that a scientifically controlled study in this area would be richly rewarding."¹ It took 25 years before McDiarmid et al. published a randomised trial (N=19+21). We were unable to find other randomised trials. McDiarmid et al. could not show an overall beneficial effect but also found that in a subgroup of patients with infected superficial ulcers UST appeared to improve the rate of healing.²

UST has been used in the treatment of experimental wounds in animals mostly with positive results.³⁻⁶ Negative results were also reported.⁷ Research in cultured fibroblasts indicates that UST can enhance collagen production.⁸ As so often, it is doubtful whether such findings can be extrapolated to pressure ulcers in humans. They do, however, provide a rationale to perform clinical trials.

Especially in the area of pressure ulcers, where some 2,200 topical preparations alone have been recommended over the years,⁹ there are many treatments of which a few small positive trials may be found with some biological plausibility connected to them. We chose to investigate UST because we found it to be controversial in a survey.¹⁰ One out of every five Dutch nursing home physicians and one out of every four Dutch supervisory nursing home nurses think that UST is effective in the treatment of grade III pressure ulcers, whereas almost one in two (one in three for the nurses) think it is completely ineffective. To us, this is an area where clinical trials are most informative. Regardless of their outcomes, trials may change people's opinions, a first step in changing their treatment choices. We thought that the evidence of the usefulness of UST in wound healing was, on balance, still equivocal. Consequently, we performed a sham UST controlled randomised trial in an attempt to further clarify the usefulness of UST in the treatment of pressure ulcers.

Patients and methods

An elaborate description of the study design can be found elsewhere.¹¹ The trial had a full factorial design. The second experimental intervention was twice daily supplementation of either 500 or 10 mg of ascorbic acid.¹² Therefore, some of the exclusion criteria pertain to the ascorbic acid part of the trial. We recruited patients with pressure ulcers grade II, III, or IV from 11 nursing homes and one hospital, located in the south of the Netherlands. If a patient had multiple ulcers, we used two hierarchical criteria to choose one ulcer for inclusion in the trial.

First, we preferred ulcers located on the trunk. Second, we chose the most serious one. Exclusion criteria were difficulties with swallowing or frequent vomiting, osteomyelitis in the ulcer area, idiopathic haemochromatosis, thalassaemia major, sideroblastic anaemia, Cushing's syndrome or disease, pregnancy, radiotherapy in the ulcer area, and the use of antineoplastic agents or systemic glucocorticosteroids. A high probability to drop out within the 12-week follow-up period (terminally ill patients, patients for whom surgical treatment of the ulcer - other than debridement - had been planned) also led to exclusion.

Furthermore, we excluded patients if they were already taking vitamin C supplements in excess of 50 mg per day. Patients with grade II ulcers could only participate if de-epithelialisation had persisted for at least seven days without

interruption. Patients with leg ulcers had to have a positive history of pressure on that site to be eligible. The trial was approved by the ethics committee of the University Hospital of Maastricht and written informed consent was obtained from each patient or his or her guardian before enrolment.

Patients were randomly allocated to one of two treatment groups after stratification (muscle involvement (yes /no), nursing home, and ascorbic acid supplementation (500 or 10 mg twice daily)). Randomisation was carried out in random permuted blocks (size = 4) prepared in advance with the help of a computer program.

At baseline, and after two, six and 12 weeks venous blood samples were collected. Serum samples for determination of albumin and zinc were frozen at minus 76 degrees Celsius. They were analysed in one batch after data collection had been completed.

One of the two ultrasound devices (Phyaction 796, Uniphy, Eindhoven) was gauged before the start of the trial by the Department of Biophysics at the University of Limburg, assuming the other to be similar since it consisted of similar soft and hardware. After completion of the data collection, 22 months later, both devices were gauged by the biophysicists. Table 1 shows the features of UST in the trial.

Table 1 Ultrasound therapy characteristics

frequency (MHz)	3.28*
pulse duration (ms)	2
pulse repetition frequency (Hz)	100
SATA intensity† (W/cm ²)	0.10
BNR	<4
ERA (cm ²)	4‡

* The small transducers had frequencies of 3.42 and 3.29 MHz.

† Measurements at 3 monthly intervals showed that the SATA intensities ranged between the following values (W/cm²): device 1 (large transducer) 0.08-0.10; device 2 (large transducer) 0.08-0.12. The small transducers had SATA intensities of 0.10 at all checks.

‡ The small transducers had an ERA of 1 cm².

List of abbreviations and formulas

SATA intensity: Spatial Average Temporal Average intensity
 ERA: Effective Radiating Area (at the face of the transducer)
 BNR: Beam Non-uniformity Ratio (SPTA/SATA)
 Ptot: total acoustic power

SPTA intensity: Spatial Peak Temporal Average intensity
 SATP intensity: Spatial Average Temporal Peak intensity

$$\text{SATP} = 5 \times \text{SATA}$$

$$\text{Ptot} = \text{SATA} \times \text{ERA}$$

$$\text{SPTA} = \text{SATA} \times \text{BNR}$$

As a first line quality control during the trial, the manufacturer checked the power output of both devices about every three months by means of a beam pressure balance immersed in water.

Treatment duration was determined by defining a treatment area, larger than the actual wound surface area. This was done by drawing a contour that ran parallel to the wound edge at a distance of approximately 0.75 cm on pieces of overhead transparency with a grid (1x1 cm) using a fine-tipped transparency marker. The sum of the fully enclosed squares, and the sum of the partially enclosed squares divided by two, were added to obtain a treatment area in square centimetres. We extended the wound radius by 0.75 cm because many physiotherapists we talked to believed that the wound edge played an important part in the healing of (superficial) wounds. We thought that direct treatment of the wound surface was likely to be most effective but decided to do both. Circular movement of the transducer across the wound results in insonating the central wound area more often than the areas at the periphery. By extension of the wound radius we insonated the wound margins more, thereby complying with the physiotherapists' wishes. Treatment duration was read from a table derived on the basis of the following formula: treatment area estimate divided by effective radiating area (at the face of the transducer) times 3 minutes. The minimum treatment duration was 3 minutes and 45 seconds. Wounds with a treatment area over 5 cm² were treated longer. For example, a wound with a treatment area of 10 cm² was treated for seven and a half minutes. Surface estimations were repeated regularly and treatment duration adjusted accordingly. All patients were treated once daily, 5 times per week, not during the weekends. Full compliance over 12 weeks resulted in 60 treatments. We used neutral Sonocol coupling gel (Franckline Products, Maurik). UST was guided by three main principles. First, using a thin layer of coupling gel, we tried to establish close contact between transducers and wounds. Second, we tried to establish contact between transducers and wounds at a right angle to ensure maximal absorption of sound energy. Third, transducers were moved in a circular fashion to average out intensity fluctuations in the near field. Transducers were cleaned with cold tap water and soap and put in a 2% lyorthol solution for at least 5 minutes after each treatment. Before using them on another patient any remaining lyorthol was washed off with tap water. UST with the characteristics mentioned in table 1 cannot be distinguished from the sham UST, unless a few drops of water are put on an activated probe, or the probe is immersed in a tray filled with water. We asked participating physiotherapists not to do this, after explaining to them the importance of blind conditions. Instead of a switch button with two positions, the ultrasound device had 20 codes randomly divided over the two treatment options, active or sham. Obviously, inadvertent unblinding of one treatment code left the quality of the other codes hidden.

The UST protocol was approved by a sample of Dutch education centres for physiotherapy.

More than 75 percent of the treatments were given by the main investigator (GtR) and his nurse assistant, who received training from a consultant physiotherapist. All patients lay on water beds (Semperit, Austria). Staff were instructed to reposition patients once every three hours. We provided flotation pads (Jobst, Ireland) if patients sat up and their chairs permitted installation. Local wound care was standardised and consisted of once (exceptionally twice) daily gentle cleansing or rinsing with sterile saline (0.9%) or chlorhexidine (0.1%) on gauze or in a syringe. We performed surgical debridement and used Elase™ when

indicated. Ulcers were covered by Unitulle™ or Jelonet™ paraffin gauze, followed by hydrophilic gauze and fixated with Fixomull™ or Leucopor™. Use of topical antibiotics was left to the treating physician, but discouraged by us. The investigators, nursing staff and patients were blinded as to treatment allocation. GtR and a research nurse performed most (weeks 1 to 6 and then all even weeks to 12, except during weekends) of the topical wound care themselves. Success of blinding was checked after 2 and 12 weeks.

Effect measurements

GtR and the nurse took colour slides perpendicularly to the (main) plane of the wounds at baseline and after 1, 2, 4, 6, 8, 10 and 12 weeks. If possible, we measured ulcer volumes using the method described by Berg et al.¹³ Slides were projected (in random order per patient and magnified 6.2 times) and the wound contours drawn by trained co-workers unaware of treatment allocation and follow-up week. Wound contours were scanned (Hewlett Packard Scanjet) and surface areas calculated with a computer program. In addition to absolute (cm²/week) and relative (percent change) healing rates, this program enabled us to calculate healing velocities (in cm per week) indicating at which rate the wound edges are growing toward the center. These velocities take into account that wounds with a large contour might have more healing potential than smaller ones because they have a greater number of dividing epithelial cells along their edge.

Two nursing home physicians and two senior staff nurses in nursing homes, with an interest in pressure ulcers but unaware of treatment allocation, scored all slides separately on four visual items (colour of the surrounding skin, necrotic tissue, granulation tissue, deepest tissue involved; each on a four-point scale) and then gave an overall report mark between 1 and 10 (1=bad, 10=excellent) for each ulcer. For this purpose, we prepared slide carousels carrying the slides of eight patients (four from each treatment group). In each carousel the slide order was random. Signs with regard to follow-up week were masked. In addition, panel members scored the overall clinical change (between -100% and +100%), comparing each follow-up slide with the corresponding baseline slide. In that session, the slide order for each patient was again random, except for the baseline slides, and signs on follow-up week were masked.

Statistical analysis

We carried out an intention-to-treat as well as a per protocol analysis. We defined the latter as an analysis restricted to those patients who had never had UST on their ulcer before, had an overall compliance of at least 80%, in whom no major co-interventions (except our standardised treatment consisting of 3 hourly repositioning, waterbed, flotation pad and protocolled topical wound care) occurred and whose effect measurements were relatively unproblematic.

Co-variables

The plethora of co-variables prevented the standard use of multivariate analysis. Therefore, we grouped together baseline variables into eight clinically cogent clusters, and used these to control confounding.¹⁴ Appendix 1 shows the eight clusters and their most important component variables. The partitioning code was

broken only after all cluster variables and outcome variables were defined and cut-off points for independent variables chosen. We estimated missing values on independent variables using information on relevant baseline data from cases that had complete information on those variables. To do this, we used linear regression in which continuous variables were trichotomised in order to avoid unnecessary assumptions of linearity. For instance, to estimate a missing value on height (one case), information on sex, weight and age (the latter two in tertiles) was used.

Outcome variables

We used the Kaplan-Meier method to calculate wound survival times and Cox proportional hazards analysis to calculate the ratio of the wound closure probabilities per unit time. Absolute mean surface reductions (cm^2/week) were calculated by fitting a straight line through the surface area values for each patient. We calculated the relative changes in surface area (percent/week) by subtracting a patient's baseline value from his last value. This difference was then divided by baseline value and time interval. The potential to epithelialise is related, at least in superficial wounds, to the length of the wound edge (i.e. the number of dividing epithelial cells). Therefore, we also calculated mean healing velocities (cm/week), indicating how rapidly the edge moves toward the centre of the wound. Mean changes per week in report marks were calculated by fitting a straight line through the report marks for each patient. Mean overall clinical changes per week were calculated by taking the mean of the panel's judgments for each patient.

The influence of loss to follow-up on the study outcome was tested in a sensitivity analysis in which a patient's trend was extrapolated either using the sham group trend or the trend of the group the patient had been allocated to. Deletion was a third option. We prefer using the sham group trend for extrapolation because it is the best estimate of the natural course (placebo effects included) in these patients. We present results from that analysis in the tables.

We report differences with their 90 percent precision intervals (also called confidence intervals), allowing easy one-tailed testing of the null hypothesis at a P-value of 5 percent. Readers can choose any desired precision interval for two important outcome variables using the P-value curve of figure 3.

Results

Eighty-eight patients were randomised in 1991 and 1992. After two and 12 weeks, nurses, physiotherapists and GtR and his assistant were invited to guess the treatment allocation and to indicate their certainty on a scale from 1 to 100%. In about 85% of the cases the three groups of workers indicated maximal doubt. In the remaining cases the number of incorrect guesses exceeded the number of correct ones, although the correct ones were guessed with slightly more certainty. After 12 weeks, nurses' guesses did not indicate any unblinding. Physiotherapists correctly guessed allocation in eight cases and incorrectly in five cases with, on average, 92 and 75 percent certainty respectively, indicating no large problems in blinding. Due to jamming of radios and other technical problems, the assistant and GtR had broken the code in 7 patients with (near) certainty. In two other cases they made an incorrect guess.

There were five deaths and one withdrawal in the ultrasound and three deaths and two withdrawals in the sham group respectively. Two patients complained of UST being painful at times, one in both groups. Other side-effects were not reported. Seven patients died and two withdrew before effect measurements at six weeks. One patient died and one withdrew after six weeks of follow-up. For the latter two cases we estimated missing outcome variable values by extrapolating their own trend instead of using the group trend substitution mentioned earlier.

Results: Intention-to-treat analysis

Table 2 shows the extent of baseline similarity of the treatment groups at the level of the cluster variables and table 2A of some important separate variables.

Table 2 Percentage of patients across levels of the prognostic cluster variables for each treatment group. Each cluster variable is constructed of separate baseline variables (see appendix 1)

	ultrasound (N=45)	sham (N=43)
wound status		
bad	35.6	32.6
moderate	53.3	53.5
good	11.1	14.0
nutritional status		
bad	68.9	72.1
usual	31.1	27.9
vitamin C		
≤ 2 mg/L	24.4	27.9
2 - 4 mg/L	24.4	37.2
> 4 mg/L	51.1	34.9
mobility		
bad	35.6	46.5
usual	64.4	53.5
subcutaneous cushioning		
bad	11.1	27.9
usual	88.9	72.1
care level		
bad	31.1	39.5
usual	68.9	60.5
concomitant diseases		
bad	17.8	23.3
usual	82.2	76.7
overall pressure ulcer status		
bad	73.3	69.8
usual	26.7	30.2

Figure 1 shows the wound survival times by means of Kaplan-Meier curves. The two curves do not reveal significant differences between the groups. A Cox proportional hazards analysis in which the wound survival ratio was adjusted for differences at baseline yielded a hazard ratio of 1.08 (PI from 0.56 to 2.06), indicating no larger wound closure probability per unit time in the ultrasound group.

Table 2a Distribution of a selection of separate baseline variables for each treatment group. For continuous variables the median (and in parentheses the 25th and 75th percentile) is given

	ultrasound (n=45)	sham (n=43)
age of ulcer at randomisation (days)	92 (45-224)	86 (27-200)
grade II & III (%)	80.0	83.7
ulcers located on the trunk (%)	60.0	58.1
report mark (1=bad;10=excellent)	6.5 (5.5-7.0)	6.0 (5.5-7.0)
wound surface area (cm ²) (%)		
0.01- 1.00	42.2	34.9
1.01- 5.00	40.0	44.2
5.01-10.00	15.6	11.6
> 10	2.2	9.3
wound volume* (ml) (%)		
0.01- 1.00	36.4	50.0
1.01- 5.00	45.5	35.7
5.01-10.00	18.2	0.0
> 10	0.0	14.3
body mass index (kg/m ²)	21.4 (18.2-23.1)	20.8 (18.9-24.8)
serum albumin (g/L)	31.0 (28.6-33.9)	31.3 (29.3-33.2)
serum zinc (μmol/L)	11 (11-13)	12 (10-13)
hemiplegia (%)	11.1	25.6
diabetes mellitus (%)	13.3	32.6
time in bed (h/24h)	17.2 (14.4-24.0)	16.0 (14.0-20.5)
exposure to faeces (min/24h)	26 (5-62)	30 (13-120)
exposure to urine (min/24h)	180 (0-510)	120 (0-480)

* Available for 11 and 14 patients in the ultrasound and sham group respectively.

Figure 1. Kaplan-Meier wound survival curves for all 88 patients (intention-to-treat analysis). The solid line and the broken line represent the survival curves for the ultrasound and sham group respectively. P-value = 0.61 (log rank test, one-tailed).

Table 3 shows the crude and the adjusted results for the other outcome variables. Figure 3 provides extra data for absolute surface reductions and clinimetric changes. There are no clear indications that ultrasound is superior to sham treatment. The results of two analyses in which we dealt with missing values on

outcome variables differently (sensitivity analysis) were almost identical to the ones presented here.

Table 3. Results of intention-to-treat analysis of outcome variables of surface, volume, and clinimetric changes

	ultrasound (n=45)	sham (n=43)	ultrasound minus sham	adjusted difference (PI)*
mean surface reduction (cm ² /week)	0.18	0.31	- 0.13	- 0.12 (- 0.27; 0.03)
mean surface reduction (percent/week)	22.91	13.82	9.09	8.27 (- 2.31; 18.85)
mean healing velocity (cm/week)	0.18	0.13	0.05	0.05 (- 0.04; 0.13)
mean volume reduction† (ml/week)	- 0.29	0.42	- 0.71	- 0.72 (- 1.22; - 0.22)
mean volume reduction‡ (percent/week)	- 4.12	15.84	-19.96	-17.41 (-51.35; 16.53)
overall clinical assessments from slides				
mean improvement in report mark per week‡	0.71	0.46	0.26	0.22 (- 0.14; 0.57)
mean clinical improvement (percent/week)§	27.40	16.51	10.90	9.15 (- 1.44; 19.73)

* PI = 90 percent precision interval; other intervals can be read from figure 3.

† Volume measurements were available for 11 and 14 patients in the ultrasound and sham group respectively.

‡ Improvements (changes) were scored on a scale from 1 (bad) to 10 (excellent).

§ Improvements (changes) were scored on a scale from -100 to +100 percent.

Figure 2. Kaplan-Meier wound survival curves for 64 patients (per protocol analysis). The solid line and the broken line represent the survival curves for the ultrasound and sham group respectively. P-value = 0.71 (log rank test, one-tailed).

Results: per protocol analysis

We restricted the per protocol analyses to 64 patients. Three patients were excluded only from analyses pertaining to wound surface areas. We decided on the exclusions before the partitioning code was broken. Four patients had had some form of UST before randomisation, one patient was found later to be ineligible, 13 patients had received less than 80% of the USTs, eight had received a potentially powerful co-intervention during the trial, e.g. specially adapted wheelchairs in cases of sacral ulcers, and in five effect measurements were considered unreliable, usually due to the wound surface areas depending

considerably on the degree of traction applied to the wound edge during photography. Four patients were excluded for more than one reason. Figure 2 and table 4 show that this analysis broadly confirms the results of the intention-to-treat analysis. The Kaplan-Meier curves are not significantly different between the groups. The Cox hazard ratio was 1.08 (PI from 0.44 to 2.66). Again, the results of two analyses in which we dealt with missing values on outcome variables differently were almost identical to the ones presented here.

Table 4. Results of per protocol analysis of outcome variables of surface, volume, and clinimetric changes*

	ultrasound (n=30)	sham (n=31)	ultrasound minus sham	adjusted difference (PI)†
mean surface reduction (cm ² /week)	0.20	0.33	- 0.13	- 0.14 (- 0.35; 0.07)
mean surface reduction (percent/week)	26.94	16.01	10.92	13.13 (- 1.61; 27.87)
mean healing velocity (cm/week)	0.21	0.14	0.07	0.07 (- 0.04; 0.18)
mean volume reduction‡ (ml/week)	0.16	0.48	- 0.33	not enough data
mean volume reduction‡ (percent/week)	29.17	11.09	18.08	not enough data
overall clinical assessments from slides§				
mean improvement in report mark per week	0.79	0.52	0.27	0.31 (- 0.17; 0.78)
mean clinical improvement (percent/week)¶	30.11	17.54	12.57	13.32 (- 0.84; 27.49)

* This analysis was restricted to those patients in whom compliance was at least 80%, no major co-interventions (except our standardised treatment consisting of 3 hourly repositioning, waterbed, flotation pad and protocolled topical wound care) occurred and whose effect measurements were relatively unproblematic. Decisions on exclusions were made before the partitioning code was broken.

† PI = 90 per cent precision interval.

‡ Volume measurements were available for only 3 and 6 patients in the ultrasound and sham group respectively.

§ These measurements pertain to 32 and 32 patients in the ultrasound and sham group respectively.

|| Improvements (changes) were scored on a scale from 1 (bad) to 10 (excellent).

¶ Improvements (changes) were scored on a scale from -100 to +100 percent.

Figure 3. P-value curve from the intention-to-treat analysis. The x-axis (bottom) represents the surface reduction (cm²/week) as well as (top) the change in report marks on a scale between 1 and 10. The sigmas below the figure indicate the localisation of treatment differences (intervention minus control) one and two standard deviations (to both sides) from our estimate and facilitate the construction of 68% and 95% precision intervals respectively. The point estimate (P=0.5) of the adjusted difference in surface reduction is -0.12 cm²/week and for the adjusted change in report mark it is +0.22. For example, for the hypothesis of a true difference of +0.06 cm²/week (or +0.65 report mark points), the figure shows that the probability to find the measured or a larger difference is 95%. In this figure, P-values higher than 50% should be subtracted from 100%, which leads to a value of 5% in this example.

Results: multivariate subgroup analyses

We carried out three additional analyses to explore the possibility that the effects of UST differed over special subgroups. We focused on baseline surface area (≤ 1 vs $1-10 \text{ cm}^2$), mobility (no spontaneous body movements and movements that are destructive with regard to the ulcer vs at least some (non-destructive) spontaneous body movements), and infection (colour of the surrounding skin is red or any degree of necrosis vs otherwise). The latter was suggested by the positive results in infected wounds in the trial by McDiarmid et al.² In these analyses the influence of other variables was adjusted for by means of the cluster variables. Table 5 shows four differences of marginal statistical significance. Three of those are negative differences, for which we do not have a reasonable explanation. Surprisingly, we found a positive difference in small wounds. Actually, we conjectured that UST would be more effective in larger wounds only, because in such wounds UST would have a greater potential to produce its beneficial effects (more fibroblasts, more granulation tissue). Therefore, we find the tendency for UST to be more effective in small wounds hard to explain. We believe that these subgroup findings are due to chance and it would be useful to see whether they will be confirmed in future research.

Table 5. Results of three multivariate subgroup analyses of mean surface reduction (cm^2/week)

	number of patients		adjusted difference (PI)*
	intervention	control	intervention minus control
baseline surface area (cm^2)			
≤ 1	19	15	0.21 (-0.00;0.42)
1.01 - 10	25	24	-0.15 (-0.31;0.01)
spontaneous body movements			
at least some (non-destructive)	10	13	-0.01 (-0.32;0.29)
none or destructive	35	30	-0.17 (-0.35;0.00)
wound infection			
clean	7	6	0.14 (-0.29;0.57)
infected	38	37	-0.16 (-0.33;0.00)

* PI = 90 percent precision interval.

Discussion

A useful interpretation of our findings presupposes the internal validity of the trial. Therefore, we shall briefly comment on that first. Table 2a shows that the sham group had a greater proportion of patients with very large ulcers, hemiplegia, and diabetes, which might be a prognostic disadvantage. Baseline similarity on the level of the cluster variables was good for four out of eight clusters, leaving some room for confounding. However, when we used the clusters in a multivariate analysis to correct for potential confounding, the adjusted differences were close to the crude ones.

Compliance was higher than 80% in 75 patients. We tried to establish similar circumstances, apart from the intervention, in both treatment groups by standardising body support measures and topical wound care, and strict blinding. Because the main investigator and the nurse assistant personally carried out topical wound care most of the time, the latter was standardised to a high degree. Measurement bias was eliminated by working under blinded conditions, which was almost completely successful. Where blind conditions were compromised, standardised procedures probably prevented major bias. We assessed the impact of loss to follow-up, which was 12.5 percent, by doing the analyses under three different assumptions, i.e. a sensitivity analysis. The results of these were almost identical. In conclusion, we think that our trial is internally valid.

Let us turn to external validity. The evidence from randomised trials in humans on the efficacy of UST in wound healing and the healing of pressure ulcers in particular is scarce and contradictory. To a lesser extent, this also applies to laboratory research. There are three randomised trials of UST in venous ulcers. Callam et al. reported positive results in a trial where the control group received only standard treatment, no sham UST.¹⁵ Lundeborg and Eriksson and colleagues unsuccessfully tried to reproduce Callam et al's findings in two trials that were similar to the one by Callam et al., but sham UST controlled.^{16,17} We found two controlled, but non-randomised trials in this area^{18,19} showing positive results. The only randomised trial in pressure ulcers that we know of was fairly similar to ours in the choice of the UST parameters.² McDiarmid et al. were unable to show an overall beneficial result, but reported a positive result in the subgroup of patients with infected ulcers. With hindsight they reasoned that slowly healing infected wounds offer scope for improvement in contrast to clean sores that are already healing at a (near) maximum rate.² We could not confirm their findings in a subgroup analysis. A Kaplan-Meier analysis in this subgroup showed no treatment differences either (figure 4).

Figure 4. Kaplan-Meier wound survival curves for 75 patients with an infected wound. The solid line and the broken line represent the survival curves for the ultrasound and sham group respectively. P-value = 0.46 (log rank test, one-tailed).

Just as in the McDiarmid trial we judged infection from wound inspection (red edge or necrosis). No cultures were made. Our subgroup of patients with infected wounds consisted of 75 persons.

A problem with formal testing of UST is the large number of treatment parameters involved (table 1), each of which can be varied. By using the literature and asking experts on physiotherapy in the Netherlands, we tried to choose the parameters with the highest chance of producing beneficial effects. We gave the therapy a maximal chance to show its efficacy. However, we could not demonstrate clear beneficial effects under optimal circumstances. This probably reflects the low therapeutic potential of other forms of UST in the treatment of pressure ulcers as well.

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Appendix 1. Approximate definition of the cluster variables using baseline variables.

Wound status (3 levels)

bad: muscle involvement and an estimated time needed for closure of more than 12 weeks, or ulcer has been present for more than 180 days.

good: no muscle involvement and a median panel report mark ≥ 7 (1=bad, 10=excellent) and ulcer has been present for 30 days or less.

normal: otherwise.

Nutritional status (2 levels)

bad: severely undernourished (clinical impression) or serum albumin < 30 g/L or upper arm fat area < 10 th percentile (adjusted for sex and age) or upper arm muscle area < 10 th percentile (adjusted for sex and age).

normal: otherwise.

vitamin C (plasma) (3 levels)

bad: ≤ 2 mg/L; intermediate: 2-4 mg/L; good: > 4 mg/L.

Mobility (2 levels)

bad: patient moves destructively with regard to ulcer (judgment of staff) or is paralysed.

normal: otherwise.

Subcutaneous cushioning (2 levels)

bad: ulcer on the trunk and the sum of 4 skinfolds < 3 cm, or ulcer on the trunk and weight over 70 kg and sum of 4 skinfolds > 6 cm.

normal: otherwise.

Care level (2 levels)

bad: insufficient general or topical wound care, especially during weekends, (investigators' judgment) or a sacral or ischial ulcer is combined with a daily faecal exposure of at least 2 hours.

normal: otherwise.

Concomitant diseases (2 levels)

bad: a positive cardiovascular history and paralysis.

normal: otherwise.

Overall pressure ulcer status (2 levels)

bad: more than one grade II or grade III ulcer or any number of grade IV ulcers or has suffered from pressure ulcers before.

normal: otherwise.

Chapter 7

Summary and closing remarks

This chapter is especially aimed at the quick reader who wants to know in less than 15 minutes what our findings are, how they were obtained, and why we chose to study the effects of vitamin C and ultrasound in the treatment of pressure ulcers.

Conclusions

Let us start, for a change, with the conclusions. Our findings indicate that, in patients with pressure ulcers, the twice daily oral intake of 500 mg of vitamin C does not accelerate wound healing (chapter 5). Similarly, we found that insensitising pressure ulcers with (pulsed, low dose) ultrasound is a waste of time (chapter 6).

Study methods

Eighty-three nursing home and five hospital patients with pressure ulcers participated in our trial. They were randomly allocated to receive one of four treatment combinations: (1) twice daily supplementation of 10 mg vitamin C, and sham ultrasound, (2) twice daily supplementation of 10 mg vitamin C, and true ultrasound, (3) twice daily supplementation of 500 mg vitamin C, and sham ultrasound, or (4) twice daily supplementation of 500 mg vitamin C, and true ultrasound. We employed random permuted blocks (size=4) for treatment allocation after prestratification on ulcer grade and centre. Before treatment started, we collected information on many prognostic indicators of wound healing in each patient. Examples are the age of the ulcer at the day of inclusion in the trial, patient mobility, a few blood constituents, nutritional status, and previous treatments. The complete set of indicators is summarised in table 5 of chapter 3 (page 43). The measurement of these indicators enabled us to refine the analysis. All patients lay on water beds. Topical wound care was standardised.

Effervescent tablets containing 10 or 500 mg of ascorbic acid were given to the patients daily, in the morning and early evening. This was continued until the ulcer had healed or 12 weeks had passed, whichever occurred first. Pulsed, low dose ultrasound (or sham ultrasound) treatment was given five times per week, directly on the wound surface, until the wound had healed or 12 weeks had passed. These treatments were usually given by the investigators, who had received training from a consulting physiotherapist. The physical ultrasound parameters are given in table 2 of chapter 3 (page 36). Daily treatment duration depended on surface area.

Patients, investigators, nurses, and participating physiotherapists were strictly blinded to treatment allocation. After two and twelve weeks we checked whether

blinding had been successful by inviting them to guess the treatments for each patient.

Data collection took place over 22 months, in 1991 and 1992. We recorded the day of inclusion and of wound closure. This permitted an analysis of the 'wound survival data'. In addition, we took colour slides at baseline and after 1, 2, 4, 6, 8, 10, and 12 weeks. The slides were used to calculate changes in surface areas. If possible, we also measured wound volumes. Finally, a blinded panel of experts rated all the slides on a few clinical rating scales.

A protocol for data analysis was written before the start of the data analysis. It contained some main principles: first, we decided to present the outcome of an intention-to-treat analysis and of an analysis restricted to a group of patients in which everything (compliance, lack of co-interventions, effect measurements) went the way we had planned it. We used the term 'per protocol analysis' for this latter analysis. Second, we took all decisions on outcome variables and on patients to be excluded from the per protocol analysis before we broke the partitioning code. Third, we grouped the multitude of prognostic indicators into eight clinically cogent cluster variables, which we used for control of confounding. Formation of these cluster variables was also done before the partitioning code was broken. Fourth, the impact of missing values on effect measurements was assessed by a sensitivity analysis employing three reasonable assumptions.

The ultimate aim in the care for patients with pressure ulcers is, of course, closure of the wound. This can be simply summarised as follows. Of the 88 patients with pressure ulcers in the trial 37 (42%) healed within 12 weeks. In the high dose vitamin C group this was 37% compared to 47% in the reference group. In the ultrasound group 40% healed compared to 44% in the group that received sham ultrasound. To obtain a more balanced picture taking into account the exact timing of wound closures, the reader is referred to the wound survival curves in chapters 5 and 6 (pages 70, 71 and 85, 86 respectively). The use of the other outcome measures employing reductions in wound surface area and volume per week, and the clinical rating scales did not alter this simple summary of the outcomes to any significant extent.

Why this study?

Most reviews and books on vitamin C and wound healing point out that daily intakes of about 60 mg are sufficient for optimal wound healing. However, many tend to make an exception for pressure ulcers, referring to the results of a trial published in 1974. This trial ($N=2 \times 10$) was performed among surgical patients with pressure ulcers using the same dosage as we did. The effects after one month were clearly in favour of the supplemented group. The well-known role of vitamin C in the synthesis of stable collagen was used to explain the findings. Replication of these findings would be of interest to clinicians dealing with pressure ulcers, but would also raise the question of what makes the healing of pressure ulcers so different from that of other, especially surgical wounds. In the latter case, evidence had indicated that not much could be expected from supplementation unless frank vitamin C deficiency existed.

In the case of ultrasound, also, one randomised clinical trial in pressure ulcers had been reported so far. It was much smaller than ours and less well controlled. A positive finding was reported for a subgroup consisting of patients with infected ulcers. Animal research and research on the effects of ultrasound on cells that produce collagen (fibroblasts) was used to give the results some biologic plausibility. We performed a similar subgroup analysis to explore the possibility that in our trial too a special effect might exist for infected wounds. However, we were unable to confirm this earlier finding.

Of the myriad of treatments employed or advocated to aid in the healing of pressure ulcers relatively few have been tested in controlled trials. Perhaps the fatalistic attitude of some authors who wrote that too many variables are involved in wound healing and that these cannot be adequately controlled, is responsible for this paucity of controlled studies. In the meantime, in different countries and centres, consensus meetings are being held to define accepted ways to prevent and treat pressure ulcers. Ideally, the recommendations formulated at such meetings should be based on the findings of sound clinical research. If this research is non-existent, consensus may become nonsense, as a sceptic, Petr Skrabanek, once wrote.

In a rigorous trial, we have evaluated the effectiveness of two treatments that are currently advocated in the treatment of pressure ulcers. Both failed the exam. It might be that we have a good nose for the ineffective, but we fear that vitamin C supplementation and ultrasound are no exceptions among the multitude of treatments employed in the treatment of patients with pressure ulcers today. Rigorous new trials will be needed to substantiate existing and future claims. Such trials are feasible.

Samenvatting

Ongeveer vijf jaar geleden begonnen wij met de voorbereidingen van het onderzoek dat in dit proefschrift is beschreven. In eerste instantie stelden we ons de vraag of doorligwonden sneller zouden genezen door het toedienen van extra veel vitamine C aan de patiënten. Deskundigen op het gebied van voeding en wondgenezing leken hier heil van te verwachten. Dit kwam enerzijds omdat bekend is dat vitamine C een belangrijke rol speelt bij de vorming van nieuw bindweefsel, het materiaal waarmee een wondholte bij genezing wordt opgevuld. Anderzijds hadden enkele Britse artsen in 1974 aangetoond dat de doorligwonden van patiënten die één gram vitamine C per dag (ongeveer 20 sinaasappels, maar dan in een tablet) extra kregen, aanzienlijk sneller genazen dan de wonden van patiënten die geen extra vitamine C kregen. In het onderzoek van de Britten deden helaas weinig patiënten mee. Verder had men weinig rekening gehouden met factoren die van invloed kunnen zijn op de wondgenezing buiten vitamine C om. Daardoor vertrouwden wij de uitslag van dit onderzoek niet zomaar. Bovendien vonden we het vreemd dat doorligwonden een uitzondering zouden vormen. Het is namelijk bekend dat voor een optimale genezing van andere wonden een hoeveelheid vitamine C die je binnenkrijgt met de dagelijkse voeding, zeg 70 mg, voldoende is. Als doorligwonden inderdaad een uitzondering zijn, waarbij extra veel vitamine C wel helpt, dan is dat een prachtige therapie. Immers, vitamine C heeft nauwelijks bijwerkingen en is nog goedkoop ook.

We vonden het aantrekkelijk om in één moeite meteen het effect van nóg een therapie voor wondgenezing te testen. De keuze viel daarbij op ultrageluidtherapie. Uit een enquête was ons gebleken dat ongeveer 25 procent van de Nederlandse artsen en leidinggevende verpleegkundigen in verpleeghuizen dacht dat ultrageluid zou helpen bij de wondgenezing. Echter, zo'n 40 procent geloofde daar niets van. Als er zulke grote meningsverschillen zijn, zo dachten we, is onderzoek noodzakelijk. Ook over dit onderwerp bleek slechts één redelijk goed, alweer Brits, onderzoek te bestaan. Daaruit kwamen aanwijzingen dat ultrageluid alleen helpt bij vieze, besmette doorligwonden. Dat was echter verre van zeker, omdat ook aan dat onderzoek slechts weinig patiënten meededen.

Aan ons onderzoek deden 88 patiënten mee. Tweeëntwintig patiënten kregen iedere dag twee bruistabletten met een halve gram vitamine C erin en werden tevens behandeld met ultrageluid (echt-echt). Tweeëntwintig patiënten kregen geen extra vitamine C en werden behandeld met nep-ultrageluid (nep-nep). Drieëntwintig patiënten kregen geen extra vitamine C, maar wel ultrageluidbehandeling (nep-echt). De vierde groep, van 21 patiënten, kreeg wel extra vitamine C, maar nep-ultrageluid (echt-nep).

Net voordat we met de behandelingen begonnen, verzamelden we bij iedere patiënt veel informatie over andere factoren die de wondgenezing zouden kunnen beïnvloeden. Als voorbeeld noemen we de voedingstoestand en de ernst van de

wond. Uiteraard zagen we erop toe dat de gewone behandelingen die de patiënten voor hun doorligwonden kregen, gewoon werden voortgezet. In verband met het onderzoek zorgden we echter dat die gewone behandelingen zoveel mogelijk hetzelfde waren voor alle patiënten. Zo lagen ze allemaal op waterbedden. Patiënten die een deel van de dag in een stoel doorbrachten, kregen tevens speciale geleikussens. Ook de directe verzorging van de wonden vond plaats volgens stricte regels. Dat kon omdat de wondverzorging grotendeels door de onderzoekers werd gedaan.

Om de effecten van de vitamine C toediening en het ultrageluid op de wonden te meten, hielden we bij wanneer na de start van onze behandelingen de wond eventueel genezen was. Daarnaast maakten we 1, 2, 4, 6, 8, 10 en 12 weken na het begin kleurendia's van de wonden. Zo ontstond van de wond van elke patiënt een serie dia's. De dia's werden gebruikt om veranderingen in wondoppervlakte te meten. Daarnaast lieten we ze zien aan een panel van deskundigen. Het panel beoordeelde op die manier de veranderingen die meer te maken hebben met het uiterlijk van de wonden, zoals de kleur van de wondrand en de hoeveelheid pus. Tenslotte maten we, indien mogelijk, de inhoud van de wonden omdat je die op een dia niet goed kunt beoordelen. Steeds zorgden we ervoor dat de personen die hun oordeel moesten uitspreken over de vooruitgang van de wonden niet wisten in welke behandelgroep de betreffende patiënt zat. Zo kon men zijn oordeel steeds objectief geven.

Na twaalf weken waren 37 van de 88 wonden genezen; 16 in de groep patiënten die extra veel vitamine C hadden gekregen en 21 in de groep die we niets extra's hadden gegeven. In de groep die met ultrageluid was behandeld, genazen 18 wonden binnen 12 weken, terwijl er 19 genazen in de groep die geen echt ultrageluid had gekregen. Berekeningen waarmee we keken of de snelheid waarmee de wonden dichtgroeiden (bijvoorbeeld in vierkante centimeters per week) in de ene behandelgroep anders was dan in de andere, leverden hetzelfde resultaat op: geen duidelijke verschillen.

Onze conclusie luidt dat vitamine C en ultrageluidtherapie geen gunstige invloed hebben op de genezing van doorligwonden.

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Dit dankwoord kan niet compleet zijn. Dit onderzoek is het product van de inspanningen van honderden mensen. Het is ondoenlijk op deze plaats iedereen persoonlijk te bedanken. Een aantal personen en instanties worden in de betreffende hoofdstukken bedankt. Ik kan slechts hopen dat ik degenen die ik hier vergeet, mijn dankbaarheid eerder al heb getoond.

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Toen het ten tweeden male digitizen van honderden wondontrekken onontkoombaar leek en Annemie Mordant en Ingeborg Poorterman reeds een lichte hoofdpijn voelden opkomen, redde Tonie van Montfort ons door een fraai computerprogramma in elkaar te knutselen dat automatisch oppervlaktes en omtrekken uitrekende. Zijn broer Harry van Montfort zorgde dat het programma ook 's nachts zijn werk deed zodat we toch nog op zomervakantie konden. De mensen van de scanruimte van het ICA waren erg gastvrij en lieten ons een tiental ochtenden hun scanner gebruiken.

De vakgroep Anatomie/Embryologie stelde haar verticaal hangende diaprojector beschikbaar evenals haar digitizer. Vooral Johan Hekking en Henk van Mameren wil ik hier bedanken.

Dit onderzoek was nooit afgekomen zonder de inzet en toewijding van vier vrouwen. Henriëtte van Houtem, jij hielp mee het onderzoek van de grond te krijgen en bij het uitvoeren van de enquête die hoofdstuk 2 vormt. Marleen Palland, jouw humor en relativiseringsvermogen hielden me op de been in die onwennige beginfase van de gegevensverzameling. Hilde Sielhorst, jouw organisatietalent zorgde ervoor dat we 's avonds voor het 8 uur journaal thuis waren in die vier maanden dat we dagelijks op en neer naar Venlo reden. Je oog voor detail is de kwaliteit van het onderzoek buitengewoon ten goede gekomen. Ingeborg Poorterman, jouw nauwgezetheid in de fase van gegevenscontrole en analyse zorgden ervoor dat ik vertrouwen heb in de cijfers die we geproduceerd hebben.

Een opsomming van wat Fons, the amazing, Kessels voor dit onderzoek heeft gedaan zou bijna een apart hoofdstuk vergen. Fons, eigenlijk hebben we je te laat bij het onderzoek betrokken. Steeds wanneer we iets wilden randomiseren - en we waren er dol op - schreef jij de programma's. Je adviseerden ten aanzien van de analyse waren onmisbaar. Ik heb veel van je geleerd en hoop in de toekomst nog meer van je te leren. Jouw eigenzinnige ideeën strekken zich uit ver over de grenzen van de epidemiologie en biostatistiek. Van jou leerde ik de 'ouwe mannenpraat' te wantrouwen en althans te proberen zelf na te denken.

Paul Knipschild, van jou leerde ik wat het betekent serieus literatuuronderzoek te doen, hoe leuk het is om in de contramane te zijn, hoe belangrijk om het ingewikkelde eenvoudig, maar correct weer te geven, en dat eerlijkheid het langste duurt, ook in onderzoek. Jij was nooit te beroerd om mee op pad te gaan als er weer eens een commissie overtuigd moest worden van de noodzaak mee te doen aan ons onderzoek. Precies op de tijdstippen dat ik een oppepper nodig had zorgde jij voor een aanvulling op mijn verzameling CDs en cassettes. Je schrijftalent vergrootte de leesbaarheid van dit proefschrift aanzienlijk. Verder stond je me toe op sommige punten eigenwijs te zijn en zelf verantwoordelijkheid te dragen.

Mijn dank gaat ook uit naar mijn (ex-) collega's van de vakgroep Epidemiologie. Toen mijn vervangende dienstplicht er in 1989 opzat en de vakgroep mij een

baan(tje) als AIO aanbood nam ik dat vooral aan omdat ik de sfeer zo prettig vond.

Erik van Rossum las het manuscript door en gaf me waardevolle adviezen ten aanzien van de lay-out, die tenslotte perfect werden verwezenlijkt door Thum W.P. Aarts. Bob Wilkinson schaaftde het Engels bij zodat we ons ook in het buitenland niet hoeven te schamen. Ron Schellings bezorgde het manuscript veilig bij de drukker.

Tenslotte wil ik mijn ouders bedanken voor hun nimmer aflatende vertrouwen in mij.

Curriculum Vitae

Gerben ter Riet werd geboren op 9 december 1960 te Enschede. Na het behalen van zijn VWO B examen aan het Kottenparkcollege te Enschede in 1979 studeerde hij geneeskunde aan de Rijksuniversiteit Limburg te Maastricht. In 1987 behaalde hij het artsdiploma. Hij vervulde de eerste drie maanden van zijn vervangende dienstplicht bij de vakgroep Keel Neus en Oorheelkunde, waar hij zich bezighield met de electrofysiologie van de middenoorspierreflex in de rat. De vervangende dienstplicht werd afgerond bij de vakgroep Epidemiologie, waar hij zich bezighield met literatuuronderzoek naar de effectiviteit van alternatieve geneeswijzen en acupunctuur in het bijzonder. In 1989 werd hij Assistent in Opleiding (AIO) bij de vakgroep Epidemiologie. Hij rondde het in dit boek beschreven onderzoek af als onderzoeksmedewerker bij de Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO). Sinds 1 februari 1994 werkt Gerben ter Riet als universitair docent bij de vakgroep Epidemiologie van de Rijksuniversiteit Limburg te Maastricht.