

Health-related quality of life in patients with chronic wounds before and after treatment with medical ozone

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Abstract

Ozone therapy has been used to treat numerous diseases. Indications of its therapeutic application are increasing, and evidence for its usefulness is growing. Evidence of its antibacterial and proliferative activity suggests its efficacy in treating chronic wounds. The current study evaluated the effect of ozone therapy on the health-related quality of life of patients with chronic wounds.

In the present cross-sectional study, the health-related quality of life was evaluated in 86 patients with chronic wounds undergoing ozone therapy. To measure quality of life, 2 previously established questionnaires were used, the Cardiff wound impact questionnaire and the SF-36 questionnaire. Questionnaires were completed through interviews with the patients.

A total of 86 patients with chronic wounds undergoing ozone therapy participated in this study. The mean age of participants was 58.91 years; 69.8% of them were male, 91.9% had diabetes mellitus, and 50% were receiving insulin therapy. Patients were under local (26.7%), systemic (9.3%), and local plus systemic (64%) protocols of ozone therapy. Mean overall quality of life reported by the patients was 6.2, and mean overall quality of life satisfaction was 6.02 (measured by the Cardiff Wound Impact Questionnaire). Mean physical quality of life measured by the SF-36 questionnaire was 39.12, and mean mental quality of life was 44.37 (measured by the same questionnaire). Among the included variables, the number of ozone therapy sessions was the strongest predictor of quality of life in both questionnaires and remained significant after different levels of adjustment.

In addition to the significant improvement observed in the healing of chronic wounds, medical O₃ therapy has also shown to effect a significant improvement in the health-related quality of life of patients and could be a valuable therapeutic option in chronic wound cases.

Abbreviations: ACTH = adrenocorticotrophic hormone, CLEU = chronic lower extremity ulcers, CRH = corticotropin-releasing hormone, cortisol, DHEAS = dehydroepiandrosterone sulfate, O₃ = medical ozone, QoL = quality of life.

Keywords: chronic wounds, ozone-therapy, quality of life

1. Introduction

According to the latest publications, chronic lower extremity ulcers (CLEU) are known as a major global health problem as well as a common metabolic disorder. In the United States population alone, the incidence of CLEU is 2.4 to 4.5 million people.^[1] Chronic wounds can be classified as vascular ulcers (e.g., venous and arterial ulcers), diabetic ulcers, and pressure ulcers.^[2] In CLEU cases, through accelerated atherosclerosis and microvascular changes, some major complications are observed,

including retinopathy, neuropathy, cardiomyopathy, and nephropathy.^[3] In this regard, chronic wounds are related to complications which often lead to limb amputation.^[4] Moreover, these ulcers in 60% to 70% of patients lead to the loss of the patient's quality of life (QoL) and are a common cause of morbidity.^[5] Feelings of frustration, anxiety, isolation, depression, and low self-esteem, and a negative self-concept are the attributes of QoL at any stage of the life cycle, and all life domains are significantly affected in CLEU patients.^[6–8]

Patients with CLEU experience loss of limb sensation and foot deformity through decreases in perfusion, angiopathy, and neuropathy which interfere with the process of wound healing. Some inaction of gram-positive and gram-negative organisms involved in the inhibition of wound healing showed an antibiotic resistance during treatment.^[9] Thus, increasing blood perfusion and suppressing local infection is known as the central goals for CLEU treatment.

Several studies have proven the safety and efficacy of medical ozone (O₃) therapy on patients with chronic wounds such as diabetic foot ulcers.^[10–14] Generally, O₃ is an unstable molecule derived from 3 oxygen atoms, and its pulmonary toxicity through O₃ direct inhalation has been shown.^[15] Medical usage of O₃ began in the 19th century, and through the years, different medical O₃ delivery routes for the treatment of CLEU, such as autohemotherapy, insufflation, and local administration, have been developed.^[16,17] Antioxidant enzyme stimulation, growth factor regulation, increasing local blood infusion, and

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antibacterial activity are the beneficial roles of O3 therapy in chronic wound improvement.^[17,18] While some clinical trials have proven the significant therapeutic potential of O3 therapy on CLEU cases, QoL in these patients before and after treatment is one of the important unknown prospects for developing this therapeutic method in clinical approaches. Therefore, the aim of this study was to evaluate the effect of medical O3 therapy for various causes of chronic wound, including diabetes, vascular diseases, chronic pressure, and osteomyelitis, on patients' health-related QoL.

2. Methods

2.1. Patients

This cross-sectional study employed 2 questionnaires for assessing Cardiff Wound Impact. The first questionnaire was specifically designed to measure QoL in people with ulcers, and the next general questionnaire was used to assess health-related QoL. Health-related QoL was evaluated in 86 patients with chronic wounds undergoing O3 therapy in Baghiyatalah Ozone Therapy Research Center, Tehran, Iran.

O3 therapy was done based on the Madrid Declaration on Ozone Therapy as approved by the International Scientific Committee of Ozone Therapy.^[19] In brief, treatment included the following techniques: Local ozone therapy, minor hemotherapy, and major hemotherapy. Ozolive gel and ozone solutions were also used for dressing.

2.2. Questionnaires and measure of quality of life

To measure QoL, 2 previously developed questionnaires, the Cardiff wound impact questionnaire and the SF-36 questionnaire, were used. The SF-36 questionnaire is a general questionnaire for assessing health-related quality of life. The questionnaire results from a valid study called Medical Outcome Study. It is one of the most popular questionnaires for assessing health-related lifestyle and has been used on a large scale over many years. Generally, this questionnaire assesses 8 areas: physical function of the individual; individual limitation of function due to reduced physical health; individual functional limitations due to decreased mental health; energy/fatigue; mental health; social function; pain; and general health.^[20] A single medical doctor who is expert in both the English language and chronic wound management interviewed the patients to complete the questionnaire.

Although an approved Persian language translated version of the SF-36 questionnaire was available, a localized version of the Cardiff Wound Impact questionnaire was prepared. After obtaining permission from the main designers of the questionnaire, it was translated from English to Persian and back-translated from Persian to English under the supervision of specialists to obtain a localized version of the Cardiff Wound Impact Questionnaire. Both the SF-36 and Cardiff Wound Impact questionnaires are comprised of 19 main items: age, sex, place of residence, education, marital status, home status, diabetes, hypertension, ischemic heart disease, kidney failure, ozone therapy sessions, methods of ozone therapy, history of wound debridement, history of amputation, hospitalization, combined antibiotic treatment, wound healing status, independence, and frequency of meeting family members. The first questionnaire specifically measures quality of life in patients with lower extremity wounds, and the latter measures general health-related quality of life independent to the background disease of

the patients. In total, 86 patients with chronic wounds undergoing O3 therapy participated in the current study. In all steps of this study, signed written consent was obtained from the patients, and 2 expert physicians completed the questionnaires through interviews.

Prior to conducting this research, the details of it were presented and confirmed at a Research Ethics meeting on 01/06/2014 with registration no. 5904/5/340.

2.3. Data analysis

Data was analyzed using software SPSS ver. 20, during which averages questions as explained above, and taking into account the different groups to compare the average of independent test *t* test and the results were reported. Values are shown as means \pm SD, and a *P* value less than .05 ($P < .05$) was considered significant.

3. Results

Overall, the QoL of 86 patients with chronic wounds was assessed. Mean age of the participants was 58.91 years, 69.8% were male, 91.9% had diabetes mellitus, and 50% were undergoing insulin therapy. Patients were under local (26.7%), systemic (9.3%), and local plus systemic (64%) protocols of ozone therapy. Mean overall QoL reported by the patients was 6.2, and mean overall QoL satisfaction was 6.02 (measured by the Cardiff Wound Impact questionnaire). Mean physical QoL measured by the SF-36 questionnaire was 39.12, and mean mental QoL was 44.37 (measured by the same questionnaire). Among the included variables, the number of ozone therapy sessions was the strongest predictor of QoL for both questionnaires, and it remained significant after different levels of adjustment. Table 1 shows the variables and data interpretation.

Results of the current study showed a significant correlation between history of amputation and patient QoL in both questionnaires (SF-63 = $P < .103$ and Cardiff = $P < .078$) (Tables 2 and 4). Unlike history of amputation, there was an opposite interaction between QoL and combined antibiotic treatment in both questionnaires (SF-63 = $P < .083$ and Cardiff = $P < .0021$) (Tables 2 and 4).

Again, the results of multivariate regression analyses in both questionnaires proved that there is a correlation between O3 therapy and patient QoL (Tables 3 and 5). In the SF-63 questionnaire, multivariate regression analysis showed a significance in number of sessions ($P < .000$) and independence ($P < .000$). A direct and significant relation between degree of education and QoL was also seen ($P < .013$). Analysis proved that there is an opposite interaction between QoL and the methods of O3 therapy ($P < .013$) (Table 3). In the Cardiff questionnaire as in the SF-63, multivariate regression analysis showed a significant correlation between number of O3 therapy sessions ($P < .001$) as well as independence ($P < .002$) and patient QoL. Combined antibiotic treatment and methods of O3 therapy had a direct and significant correlation ($P < .041$ and $P < .004$, respectively) with QoL (Table 5).

Multivariate regression analysis for PCS from the SF-63 questionnaire showed that number of O3 therapy sessions as the main independent variable has a direct significant correlation with QoL ($P < .001$). Moreover, independence and methods of O3 therapy had a significant relation ($P < .002$ and $P < .001$, respectively). There was an opposite correlation between history

Table 1**Variables and data interpretation.**

Row	Variable	Role (independent, dependent, background, confounder)	Quantitative		Qualitative		Scientific definition	Unit
			Continuous	Discrete	Nominal	Ranking		
1	Quality of life	Dependent				*	Patients' satisfaction with life by questionnaire SF-36 will be measured.	
2	Ozone	Independent	*				Three-atomic oxygen molecules	Micrograms per millilitre.
3	Age	Background	*				The number of person years of life	Year
4	Gender	Background			*		Every gender	Male female
5	Income	Background	*				The monthly income of the household head	Rial
6	Education	Background				*	Everyone at school and university education	Last educational certificate
7	Location	Background			*		Location persons	Tehran / non-Tehrani
8	Marital status	Background			*		Single or married patient	Single married
9	Chronic wounds	Background			*		A sore that lasts more than 3 months	The presence or absence of chronic wounds
10	Background disease	Background		*		*	Any medical condition diagnosed in patients.	Yes/no
11	Cell therapy	Background		*		*	Any medical treatment for wounds in addition to ozone as well as any medical treatment for the Background disease.	Yes/no
12	Debridement of wounds	Background		*		*	History of any surgical wound debridement patient.	Yes/no

of amputation and patient QoL ($P < .040$) (Table 6). Additionally, multivariate regression analysis for MCS from the SF-63 questionnaire proved again that number of O3 therapy sessions is the main independent variable and has a direct significant correlation with QoL ($P < .012$). Similarly, the patient's independence and education had significant correlations with QoL ($P < .013$ and $P < .020$, respectively) (Table 7).

Table 2**The relation between studied variables and QoL for SF-63 questionnaire.**

variable name	β	P value
Age	-0.038	.774
Sex	-0.009	.933
Place of living	-0.066	.546
Education	0.028	.779
Marital status	-0.105	.335
Home status	0.105	.335
Diabetes	0.090	.408
Hypertension	-0.017	.887
Ischemic heart disease	-0.019	.863
Kidney failure	-0.151	.166
Ozone therapy sessions	0.521	<.001
Methods of ozone therapy	-0.053	.626
History of wound debridement	-0.054	.618
History of amputation	-0.177	.103
Hospitalization	-0.063	.562
Combined antibiotic treatment	-0.188	.083
Wound healing or not	0.359	.001
Independence	0.355	.001
Frequency of meeting family members	0.052	.633

Values are means \pm SD.

* $P < .05$.

4. Discussion

In the Cardiff Wound Impact questionnaire used in the final model of regression analysis, presence or absence of antibiotic treatment, independent living ability, and QoL in addition to number of ozone therapy sessions were associated with ozone therapy. Antibiotic therapy and the ability to live independently were inversely proportional to QoL. Ozone therapy for localized to systemic treatment was associated with a higher QoL. The ozone treatment system for systemic plus topical treatment was associated with a higher QoL.

In the SF-36 questionnaire used in the final model regression analysis, level of education, ability to live independently, and QoL in addition to number of ozone therapy sessions were

Table 3**Multivariate regression analysis for SF-63 questionnaire.**

Variable name	β	P value
Age	-0.144	.235
Sex	0.084	.383
Place of living	-0.005	.958
Education	0.278	.013
Home status	0.050	.597
Ozone therapy sessions	0.564	0 > .000
Methods of ozone therapy	-0.232	.013
History of wound debridement	0.078	.470
History of amputation	-0.186	.059
Hospitalization	-0.103	.247
Combined antibiotic treatment	-0.138	.118
Wound healing or not	0.011	.920
Independence	0.371	0 > .000

Values are means \pm SD.

* $P < .05$.

Table 4**The relation between studied variables and QoL for Cardiff questionnaire.**

Variable name	β	P value
Age	0.052	.635
Sex	-0.031	.778
Place of living	0.120	.272
Education	-0.131	.229
Marital status	0.100	.359
Home status	-0.111	.310
Diabetes	-0.026	.813
Hypertension	0.065	.554
Ischemic heart dicesis	0.064	.558
Kidney failure	0.117	.283
Ozone therapy sessions	-0.515	<.001
Methods of ozone therapy	0.117	.283
History of wound debridement	0.059	.591
History of amputation	0.191	.078
Hospitalization	0.058	.596
Combined antibiotic treatment	0.249	.021
Wound healing or not	-0.384	<.001
Independence	-0.309	.004
Frequency of meeting family members	-0.099	.346

Values are means \pm SD.* $P < .05$.

associated with ozone therapy. This means that the ability to live independently and QoL are in direct proportion to level of education. Similar to the Cardiff Wound Impact assessment, ozone therapy for localized to systemic treatment was associated with a higher QoL. The ozone treatment system for systemic plus topical treatment was associated with a higher QoL. The SF-36 questionnaire is divided into 2 parts. The PCS part is related to the physical dimension of QoL, and the MCS part relates to the mental aspect of QoL.

In the PCS, the final model regression analysis showed that, in addition to number of ozone therapy sessions, history of amputation, the ability to live independently, and QoL were associated with ozone therapy. This means that the ability to live independently and QoL has amputation directly and inversely proportional to the QoL. Similar to the previous 2, treatment with ozone locally to systemic treatment was associated with a higher QoL. The ozone treatment system for systemic plus topical

Table 5**Multivariate regression analysis for Cardiff questionnaire.**

Variable name	β	P value
Age	0.083	.502
Sex	-0.057	.562
Place of living	-0.004	.968
Education	0.050	.654
Home status	0.010	.916
Ozone therapy sessions	-0.575	<.001
Methods of ozone therapy	0.0273	.004
History of wound debridement	-0.070	.527
History of amputation	0.168	.095
Hospitalization	0.073	.426
Combined antibiotic treatment	0.186	.041
Wound healing or not	-0.056	.606
Independence	-0.307	.002

Values are means \pm SD.* $P < .05$.**Table 6****Multivariate regression analysis for PCS of SF-63 questionnaire.**

Variable name	β	P value
Age	-0.158	.186
Sex	0.094	.319
Place of living	-0.059	.524
Education	0.137	.206
Home status	0.041	.664
Ozone therapy sessions	0.564	<.001
Methods of ozone therapy	-0.308	.001
History of wound debridement	-0.060	.573
History of amputation	-0.200	.040
Hospitalization	-0.034	.700
Combined antibiotic treatment	-0.128	.143
Wound healing or not	0.031	.766
Independence	0.290	.002

Values are means \pm SD.* $P < .05$.

treatment was associated with a higher QoL. Here, there was no significant relationship between level of education and QoL.

This means that the ability to live independently and QoL are directly proportionate to level of education. Here, history of amputation was not related to QoL. The change was remarkable in this part of the power relationship between independent living and QoL with QoL psychological than physical strength. Moreover, the types of ozone therapy and QoL in this area had no significant relationship.

A review of the literature revealed that, to the best of the authors' knowledge, no assessment of QoL in patients treated with ozone has been done.^[21] It is estimated that ozone therapy acts through stimulation of the neuroendocrine system. Although the exact mechanism is unclear, an euphoric feeling of liberation is involved. It is proposed that these hormones, including adrenocorticotrophic hormone (ACTH), corticotropin-releasing hormone (CRH), cortisol, dehydroepiandrosterone sulfate (DHEAS), growth hormones, endorphins, and neurotransmitters, when injected with ozone-rich blood to the body, are released.^[16] Another hypothesis is that, as the results of this study suggest, because ozone therapy is effective in wound healing, this healing enhances QoL for the patients. The relationship between elevated ozone therapy and improved QoL can be attributed to

Table 7**Multivariate regression analysis for MCS of SF-63 questionnaire.**

Variable name	β	P value
Age	0.024	.868
Sex	0.019	.869
Place of living	0.068	.549
Education	0.311	.020
Home status	0.171	.135
Ozone therapy sessions	0.331	.012
Methods of ozone therapy	-0.029	.792
History of wound debridement	0.242	.065
History of amputation	-0.039	.737
Hospitalization	-0.073	.495
Combined antibiotic treatment	0.005	.961
Wound healing or not	-0.103	.417
Independence	0.279	.013

Values are means \pm SD.* $P < .05$.

wound healing. However, in the current study, multivariate regression analysis of final recovery or wound healing was not significantly associated with QoL.

Due to the high number of ozone therapy sessions associated with increased QoL, as shown in the current study, the strongest predictor of QoL was number of ozone therapy sessions. Another variable that was directly related to QoL in the current study was the ability to live independently. The ability to live independently with all models of the Cardiff and SF-36 questionnaires had a direct and significant relationship with QoL. This relationship is also evident, and it seems rational. Interestingly, the relationship of these variables is more significant with physical health than with mental health. The relation between physical health and QoL is more powerful both clinically and statistically. Reputable studies have achieved results in line with the current findings. For example, Fortin et al.^[22] evaluated the relationship between comorbidities and QoL. The greater the number of comorbidities was more individual, he also reduced QoL. In the current study, 2 main questionnaire study was not associated in the final model regression analysis. But the SF-36 divided into 2 physical and mental, although a history of amputation of the mind was not related to the variable part of the beauty of this questionnaire, is a direct connection that after entering the other variables in the regression equation is still significant.

In the current study, despite the fact that number of treatments and QoL were directly associated with ozone, the ozone therapy was inversely associated with QoL. This means that those patients who were only treated locally had a better quality of life than others. At first glance, it seems that treatment with ozone is more severe and QoL is further reduced. The reason for this relationship is the severity of the wounds. The larger wounds, more and more fluid design are needed to systemic therapy, ozone therapy by topical, and systemic treatment to both changes. Thus, it seems that this connection is strongly related to the type of wounds receiving ozone therapy. A case in point is the relationship of ozone therapy with both scale and QoL. It is hypothesized that QoL is even enhanced with ozone protection, because it suggests that ozone can improve mental QoL. The same is the case for antibiotic therapy as seen in the current study.

In the Cardiff questionnaire, antibiotic treatment was inversely related to QoL. Here, too, the problem arises that the wounds are likely more serious and more infectious diseases are treated with antibiotics. The patients also have a lower QoL. Therefore, antibiotic therapies are those that have a lower QoL and the reversed antibiotic treatment and QoL is a false relationship. It is noteworthy that this negative association was significant only in the Cardiff questionnaire; and any components of the SF-36 questionnaire, physical, and psychological regression.

Many studies have examined QoL in Iran as part of their expression is not unpleasant. In this study, the SF-36 questionnaire was used to evaluate QoL. The total mean scores of physical (PCS) and mental (MCS) QoL in these patients were 55.01 and 63.86 points, respectively, corresponding to both of our study are higher ($P < .001$). Of course, it is known that the participants in the current study were healthy normal citizens of Tehran. In this study, factors that were associated with QoL and health included age, gender, and economic status. Older age, female gender, and weaker economic situation had direct correlations with the physical deterioration of QoL. While that does not play an important role for mental health, age and gender were not significant. In this study, there was no significant relationship between physical or mental QoL in contrast to our study, education or living independently or with family.

As mentioned above, this study was conducted on healthy subjects. Other studies, however, have been conducted on a variety of Iranian patients. For example, one study assessed 101 patients with nonmalignant chronic pain caused by disease recommend the suffering of samples. In it, overall QoL and overall mental health QoL were 43.37 and 46.95, respectively. The study also reported lower overall QoL in older people.^[22,23]

Another study examined the QoL of patients with type II diabetes. This study was conducted in 2012 and with a large sample size ($n=3472$). It investigated QoL in 3472 Iranian people with type 2 diabetes with a mean age of 59.4 years and the factors related to it.^[24]

In this study, unlike the previous two studies, the SF-36 questionnaire was not used; thus, a direct comparison with the scores in the current study was not possible. However, the existence of possible factors affecting the QoL of diabetic patients in this study is remarkable. Overall, female gender, lower education, having a steady job, longer duration of diabetes, hospitalization due to diabetes in the year before the study, diabetic foot ulcers, nephropathy, and retinopathy were factors that had a relationship with a lower QoL. The project researchers concluded that the QoL of diabetic patients in Iran is significantly lower.^[24] Ironically, the very existence of diabetic foot ulcers in people is directly and strongly associated with a reduced QoL. In this study, variables such as marital status, type of diabetes (such as untreated, nutritional therapy, lifestyle changes, and drug treatment), city of residence, and cardiovascular diseases had an effect on QoL.

One study published in 2014 investigated 1232 patients who had recently been infected with diabetic foot ulcers. This study with diabetes data gathered from 14 centers in 10 European countries was valid. As in previous studies, the SF-36 questionnaire and the Euro-QoL-5D were used.

Among other factors, patient QoL will be affected by size of the wound, limb ischemia, increased serum levels of CRP, clinical diagnosis of infection, and polyneuropathy, all of which are related to reduced QoL.^[25]

To the best of the authors' knowledge, the current study is the only study that examines the QoL in patients treated with ozone. The sectional nature of the study makes it harder to make a causal link between categorical variables. The small sample size indicates that all relationships between variables are not perfectly efficient. Therefore, it is possible that other relationships between these variables are present in higher sample volumes.

5. Conclusion

Patients with chronic wounds have considerably decreased QoL and need special care. Medical O₃ therapy appears to increase health-related QoL among these patients and could be a valuable therapeutic option. It seems that the application of medical O₃ therapy, in addition to its positive effects on the healing process of chronic wounds, can significantly improve and increase QoL in patents. The current study has proven again that O₃ therapy can be a safe, efficient, and highly potential therapeutic method for improving QoL in cases with chronic wounds.

Author contributions

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