Hyperbaric oxygen therapy in the treatment of skin ulcers due to calcific uraemic arteriolopathy: experience from an Australian hyperbaric unit

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Key words
Calciphylaxis, hyperbaric oxygen therapy, chronic wounds, outcome

Abstract
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Introduction: Calcific uraemic arteriolopathy (CUA), also known as 'calciphylaxis', is a syndrome of ischaemic necrotic ulcers occurring in uraemic patients with end-stage renal failure. It is a debilitating condition with a high morbidity and mortality. Hyperbaric oxygen (HBO) has been used to treat such wounds for many years but evidence of its efficacy is limited.
Aim: We aimed to study the efficacy of HBO on the healing of problem ulcers secondary to CUA.
Method: A retrospective case review of all patients with chronic skin ulcers secondary to CUA treated at the Alfred Hospital Hyperbaric Unit from July 1997 to March 2006 (n = 20).
Results: HBO was beneficial in eleven (55%) patients, with six of these (30%) experiencing complete resolution of their ulcers on completion of their treatment. Advancing age was identified as a predictor of a positive outcome (P = 0.02). There was no statistical correlation between the number of HBO treatments and ulcer healing.
Conclusion: HBO can benefit patients with chronic non-healing wounds secondary to CUA, but its precise role remains undefined.

Introduction

Calcific uraemic arteriolopathy (CUA), also known as 'calciphylaxis', is a syndrome of ischaemic necrotic skin ulcers caused by subcutaneous and small vessel calcification. It occurs mainly in patients with uraemia caused by end-stage renal failure (ESRF). Hypercalcaemia, hyperphosphataemia and hyperparathyroidism are also thought to be precipitating factors and can feature as part of the syndrome. The condition usually presents as nodules of subcutaneous calcification that develop into painful violaceous ulcers (*livedo reticularis*) which become progressively necrotic.[1] Secondary infection of the ulcers is common in the setting of underlying uraemia and immune compromise. This can progress to sepsis, which is associated with a mortality of 60–80%.[2] CUA more commonly affects females and younger patients on long-term dialysis and has a prevalence of up to 4% in patients undergoing haemodialysis.[3]

The term calciphylaxis was first used by Sleye in 1962 when he induced metastatic soft tissue calcification in rats in a two-stage process. He first sensitised rats with Vitamin D analogues and parathyroid hormone (PTH) and then, after a critical period, challenged them with injections of irritant substances (egg albumin, iron) or local trauma.[4] The areas of skin challenged developed the characteristic ulceration described above. The word was coined because the mechanism of calcification was proposed to be a hypersensitivity reaction, and originates from the combination of calcium and anaphylaxis.

Calciphylaxis was first described in humans by Rees and Coles in 1969 who found medial calcification and intimal hyperplasia of arterioles occurring in the presence of uraemia.[5] The arteriolar calcification led to ischaemic tissue necrosis which then itself became calcified and necrotic.[1] Skin breakdown and wound development was then triggered by minor trauma and progressed to extensive ulceration. In 1998, Coates et al found that the previously described derangements in calcium, phosphate and PTH were often not present in patients with calciphylaxis and so proposed the use of a more descriptive term of "calcific uraemic arteriolopathy" (CUA).[6]

Hyperbaric oxygen (HBO) therapy involves breathing 100% oxygen at an elevated ambient pressure, usually 203–253 kPa. In hypoxic tissue, such as that found in and around problem ulcers, it restores tissue oxygen tension ($P_{tc}O_2$) to physiologically normal or supra-normal levels. This enhances fibroblast proliferation, collagen formation and angioneogenesis to aid ulcer healing. Wound healing may also be enhanced by systemic effects such as the mobilization of vasculogenic stem cells.[7] The elevation of $P_{tc}O_2$ also improves neutrophil function and polymorphonuclear leukocyte-mediated bacterial killing of organisms commonly found in associated ulcer infection.[2,8] It is by these mechanisms that HBO probably exerts its effect in CUA.

HBO has been used in the treatment of CUA wounds for many years but published evidence of its efficacy is limited to isolated case reports and small case series.[2,9–14] The first case series by Podymow and colleagues reported complete

healing in two out of five patients with CUA.[2] A year later Basile *et al* published a larger series of nine patients with distal lesions, eight of whom had their ulcers heal after an average of 41 HBO treatments.[9] Not all reports have shown benefit, however, and HBO has failed to become a universally accepted treatment.[13] This review aimed to study the benefit of HBO in those patients treated at the Alfred Hospital, Melbourne.

Methods

After submission to the Hospital Ethics Committee, the study was approved as a quality assurance project. All patients treated at The Alfred Hospital Hyperbaric Unit for chronic non-healing skin ulcers secondary to CUA from July 1997 to March 2006 inclusive were retrospectively studied. Patients were identified by searching the unit patient database (FileMaker Pro 5.5, Filemaker Inc, Santa Clara, California). Patient information was obtained regarding age, gender, cause for renal failure, presence of diabetes, dialysis type and the distribution of CUA lesions. Lesions were defined as either 'proximal', referring to lesions of the trunk, buttocks or upper thighs, or 'distal', referring to lesions of the arms and lower legs. Where both proximal and distal lesions were present, patients were assigned to the proximal group (being indicative of more extensive disease).

HBO data retrieved included the duration and number of treatments, and the degree of pressurisation. Patients typically received HBO for 90 minutes at between 203 and 243 kPa for five days per week. A therapeutic course of treatment was, for the purpose of this study, defined as more than two weeks (ten treatments) of therapy as this is the minimum prescribed to treat non-healing wounds of other aetiologies at our institution. Eight patients who received less were considered to have been withdrawn before receiving a therapeutic dose and were therefore excluded from further study. Patients were defined as having multiple treatment courses if there was a break in treatment of more than one month.

Efficacy of HBO was assessed using a six-point outcome score (Table 1), which was created from outcome measures used in the previous case studies.[2,9] This was aided by photographs when available. In the absence of photographs, outcome was based on the wound assessment made in the medical record. Healing was defined as a stepwise improvement of the ulcers evidenced by resolution of necrotic areas, granulation, reduction in wound size, and subsequent scar formation. Outcome assessment was made when each patient's treatment at the hyperbaric unit came to an end. Patient follow up was undertaken in mid 2008, aiming to evaluate mortality and progression of wounds subsequent to treatment.

Table 1
Six-point score used to assess healing in skin ulcers due to CUA

Score	Description
0	Severe deterioration leading to morbidity/mortality
1	Increase in wound size/necrotic tissue area
2	No change
3	Healing of necrotic areas with granulation tissue
4	Reduction in wound size
5	Scar formation/resolution of wound

Results were analysed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA). Relationships between continuous variables were determined using Spearman correlation coefficients, whilst relationships between continuous and categorical variables were determined using Wilcoxon rank sum tests. A two-sided P-value of 0.05 was considered to be statistically significant.

Results

Twenty-eight patients with a diagnosis of CUA were identified from the hyperbaric unit database. Eight of the 28 patients received ten treatments or fewer (median 2.5, range 0–7) and were excluded from further analysis. Reasons for discontinuation or refusal of therapy included patient refusal, anxiety/claustrophobia, respiratory co-morbidity and withdrawal by referring medical staff for palliation. Of the remaining twenty patients, two patients had missing data pertaining to their calcium/phosphate levels. The mean age of the treated patients was 56 years (SD 10.7) and twelve were female. Study patient characteristics are summarised in Table 2. The study group received between 17 and 83 treatments (median 51, mean 50.6) and five patients received more than one course of HBOT (median 1, range 1-3).

Eleven of the 20 patients treated had improvement in their wounds with HBO (an outcome score of 3 or more), of whom six healed completely. The five patients who received multiple courses all showed improvements in healing by the end of each course, only to subsequently deteriorate and require further treatment. Surgical debridement, skin grafting, antibiotics and wound care were administered as indicated.

In half of the patients, the decision to stop HBO was due to factors external to the hyperbaric physician. Reasons included being stopped by referring physician (three patients), withdrawal for palliation (two patients), attendance issues (two patients), patient decision (two patients) and death due to other causes (one patient). No demonstrable dose-response relationship was seen between the number of HBO sessions and ulcer healing (P = 0.42).

There were no statistically significant correlations between wound healing and gender, diabetic co-morbidity, or the type of dialysis therapy used to treat the renal failure (Table 3). Similarly, normal serum calcium and potassium levels at the time of assessment, or a history of parathyroidectomy,

Table 2
Clinical data for patients undergoing HBO for skin ulcers secondary to CUA (n = 20)

Age	Sex	Aetiology	Type of dialysis	Previous PTH surgery	Serum Ca^{2+}/PO^{4-}	Ulceration site (biopsy-proven)	HBO treatments	Outcome score	Additional therapy
45	M	Diabetic nephropathy	PD	Yes	Normal	Distal (No)	77	5	
31	F	Lupus nephritis	HD	Yes	Normal	Proximal (Yes)	76	1	Debridement
73	F	Diabetic nephropathy	PD	Yes	Normal	Distal (No)	75	4	Debridement and skin grafting
42	F	Glomerulonephritis	PD	Yes	Normal	Proximal (No)	37	2	
63	M	IgA nephropathy	HD	Yes	Normal	Distal (Yes)	52	1	
42	F	Hypertension	HD	No	Normal	Distal (No)	45	1	
63	M	Hypertension	HD	No	Elevated	Distal (Yes)	60	5	Debridement and skin grafting
58	M	Diabetic nephropathy	HD	Yes	Unknown	Distal (Yes)	20	4	
65	F	Lupus nephritis	None	Yes	Normal	Distal (Yes)	79	5	
46	M	Reflux nephropathy	None	Yes	Normal	Distal (No)	33	0	Debridement and BKA
58	F	Hypertension	HD	Yes	Normal	Distal (No)	83	2	Debridement
58	F	Reflux nephropathy	HD	No	Elevated	Proximal (No)	33	2	Parathyroidectomy
62	M	Diabetic nephropathy	HD	Yes	Normal	Proximal (Yes)	79	3	Debridement
67	F	Obstructive nephropathy	HD	No	Unknown	Proximal (No)	54	2	
68	F	Hypertension	HD	Yes	Normal	Proximal (Yes)	50	5	Surgical debridement
53	F	Reflux nephropathy	HD	Yes	Normal	Distal (Yes)	17	3	Died during HBO (sepsis)
57	M	Diabetic nephropathy	HD	No	Normal	Distal (Yes)	35	1	
64	F	Polycystic kidneys	PD	No	Normal	Distal (No)	22	5	
49	M	Diabetic nephropathy	PD	No	Normal	Distal (No)	28	3	Debridement
62	F	Glomerulonephritis	HD	No	Normal	Distal (Yes)	57	5	

PD – Peritoneal dialysis, HD – Haemodialysis, PTH – parathyroid, BKA – below-knee amputation

Table 3
Statistical correlation between patient characteristics and skin ulcer healing (outcome) when treated with HBO

Patient characteristic	P-value
Advancing age	0.02
Gender	0.73
Number of HBO treatments	0.42
Site of CUA lesion	0.39
Type of dialysis	0.42
Co-existing diabetes	0.54
Abnormal Ca^{2+}/PO^{4-}	0.94
History of previous parathyroidectomy	0.63
CUA proven on biopsy	0.45

was not a predictor of a successful outcome. There was no correlation between the site of the lesion and a worse outcome (P = 0.39). Advancing age was the only predictor of positive outcome (P = 0.02), older patients tending to do better with HBO.

Follow-up information was available for 16 of the 20 patients. Ten had died and six remained alive at a mean follow up of 51 weeks. Of the nine patients who had not responded to HBO (scores of 1 or 2), two were unable to be contacted and the other seven had died; two patients immediately followed cessation of HBO and withdrawal of active therapy and, in the remaining five, the longest survival was 15 weeks. In contrast, of the five patients who had healed at the end of their courses of HBO, the four who were contactable were alive and had remained healed after 12, 34, 46 and 89 weeks. One had experienced new CUA lesions at a previously unaffected site but these had again responded completely to HBO treatment. Of the four patients with a very limited response to HBO (score of 3), one was not contactable, and one died of systemic sepsis shortly after ceasing HBO, but the other two continued to heal and remained alive after 27 and 98 weeks. The two patients who substantially, but not completely, healed (score of 4) both survived for a further four years.

Discussion

In our study, the age, sex distribution and prevalence of diabetes in the patients were all similar to those of the two previous published series.[2,9] However, we were unable to reproduce a healing rate of 89% (8 of 9 patients) described in Basile's case series.[9] By comparison, only 30% of our patients experienced a complete resolution of their ulcers, similar to the original series by Podymow et al.[2] This study, combined with our own, probably represents a more accurate picture of the healing rate for CUA ulcers. Historically, a worse outcome has been associated with patients with proximal lesions. In our study, more patients had proximal lesions (six patients), but on analysis we found no correlation between the site of the lesion and a worse outcome.

The high mortality at follow up probably reflects the natural history of patients who develop CUA but there are insufficient data in our series and in the literature to confirm this. Response to HBO appears to be a predictor of mortality, the eight early deaths all occurring in patients with poor or no response.

Of the patient factors studied, age was a significant predictor of success with older patients being more likely to have a positive outcome with HBO. The exact reason for this cannot be ascertained from our study. However, it may be reasonable to postulate that more aggressive forms of CUA, renal failure, or of the underlying cause of said renal failure are seen in younger patients. Whatever the reason, it would be difficult to base a decision to treat with HBO on age alone – the patient with the most dramatic turnaround from life -threatening, extensive proximal disease to good long-term function was only 45 years old.

Regarding HBO, all treatments were given at pressures between 203 and 243 kPa, but there was no relation between the pressure or number of treatments and outcome. Thus the selection of which patients will respond to HBO, and the most effective treatment regimen (number of sessions) remains largely inconclusive.

A multimodal, multidisciplinary approach to treatment is usual for CUA. The complex nature of calciphylaxis and its co-morbidities can produce many barriers to successful treatment. In half of our patients, the decision to stop treatment was not made by the hyperbaric physician. For some patients, receiving daily hyperbaric oxygen therapy in conjunction with intermittent dialysis and inter-hospital transfer is too demanding. Close liaison between patient, renal unit and hyperbaric unit is essential to improve efficiency and minimise the chance of patients missing valuable dialysis or HBO. During periods of HBO, many of our patients received dialysis at The Alfred to avoid patients spending time and energy commuting between treatment centres.

In addition to providing HBO, most hyperbaric units can provide an important coordinating role due to their position of being able to review patients daily and follow the progress of healing. Routine wound care and antibiotics when necessary are administered. CUA skin ulcers are often associated with severe ischaemic pain and distress. Pain management and psychological support are other aspects of treatment well managed by hyperbaric physicians many of whom have a background in anaesthesia.

Referral for surgical debridement and skin grafting may also be necessary. Half of our patients healed after skin grafting. A key role for HBO may be as a pre-operative optimizer of the wound base by improving the microcirculation and encouraging healthy granulation prior to skin grafting. However care must be taken in patients with widespread

calcific deposits. The donor site must first be investigated for the presence of calciphylaxis as new ulcers can be generated from the surgical insult. On the evidence of this study, grafting may be best reserved for older patients with isolated lower limb CUA.

Control of calcium and phosphate levels and surgical parathyroidectomy are recognised treatments for CUA. A retrospective case series by Angelis and colleagues reported an 80% healing rate in patients who underwent parathyroidectomy.[3] This was reinforced by a recent study by Duffy and colleagues who retrospectively studied two cohorts of patients with CUA ulcers. Those treated with total or partial surgical parathyroidectomy (six patients) demonstrated a 100% healing rate compared with those treated with medical therapy (nine patients) of whom only two had improvement in the skin lesions. The surgery group also showed a survival benefit over the 80-month follow up (median survival 39 versus three months using Kaplan-Meyer analysis).[15] The majority of our patients had previously undergone parathyroidectomy and had good control of calcium and phosphate prior to starting HBO. Given this was a group who had largely failed to show ulcer healing despite 'conventional' therapy our 30% healing rate may represent significant benefit, but without comparative controls no definitive conclusions can be drawn.

A common observation in our patients was that the severe pain often associated with CUA lesions usually diminished and in some cases ceased after several weeks of treatment with HBO, but unfortunately objective scoring of this was not undertaken. This is something which deserves further study: if HBO can contribute to an improved quality of life by reducing pain then it may be justifiable, even in some terminal cases. It is important to qualify this with the fact that for some patients, the logistics of travel to a hyperbaric facility could represent an inappropriate burden during the final weeks of life.

When examining therapeutic options for CUA in the absence of higher order evidence, it is useful to consider mechanisms of action. Medical and surgical therapies involve controlling metabolic derangement to arrest or reverse the process of systemic calcification. In contrast HBO acts to reverse tissue hypoxia at the wound site and as such can be considered a local treatment for hypoxic ulceration but not for the underlying CUA (Table 4). However, a further observation in our patients was that long-term responders reported softening and improved flexibility of their tissues. This may represent some reversal of the CUA process but assuming any causal relationship would be inappropriate at this stage.

The pathogenesis of CUA is incompletely understood. However, it is reasonable to postulate that calcium deposition in small vessels will lead to local tissue hypoxia around the wound margins akin to many chronic wounds. Restoration of tissue normoxia, the goal of therapy in hypoxic wounds, may be difficult to achieve in patients with arterial calcification leading to a reduced macro-vascular blood flow. Any benefit demonstrated from HBO in calciphylaxis seems just as likely to be due to enhanced neutrophil function in patients with multiple barriers to healing, including diabetes and uraemia. In addition, optimising neutrophil function may render the patient resistant to secondary infection, the commonest cause of death in CUA.

This study reflects our belief that prolonged treatment with HBO is often required to heal these wounds. We believe this probably induces microvascular angioneogenesis not only in hypoxic areas at the wound site but also at other sites of calcification. This may in turn provide some degree of protection from ischaemic injury to these sites in the future.

The results of this study can be compared with the recently published interim analysis of the study by Hawkins et al, which evaluates outcomes of chronic hypoxic wounds treated with HBO.[16] This prospective study of 110 patients showed an overall good response in 52.3% receiving HBO. Skin ulcers due to CUA were not examined as a subgroup in this report but analysis of wounds caused by peripheral vascular disease and venous disease demonstrated a good response in 23.5% and 45.5% respectively at the end of treatment with HBO. The healing rate of 30% in our study is, therefore, consistent with these results and supports the view that whilst HBO is not a cure-all for refractory wounds, it is at least one treatment option for patients with skin ulcers secondary to CUA. However, patients should be informed of the potentially prolonged treatment course that may be required and the effect this may have on other aspects of their ongoing medical care.

For the future, there have recently been a number of case reports of treatment of CUA with agents aimed at modifying calcium and/or phosphate kinetics, including chelating agents and bisphosphonate therapy.[17,18] It seems reasonable to speculate that such strategies could be synergistic with

Table 4
Therapeutic options for patients with CUA

	Systemic therapies	Wound therapies
Medical		
	Reduce dialysate calcium	Topical antibacterial preparations
	Anticoagulation	HBO
	Phosphate binders	
Surgical		
	Parathyroidectomy (partial or total)	Wound debridement
		Skin grafting
General		
	Antibiotics	Avoid triggering factors
	Analgesics	

HBO in managing this difficult problem but this remains to be explored.

Limitations of our study are those inherent in all retrospective reviews, such as record keeping and a lack of comparative controls. Patients who received more than one treatment course all showed improvement with each course but analysis was done on the patient's eventual outcome rather than that of the individual course, as this would have positively biased the outcome. Out of necessity, the outcome score was developed from previously published wound assessment outcomes but has not been validated. More robust, prospective studies of CUA therapeutics will probably need to be multi-centred and given the difficulty in organizing and funding randomized trials, this would seem an ideal area for a well-designed registry.

Conclusion

In a proportion of our CUA patients, HBO was beneficial in improving ulcer healing and resolution. However, this study does not support the healing rates achieved in the largest previous study. The ability to predict from clinical signs and symptoms which patients will benefit, and the most effective HBO regimen remains undefined. Given CUA is a painful and debilitating condition, it remains reasonable to consider HBO as part of the multidisciplinary, multimodal treatment approach in those patients able to undertake the prolonged treatment that is often required. Prospective, case-controlled trials are needed to clearly define the healing effect of HBO in this condition.

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