Clinical observations supporting a vasodilatory effect of the modified papaya extract OPAL001

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Abstract

Vascular insufficiency is a major reason for the development and perpetuation of chronic wounds. It is plausible that agents that cause vasodilation may promote wound healing. The OPAL process is where ripened fruit is treated by homogenisation, heat treatment, alkalisation and filtration of the pulp. OPAL 001 uses papaw and peach fruits mixed 10: 1 by volume. This article presents four cases of non-healing ulcers that provide clinical observational support for the hypothesis that OPAL products facilitates healing by causing vasodilation of the blood vessels around the wound.

Key words: venous ulcer, arterial ulcer, diabetic ulcer, pressure ulcer, wound therapy, vasodilation.

Background

Chronic skin ulceration is a major problem, causing a large burden of morbidity and community costs. The prevalence of chronic wounds in Australia is up to 3.0 per 1000 in adults over 60[1,2]. The most common cause is venous ulceration[1]. Many forms of ulcers are prone to recurrence.

Chronic ulceration is due to the cellular systemic changes associated with ageing, repeated ischaemia-reperfusion injury and bacterial colonisation with resulting inflammatory host response[3]. Ageing tissues are more susceptible to injury than are younger tissues. Ischaemia underlies the pathogenesis of chronic diabetic wounds, pressure wounds and venous ulceration. In venous ulceration, the normal arterial/venous pressure gradient is lost, causing stasis and effective ischaemia[3]. When arterial circulation is re-established, improved blood flow leads to a restoration of an inflammatory response, established by the release of leukotrienes, and to the release of proinflammatory cytokines and oxygen free radicals. This blocks nitrous oxide mediated vasodilation and results in secondary ischaemia[4]. Wound healing, therefore, requires that cyclic ischaemia and reperfusion is prevented by consistent perfusion[4]. Bacterial colonisation further stimulates the release of inflammatory cytokines and superoxide, facilitating the secondary ischaemia described above[3].

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Carica Papaya (pawpaw) has been used widely as a wound healing agent, particularly in many resource-poor countries where its ready accessibility is attractive[5]. OPAL A is a filtrate produced through homogenisation, heat treatment, alkalisation and filtration of the pulp of ripened *C. Papaya* (the OPAL process). Preclinical work indicates the possibility that OPAL A facilitates wound healing; however, the mechanisms through which OPAL A may facilitate this process are unclear and are under investigation. Hypothesised mechanisms include vasodilation, inhibition of proinflammatory responses, and/or antioxidant effects[6]. OPAL001 filtrate is a mixture of OPAL A filtrate and OPAL M filtrate, a filtrate manufactured from peach by the OPAL process, in a 10:1 ratio by volume.

Given that vascular insufficiency is a major reason for the development and perpetuation of wounds, it is plausible that agents that cause vasodilation may promote wound healing. This article presents four cases that provide clinical observational support for the hypothesis that OPAL001 improves healing by causing vasodilation of the blood vessels around the wound. The aim of the observations was to provide objective evidence that wound healing had indeed taken place after months to years of failed treatments with other therapies.

The first three patients were treated by the inventor of the OPAL process (who was not a physician) between 2001 and 2004. The author was asked to review the cases from the perspective of an independent, academic general practitioner (GP). This was done by thorough review of the case notes from the patient's GP, domiciliary nurse, specialist letters and

hospital records, where available, and from the photographic record maintained by the inventor. The patients were also interviewed and examined by the author in 2007. The final case was one treated by the author directly in 2008. Permission to publish these case records was given by each patient, and approved by the Human Research Ethics Committee of the University of Queensland (number 2011000413).

Case 1: Pressure ulcer from quadriplegia

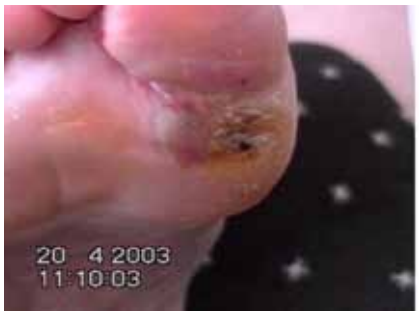
A 44-year-old man who became a quadriplegic at the age of 19 had a history of diabetes mellitus, atrial fibrillation and hypertension, and was a regular smoker. In October 2001, he developed a pressure area over the left greater trochanter as a result of lying in a wet (normal) bed and not being rotated regularly during hospitalisation for treatment of a urinary tract infection. The pressure area progressed to a Grade 4 ulcer with a sinus extending to the bone. On 24 March 2002, the dimensions of the ulcer were 5 x 5 cm. A computerised tomography (CT) scan of the area revealed a 2.5 x 2.5 cm deep abscess with no bony involvement. Between 100 and 150 ml of yellow serous fluid was discharging from the wound every 24 hours. The patient was admitted to hospital in April 2002 to have the ulcer drained and debrided.

Subsequently, the patient's ulcer was treated daily at his home by domiciliary nurses who used a wick to assist sinus drainage. Treatments included topical antiseptic (Betadine) and Bioptron light. Despite treatment, the sinus remained a 5 x 5 cm defect with the edges of the wound inflamed. An ostomy bag was used to collect the serous fluid. The skin was cleaned and the sinus flushed with saline twice weekly.

The ulcer proceeded to heal slowly. In October 2002 the dimensions were 3 x 3 cm, reducing to 2 x 2 cm in June 2003. However, the depth of the ulcer did not improve. The bottom of the wound could be visualised at 2 to 3 cm, but a sinus leading into the base of the wound was of indeterminate depth. The volume of discharge still required an ostomy bag.

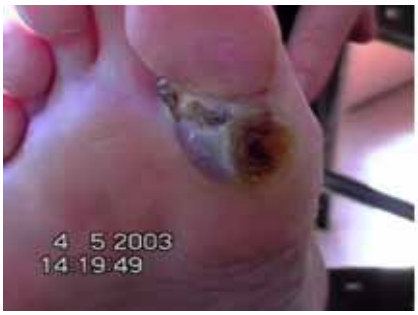
From July to October 2003, OPAL001 cream was applied (by domiciliary nurses) between the internal border of the wafer and the edge of the wound once per day, applied between the internal border of the wafer and the edge of the wound. The skin around the ulcer and the edge of the wound changed from red and inflamed to pink and healthy looking. In September 2003, the wound was clean but there was no change in size. Up to October there was no change in the sinus depth or the discharge. A decision was made to use undiluted OPAL001

Figure 1. Diabetic foot ulcer treated with OPAL A.



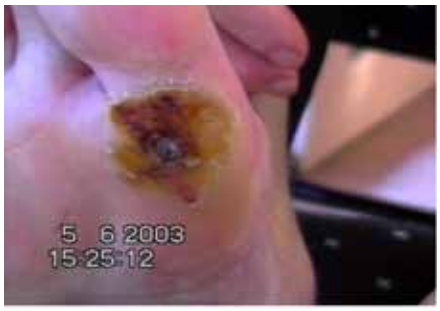
A. Baseline thickened, dead skin is present at the medial aspect of the skin over the metatarsophalangeal joint. Possible blistering extending towards the lateral aspect of the base of the great toe. There may be infection beneath this area.

Date: 20 April 2003



B. Two weeks after baseline. The extent of non-viable tissue is now clear.

Date: 27 April 2003



C. Six and a half weeks after baseline. Last photo available. Eschar is confined to the skin overlying the base of the metatarsophalangeal joint. The eschar is dry and lifting at the edges. The skin in the interdigital space and between the space and the eschar is healthy.

Date: 5 June 2003

filtrate in the wound itself. Approximately 10 ml of filtrate was applied directly into the sinus with each dressing change. One day after the first application of the OPAL001 filtrate, the discharge from the sinus changed from a yellowish serous fluid to a heavily blood-stained serous fluid. Within a couple of weeks, the sinus began to reduce in size. The patient reported a stinging sensation where the OPAL001 filtrate contacted the skin. This was abated by diluting the filtrate with an additional 25% of sterile water.

After two weeks of treatment with the filtrate, the ulcer was about 1.5 to 2.0 cm in diameter and had a clean granulating base. By May 2004 the ulcer was 1.2 cm in diameter. In June 2004, the patient underwent elective surgery (for which he had been on the waiting list for three years) to close the remaining defect and protect the area with a rotation flap of skin and muscle. The surgery was successful. The patient continues to apply OPAL001 cream to the area to keep the scar soft. He reported that when he did not apply the cream for two to three weeks, the scar began to feel tighter and became a little red. No photographs were taken of this ulcer.

Case 2: Diabetic foot ulcers

This patient was a 56-year-old man with insulin-dependent type II diabetes associated with peripheral neuropathy, small and large vessel disease in his legs, and retinal disease. He had a 30-year history of heavy drinking and nutritional deficiency. He suffered multiple foot ulcers, which ultimately led to gangrene and amputation of three toes from the left foot between 2000 and 2002. The patient lives alone and has three adult children who live interstate.

In April 2003, the patient had developed two ulcers, one between the first and second digits of the right foot, and an infected lesion on the tip of the left fourth toe. He was being considered for amputation of the infected toe. Home-based treatment of both lesions with OPAL001 filtrate and cream was commenced in April 2003. Filtrate was applied to the ulcer bed of both lesions and cream applied to both forefoot and sole on each foot.

Right foot

After one week, non-viable tissue became clearly delineated, and was considerably larger than initial inspection indicated. The eschar dried out and began to reduce in size and separate over the next week (Figure 1). The interdigital skin healed first and was completely replaced with normal skin. After six weeks of treatment, the eschar was approximately one-third of its original size. The nail, which had been affected by probable ischaemia and chronic fungal infection, lifted off and a healthy nail had begun to regrow within six weeks of commencing treatment.

Left fourth toe

The infected lesion at the tip of the fourth toe on the left foot dried up two weeks after OPAL001 treatment commenced (Figure 2). The dried skin steadily lifted off, revealing healthy skin. The adjacent nail, which was badly affected by what appeared to be a fungal infection and probable ischaemia, lifted off and was replaced by normal nail. The ulcer at the tip of the toe, the nail bed and the ulcer on the right foot had not healed fully by the time the photographic record had been completed in June 2003.

The pain from the ulcers decreased after treatment and the patient was able to walk freely. The patient was reviewed by staff at his local hospital at a pre-planned review in September 2003, with the view to further amputation of the fourth toe on

the left foot. The doctor discharged him from the clinic on the basis that the ulcer had healed fully.

I examined the patient for the first time on 27 July 2007. The skin and nails of both feet were completely healthy, and had remained so since 2003. He was using OPAL001 cream on both feet routinely. This episode was the first time the patient's foot ulcers had healed fully and surgery was not required.

Case 3: Venous ulceration

A 75-year-old, intellectually disabled, but otherwise healthy man had long-standing left leg varicose veins. As a result, he has had multiple venous ulcers between the left knee and ankle, which usually took months to heal. He has had two operations attempting to improve his venous circulation.

In early 2004, he apparently developed a skin tear, which progressed to a venous ulcer overlying the shin on the left leg, with dimensions of approximately 7 x 4 cm. There was a flap of normal skin attached to the proximal margin and the base of the wound extending to the centre of the ulcer. The patient attended his GP's surgery three times weekly for dressings. He was prescribed antibiotics four times for coexisting cellulitis and he wore graduated compression stockings. The ulcer continued to grow in spite of this treatment. The ulcer was present for approximately six months before the patient started home-based treatment with OPAL001 filtrate and cream in June 2004. The ulcers were treated with OPAL001 filtrate placed in the ulcer cavity and OPAL001 cream around the periphery of the lesion. The quality of the surrounding skin improved and the ulcer base appeared much cleaner within a week (Figure 3). New skin began growing from the edge of the lesion and from the central skin flap. New skin developed much more quickly from the central skin flap than from the periphery of the wound. Healing of about two-thirds of the ulcer was achieved in the first two months. This rate of healing was much faster than the healing of the patient's previous ulcers. Closure of the remaining third of the ulcer took a much longer period of time, with complete closure of the ulcer taking approximately six months. There were another couple of episodes of cellulitis that impeded healing during this time, both treated with antibiotics.

The patient's carers treat new ulcers with the OPAL001 filtrate, saline washes and exposure to sunlight. New ulcers heal promptly. The carers use OPAL001 cream to improve skin quality when the skin becomes dry and flaky.

Case 4: Generalised small vessel arteriopathy

This 85-year-old lady suffered from generalised arteriopathy. She had suffered five strokes and was completely dependent for all personal care and activities of daily living, which were provided in an aged care facility. Her mental capacity was intact.

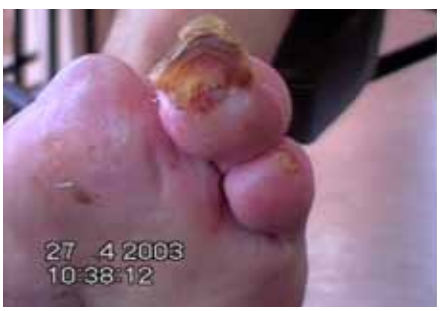
She developed a large squamous cell carcinoma on her left temple. This was treated with excision and a full-thickness skin graft in February 2008. The graft failed to take and demonstrated very poor skin quality, an ulcerated area centrally and several areas where the edge of the graft had necrosed. Arteriolar disease which compromised the ability of the graft to take was hypothesised. OPAL001 treatment was commenced in April 2008 (Figure 4). Filtrate was applied to the ulcer and cream to the rest of the graft and about one centimetre of surrounding skin.

By one month, the quality of the skin improved markedly. Areas of necrosis were more sharply defined then self-debrided to reveal clean, granulating beds. The ulcers then closed progressively over the subsequent eight weeks and complete healing was achieved 12 weeks after commencement of the treatment.

Figure 2. Diabetic toe ulcer treated with OPAL A.

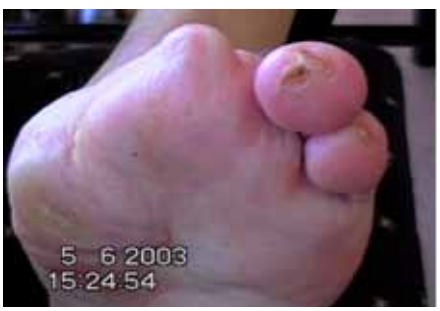
A. Baseline (commencement of treatment). The tip of the toe is necrotic and probably infected. The nail is grossly abnormal.

Date: 20 April 2003



B. One week after baseline. The tip of the toe is clean and drying out. The skin on the plantar aspect of the ulcer appears healthy.

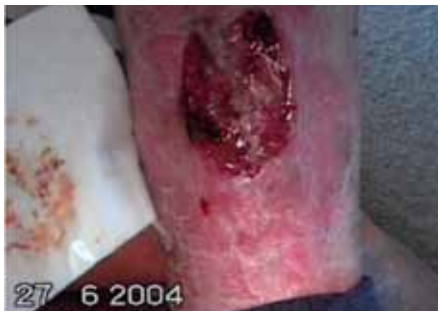
Date: 27 April 2003



C. Seven weeks after baseline. Only one lesion remains in the small central area, which is now shallow and dry. The nail is regrowing.

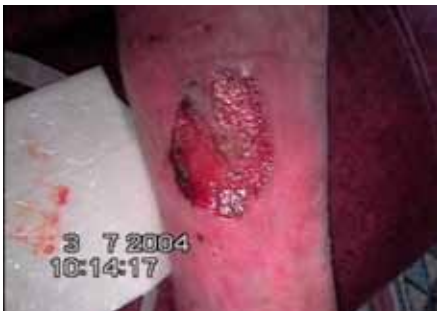
Date: 5 June 2003

Figure 3. Non-healing varicose ulcer treated with OPAL A



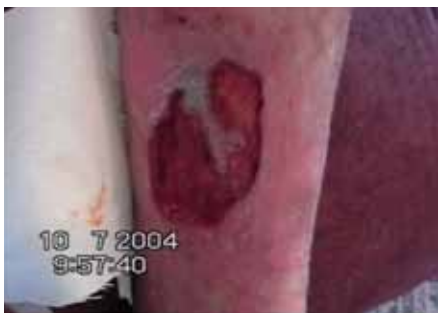
A. The ulcer is approximately 7 x 4 cm. There is a tag of normal skin in the centre of the ulcer. The base probably has low-grade infection and the edge of the wound is inflamed.

Date: 27 June 2004



B. The ulcer base is now very clean. Inflammation of the wound edge has completely resolved. Skin quality has improved markedly

Date: 3 July 2004



C. New skin arising from all wound edges is visible.

Date: 10 July 2004

D. The medial aspect of the ulcer has closed over, but healing is slower in the medial aspect of the original wound. , There is narrowing of the middle section of the remaining wound. The wound looks cleaner.

Date: 26 September 2004

Discussion

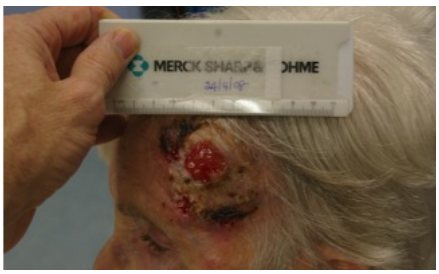
Each of the patients had chronic medical conditions which both caused skin ulceration and mitigated against their prompt healing. All four had tissue ischaemia as the underlying process. Three of these had an arterial origin. Cases two and four had underlying arteriolar disease, which left the skin vulnerable to non-healing of external insults. Case one had quadriplegia and suffered a pressure ulcer.

In each of these three cases that had an arterial origin, the OPAL001 treatment appears to have improved arteriolar circulation, but only in tissue which was ischaemic and not necrotic. In cases two and four, areas of questionable viability declared themselves as necrotic at the commencement of the treatment, with the development of an eschar, which subsequently lifted off. It may be that reperfusion injury described above facilitated this change because of unreliable reperfusion to this tissue. Tissue which was sufficiently viable progressed to healing. This principle appears to be further supported by case two where OPAL001 cream had been applied daily to the entire forefoot and sole so the toes were treated as well. Diseased nails on the toes of both feet separated and were replaced by new, healthy nail. Moreover, the quality of the skin around the ulcer improved markedly and rapidly in all four cases.

In case one, there was limited improvement when OPAL001 cream was applied to the skin around the deep ulcer, but not the ulcer bed itself. The application of undiluted filtrate to the ulcer cavity led to previously straw-coloured exudate becoming blood-stained within 24 hours. It seems that blood supply to the ulcer bed was encouraged quite rapidly. Closing in of the sinus commenced from that point.

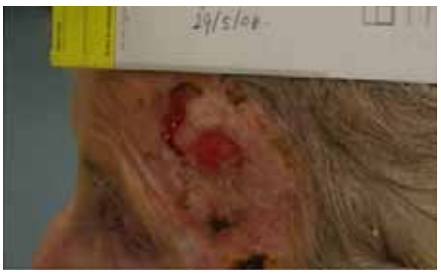
The patient in case three had venous ulceration, with no arterial insufficiency. Here it may have been that both arterioles and venules were dilated, facilitating local improvement in the overall circulation. Alternatively, arterioles only may have dilated, leading to a re-establishment of the normal pressure gradient in the treated area. In this case, the initial improvement and closure of the wound was quite rapid, which was followed by healing at a rate more in keeping with that expected in normal skin. It may be that OPAL001 normalised the skin micro-environment, allowing healing to take place at the normal rate.

Figure 4. Failed skin graft treated with OPAL A



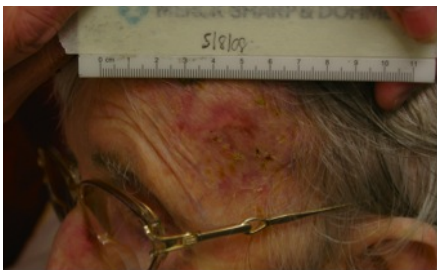
A. Failed skin graft two months after removal of large SCC. Central ulcer, necrosis of skin edge and very poor graft quality. OPAL A commenced.

Date: 24 April 2008



B. Four weeks post-treatment. Skin quality now normal. Necrotic tissue removed and all ulcers clean

Date: 29 May 2008



C. Twelve weeks post-treatment. Graft fully healed.

Date: 05 August 2008

The hypothesis that OPAL A causes vasodilation has been tested. A vasodilatory action probably mediated protection against oxidation of nitric oxide was identified[7]. OPAL-modified papaya also has an anti-inflammatory effect[8]. A possible wound debriding effect is currently being investigated.

These case reports present promising findings and join an early case report series on treatment of pressure ulcers in quadriplegics[9] which report promising findings in this population. This encouraging preclinical evidence has to be confirmed by formal randomised controlled trial. This is currently in progress, where OPAL A filtrate and cream are being tested in a single, blind, randomised, placebo controlled clinical trial on ulcers that are resistant to healing (Woodward, personal communication).

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