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Original Article

Hyperbaric oxygen in the treatment of calciphylaxis: A case series and literature review

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SUMMARY AT A GLANCE

Calciphylaxis is often a pre-terminal event in dialysis dependent kidney disease, with obese and diabetic patients at highest risk. The role of hyperbaric oxygen therapy (HBOT) in the treatment of calciphylaxis has been unclear, with the therapy often being used as a last therapeutic resort. This paper is possibly the largest case series of HBOT use for the treatment of calciphylaxis and provides useful insights into its place in managing the disease.

ABSTRACT:

Aims: **Calcific uraemic arteriolopathy (CUA) or calciphylaxis is most commonly seen in end-stage renal disease and is associated with significant morbidity and mortality. The aim of this study was to determine whether hyperbaric oxygen therapy (HBOT) is effective in healing calciphylaxis lesions and to determine if there are any patient factors that can predict wound healing and patient survival.**

Methods: **We identified by retrospective review all cases of CUA referred to our institution for treatment with HBOT. We documented the clinical and biochemical parameters of this patient population, the size and distribution of the lesions as well as wound outcomes and patient survival following treatment.**

Results: **A total 46 patients were identified with CUA associated with renal failure. Of the 46 patients, only 34 received a full course of HBOT. The balance was deemed unsuitable for treatment or was unable to tolerate treatment and was palliated. Of the 34 patients that received a full course of HBOT, 58% showed improvement in their wound scores, with more than half of these patients having complete healing of their wounds. The balance did not benefit from the therapy and had a very poor prognosis. Those that benefited from HBOT survived on average for more than 3 years. The only factor significantly associated with improved wound healing and survival was diabetes.**

Conclusion: **This retrospective analysis suggests a role for HBOT in the treatment of CUA with more than half of the treated patients benefiting and surviving for an average of more than 3 years.**

Calcific uraemic arteriolopathy (CUA) or calciphylaxis is a debilitating condition most commonly seen in end-stage renal disease. It has become increasingly recognized in the dialysis population with an estimated prevalence of 4.1%.[1] It appears to be more common in females and in those with diabetes and obesity.[2–4]

CUA is characterized by the development of cutaneous lesions such as erythematous nodules or indurated plaques. These can rapidly evolve to become painful necrotic ulcers, predisposing to infection, sepsis and death.[5,6] CUA has an exceptionally high morbidity and mortality; proximal and ulcerated lesions carry the poorest prognosis with mortality as high as 80%.[7]

The key histological finding is that of cutaneous arteriolar medial calcification, subintimal fibrosis and intravascular thrombosis.[8] The exact pathogenesis underlying this remains poorly understood. It is thought that an elevated calcium phosphate product in the presence of hyperparathyroidism can lead to 'metastatic calcification'.[9] This is supported by the fact that an elevated parathyroid hormone (PTH) and calcium phosphate product are commonly observed in CUA.[4,10] Therapy has focused on correcting derangements of

calcium, phosphate and PTH in addition to supportive care with antibiotics, wound debridement and dressings as well as nutritional support.[11] Despite these measures, outcomes have remained poor and therefore attention has turned to newer therapies such as sodium thiosulphate[12–14] and hyperbaric oxygen therapy (HBOT).[15]

HBOT consists of breathing 100% oxygen at pressures higher than ambient pressure (1 atmosphere absolute (ATA)) while the patient is situated inside a sealed treatment chamber. Patients with CUA typically receive 20–30 treatments of 100 and 110 min at pressures between 2.0 and 2.4 ATA. This allows for the delivery of normal or supra-normal levels of oxygen to hypoxic tissues like those found in CUA ulcers and promotes wound healing through fibroblast proliferation and angiogenesis while also aiding oxygen-dependent neutrophil bactericidal activity.[16,17]

Our aim was to determine whether HBOT is effective in healing calciphylaxis lesions and to determine if there are any patient factors that can predict wound healing and patient survival.

METHODS

A retrospective review was conducted on all patients with confirmed or assumed CUA in association with end-stage renal failure treated at the Alfred Hospital Hyperbaric Unit over a 13 year period between June 2000 and July 2013 inclusive. Local ethics approval for conduction of the study was granted by the Alfred Hospital Ethics and Research Department. Patients were identified by searching the Hyperbaric Unit patient database and Renal Unit records.

Basic patient demographics were obtained including: age, gender, cause of renal failure, dialysis type, previous renal transplantation and length of time on dialysis. The incidence and duration of diabetes and history of parathyroidectomy were also recorded. Concomitant medication including warfarin, cinacalcet and sodium thiosulphate was recorded. The CUA lesions were characterized according to site, distribution and size. Details of HBOT for each patient included: number of treatments, duration of treatment and any hyperbaric-related complications.

At the completion of each patient's treatment course, the effect of hyperbaric therapy on wound outcome was evaluated using a four-point outcome score. The response to treatment was graded as wound deterioration (0 score), no change (1), partial healing or reduction in wound size (2) or complete healing (3). This was facilitated by clinical photography when available. In the absence of photographs, outcome was based on wound assessments made in the medical record. Patient follow-up was undertaken where possible until July 2013.

Statistics

Continuous data were described as either mean (standard deviation (SD)) or median (interquartile range) if not normally distributed. Univariate and multivariate analysis of factors associated with wound healing and survival was performed. All analyses were performed using the statistical package STATA 13 (StataCorp, College Station, TX, USA).

RESULTS

A total of 46 patients with a diagnosis of CUA associated with chronic kidney disease were referred to our institution for treatment with HBOT between June 2000 and July 2013 inclusive. One of these patients had a functioning renal transplant and was not receiving renal replacement therapy at the time they developed CUA but was included in the analysis.

Baseline clinical details

The mean age of the 46 patients identified was 61 years (SD ± 11.7) and 29 (63%) were female (Table 1). Thirty patients (65%) had a wound biopsy to confirm the diagnosis of CUA. Nine patients were receiving peritoneal dialysis (PD) and 34 patients were on haemodialysis (HD). Two patients had chronic kidney disease but were not on dialysis and one had a functioning renal transplant. The mean time on dialysis prior to presentation was 3.3 years (SD ± 5.0). Twenty-three patients (50%) had diabetes with an average time from diagnosis to presentation of 17 years (SD ± 8.5).

Parathyroidectomy was performed in 22 cases at a median of 6.3 (95% confidence interval (CI) 3.1–12.9) months prior to referral. The distribution is skewed with six cases having parathyroidectomy 4–6 weeks prior to commencement of HBOT. Only one of these was considered an emergency parathyroidectomy in the surgical notes. Thirteen patients were concomitantly taking warfarin at initial assessment. Phosphate binder used included calcium carbonates (6), aluminium salts (2), sevelamer (6) and lanthanum (1). One patient was on calcitriol at the time of referral.

Thirty-one (67%) patients had lesions in the distal part of their limbs, 11 patients (24%) had more proximal lesions and 4 patients (9%) had both proximal and distal lesions. The size of lesions varied from less than 25 cm^2 (30%), 25 cm^2 to 100 cm^2 (50%) and greater than 100 cm^2 (20%) in surface area. All patients were also managed with surgical debridement, skin grafting, antibiotics and wound care as indicated.

The mean PTH level in 27 patients where this was recorded was 24.7 pmol/L (SD ± 31.5) (normal 1.5–5.8 pmol/L). The corrected calcium and phosphate in 32 patients where this was recorded was 2.37 mmol/L (SD ± 0.45) and 1.65 mmol/L (SD ± 0.53) respectively. The mean calcium phosphate product was 3.59 $mmol^2/L^2$ (SD ± 1.44) (Table 2).

Hyperbaric treatment

Twelve of the 46 patients were unable to complete more than 10 hyperbaric treatments. Four were withdrawn by the treating renal unit, five were unable to tolerate HBOT and in one patient, a decision was made to commence palliation. All eventually had active treatment withdrawn and died soon after. The demographics of this group of patients did not

Table 1 Patient demographics

		All patients $n = 46$	Adequate HBOT $n = 34$	Inadequate HBOT $n = 12$	*P*-value
Gender (M : F)		17:29	15:19	2:10	0.52
Age (mean ± SD)		61.0 (11.7)	59.7 (11.4)	64.7 (12.0)	0.09
Cause of renal failure *n* (%)	Diabetes	18 (39.1%)	13 (38.2%)	5 (41.6%)	0.95
	HT/renovascular	5 (8.8%)	4 (11.7%)	1 (8.3%)	
	Glomerulonephritis	9 (19.6%)	7 (20.6%)	2 (16.7%)	
	Other/unknown	14 (21.9%)	10 (29.4%)	4 (33.3%)	
Dialysis modality *n* (%)	Haemodialysis	34 (73.9%)	25 (73.5%)	9 (75%)	0.49
	Peritoneal dialysis	9 (19.6%)	7 (20.6%)	2 (16.6%)	
	Renal transplant	1 (2.2%)	1 (2.9%)	0	
	CKD	2 (4.3%)	1 (2.9%)	1 (8.3%)	
Comorbidities *n* (%)	Diabetes	23 (50.0%)	17 (50.0%)	6 (50.0%)	0.10
	Vasculopathy	13 (28.3%)	12 (35.2%)	1 (8.3%)	
	Ischaemic heart disease	20 (43.5%)	15 (44.1%)	5 (41.6%)	
Calciphylaxis distribution *n* (%)	Proximal	11 (23.9%)	10 (29.4%)	1 (8.3%)	0.50
	Distal	31 (67.4%)	23(67.6%)	8 (66.7%)	
	Both	4 (8.7%)	1 (2.9%)	3 (25.0%)	
Lesion size *n* (%)	<25 cm^2	14 (30.4%)	12 (35.3%)	2 (16.7%)	0.27
	25–100 cm^2	23 (50.0%)	17 (50.0%)	7 (58.3%)	
	>100 cm^2	9 (19.6%)	6 (17.6%)	3 (25.0%)	

Variables compared by *t*-test (parametric data) or Wilcoxon rank sum test (non-parametric data and counts). CKD, chronic kidney disease; F, female; HBOT, hyperbaric oxygen therapy; M, male; SD, standard deviation.

Table 2 Outcomes and interventions for the 34 patients treated with adequate HBOT

Wound outcome score	Description	Total (%) $n = 34$	Parathyroidectomy $n = 18$	Sodium thiosulphate $n = 6$}	1 year survival $n = 17$
0	Wound deterioration	12 (35%)	7 (38.8%)	0	2 (11.8%)
1	No change to wound size	2 (6%)	1 (5.6%)	0	
2	Partial healing or reduction in wound size	9 (26%)	4 (22.2%)	2 (33.3%)	15 (88.2%)
3	Complete healing of wound	11 (32%)	6 (33.3%)	4 (66.7%)	

HBOT, hyperbaric oxygen therapy.

differ significantly from the group that tolerated an adequate course of HBOT (Table 1). This group of patients was excluded from further analysis.

Patient survival and the effects of hyperbaric oxygen on wound healing were only analysed in the 34 patents that completed an adequate course of HBOT. These patients had an average of 44 treatments (SD ± 22). Hyperbaric treatment was completed in a mean of 55.3 (95% CI 42.5–67.9) days. Five patients received multiple courses of HBOT (four patients: two courses, one patient: three courses). Twelve hyperbaric oxygen-related complications (0.8%) occurred in 1550 treatments (4 barotrauma, 3 anxiety events, 3 episodes of nausea and 2 patients with temporary myopia).

Wound outcome

Of the 34 patients that received adequate HBOT, 12 (35%) had deterioration in their wound (wound score of 0) and 2 (6%) had no change (wound score of 1). Nine (26%) had improvement in their wound (wound score 2) and 11 (32%) had complete wound healing (wound score of 3) (Table 2). There was no difference in outcome depending on the wound size. If an adequate course of HBOT occurred, the heal rate was 64% for lesions <25 cm^2 and between 25 and 100 cm^2, and 50% for lesions over 100 cm^2 in size ($P = 0.75$) (Fig. 1). There were nine patients on PD of whom six were successfully treated (67%). There were 25 on HD of whom 14 (56%) were successfully treated ($P = 0.59$).

Patient survival

Of the 14 patients that had deterioration or no improvement in their wound with HBOT (wound score 0–1), 1 was lost to follow-up and all others were deceased at last review. Eleven of the 13 died within 1 year of treatment and the remaining 2 patients died within 2 years of treatment. Of the 20 patients that had a response to HBOT (wound score 2–3), 13 were alive at last follow-up (mean follow-up 6 years, range 1–13 years) and 7 were deceased (mean survival 38.4 months, range 8–68 months).

Multivariate regression was performed on patients in whom complete data were available for the factors that

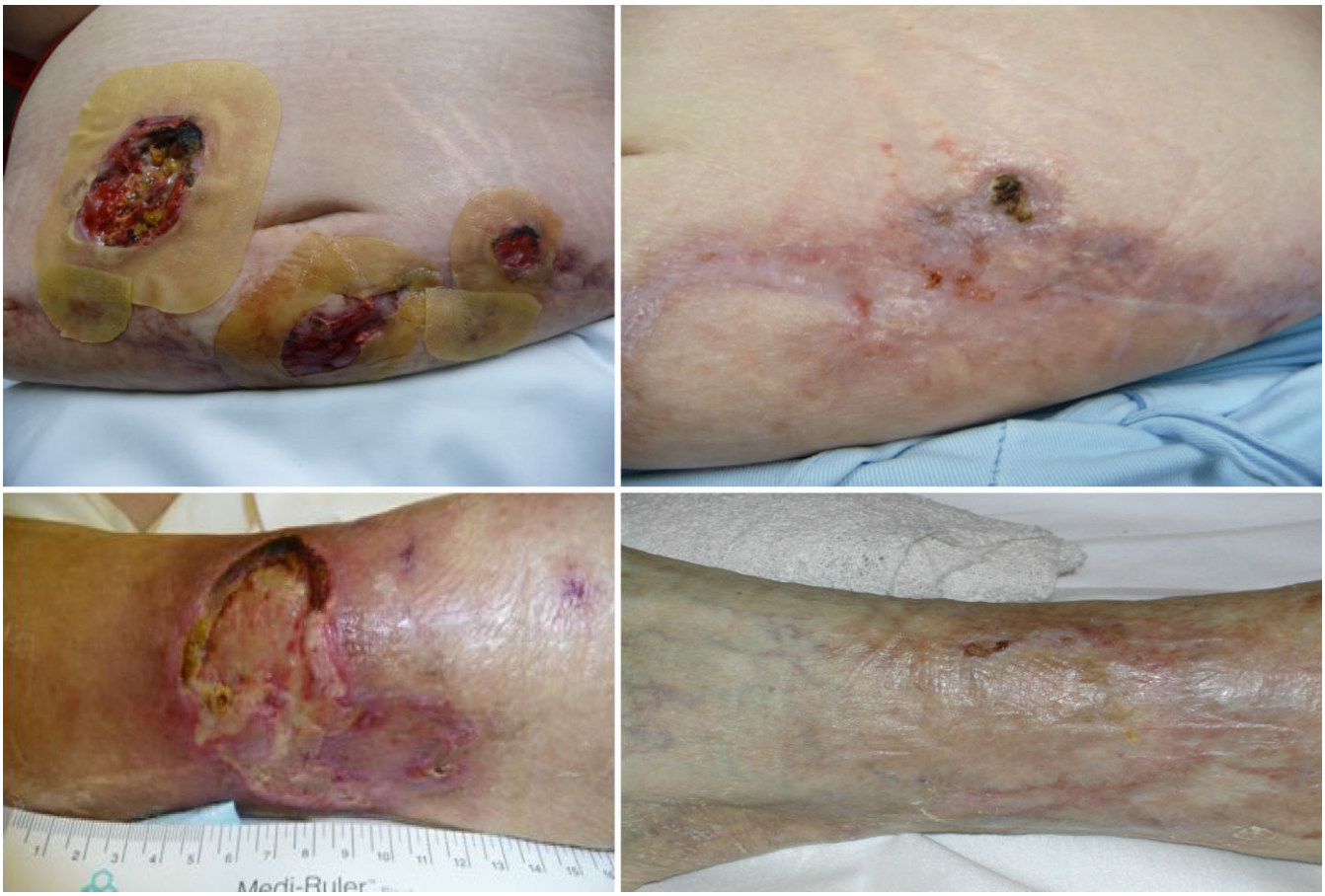

Fig. 1 Calciphylaxis lesions in abdominal distribution (upper panels) and lower limb distribution (lower panels) demonstrating size of lesions prior to hyperbaric oxygen course and following treatment.

were examined. Diabetes was the only factor significantly associated with improved wound healing ($P < 0.05$) and improved mortality ($P < 0.05$). Of the 17 diabetic patients who completed a course of HBOT, 13 (76.5%) had a wound outcome score of 2 or 3 whereas in the 17 non-diabetics, only 7 (41%) showed wound improvement with HBOT ($P = 0.04$). Median survival after HBOT was significantly longer for diabetics at 59.9 months *versus* 8.6 months for non-diabetics ($P = 0.03$).

Age, gender, mode of dialysis, time on dialysis, parathyroidectomy, warfarin, lesion distribution and size, PTH level, calcium, phosphate, calcium phosphate product and the use of sodium thiosulphate had no statistically significant impact on wound healing or mortality.

DISCUSSION

Our case series represents the largest group of patients with CUA referred for HBOT reported to date, with 46 patients being assessed in total. Fifty-eight per cent of those patients that received a sufficient course of HBOT demonstrated improvement in their wounds with almost half of these patients having complete healing of their wounds. Patients were referred for consideration of HBOT usually as a result of failure to respond to conventional and supportive measures. Referral was often made to our centre as a 'last resort' and is reflected in the large number of patients deemed not suitable for HBOT, most of who were withdrawn from dialysis and died soon after.

The CUA lesions in our series seemed to occur slightly more commonly in females, presenting in general several years after dialysis commencement. The patient group was young for a dialysis population, with the average age being 61 years. Half of the patients assessed were diabetic, mostly of long duration. Almost a third of patients were on warfarin at the time of presentation. Hyperparathyroidism was common but not universal among the population. Imbalance of calcium phosphate product was also only modest in those patients for which data were available. The bulk of lesions were distal but up to one-third of patients had proximal lesions. Other smaller case series make similar observations about the pattern of disease occurring more commonly in females, in a younger age group, many of whom are diabetic (and obese) and on warfarin.[2,4,10]

Table 3 Prior studies of the influence of hyperbaric oxygen therapy (HBOT) on calciphylaxis

Author	Year	Cohort	No. of HBOT treatments (range)	Other interventions	Outcome	Comments
Podymow *et al*.[15]	2001	5	25–35	Nil	60% improved 40% healed	Diabetic 80% Distal 40%
Basile[20]	2002	11	20–108	PTHX	89% improved 73% healed	Diabetic 27% Distal 100%
Dwyer *et al*.[21]	2002	1	23	Not reported	100% healed	Diabetic 0% Distal 100%
Edsell *et al*.[22]	2008	20	17–83	PTHX	55% improved 30% healed	Diabetic 30% Distal 70%
Rogers *et al*.[23]	2008	12	7–41	Not reported	92% healed	Diabetic 33% Distal 40%
Arenas *et al*.[24]	2008	2	20–30	Cinacalcet, STS, PTHX, sevelamer	100% improved	Diabetic 0% Distal 50%
Alikadic *et al*.[25]	2009	1	19	Iloprost infusion	100% healed	Diabetic 0% Distal 100%
Baldwin *et al*.[26]	2011	7	10–65 HBOT in 6 pts only	Cinacalcet, sevelamer, STS	86% healed	Diabetic 57% Distal 86%
New *et al*.[27]	2011	5	25–30 HBOT in 2 pts only	Calcitriol, cinacalcet , STS, PTHX, sevelamer	80% healed	Diabetic 20% Distal 100%
Malabu *et al*.[28]	2012	6	Not reported	Cinacalcet, STS, PTHX	50% healed	Diabetic 66% Distal 66%
Savoia *et al*.[29]	2013	4	Not reported HBOT in 3 pts only	Cinacalcet, STS	75% improved	Diabetic 25% Distal 75%

PTHX, parathyroidectomy; pts, patients; STS, sodium thiosulphate.

While it is tempting to implicate high calcium phosphate product combined with severe hyperparathyroidism in the pathogenesis of CUA, others like ourselves have also observed the disease occurring in patients with only modest derangements in these parameters.[15] Similarly, while many patients had undergone parathyroidectomy prior to referral, a large number had not. The role for urgent parathyroidectomy in CUA remains unclear with some case series suggesting a benefit of this procedure on disease outcome[18] and others not.[19]

Previous reports of the use of hyperbaric oxygen in calciphylaxis have been limited to small series or case reports (Table 3).[15,20–30] In these reports, patients have often failed to respond to conventional therapies including wound debridement, antibiotic therapy and parathyroidectomy and had complete wound healing with HBOT. It is worth noting the high prevalence of diabetics with CUA in these reports but not all diabetics responded completely to HBOT. In contrast, diabetics in our series were associated with improved wound outcome. This observation has not previously been reported. Recent meta-analysis suggests a clear benefit of HBOT for treatment of simple diabetic foot ulcers,[31] and this may partly explain the benefit we observed in diabetics with CUA. Non-diabetics with complete peripheral vascular occlusion contributing to CUA may benefit less from HBOT as higher arterial partial pressures of oxygen may fail to reach the wound bed. Small vessel diabetic disease as part of CUA may benefit greater from HBOT because of improved local tissue oxygenation. Indeed, some studies have measured changes in wound area transcutaneous oxygenation pressure with HBOT and correlated this with wound outcomes.[15] While such measurement was not available for our patient population, demonstrating improved tissue oxygen in diabetic patients with CUA treated with HBOT *versus* non-diabetic patients treated similarly, may go some way to support this hypothesis.

More important than wound response to treatment in CUA is overall patient survival. While it may be possible to induce wound healing of CUA with a variety of therapies, any intervention, especially costly ones such as HBOT, needs to demonstrate mortality benefit as well. Few studies have looked at long-term mortality in patients with CUA treated with HBOT. In our patient population, failure to respond to treatment was almost universally fatal mainly due to withdrawal of therapy and palliation. This most likely reflects the patient population referred to our service for consideration of HBOT treatment as a 'last resort'. In those that did respond to HBOT, 13 were alive at last review with a mean follow-up of 6 years. Of the seven deceased patients that responded to HBOT, mean survival was 38.4 months. Rogers *et al*.[23] were similarly able to demonstrate mean survival of 25.5 months in their patients that responded to HBOT. Although this was significantly worse than their matched controls, it still equated to an average of just over 2 years of survival if responding to treatment, and in our patient population over 3 years of survival.

The number of HBOT sessions that are thought to be sufficient to demonstrate a response in tissue healing remains unclear. As is evident from the published literature,

the number of prescribed treatment sessions can vary over a wide range (Table 3). In our cohort of patients, the mean number of HBOT sessions was 44 (±22). The authors can only suggest frequent clinical assessment of wounds and surrounding tissue to gauge response to HBOT. Serial clinical photography may aid in this assessment. Some authors[15] have suggested the efficacy of HBOT may be demonstrated by increased transcutaneous oxygen pressure in CUA lesions but this has not been universally applied.

HBOT is associated with some risks of adverse effects including damage to ears, sinuses and lungs from the effects of pressure, temporary worsening of short-sightedness, claustrophobia and oxygen poisoning. Although serious adverse events are rare, HBOT cannot be regarded as an entirely benign intervention. Oxygen toxicity seizures are a known complication of HBOT. During the first 20 years of operation of the Freemantle Hospital Hyperbaric Medicine Unit for example, oxygen toxicity seizures occurred at a rate of 1/1650 treatments.[32] In our case series, over a total of 1550 HBOT, there were only a few noted side effects of treatment, most of them mild and self-limiting. There were no reported cases of oxygen toxicity seizures.

Limitations

This study was limited by the biases inherent in retrospective case series. Incomplete data obtained from medical records and the lack of comparative controls limit our findings to observations only. As HBOT was in many cases considered a 'last resort' for patients, the population we were treating had already failed conventional therapies. This inevitably meant patients had already had prolonged hospitalization with all its associated morbidity prior to arriving at our institution.

It was not possible to compare the effects of newer agents that may play a role in the prevention of CUA such as cinacalcet, or in the treatment of CUA such as sodium thiosulphate as these agents were not available to all patients in this cohort. Whether the use of these agents will affect the profile of patients developing CUA and being referred for HBOT remains to be seen. It has been suggested that thiosulphate may be synergistic with HBOT to heal CUA.[33] As single-centre randomized controlled clinical trials are unlikely to be practical in this patient population, we suspect it will remain difficult to identify the best modality of treatment for this condition for some time to come.

CONCLUSIONS

Our data certainly suggest that HBOT should continue to be considered as a viable and safe therapeutic option as part of a multimodal approach for the treatment of CUA. It is most likely that no single intervention will prove most beneficial in this patient population but rather early initiation of multimodal therapies is likely to produce the best patient outcomes. Whether early introduction of HBOT in combination with newer therapies such as sodium thiosulphate will prove to be of benefit remains to be seen.

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