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Therapeutic outcomes evaluation of adjuvant hyperbaric oxygen therapy for non-healing diabetic foot ulcers among sudanese patients

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ABSTRACT

Background and aims: Diabetic foot ulcers (DFUs) are common complications of diabetes that frequently lead to amputation and disability. Despite some promising results in using hyperbaric oxygen therapy (HBOT) for DFUs treatment, its efficacy is still debatable. The aim of this study was to evaluate the therapeutic outcomes of adjuvant HBOT in non-healing DFUs treatment.
Methods: A descriptive, retrospective, hospital-based study was conducted at Al–Mo'alem Medical City-Khartoum, Sudan from August to December 2018. Medical records of Type 2 diabetic patients, treated with HBOT plus standard wound care for DFUs, were included in the study. Data were analyzed by simple descriptive statistics and logistic regression. $P \leq 0.05$ was considered statistically significant.
Results: The study results showed that 51.7% of patients had Wagner grade-3 ulcers and 28.3% had complete loss of protective sensation. Almost 61% of patients achieved complete ulcer healing while 16.7% underwent amputation. Twenty percent of patients treated with HBOT experienced ear barotraumas as adverse effects. Protective sensation (OR = 6.00, 95% CI = 1.79–20.16, $p = 0.004$) and more sessions of HBOT (OR = 17.35, 95% CI = 4.51–66.73, $p = 0.000$) were positive predictors of complete ulcer healing. Loss of protective sensation (OR = 0.17, 95% CI = 0.05–0.63, p = 0.007) was an indicator of amputation.
Conclusions: Treatment with adjuvant HBOT enhanced ulcer healing and reduced amputation rate in patients with non-healing DFUs. HBOT could be considered a relatively safe intervention.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder with short and long-term complications [1]. Diabetic foot ulcers (DFUs) are common and serious complications of diabetes that necessitate high care from patients, community, and healthcare systems [2].

Epidemiological studies revealed that the global prevalence of DFUs was 6.3%, and Africa has the second-highest prevalence of DFUs worldwide (7.2%). The rising prevalence of diabetes worldwide is associated with an increased incidence of lower limb amputations due to foot ulcers [3,4].

Diabetes is a serious health threat that is growing faster in low- and middle-income countries [5]. In Sudan, the prevalence of type 2 DM in 2019 was estimated to be 20.8%, with 18.1% of diabetic patients in Khartoum city suffering from DFUs [6,7]. Amputation, as a serious complication of DFUs, has increased dramatically in recent years in Sudan. During the period from June 2006 to May 2007, 19.2%, of patients with diabetic septic foot underwent lower limb amputation in Omdurman Teaching Hospital-Sudan [8]. Remarkably, the rate of amputation had increased to 54.7% in Wad Medani Teaching Hospital-Sudan in 2016 [9].

DFUs treatment aims to reduce complications and improve the patients' quality of life. In general, the standard therapy for DFUs includes patient education, glycemic control optimization, wound debridement, dressing, off-loading, antibiotics for active infections,

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vascular assessment and surgery [10]. Other therapies such as acellular matrix and hyperbaric oxygen therapy (HBOT) have shown promise in the treatment of DFUs [10–12]. HBOT has been used as an adjuvant therapy for the treatment of non-healing DFUs, gas gangrene, acute traumatic ischemia, and necrotizing soft tissue infections. Moreover, HBOT has been indicated for refractory osteomyelitis, delayed radiation injury, compromised grafts and flaps, and acute thermal burn injury [13].

HBOT improves oxygen delivery to stressed and hypoxic tissues. Therefore, it reduces inflammation, vasoconstriction, and angiogenesis [14]. In addition, HBOT promotes ulcer healing by direct and synergistic antimicrobial activity [15].

In HBOT, the patient intermittently breathes pure oxygen in a hyperbaric chamber that pressurized to greater than 1 atm [10]. Breathing 100% pure oxygen at 1.5–3 times atmospheric pressure is generally recommended. Although there is no consensus regarding the optimum numbers of HBOT sessions, more than 20 sessions were recommended by some reports to achieve therapeutic goals [16–19].

HBOT is generally well tolerated with rare complications. The most documented side effects of HBOT include middle ear, sinus and dental barotraumas, as well as reversible hyperoxic myopia. In rare cases, pulmonary barotrauma, oxygen toxicity seizure, cataract, and claustrophobia may occur [20,21]. HBTO is absolutely contraindicated for patients with pneumothorax. It is relatively contraindicated for Eustachian tube dysfunction, uncontrolled hypertension, congestive heart failure, chronic obstructive pulmonary disease/asthma, claustrophobia, recent eye or thoracic surgery, history of seizures and fever [22].

Despite being reported as an effective therapy in improving the clinical outcomes of patients with non-healing DFUs [21,23], the efficacy of HBOT is still debatable [24,25]. This study was conducted to evaluate the therapeutic outcomes of adjuvant HBOT among DFUs patients in terms of complete ulcer healing, amputation rate, and incidence of adverse effects.

2. Methods

2.1. Study design and populations

A descriptive, retrospective, hospital-based study was conducted at Al–Mo'alem Medical City-Derby wound care center in Khartoum city, Sudan. This center provides both conventional wound care and HBOT for patients with chronic wounds. Continuous supervision and monitoring are provided by qualified medical professionals who had been trained in wound care and hyperbaric oxygen therapy. The center is equipped with two hyperbaric oxygen chambers, each contains 14 seats. The study populations were diabetic patients treated with HBOT for wounds, during the period from August to December 2018.

2.2. Inclusion criteria

All medical records of type 2 diabetic patients, treated with HBOT plus standard wound care for DFUs, were included in the current study. The selected patients had failed a four-week course of conventional wound treatment before starting HBOT. One hundred and twenty patients with DFUs had met the inclusion criteria.

2.3. Exclusion criteria

Patients with cardiac problems, asthma, uncontrolled diabetes (Hemoglobin A1c $\geq$ 7% or random blood glucose $^{>}$200 mg/dL, before and/or during treatment) [26], and uncontrolled hypertension (Systolic/diastolic blood pressure $\geq$ 140/90 mmHg) [27] were excluded from the study because they are relatively at risk of HBOT side effects. Patients with wounds localized in other parts of the body were excluded. Medical records with incomplete data were also excluded.

2.4. Study setup of HBOT

The patients breathed pure oxygen inside the hyperbaric oxygen chamber which was adjusted at 2.5 atm absolute (ATA). Each patient spent 90 min/day inside the hyperbaric chamber for 6 days/week. Generally, the number of required sessions depends on the severity of the ulcer. During HBOT, the patients received standard wound care including surgical debridement, dressings, wound offloading, vascular assessment, glycemic control, and treatment of active infections [13]. All treatment modalities were provided under the supervision of qualified and expert physicians and nurses. After completion of HBOT sessions, patients were followed up for 12 months with scheduled visits every 4–6 weeks to ensure there is no ulcer recurrence.

2.5. Evaluation of ulcer's characteristics

Ulcer's characteristics (ulcer's grades, protective sensation, and ulcer healing) had been evaluated by an expert and qualified physician in wound care. DFUs were classified according to Wagner ulcer classification system [28]. A superficial diabetic ulcer represents Grade 1. Grade 2 is defined as an extension of ulcer to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis. Grade 3 is a deep ulcer with abscess, osteomyelitis or joint sepsis. Grade 4 is described as gangrene localized to a portion of forefoot or heel, and grade 5 is extensive gangrenous involvement of the entire foot.

Patients were examined for loss of protective sensation using both monofilament (size 2.83–6.65) and vibration tests [29]. The application of monofilaments started from light (size 2.83–3.61) and progressed to heavy filaments (size 5.07–6.65). The ability to sense light filaments designates normal sensation while the inability to sense heavy filaments indicates loss of protective sensation. Vibration testing was conducted using 128-Hz traditional tuning fork. Complete ulcer healing is defined as optimal epithelialization without drainage while the failure of ulcer healing is described as a re-epithelialization failure [30].

2.6. Data collection tool

Data were manually collected from paper-based medical records. The data collection sheet was developed by the researchers according to the research objectives and reviewed by qualified experts. The first section of the data sheet included socio-demographic characteristics, medical history, and co-morbidities. The second section covered the ulcer characteristics, including ulcer location, classification, and the degree of sensation. The third section contained the number of HBOT sessions, HBOT side effects, degree of ulcer healing, and amputation rate.

2.7. Statistical analysis

Statistical package for social science software (SPSS, version 21) and Microsoft Excel programs were used for analysis. Simple descriptive statistics such as frequency and percentage were used to describe the distribution of clinical characteristics of the patients and therapeutic outcomes. For categorical variables, Pearson's Chi-square test was used to assess the association between therapeutic outcomes (ulcer healing and amputation) and demographic/clinical characteristics of the patients. Logistic regression analysis was used

to describe the relationship between the dependent (therapeutic outcomes) and independent (demographic/clinical characteristics) variables. Hosmer and Lemeshow goodness of fit and Negelkerke pseudo R^2 tests were assessed. *P*-value ≤0.05 was considered statistically significant.

2.8. Ethical approval

Ethical clearance was obtained from Khartoum University, Faculty of Pharmacy, Research Board (Research Ethics Committee, No. 36-14-7-2018) before starting the research. In addition, permission to conduct the research was granted by the general manager of the wound care center. Privacy and confidentiality of patients' information were insured by using coded data collection sheets and the soft copy of the data was password-protected.

3. Results

3.1. Demographics and medical history of patients

The majority of the patients (69.2%) were male; and 44.2% were above sixty years old. Most patients (66.7%) were living in Khartoum state. Twenty-five percent of patients were smokers. About one-third of patients (31.7%) had comorbidities, with 26.7% and 5% had hypertension and hyperlipidemia, respectively. Regarding current medications, 68.3% of the patients were on insulin therapy. Antibiotics and antihypertensive medications were prescribed to 47.5% and 26.7% of the patients, respectively (Table 1).

3.2. Ulcer characteristics

Ulcers were classified according to Wagner grades. Almost 52% of patients had Wagner grade-3 ulcer and 46.7% had toe's ulcers. Monofilament and vibration tests were used to evaluate the protective sensation in all patients. Mild to moderate sensation was detected in 71.7% of patients (Table 2).

Table 1
Demographics and medical history of patients (N = 120).

Variables	Frequency (%)
Gender	
Male	83 (69.2%)
Female	37 (30.8%)
Age group (years)	
18–40	4 (3.3%)
40–60	63 (52.5%)
˃ 60	53 (44.2%)
Living area	
Khartoum locality	80 (66.7%)
Others (outside Khartoum locality)	40 (33.3%)
Habits	
Cigarette smoking	30 (25.0%)
Tobacco	2 (1.7%)
Non-smokers	88 (73.3%)
Co-morbid conditions	
Hypertension	32 (26.7%)
Hyperlipidemia	6 (5.0%)
Without co-morbidity	82 (68.3%)
Current medications[a]	
Insulin	82 (68.3%)
Oral hypoglycemic drugs	44 (36.7%)
Antibiotics	57 (47.5%)
Antihypertensive drugs	32 (26.7%)
Aspirin	13 (10.8%)
Lipid lowering drugs	6 (5.0%)

[a] A patient might receive more than one medication.

Table 2
Ulcer characteristics among diabetic patients with foot ulcer (N = 120).

Variables	Frequency (%)
Ulcer location	56 (46.7%)
Toe	24 (20.0%)
Planter	14 (11.7%)
Dorsum	26 (21.7%)
Others[a]	
Wagner ulcer classification[b]	20 (16.7%)
Grade 2	62 (51.7%)
Grade 3	20 (16.7%)
Grade 4	18 (15%)
Grade 5	
Examination of peripheral neuropathy	120 (100%)
Monofilament and vibration tests	
Sensation	86 (71.7%)
Moderate/mild	34 (28.3%)
No sensation	

[a] Others: Patients with ulcers involving the foot and extending upwards to the ankle or leg.
[b] Grade 2: Extension of ulcer to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis. Grade 3: Deep ulcer with abscess, osteomyelitis, or joint sepsis. Grade 4: Gangrene localized to portion of forefoot or heel. Grade 5: Extensive gangrenous involvement of the entire foot.

3.3. Degree of ulcer healing and numbers of HBOT sessions

Two-thirds of patients (66.7%) received 20 or less HBOT sessions (an average of 20.8 ± 11.9). Most patients (60.8%) achieved complete ulcer healing while 28.3% exhibited partial recovery. Among the treated patients, only 20% experienced ear barotraumas, and 16.7% underwent amputation (Table 3).

3.4. Factors associated with clinical outcomes

A significant association was observed between ulcer healing and neuropathy (loss of sensation) ($p = 0.05$). Moreover, ulcer healing was significantly associated with the number of HBOT sessions ($p = 0.000$). On the other hand, amputation was significantly associated with ulcer location ($p = 0.046$), neuropathy degree ($p = 0.018$), number of HBOT sessions ($p = 0.003$), and antibiotics use ($p = 0.03$) (Table 4).

The predictors of positive therapeutic outcomes after HBOT (complete ulcer healing and absence of amputation) were explored using logistic regression. Protective sensation ($\beta = 1.81$, S.E = 0.63, $p = 0.004$) and more sessions of HBOT ($\beta = 2.95$, S.E = 0.71, $p = 0.000$) were positive predictors of complete ulcer healing. According to the odds ratio, patients undergoing more than 20 sessions of HBOT had 19 fold chances to get complete ulcer healing than patients undergoing less than 20 sessions (OR = 19.09, 95%

Table 3
Degree of ulcer healing and numbers of HBOT sessions.

Variables	Frequency (%)
No. of HBOT sessions	80 (66.7%)
≤ 20	40 (33.3%)
˃ 20	
Degree of ulcer healing	73 (60.8%)
Complete healing	34 (28.3%)
Partial healing	13 (10.8%)
No healing	
HBOT side effects	24 (20.0%)
Ear barotraumas	96 (80.0%)
None	
Amputation	20 (16.7%)
Yes	100 (83.3%)
No	

Table 4
Association between patient clinical characteristics and treatment outcomes (N = 120).

Variables	Total	Treatment Outcomes					
		Ulcer healing			Amputation		
		Complete healing	No/Partial healing	p-value	Yes	No	p-value
Age (years)	4	2 (50.0%)	2 (50.0%)	0.883	1 (25.0%)	3 (75.5%)	0.890
18–40	63	38 (60.3%)	25 (39.7%)		10 (15.9%)	53 (84.1%)	
40–60	53	33 (62.3%)	20 (37.7%)		9 (17.0%)	44 (83.0%)	
˃ 60							
Ulcer location	56	41 (73.2%)	15 (26.8%)	0.080	5 (8.9%)	51 (91.1%)	0.046*
Toe	24	12 (50.0%)	12 (50.0%)		7 (29.2%)	17 (70.8%)	
Planter	14	7 (50.0%)	7 (50.0%)		1 (7.1%)	13 (92.9%)	
Dorsum	26	13 (50.0%)	13 (50.0%)		7 (26.9%)	19 (73.1%)	
Other							
Ulcer classification	20	13 (65.0%)	7 (35.0%)	0.757	1 (5.0%)	19 (95.0%)	0.115
Grade 2	62	38 (61.3%)	24 (38.7%)		9 (14.5%)	53 (85.5%)	
Grade 3	20	13 (65.0%)	7 (35.0%)		4 (20.0%)	16 (80.0%)	
Grade 4	18	9 (50.0%)	9 (50.0%)		6 (33.3%)	12 (66.7%)	
Grade 5							
Sensation	86	57 (66.3%)	29 (33.7%)	0.050*	10 (11.6%)	76 (88.4%)	0.018*
Moderate/mild	34	16 (47.1%)	18 (52.9%)		10 (29.4%)	24 (70.6%)	
No sensation							
No. of sessions	80	38 (47.5%)	42 (52.5%)	0.000***	19 (23.8%)	61 (76.2%)	0.003**
≤ 20	40	35 (87.5%)	5 (12.5%)		1 (2.5%)	39 (97.5%)	
˃ 20							
Current medications							
Insulin	82	51 (62.2%)	31 (37.8%)	0.653	15 (18.3%)	67 (81.7%)	0.483
Yes	38	22 (57.9%)	16 (42.1%)		5 (13.2%)	33 (86.8%)	
No							
Oral anti-diabetics	44	25 (56.8%)	19 (43.2%)	0.493	6 (13.6%)	38 (86.4%)	0.498
Yes	76	48 (63.2%)	28 (36.8%)		14 (18.4%)	62 (81.6%)	
No							
Antibiotics	57	34 (59.6%)	23 (40.4%)	0.8	14 (24.6%)	43 (75.4%)	0.03*
Yes	63	39 (61.9%)	24 (38.1%)		6 (9.5%)	57 (90.5%)	
No							

*P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001.

CI = 4.77–76.45). Moreover, patients without neuropathy were 6.11 times more likely to get complete ulcer healing than patients with neuropathy (OR = 6.11, 95% CI = 1.79–20.89) (Table 5). Regarding negative predictors of amputation, patients who had protective sensation (OR = 0.15, 95% CI = 0.04–0.60) and more than 20 HBOT sessions (OR = 0.04, 95% CI = 0.01–0.34) were less likely to be amputated than patients with neuropathy and received few HBOT sessions. In addition, patients with toe ulcers (OR = 0.2, 95% CI = 0.04–0.93) have less chance to be amputated when compared to patients with dorsal/plantar ulcers (Table 5).

4. Discussion

Diabetic foot ulcers are one of the most serious complications of diabetes that lead to amputation and disabilities [31,32]. In spite of being well-known for a long time, HBOT has drawn considerable debates regarding its efficacy in DFUs treatment [33,34].

This study aimed to investigate the efficacy of adjuvant HBOT in

Table 5
Factors associated with therapeutic outcomes after HBOT (Logistic regression model).

Variables	Ulcer healing					Amputation				
	β	S.E	*P*> z	OR	95% CI	β	S.E	P> z	OR	95% CI
Age	0.05	0.47	0.91	1.05	0.42–2.62	−0.46	0.63	0.470	0.63	0.18–2.19
Sensation	1.81	0.63	0.004**	6.11	1.79–20.89	−1.89	0.70	0.007**	0.15	0.04–0.60
No. of sessions	2.95	0.71	0.000***	19.09	4.77–76.45	−3.32	1.15	0.004**	0.04	0.01–0.34
Location	0.99	0.56	0.080	2.69	0.89–8.11	−1.63	0.79	0.041*	0.20	0.04–0.93
Toe	0.25	0.72	0.728	1.29	0.31–5.32	−1.00	0.90	0.266	0.37	0.06–2.15
Planter	−0.28	0.81	0.726	0.75	0.16–3.67	−1.73	1.30	0.183	0.18	0.01–2.26
Dorsum										
Ulcer classification	0.47	0.67	0.487	1.59	0.43–5.94	0.24	1.24	0.845	1.27	0.11–14.36
Grade 3	0.67	0.82	0.418	1.95	0.39–9.75	0.55	1.39	0.693	1.73	0.11–26.12
˃ Grade 3										
Antibiotics	0.53	0.57	0.356	1.69	0.56–5.15	−1.35	0.79	0.089	0.26	0.06–1.23
Insulin	0.42	0.70	0.545	1.53	0.39–6.03	0.65	1.19	0.589	1.91	0.18–19.75
Oral anti-diabetics	0.10	0.68	0.881	1.11	0.29–4.18	−0.22	1.10	0.844	0.81	0.09–6.96
	Nagelkerke R2 = 0.377					Nagelkerke R2 = 0.419				
	Hosmer-Lemeshow: Chi-square = 10.778.					Hosmer-Lemeshow: Chi-square = 6.460.				

β: β coefficient; S.E: Standard error; OR: Odd ratio; CI: Confidence interval.
*P ≤ 0.05; **P ≤ 0.01; ***P ≤ 0.001.

DFUs treatment. According to the distribution of the study participants, most patients were males, elderly, and insulin users. Additionally, about one-third of the patients had severe diabetic peripheral neuropathy. Based on recent studies, insulin consumption, gender, age ≥50 years, peripheral neuropathy, and previous history of ulceration were identified as risk factors for developing ulcers [35,36].

Complete ulcer healing and amputation rate were assessed as indicators for clinical outcomes. Complete ulcer healing was observed in almost two-thirds of the patients with non-healing DFUs. The results of the current study showed that adjuvant HBOT could have a beneficial effect in treating patients with non-healing DFUs. According to Salama SE et al., 2018; adjuvant HBOT with conventional therapy was more effective than conventional therapy alone in the treatment of non-healing DFUs [23]. Adjuvant HBOT improved the patient's quality of life through improving ulcer healing, and reducing the risk of major amputations in patients with chronic DFUs [21,37,38]. Wagner grade-3 and grade-4 ulcers were noticed in the majority of DFUs patients investigated in this study. This result concurs well with previous findings in the literature which highlighted that ulcers were completely healed in patients with Wagner grade 2, 3, or 4 ulcers [19,39–41]. Few patients had poor response to HBOT which could be attributed to patients' noncompliance to the scheduled visits of HBOT sessions.

The majority of participants had complete ulcer recovery with a decreased minor and major amputation rate. It had been reported that amputation was less likely to occur after HBOT [21,37,38,42]. In contrast, other studies stated that HBOT neither facilitates wound healing nor reduces the rate of amputation in patients with chronic DFUs [34,43,44]. This discrepancy in findings may be due to variation in patients' characteristics such as age, diabetes duration, comorbidities, and previous amputation. Patients' non-compliance or inconsistency to medical follow-up may be additional factors [45,46].

With the exception of ear barotraumas reported by some patients, the majority of patients did not experience any side effects. Generally, HBOT could be considered a safe adjuvant therapy in DFUs treatment.

In regard to the predictors of better clinical outcomes after HBOT, complete ulcer healing was significantly associated with an increased number of HBOT sessions. In addition, more HBOT sessions and absence of neuropathy were associated with a significant decrease in amputation rate. According to Chen CE et al., 2010; patients receiving more than 20 sessions of HBOT were less prone to amputation [17]. Diabetic neuropathy is not only a risk factor of DFUs, but it negatively affects ulcer healing [36,47]. Ulcer healing appeared to be two times greater in patients with higher ulcer grades. However, ulcer classification was not recognized as a significant predictor of complete ulcer healing (OR = 1.95). Several studies highlighted that HBOT was effective in treating patients with Wagner grade-3 or higher ulcer grades [41,48]. In the current study, the patients received HBOT with standard wound care including antibiotics therapy for active infections. The study findings showed that the use of antibiotics during HBOT had no additive effect on the therapeutic outcomes of HBOT. In the literature, the synergistic effect of adjunct HBOT with some antibiotics had been reported, but it remains unproven for many antibiotics such as metronidazole [15].

Several randomized clinical trials suggested that HBOT was considered as a promising adjunctive therapy for DFUs [21,33]. The International Working Group on the Diabetic Foot (IWGDF) and the Undersea and Hyperbaric Medical Society (UHMS) guidelines recommended the use of adjuvant HBOT for Wagner Grade 3 or higher DFUs. However, there is a moderate quality of evidence supporting its use for DFUs [49,50].

5. Limitations

This study is a single-center retrospective observational study with a small sample size because of poor documentation. Therefore, it may not be representative of the general population. In addition, data were collected from paper-based records, and this process is tedious and time-consuming.

6. Conclusion

Adjunct HBOT enhanced the rate of ulcer healing and reduced the need for amputation in patients with non-healing DFUs.

More treatment sessions with HBOT and the absence of diabetic neuropathy were associated with improved ulcer healing and reduced rate of amputation.

HBOT could be considered a relatively safe intervention, with few patients experienced ear barotraumas during treatment.

7. Recommendations

- HBOT may be considered a potential adjunctive therapy in non-healing DFUs treatment. Nevertheless, multicentre, prospective large scale, randomized clinical trials are recommended to ascertain the effectiveness of HBOT.
- Further research - based on patient selection criteria for HBOT - is essential to identify patients that might benefit from this therapy.

Authors' contributions

Fadol E.M. conceived, collected the data, and drafted the manuscript. Abdoon, I. contributed to study design, analysis/interpretation of data, editing, and providing a critical revision of the manuscript. Abdalla, S.A., Osman, B., Suliman H.M and Osman, W. participated in reviewing, editing, and providing final approval of the manuscript. Mohamed E. participated in statistical analysis and interpretation of data. All authors had complete access to the study data that support the publication.

Declaration of competing interest

None.

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