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Research Article

Research Article

Ablative fractional CO_2 laser surgery improving sleep quality, pain and pruritus in adult hypertrophic scar patients: a prospective cohort study

Kaiyang Lv[1,2,†,*], Huazhen Liu[2,†], Haiting Xu[3,4], Caixia Wang[5], Shihui Zhu[2], Xiaozhen Lou[2], Pengfei Luo[2], Shichu Xiao[2,*] and Zhaofan Xia[2,*]

[1]Department of Plastic Surgery, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200092; People's Republic of China, [2]Department of Burn Surgery, the First affiliated Hospital to Naval Medical University, Shanghai 200433, People's Republic of China, [3]Department of Burn and Plastic Surgery, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong 250021, People's Republic of China, [4]Department of Plastic Surgery, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325000, People's Republic of China and [5]Shanghai Institute of Laser Technology, Shanghai 200233, People's Republic of China

*Correspondence. Kaiyang Lv, Email: lvkaiyang@hotmail.com; Shichu Xiao, Email: huangzhuoxiao4@hotmail.com; Zhaofan Xia, Email: xiazhaofan_smmu@163.com

[†]Joint first author.

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Abstract

Background: Poor sleep quality is associated with a decrease in quality of life in patients with major burn scars, combined with pruritus and pain. Few interventions have been reported to improve the sleep quality of patients with scars. In the current prospective cohort study, we investigated the efficacy of CO_2-ablative fractional laser (AFL) surgery *vs* conventional surgery in post-burn patients with hypertrophic scars with sleep quality as the primary study outcome.

Methods: In total 68 consecutive patients undergoing scar surgical treatment were recruited, including a CO_2-AFL surgery cohort ($n = 35$) and a conventional surgery cohort ($n = 33$). A subgroup from the AFL cohort was selected. Sleep quality, pain and pruritus were evaluated. Multiple linear regression analyses were performed to reveal the effect of CO_2-AFL surgery.

Results: The CO_2-AFL surgery cohort had significantly lower Pittsburgh sleep quality index (PSQI) global scores than the conventional surgery cohort after the last surgical treatment. In the subgroup of patients receiving hardware sleep monitoring, CO_2-AFL markedly increased deep sleep time, deep sleep efficiency and reduced initial sleep latency. Compared to the conventional surgery cohort, the CO_2-AFL cohort presented significantly lower pain and pruritus scores. Correlation analysis showed pain and pruritus were significantly associated with PSQI scores, and there were also significant correlations between pain and pruritus scores. Multiple linear regression analysis showed that surgery method was negatively linearly correlated with visual analog scale (VAS) pain score, brief pain inventory (BPI) total, VAS pruritus score, 5-D itch scale total, four-item itch questionnaire (FIIQ) total and PSQI total.

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Conclusions: CO_2-AFL surgery significantly improved sleep quality and reduced pain and pruritus of hypertrophic scar patients. The alleviation of sleep disorder was associated with improvement of deep sleep quality including deep sleep time and deep sleep deficiency.
Trial registration: The Chinese Clinical Trial Registry (ChiCTR200035268) approved retrospectively registration on 5 Aug 2020.

Key words: Burn scar, Ablative CO_2 fractional laser, Cardiopulmonary coupling, Sleep quality, Pain, Pruritus

Highlights

- This study demonstrates for the first time that CO_2-AFL surgery can significantly improve sleep quality, especially the deep sleep quality, of hypertrophic scar patients.
- CO_2-AFL surgery significantly reduces pain and pruritus of hypertrophic scar patients.
- This study supports use of CO_2-AFL treatment as an effective therapy for burn scar patients with sleep disorders.

Background

Hypertrophic scars following burn injury occur as a result of undue proliferation of fibroblasts and excessive collagen synthesis that lead to excessive deposition of the extracellular matrix and diminished collagen degradation during wound healing [1–3]; the incidence of pathologic scaring frequently happens after a burn wound has healed [4]. Contracture of hypertrophic scars, which is often accompanied by intense pruritus and neuropathic pain, compromises the quality of life of burn victims [5], including the occurrence of sleep disturbance [6–8]. Sleep quality is related to health and affects the balance of and satisfaction with life, and disturbance of sleep quality may lead to feelings of tension, depression, anger, fatigue and confusion [9], even suicide of the victims.

Various therapies are used for hypertrophic scaring following burn injury including burn rehabilitation massage therapy, garment pressure therapy, steroid injection and surgical excision [10–14]. Ablative fractional laser (AFL) is a novel therapeutic method for scars [15]. It generates thermal energy that is deposited in columns through the epidermis and into the dermis. These columns are evenly spaced throughout the treatment area, with the intervening areas composed of untreated viable skin, and create microscopic treatment zones [16]. The thermal energy of fractional lasers results in persistent expression of heat shock proteins and induces the production of a cascade of cytokines and growth factors, stimulating collagen production and tissue remodeling and activating fibroblasts, thereby reducing scar thickness and improving skin elasticity. Moreover, the greater the pulse energy of the lasers, the greater the degree of tissue ablation and coagulation [17–22].

AFL has been proved to provide significant, sustained improvement of mature hypertrophic burn scars, but its effect on sleep quality has not been reported. In the current prospective cohort study, we investigated the efficacy of ablative fractional carbon dioxide laser (CO_2-AFL) surgery *vs* conventional surgery in post-burn patients with hypertrophic scars, with sleep quality as the primary study outcome.

Methods

Study population

Single center data from a multicenter, prospective cohort study of risk factors for hypertrophic burn scars were analyzed [23]. This single center prospective study enrolled consecutive burn scar patients who received treatment at Changhai Hospital between May 2016 and April 2018. Patients with immature scars who were aged at least 18 years and whose time interval from burn to scar occurrence was <1 year were included. We excluded pregnant or lactating women, patients with current or recent cancer, severe systemic disease or keloids, or patients who were in a poor condition and cannot tolerate surgery under regional or general anesthesia, or had previous CO_2-AFL surgery.

Patients were assigned to undergo CO_2-AFL surgery or conventional surgery according to scar severity and patients' intent. Scar severity was jointly decided by scar area of total body surface area (TBSA) and scar location. A subgroup was selected from the CO_2-ALF surgery cohort according to the patients' will to undergo preoperative and postoperative hardware sleep monitoring. All patients provided written informed consent to surgical treatment.

The study protocol was approved by the local ethics committee of Changhai Hospital (CHEC2014086). All study participants provided written informed consent to the study.

Surgery protocols

Surgeries were performed by at least two burn surgeons with >6 years of experience in burn surgery, and the sessions of surgeries were determined by effective negotiation between doctors and patients depending on the patients' condition. Conventional surgery included scar excision and suturing, scar excision split thickness skin graft, full thickness skin graft, regional flap (e.g. V-Y plasty, and Z plasty), skin substitute and pedicle flaps. CO_2-AFL surgery was performed in one session every 4–12 weeks (UltraPulse® Encore; Lumenis, Santa Clara, CA, USA), under general anesthesia, nerve

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blocking anesthesia or lumbar anesthesia for large scars (scar surgery area >2% TBSA) or with topical 1% lidocaine cream for small scars (scar surgery area ≤2%TBSA). Large scars were treated with laser under the whole scar principle, which means all the scar area should be treated in one session of AFL surgery, and the laser should try to penetrate the bottom of the scar. Treatment depth was determined according to the estimated scar thickness [15,24]. Scars were treated in the single pulse mode, with non-overlapping pulses, at an energy density of 20–150 mJ corresponding to a treatment depth of 0.4–4 mm and treatment density of 3–5%. Immediately after laser treatment, topical compound betamethasone suspension (5 mg/mL) was applied to the surface of the treated scar. In addition, wound gel (Prontosan, B. Braun Medical Inc, Bethlehem, PA) was applied for 3–7 days for anti-infective purposees. Then, 3–10 days postoperatively, patients were allowed to receive pressure therapy. All patients received pressure therapy, silicone sheet/gel and rehabilitation therapy under the guidance of doctors during the study period.

Sleep quality and paresthetic symptom evaluation

The sleep quality of the cohort was evaluated using the Pittsburgh sleep quality index (PSQI) [25]. The PSQI has seven domains, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction over the last month. Scoring of the answers in each domain is based on a 0–3 scale, whereby 3 reflects the negative extreme on the Likert Scale and the range of the global sum is 0–21.

Pain was evaluated using the visual analog scale (VAS) [26] and brief pain inventory (BPI) [27]. BPI has domains which measure pain intensity (four items, score 0–40) and pain interference with functioning (seven items, score 0–70), respectively.

Pruritus was evaluated using the VAS for pruritus [28], the 5-D itch scale [29] and the four-item itch questionnaire (FIIQ) [30]. The 5-D itch scale has five dimensions: duration, severity, direction, interference and distribution with a total score of 5–25. A higher score indicates greater pruritus. The FIIQ has four dimensions: pruritus location (score range 1–3), pruritus degree (score range 1–5), pruritus frequency (score range 1–5) and effect on sleep (score range 0–6). The minimum score is 3, indicating the mildest pruritus and the maximum score is 19, indicating the most intense pruritus.

Evaluation of sleep quality and paresthetic symptoms, including pain and pruritus, by scales and questionnaires were performed 4–6 weeks after the last conventional surgery or AFL surgery.

Additionally, in the subgroup from the CO_2-AFL surgery cohort, objective sleep parameters were monitored using an electrocardiogram (ECG) recorder (AECG-100A, Fengsheng Yongkang Software Co, Nanjing, China) preoperatively and 1–3 days postoperatively. Cardiopulmonary coupling software (Fengsheng Yongkang Software Co.) automatically processes and analyses signals and generates pictograms for total bedtime, total sleep time, sleep efficiency (total sleep time/total bedtime), deep sleep time, light sleep time, rapid eye movement (REM) sleep time, awake time, and apnea index and initial deep sleep time [31–33].

Evaluation of sleep quality and paresthetic symptoms, including pain and pruritus, using scales were also performed both preoperatively and postoperatively in this subgroup.

Statistical analysis

The primary outcome was sleep quality and the secondary outcomes included pain and pruritus scale scores. Data are expressed as mean ± SD, and median and interquartile range (IQR) as appropriate and analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). A *chi square* test was used for categorical data and an independent sample *t* test was used for continuous variables when normally distributed. When data exhibited a significant lack of normality, a nonparametric test (such as Mann–Whitney *U* test) was used. In the subgroup of patients who underwent hardware sleep monitoring before and after CO_2-AFL surgery, a paired sample *t* test was used for continuous variables when normally distributed. A two-sided $p < 0.05$ was taken as statistically significant. Pearson correlation analysis between paresthetic symptoms and PSQI scores was performed to explore their associations. Multiple linear regressions were performed to assess the relationships between surgery method and PSQI scores, paresthetic symptoms after adjustments for sex, age, body mass index (BMI), burn area and time interval from burn to scar surgery. The predictive value of regression model was determined by R^2. $p < 0.05$ was considered significant.

Results

Patient demographic and baseline characteristics

The study flowchart is shown in Figure S1, see online supplementary material. In total, 68 patients were eligible for data analysis, including 35 patients receiving CO_2-AFL surgery and 33 patients undergoing conventional surgery. Patient demographics and baseline characteristics are shown in Table 1. The two groups were comparable in demographic and baseline characteristics except for sex distribution. The treatment area of the CO_2-AFL surgery group is larger than that of the conventional surgery group (CO_2-AFL surgery *vs* conventional surgery: 30.14 ± 17.01% *vs* 9.15 ± 5.04% TBSA, $p < 0.001$). A total of 14 patients were included in the subgroup of patients receiving CO_2-AFL surgery whose sleep quality was assessed both preoperatively and postoperatively. Subgroup demographics and baseline characteristics are shown in Table 1.

Primary outcomes

PSQI The CO_2-AFL surgery cohort had significantly lower PSQI global scores than the conventional surgery cohort (CO_2-AFL surgery *vs* conventional surgery: 8.14 ± 3.67 *vs* 11.58 ± 4.89, $p = 0.002$) 4–6 weeks after the last surgical treatment (Table 2). Moreover, patients receiving CO_2-AFL surgery had markedly lower scores in sleep quality (CO_2-AFL

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Table 1. Demographic characteristics of the study population and subgroup receiving objective sleep monitoring

Variable	Conventional therapy ($n = 33$)	CO_2-AFL ($n = 35$)	CO_2-AFL subgroup ($n = 14$)
Male (*n*)	16	27**	12
Age (years)	43.06 ± 11.34	38.60 ± 10.78	38.07 ± 12.35
BMI (kg/m^2)	23.83 ± 3.28	23.13 ± 2.63	22.24 ± 2.86
Burn area (%TBSA) (mean ± SD)	51.67 ± 22.73	48.80 ± 24.41	50.93 ± 25.49
Time interval from burn to scar surgery (months) (mean ± SD)	6.68 ± 5.55	8.28 ± 6.41	7.56 ± 5.33
Causes of injury (*n*)			
Flame	24	32	10
Others	9	3	4
Scar location (*n*)			
Head and face	19	26	12
Trunk	27	30	12
Extremities	30	30	13
Total session of treatments (mean ± SD)	2.58 ± 1.47	2.43 ± 1.65	3.07 ± 2.16
Treatment area (%TBSA) (mean ± SD)	9.15 ± 5.04	30.14 ± 17.01**	34.29 ± 16.56
Postoperative local infections (*n*)	6	5	2

**$p < 0.01$ compared with conventional therapy group. *BMI* body mass index (kg/m^2), *TBSA* total body surface area, *AFL* ablative fractional laser, *SD* standard deviation

surgery *vs* conventional surgery: 1,1–2 *vs* 2,1–2, $p = 0.011$), sleep latency (CO_2-AFL surgery *vs* conventional surgery: 2,1–2 *vs* 2,1–3, $p = 0.009$), sleep disturbances (CO_2-AFL surgery *vs* conventional surgery: 1,1–2 *vs* 2,1–3, $p = 0.010$), sleep time (CO_2-AFL surgery *vs* conventional surgery: 1.25 ± 1.07 *vs* 1.79 ± 1.05, $p = 0.043$) and daytime dysfunction (CO_2-AFL surgery *vs* conventional surgery: 1,1–2 *vs* 2,1–3, $p = 0.013$), which indicates better sleep quality (Table 2).

In the subgroup of patients receiving CO_2-AFL surgery whose sleep quality was assessed both preoperatively and postoperatively, the postoperative PSQI global score decreased significantly *vs* the baseline PSQI global score (preoperative *vs* postoperative:12.60 ± 3.27 *vs* 8.86 ± 2.50, $p < 0.001$) (Table 2), suggesting improved sleep quality. In addition, the domain scores in sleep quality (preoperative *vs* postoperative: 2.14 ± 0.66 *vs* 1.36 ± 0.63, $p = 0.001$), sleep time (preoperative *vs* postoperative: 2.21 ± 0.97 *vs* 1.43 ± 0.94, $p = 0.006$), sleep efficiency (preoperative *vs* postoperative: 2.43 ± 0.76 *vs* 1.29 ± 0.91, $p = 0.004$) and sleep disturbances (preoperative *vs* postoperative: 1.93 ± 0.73 *vs* 1.29 ± 0.61, $p = 0.022$) decreased markedly after CO_2-AFL surgery. Meanwhile, there was no noticeable change in sleep latency (preoperative *vs* postoperative: 2.14 ± 1.03 *vs* 1.71 ± 0.91, $p = 0.082$), use of sleep medications (preoperative *vs* postoperative: 0 ± 0 *vs* 0.07 ± 0.27, $p = 0.336$) and daytime dysfunction (preoperative *vs* postoperative: 1.79 ± 0.7 *vs* 1.57 ± 0.76, $p = 0.272$) (Table 2).

Subgroup hardware sleep monitoring

In the subgroup of patients who underwent sleep monitoring by ECG hardware, total time in bed (preoperative *vs* postoperative: 10.41 ± 1.39 *vs* 9.70 ± 1.35, $p = 0.017$), initial enter deep sleep time (preoperative *vs* postoperative:2.20 ± 2.01 *vs* 1.41 ± 1.66, $P = 0.03$), awakening time (preoperative *vs* postoperative:1.61 ± 0.80 *vs* 0.78 ± 0.47, $p < 0.001$) and REM sleep time (preoperative *vs* postoperative:1.97 ± 0.62 *vs* 1.54 ± 0.68, $p = 0.014$) decreased significantly after CO_2-AFL surgery (Table 2). Meanwhile, no marked change was observed in total sleep time (preoperative *vs* postoperative: 8.20 ± 1.21 *vs* 8.69 ± 1.31, $p = 0.289$), light sleep time (preoperative *vs* postoperative: 4.00 ± 1.56 *vs* 4.22 ± 1.69, $p = 0.566$), apnea index (preoperative *vs* postoperative: 14.93 ± 13.92 *vs* 18.33 ± 16.90, $p = 0.272$) and light sleep efficiency (preoperative *vs* postoperative: 0.41 ± 0.16 *vs* 0.46 ± 0.19, $p = 0.128$). Moreover, CO_2-AFL surgery significantly improved sleep efficiency (preoperative *vs* postoperative: 0.82 ± 0.08 *vs* 0.91 ± 0.05, $p = 0.001$), deep sleep efficiency (preoperative *vs* postoperative: 0.22 ± 0.10 *vs* 0.30 ± 0.15, $p = 0.02$) and deep sleep time (preoperative *vs* postoperative: 2.16 ± 1.06 *vs* 2.94 ± 1.53, $p = 0.026$) (Table 2).

Secondary outcomes

Pain Compared to patients undergoing conventional surgery, patients receiving CO_2-AFL had significantly lower VAS pain score (CO_2-AFL surgery *vs* conventional surgery: 2.65 ± 1.39 *vs* 4.12 ± 2.33, $p = 0.002$) after the last treatment (Figure 1). Consistently, evaluation with BPI showed BPI global score (CO_2-AFL surgery *vs* conventional surgery: 27.94 ± 18.20 *vs* 42.94 ± 24.62, $p = 0.006$), pain intensity (CO_2-AFL surgery *vs* conventional surgery: 10.17 ± 7.13 *vs* 15.15 ± 9.54, $p = 0.017$) and pain interference with life (CO_2-AFL surgery *vs* conventional surgery: 17.77 ± 11.41 *vs* 27.79 ± 15.63, $p = 0.003$) were significantly less severe than in patients undergoing conventional surgery (Figure 1).

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Table 2. Sleep parameters of the study cohorts and the subgroup[a]

Variables	CO_2-AFL surgery ($n=35$)	Conventional surgery ($n=33$)	Subgroup preoperative ($n=14$)	Subgroup postoperative ($n=14$)
PSQI Scales				
global score	8.14 ± 3.67	11.58 ± 4.89**	12.60 ± 3.27	8.86 ± 2.50###
sleep quality	1,1–2	2,1–2*	2.14 ± 0.66	1.36 ± 0.63##
sleep latency	2,1–2	2,1–3**	2.14 ± 1.03	1.71 ± 0.91
sleep time	1.25 ± 1.07	1.79 ± 1.05*	2.21 ± 0.97	1.43 ± 0.94##
sleep efficiency	2,1–2	2,0–3	2.43 ± 0.76	1.29 ± 0.91##
sleep disturbances	1,1–2	2,1–3*	1.93 ± 0.73	1.29 ± 0.61#
sleep medications	0,0–0	0,0–0	0 ± 0	0.07 ± 0.27
daytime dysfunction	1,1–2	2,1–3*	1.79 ± 0.70	1.57 ± 0.76
Objective Sleep Monitoring				
total time in bed (hour)	N/A	N/A	10.41 ± 1.39	9.70 ± 1.35#
total sleep time (hour)	N/A	N/A	8.20 ± 1.21	8.69 ± 1.31
initial enter deep sleep time (hour)	N/A	N/A	2.20 ± 2.01	1.41 ± 1.66#
deep sleep time (hour)	N/A	N/A	2.16 ± 1.06	2.94 ± 1.53#
light sleep time (hour)	N/A	N/A	4.00 ± 1.56	4.22 ± 1.69
REM sleep time (hour)	N/A	N/A	1.97 ± 0.62	1.54 ± 0.68#
awakening time (hour)	N/A	N/A	1.61 ± 0.80	0.78 ± 0.47###
sleep efficiency	N/A	N/A	0.82 ± 0.08	0.91 ± 0.05##
deep sleep efficiency	N/A	N/A	0.22 ± 0.10	0.30 ± 0.15#
light sleep efficiency	N/A	N/A	0.41 ± 0.16	0.46 ± 0.19
apnea index (events per hour)	N/A	N/A	14.93 ± 13.92	18.33 ± 16.90

[a]Analysis for sleep quality, sleep latency, sleep efficiency, sleep disturbances, sleep medications and daytime dysfunction compared with CO_2-AFL surgery were performed with Mann—Whitney *U* test. Analysis for global score and sleep time compared with CO_2-AFL surgery were performed with independent sample *t* test. In the subgroup, analysis for sleep parameters compared with preoperative were performed with paired sample *t* test.

Data are presented as median, IQR or mean±SD.

*p<0.05, **p<0.01 compared with CO2-AFL surgery; #p<0.05, ##p<0.01, ###p<0.001 compared with preoperative.

PSQI pittsburgh sleep quality index, *IQR* interquartile range, *SD* standard deviation, *AFL* ablative fractional laser, *REM* rapid eye movement, *N/A* not applicable

In the subgroup of patients receiving CO_2-AFL surgery, the postoperative VAS pain score was significantly lower *vs* baseline (preoperative *vs* postoperative: 5.57 ± 2.14 *vs* 3.29 ± 1.33, $p < 0.001$) (Figure 1). Evaluation with BPI revealed that CO_2-AFL surgery markedly reduced BPI global score (preoperative *vs* postoperative: 54.00 ± 18.56 *vs* 39.00 ± 13.79, $p < 0.001$), pain intensity (preoperative *vs* postoperative: 19.93 ± 7.25 *vs* 14.36 ± 5.83, $p = 0.001$) and pain interference with functioning (preoperative *vs* postoperative: 34.07 ± 11.83 *vs* 24.64 ± 8.21, $p = 0.001$) (Figure 1).

Pruritus Patients receiving CO_2-AFL had significantly lower VAS pruritus score than patients receiving conventional surgery (CO_2-AFL surgery *vs* conventional surgery: 3.57 ± 1.36 *vs* 5.82 ± 1.86, $p < 0.001$) (Table 3). In addition, patients receiving CO_2-AFL had markedly lower 5-D itch scale global score than patients undergoing conventional surgery (CO_2-AFL surgery *vs* conventional surgery: 12.34 ± 3.91 *vs* 15.06 ± 4.02, $p = 0.006$). They also had markedly lower scores in duration (CO_2-AFL surgery *vs* conventional surgery: 1, 1–2 *vs* 2, 2–3, $p = 0.008$), severity (CO_2-AFL surgery *vs* conventional surgery: 2, 2–3 *vs* 3, 2–3, $p = 0.007$) and interference (CO_2-AFL surgery *vs* conventional surgery: 4, 2–4 *vs* 5, 4–5, $p = 0.002$) than patients receiving conventional surgeries (Table 3).

Patients receiving CO_2-AFL had significantly lower FIIQ global score than patients receiving conventional surgery (CO_2-AFL surgery *vs* conventional surgery: 9.54 ± 3.58 *vs* 12.66 ± 4.14, $p = 0.001$). Moreover, patients receiving CO_2-AFL had significantly lower scores of pruritus frequency (CO_2-AFL surgery *vs* conventional surgery: 2, 2–3 *vs* 3, 3–4, $p = 0.002$), pruritus degree (CO_2-AFL surgery *vs* conventional surgery: 2, 2–3 *vs* 3, 2–3, $p = 0.018$) and effect on sleep (CO_2-AFL surgery *vs* conventional surgery: 4, 0–4 *vs* 4, 4–6, $p = 0.001$) than patients receiving conventional surgery (Table 3).

In the subgroup of patients receiving CO_2-AFL surgery whose pruritus was assessed both preoperatively and postoperatively, CO_2-AFL surgery markedly reduced VAS pruritus score (preoperative *vs* postoperative: 6.00 ± 1.41 *vs* 4.07 ± 1.21, $p < 0.001$) (Table 3). CO_2-AFL surgery also significantly decreased the 5-D itch scale global score (preoperative *vs* postoperative: 17.36 ± 3.20 *vs* 13.64 ± 4.01, $p = 0.002$) and markedly shortened the duration (preoperative *vs* postoperative: 3.07 ± 1.07 *vs* 2.14 ± 1.29, $p = 0.002$), while significantly reducing severity (preoperative *vs* postoperative: 3.21 ± 0.70 *vs* 2.64 ± 0.84, $p = 0.026$), direction (preoperative *vs* postoperative: 4.00 ± 0.96 *vs* 2.93 ± 1.00, $p = 0.002$) and interference (preoperative *vs* postoperative: 4.29 ± 0.73 *vs* 3.43 ± 1.34, $p = 0.003$) (Table 3). Meanwhile, CO_2-AFL surgery significantly decreased FIIQ global score (preoperative *vs* postoperative: 12.86 ± 2.96 *vs* 10.21 ± 2.08, $p = 0.001$), pruritus degree (preoperative *vs* postoperative: 3.29 ± 1.07 *vs* 2.36 ± 0.63, $p = 0.001$), pruritus frequency (preoperative *vs* postoperative: 3.29 ± 0.83 *vs* 2.64 ± 0.74,

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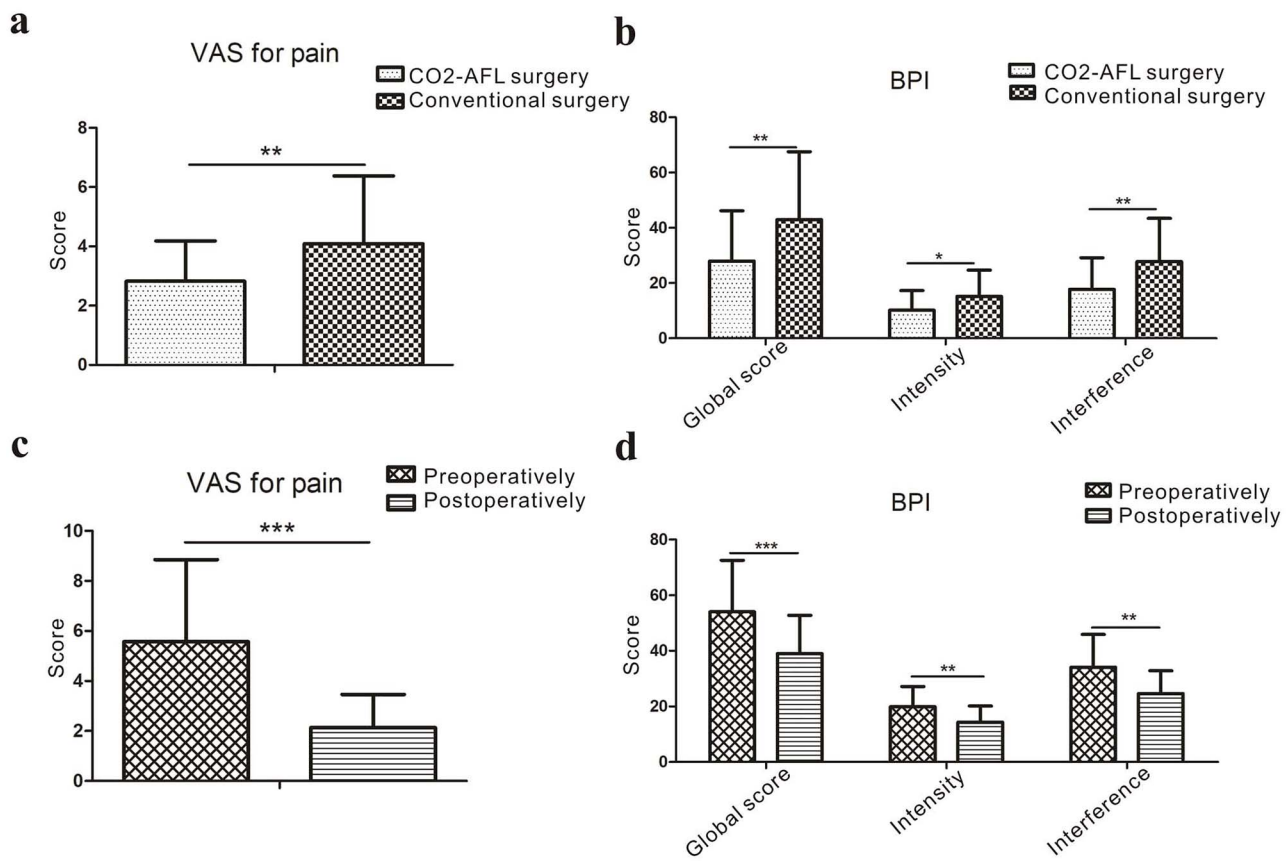


Figure 1. Pain scores of patients receiving CO_2-AFL surgery, conventional surgery and the subgroup who underwent sleep monitoring by cardiopulmonary coupling before and after CO_2-AFL surgery. (**a**) VAS scores of patients receiving CO_2-AFL surgery ($n = 35$) *vs* patients undergoing conventional surgery ($n = 33$), (**b**) BPI scores of patients receiving CO_2-AFL surgery ($n = 35$) *vs* patients undergoing conventional surgery ($n = 33$), (**c**) VAS scores of subgroup patients ($n = 14$), (**d**) BPI scores of subgroup patients ($n = 14$). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. *AFL* ablative fractional laser, *VAS* visual analogue scale, *BPI* brief pain inventory

Table 3. Priuritus evaluation of the study cohort and the subgroup[a]

Variable	CO_2-AFL surgery (n = 35)	Conventional surgery (n = 33)	Subgroup preoperative (n = 14)	Subgroup postoperative (n = 14)
VAS for pruritus	3.57 ± 1.36	5.82 ± 1.86***	6.00 ± 1.41	4.07 ± 1.21###
5-D scale				
Global score	12.34 ± 3.91	15.06 ± 4.02**	17.36 ± 3.20	13.64 ± 4.01###
Duration	1,1–2	2,2–3**	3.07 ± 1.07	2.14 ± 1.29##
Severity	2,2–3	3,2–3**	3.21 ± 0.70	2.64 ± 0.84#
Direction	3,2–4	3,3–3	4.00 ± 0.96	2.93 ± 1.00##
Interference	4,2–4	5,4–5**	4.29 ± 0.73	3.43 ± 1.34###
Distribution	2.06 ± 1.16	2.61 ± 1.20	2.64 ± 0.84	2.50 ± 1.09
FIIQ				
Global score	9.54 ± 3.58	12.66 ± 4.14**	12.86 ± 2.96	10.21 ± 2.08##
Pruritus location	2,1–3	2,2–3	2.29 ± 0.73	2.29 ± 0.73
Pruritus degree	2,2–3	3,2–3*	3.29 ± 1.07	2.36 ± 0.63##
Pruritus frequency	2,2–3	3,3–4**	3.29 ± 0.83	2.64 ± 0.74#
Effect on sleep	4,0–4	4,4–6**	4.29 ± 1.73	3.00 ± 1.30###

[a]Analysis for duration, severity, direction, interference, pruritus location, pruritus degree, pruritus frequency and effect on sleep compared with CO_2-AFL surgery were performed with Mann-Whitney *U* test. Analysis for VAS for pruritus, 5-D scale (global score and distribution) and FIIQ (global score) compared with CO_2-AFL surgery were performed with independent sample *t* test. In the subgroup, analysis for pruritus evaluation variables compared with preoperative were performed with paired sample *t* test.

Data are presented as median, IQR or mean±SD.

$^{*}p<0.05$, $^{**}p<0.01$ compared with CO_2-AFL surgery; $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ compared with preoperative.

VAS visual analogue scale, *FIIQ* four-item itch questionnaire, *IQR* interquartile range, *SD* standard deviation, *AFL* ablative fractional laser

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$p = 0.033$) and effect on sleep (preoperative *vs* postoperative: 4.29 ± 1.73 *vs* 3.00 ± 1.3, $p < 0.001$) (Table 3).

Correlation analysis between paresthetic symptoms (pain and pruritus) and PSQI

Table S1, see online supplementary material, shows correlations between paresthetic symptoms (pain and pruritus) and PSQI (total and subscales) scores. All items of pain scores showed significant positive correlations with total PSQI score ($p < 0.001$). All PSQI items except use of sleep medication were significantly positively associated with pain scores.

All items of pruritus scores also showed significant positive correlations with total PSQI score ($p < 0.01$). All global scores of 5-D itch scale and FIIQ were significantly positively associated with all PSQI items, and the VAS pruritus scores were significant positively associated with all of the PSQI items except habitual sleep efficiency.

Table 4 shows correlations between paresthetic symptoms of pain and pruritus. All items of pain scores showed significant positive correlations with all items of pruritus scores ($p < 0.01$). All items of pain scores also showed strong positive correlations with VAS pruritus scores, global score of 5-D itch scale and global score of FIIQ ($p < 0.01$).

The effect of CO_2-AFL surgery on sleep quality and paresthetic symptoms (pain and pruritus)

Table 5 shows the results of multivariate linear regression analysis for VAS pain score, BPI total score, VAS pruritus score, 5-D itch scale total score, FIIQ total score and PSQI total score, respectively, with surgery method, age, sex, burn scar area, BMI and time from burn to surgery included as independent variables. The results show that surgery method was negatively linearly correlated with VAS pain score, BPI total score, VAS pruritus score, 5-D itch scale total score, FIIQ total score and PSQI total score. For the conventional therapy cohort was labeled as 0 and CO2-AFL cohort was labeled as 1 in multiple linear regression analysis, the results means AFL surgery was negatively association with sleep quality and paresthetic symptoms, and both sleep disorder and paresthetic symptoms were improved in patients receiving AFL surgery. Age was a risk factor for increase in VAS pain score, BPI total score and 5-D itch scale total score, which means older patients with burn scar were susceptible to worse paresthetic conditions.

Discussion

Burn victims with hypertrophic scars are frequently afflicted with sleep disorders, pain and pruritus [34,35], which is associated with poor quality of life [3]. Our investigation presents the first clinical evidence that CO_2-AFL surgery significantly improved sleep quality of burn patients with hypertrophic scars. Patients also experienced significant improvement in pain and pruritus, which has also been previously reported

Table 4. Correlations between pain scores and pruritus scores of the study cohorts ($n = 68$)

Pain scores	Pruritus scores											
		5-D itch scale						FIIQ				
	VAS pruritus score	Total time	Severity	Direction	Interference	Distribution	Global score	Pruritus location	Pruritus degree	Pruritus frequency	Effect on sleep	Global score
VAS pain scores	0.615**	0.458**	0.548**	0.464**	0.525**	0.426**	0.630**	0.356**	0.262*	0.528**	0.609**	0.585**
BPI items												
Pain intensity	0.573**	0.441**	0.596**	0.509**	0.499**	0.460**	0.643**	0.396**	0.393**	0.534**	0.656**	0.645**
Pain interference with functioning	0.589**	0.430**	0.554**	0.487**	0.545**	0.487**	0.650**	0.469**	0.423**	0.565**	0.627**	0.673**
Global score	0.594**	0.442**	0.581**	0.505**	0.538**	0.486**	0.660**	0.450**	0.420**	0.564**	0.650**	0.675**

*$p < 0.05$, **$p < 0.01$.
VAS visual analogue scale; *BPI* brief pain inventory; *FIIQ* four-item itch questionnaire

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Table 5. Multiple linear regression analysis of the relationship between paresthetic symptom (pain and pruritus) and surgery method ($n = 68$)[a]

Dependent variables	Surgery method*				Age			
	β	95% CI	*P*	R^2	*β*	95% CI	*P*	R^2
VAS pain score	−1.051	−1.997 to 0.105	0.030	0.277	0.061	0.018–0.103	0.006	0.277
BPI total	−10.499	−21.476 to 0.477	0.060	0.222	0.497	0.001–0.994	0.050	0.222
VAS pruritus score	−2.109	−2.975 to 1.242	0.000	0.355	–	–	–	–
5-D itch scale total	−2.223	−4.203 to 0.243	0.028	0.248	0.097	0.008–0.187	0.034	0.248
FIIQ total	−2.75	−4.764 to 0.737	0.008	0.214	–	–	–	–
PSQI total	−3.532	−5.824 to 1.240	0.003	0.178	–	–	–	–

*Conventional therapy cohort was labeled as 0 and CO_2-AFL cohort was labeled as 1 in SPSS.

[a]Multiple linear regressions were performed with VAS pain score, BPI total, VAS pruritus score, 5-D itch scale total, FIIQ total and PSQI total as dependent variables, respectively, and independent variables were surgery method, sex, age, body mass index (BMI), burn area and time interval from burn to scar surgery for each dependent variable.

VAS visual analogue scale, *BPI* brief pain inventory, *FIIQ* four-item itch questionnaire, *PSQI* pittsburgh sleep quality index

[36], which may partly clinically explain the sleep quality improvement.

Our study compared the effect of CO_2-AFL surgery *vs* conventional surgery on hypertrophic scar patients and found that CO_2-AFL surgery was more effective than conventional surgery in decreasing PSQI global scores. In the subgroup study, CO_2-AFL surgery also caused a significant reduction in the postoperative PSQI global score *vs* the baseline. To find the internal mechanism of sleep scale improvement, we performed sleep monitoring of the subset of patients *via* cardiopulmonary coupling hardware, which demonstrated that CO_2-AFL surgery significantly improved the sleep efficiency, with reduced total time in bed, initial sleep latency, REM sleep time and awakening time. All the above parameters may contribute to the improvement in sleep efficiency and deep sleep efficiency. It suggested that CO_2-AFL surgery improves the sleep quality by improving the deep sleep quality, including deep sleep time and deep sleep deficiency, rather than the light sleep quality. On the other hand, evaluation by PSQI showed that these patients exhibited no significant change in sleep efficiency between the CO_2-AFL surgery cohort and the conventional surgery cohort. The discrepancy in sleep latency by PSQI and cardiopulmonary coupling monitoring could be explained by the greater sensitivity of real time monitoring *via* cardiopulmonary coupling hardware.

As correlation analysis showed, pain and pruritus of the scar sites could significantly interfere with sleep quality (Table S1) [37], which means alleviation of pain and pruritus could help to improve the sleep quality of patients. The multiple linear regression analysis showed that surgery method had a negative association with sleep quality scores and paresthetic symptom scores, and both sleep disorder and paresthetic symptoms were improved in patients who received AFL surgery, which confirms the beneficial effects of AFL surgery for patients with large areas of burn scars.

We found that CO_2-AFL surgery was significantly more effective than conventional surgery in reducing pain intensity and interference with daily life by pain, and also caused a significant decrement of VAS pain scores, which may be associated with improving sleep quality in hypertrophic scar patients. Pruritus could also adversely impact on quality of life and interfere with a patient's sleep [36]. Our study showed that CO_2-AFL was significantly more effective than conventional surgery in alleviating VAS for pruritus. It was also more effective in reducing duration, severity and interference of pruritus while having no impact on distribution between the two cohorts. The correlation analysis between pain scores and pruritus scores showed there were comprehensive positive correlations between all items of pain and pruritus scores, which means the combination of pain and pruritus may aggravate the symptoms of sleep disorders and make them more difficult to correct, making it more reasonable that interventions improving pain and pruritus could also improve sleep disorders.

The mechanism of scar pain and pruritus is associated with the inflammatory response and proliferation of the vasculature of hypertrophic scars [7]. CO_2-AFL could lead to apoptosis of fibroblasts in the microthermal zones and down-regulation of transforming growth factors and basic fibroblast growth factor [19,38], which would accelerate the maturation of hypertrophic scars, reducing the inflammatory response and decreasing the proliferation of the vasculature and the edema associated with the scar tissue (Figure 2). It is reasonable to accept that AFL is effective in the treatment of pain and pruritus of hypertrophic scars, though the exact mechanism still needs further research.

We also attribute the effect of AFL on the improvement of pain and pruritus of hypertrophic scars to the laser-assisted delivery of corticosteroid (a betamethasone suspension in our study), which enhances the effect of AFL treatment on hypertrophic scars [39,40]. Besides, full area of scars AFL treatment usually treat the area of the scar as large as possible in a single session and made a larger treatment area of CO_2-AFL group than conventional therapy group, which would lead to a better outcome of the CO_2-AFL group.

Our study still has some limitations. First, all the patients are from a single center, limiting the sample size of our final cohort. Nevertheless, we were able to demonstrate statistical

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Figure 2. Case presentation of a burn patient with large area scar. (**a** and **c**) 20-year-old male after a 95% TBSA flame burn in a fire accident. There were severe congestive hypertrophic scars all over the whole body when the wound healing was finished. He suffered from severe scar pruritus every day and night which kept him awake and he scratched the new body surface every 2–3 h at night. Silicone gel/silicone gel sheeting, pressure therapy and rehabilitation therapy were routinely performed which did not improve the sleep quality and paresthetic symptoms, and the symptoms got worse even 7 months after the burn. Then he was transferred to the department of burns, Changhai Hospital for further treatment. (**b** and **d**) The patient received four sessions of whole-body AFL surgery under general anesthesia and two sessions of local AFL surgery under local anesthesia in 7 months. The laser treatments accelerated the maturation of the scar and significantly improved the sleep quality and scar pruritus right after the second session of AFL surgery. The congestive scars appearance of the whole body was normalized, and his contracture of neck was improved significantly. No scar tissue was ever excised and no surgical surgery was performed during the 7 months. *AFL* ablative fractional laser, *TBSA* total body surface area

improvement in sleep disorder and paresthetic symptoms in the relatively small cohort. Second, randomized and blinded methods were not applied in this study, which would increase the bias of the study, potentially influencing the grading of the sleep quality and paresthetic symptoms of scars by both providers and patients. We remind readers to bear this in mind when applying the conclusions of the study.

Conclusions

Our study has demonstrated that CO_2-AFL surgery significantly improved sleep quality, especially deep sleep quality, and reduced pain and pruritus of hypertrophic scar patients, which may provide an effective tool to improve the quality of life and sleep quality of the population with large area immature burn scars. Together with previous studies focused on mature scar treatment, we consider CO_2-AFL treatment as an effective treatment for the whole course of scar proliferation.

Abbreviations

AFL: Ablative fractional laser; BMI: body mass index; BPI: brief pain inventory; ECG: Electrocardiogram; FIIQ: four-item itch questionnaire; IQR: Interquartile range; PSQI: Pittsburgh sleep quality index; REM: Rapid eye movement; TBSA: Total body surface area; VAS: Visual analogue scale.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KL, SX and ZX designed the study. All authors managed the study with regard to surgery, patient care and data collection. KL and HL analysed the data, which was interpreted by all other authors. KL and HL wrote the first draft of the manuscript which was reviewed, modified and approved by all other authors. All the authors vouch for the accuracy and completeness of the data reported and for the fidelity of the study to the protocol.

Ethics approval and consent to participate

The study protocol was approved by the local ethics committee of Changhai Hospital (CHEC2014086). All study participants provided written informed consent to the study.

Consent for publication

Informed consent has been obtained from the subjects (or their guardians) as specified in the ICMJE recommendations.

Conflict of interest

None declared.

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