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A Nonrandomized Trial of the Effects of Near-Infrared Photobiomodulation Therapy on Bell's Palsy with a Duration of Greater Than 8 Weeks

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Abstract

Objective: To determine whether photobiomodulation therapy (PBMT) by class IV Multiwave Locked System laser treatment as an adjunctive therapy could relieve symptoms in patients with Bell's palsy with a duration of greater than 8 weeks.

Materials and methods: This nonrandomized controlled trial was conducted from January 2020 to December 2022. Patients were eligible if they had Bell's palsy with a duration of greater than 8 weeks at the out-patient department of otorhinolaryngology in Beijing Tongren Hospital. The control group consisted of patients recruited between January 1, 2020, and December 31, 2020. The PBMT group consisted of patients recruited between January 1, 2021, and December 31, 2022. In this study, the PBM used has a wavelength of 808 and 905 nm, 1.2 W power (808 nm is 1 W, 905 nm is 200 mW), continuous mode emission (808 nm) and pulsed mode emission (905 nm), 8.35 J/cm^2 dosimetry, administered 3 times per week, 72 times of total treatment. The primary outcome measures included the House–Brackmann facial nerve grading system, the Sunnybrook facial grading system, and the Facial Clinimetric Evaluation Scale (FaCE). Secondary outcome measures comprised electroneurography, electromyography, and the blink reflex.

Results: A total of 54 participants were included (27 in the control group and 27 in the photobiomodulation group). After 6 months, the House–Brackmann grading system [risk difference, –0.59, confidence interval (95% CI), –0.81 to –0.38, relative risk, 0.27, 95% CI, 0.13–0.56, $p < 0.001$], Sunnybrook facial grading system (21.14, 95% CI, 11.71–30.58; $p < 0.001$), and FaCE (–0.20, 95% CI, 0.41–0.02; $p = 0.07$) had significant difference between the two groups. Latency of ala nasi muscle (10.92, 95% CI, 5.58–16.27; $p < 0.001$) was not statistically significant after treatment compared with the control group; however, most of the electrophysiological examinations have significant difference between the two groups, respectively.

Conclusions: The results of this study suggest that PBMT may relieve symptoms for patients with Bell's palsy with a duration of greater than 8 weeks.

Trial Registration: ClinicalTrials.gov Identifier: NCT05585333.

Keywords: Bell's palsy, photobiomodulation, a nonrandomized trial, ENoG, EMG, class IV laser

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Introduction

BELL'S PALSY CAN be caused by a variety of etiological factors, including viral infection, autoimmune disease, diabetes mellitus, emotional factors, stress, and iatrogenic factors.[1,2] It leads to facial weakness or paralysis, impaired or altered taste, hyperacusis, and decreased salivation and tear secretion.[3–5] In addition to functional and aesthetic issues, facial paralysis can hinder face-to-face communication and cause disabling psychological complications.[6,7]

Different treatments have been proposed to achieve rapid recovery without significant sequelae. Such treatments include botulinum toxin,[6,8,9] acupuncture,[10–12] facial expression exercises,[13,14] corticoids,[1,5] antiviral drugs,[15,16] electrical stimulation,[17,18] and photobiomodulation therapy (PBMT).[19–21] However, some of patients exhibited an incomplete recovery. If the disease course persists for >8 weeks, the residual symptoms are difficult to eliminate.[3,4]

Although the underlying mechanism of PBMT in the treatment of facial paralysis is still unclear, several low-level laser therapy (LLLT) studies suggest that PBMT has been suggested for the treatment of Bell's palsy demonstrating an immediate pain decrease as well as an anti-inflammatory effect.[19,20,22,23] However, there are only a few studies on Bell's palsy over 8 weeks by PBMT.[24,25] The aim of our study was to evaluate the effectiveness of PBMT in patients undergoing Bell's palsy over 8 weeks by subjective scale and electrophysiological testing.

Materials and Methods

Study design and setting

This nonrandomized controlled trial, a 30-month, single-center study, was conducted at the out-patient department of otorhinolaryngology in Beijing Tongren Hospital, Capital Medical University, Beijing, China. Given the nature of the interventions, randomization and blinding were not possible and a nonrandomized controlled trial was found to be most suitable. In phase 1 (January 1, 2020, to December 31, 2021), data were collected from patients in control group. In phase 2 (January 1, 2021, to December 31, 2022), data were collected from patients in PBMT group.

The Ethics Committee of the Beijing Tongren Hospital, Capital Medical University, approved the study (TREC2022-KY075). The study was registered at ClinicalTrials.gov (NCT05585333). This report follows the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) reporting guideline for nonrandomized controlled trials. The protocol is available in Supplementary Data.

Study population

Patients with Bell's Palsy with a duration of greater than 8 weeks were selected. All the patients were recruited by the department of otolaryngology in Beijing Tongren Hospital. Also, patients were eligible for House–Brackmann grading system (HB) greater than or equal to grade 3. They were adults older than 18 and younger than 60, and had not received medicine before 2 weeks of trial, such as prednisolone.

We exclusion HB grade 6, or greater than 90% denervation on electroneuronography (ENoG), or no voluntary electromyography (EMG) activity, or no latency of early (R1) and late (R2, R2′) components in blink reflex patients, because we met poor efficacy of PBMT according to a previous study. Exclusion criteria also included serious mental illness or social problems, and neurological disorders, in addition to systemic disease, such as severe diabetes, malignant tumors, and other serious consumptive diseases, planning for pregnancy, in pregnancy, or lactation. All participants provided written informed consent before the start of the study.

Interventions

Patients in the control group received no intervention but were free to pursue therapies if desired. Patients in the PBMT group received 72 sessions of PBMT (3 times per week). PBMT used a class IV Multiwave Locked System (MLS) laser (Mphi laser; ASA Srl, Vicenza, Italy) (Table 1).

In the PBMT group, we chose nine points, including mastoid, preauricular, temple, frontalis muscle, zygomatic muscle, buccinator muscle, masseter, orbicularis oris, and depressor anguli oris. All these points are near the superficial roots of facial nerve. Laser probe directly contacts with skin of the nine points on the affected side. The probe was fixed on each point for 1 min. In this study, the PBM used has a wavelength of 808 and 905 nm, 1.2 W power (808 nm is 1 W, 905 nm is 200 mW), continuous mode emission (808 nm) and pulsed mode emission (905 nm), 8.35 J/cm^2 dosimetry, 26.22 J for each point, administered 3 times per week, 72 times of total treatment.

Also, patients in the PBMT group wore safety glasses to prevent eye damage during the laser sessions. All treatments were performed in the outpatient clinic by the same deputy chief physician.

Outcome measure

Primary outcome comprised the House–Brackmann grading system (HB), Sunnybrook facial grading system (SB), and Facial Clinimetric Evaluation Scale (FaCE). Secondary outcome measures comprised electrophysiological testing, including ENoG, EMG, and blink reflex. All of the outcome measures were conducted on the 1st and 180th days after informed consent.

HB was used to evaluate the facial motor function.[26–28] The prognoses of grade 3 or higher were abnormal. All the HB grading was assessed by the same medical chief physician. SB grading is a 13-item questionnaire that used to evaluate the facial movement of patients.[29–31] FaCE is a 15-item self-reported questionnaire that used to assess facial impairment and disability after facial paralysis. It includes six independent domains: social function, facial movement, facial comfort, oral function, eye comfort, and lacrimal control.[32–34] All the operations of HB and SB grading and FaCE were by the same chief physician.

ENoG and EMG are now the most important facial electrophysiological examinations.[35] ENoG involves recording the compound muscle action potentials (CMAPs) and latencies of muscles, including orbicularis oculi, frontalis muscle, orbicularis oris, and ala nasi muscle.[36–40] A percentage of degenerated nerve fibers is calculated by the amplitude of the CMAPs, a side difference of 30% or bigger is considered pathologic.[35] EMG is an electrophysiologic

Table 1. Photobiomodulation Therapy Parameters

Device information	Manufacturer	ASA (S.r.l., Vicenza, Italy)	
	Model identifier	MLS laser, Mphi	
	Year produced	2020	
	No. of emitters	1	
	Emitter type	NIR laser with two synchronized laser diodes	
Irradiation parameters		Laser diode 1	Laser diode 2
	Center wavelength	905 nm	808 nm
	Operating mode	Pulsed wave	Continuous wave
	Power	200 mW	1000 mW
	Peak radiant power	75 W	1.0 W
	Frequency range	1–2000 Hz	
	Power level	50%	
	Target area diameter	ø 2 cm	
	Beam profile	Two laser beams work simultaneously and synchronously with coincident propagation axes	
	Application technique	Contact	
	Irradiance or power density	0.19 W/cm^2	
	No. of points irradiated	9 points	
	Duration of each treatment session	540 sec	
	Dose of each point	26.22 J	
	Dose in the form of energy density	8.35 J/cm^2	
	Cumulative dose of each treatment session	235.98 J	
	Frequency of treatment	3 times per weeks	
	Total treatment session	72 times	

MLS, Multiwave Locked System.

measure by recording motor unit action potentials (MUAPs) in the depressor anguli oris, frontalis muscle, and orbicularis oris.[41] The blink reflex test is to measure the facial nerve since the blink reflex delivers information on facial nerve function with normal trigeminal function.[42–44]

In blink reflex testing, two responses, R1 and R2, are analyzed. R1 is the fast ipsilateral response of the orbicularis oculi muscle with a latency of about 10–12 ms. The second bilateral response R2 has a latency of about 30–41 ms. The R1 latency higher than 12 ms or the R2 latency higher than 41 ms is considered pathologic. The R2 latency differences between both sides higher than 8 ms are considered pathologic.

Dantec Keypoint 4 (Medtronic Inc., Danmark) device was used for electrophysiological testing. All the operations were by the same examiner.

Statistical analyses

With an expected effective rate of 61% in the PBMT group and 15% in the control group with 90% power and a two-sided α of 0.05, the required sample size was 42 patients (21 in each group) using PASS 11.0 software (NCSS, Kaysville, UT). Considering a 20% dropout rate, 52 patients per group will be required.

Effective rate was based on our previous study according to a clinical practice guideline of Bell's palsy and a clinical practice guideline of facial nerve electrodiagnostics for patients with facial palsy. The HB grading of grade 3 or higher, or CAMPs with a side difference of 30% or bigger are considered abnormal.

All the analyses of patients with Bell's palsy over 8 weeks were preformed based on the full analysis set. Differences in patient characteristics between both groups were analyzed by means of chi-square tests (χ^2), Fisher's exact tests, Student *t*-tests, or nonparametric tests, as appropriate. Demographic data were analyzed by means of chi-square tests (χ^2) or Fisher's exact tests, Student *t*-tests or nonparametric tests based on different data types.

Continuous variables were reported as mean with standard deviation-associated confidence interval (95% CIs). The data of SB grading, FaCE, ENoG, and EMG were all analyzed by Student t-tests or nonparametric tests, as appropriate. Categorical variables were summarized with frequencies and percentages. Their distributions were assessed with chi-square tests or Fisher's exact tests. We compared the proportions of abnormal HB, ENoG, and blink reflex results in the PBMT groups and control group using risk differences (RDs) and relative risks (RRs) with associated 95% CIs.

All statistical computations were carried out with SAS version 9.4 (SAS Institute, Cary, NC). All reported *p* values were two-sided and were declared statistically significant when <0.05. All graphic representations were performed using GraphPad PRISM, version 8 (GraphPad Software, La Jolla, CA).

Results

Between January 2020 and December 2021, 88 patients were screened for eligibility, and 66 patients were included (control group, 34; PBMT group, 32). Due to COVID-19, 5 participants (control group, 2; PBMT group, 3) were unable to travel to the hospital. Finally, 54 were included in the analysis, with 27 in the control group and 27 in the PBMT group, as shown in the patient flowchart (Fig. 1). Patient- and treatment-related characteristics are presented in Table 2. In the PBMT group, two participants who were considered to have complete recovery from facial paralysis ended therapy after 2 months of treatment. The study comprised all 27 patients in the PBMT group.

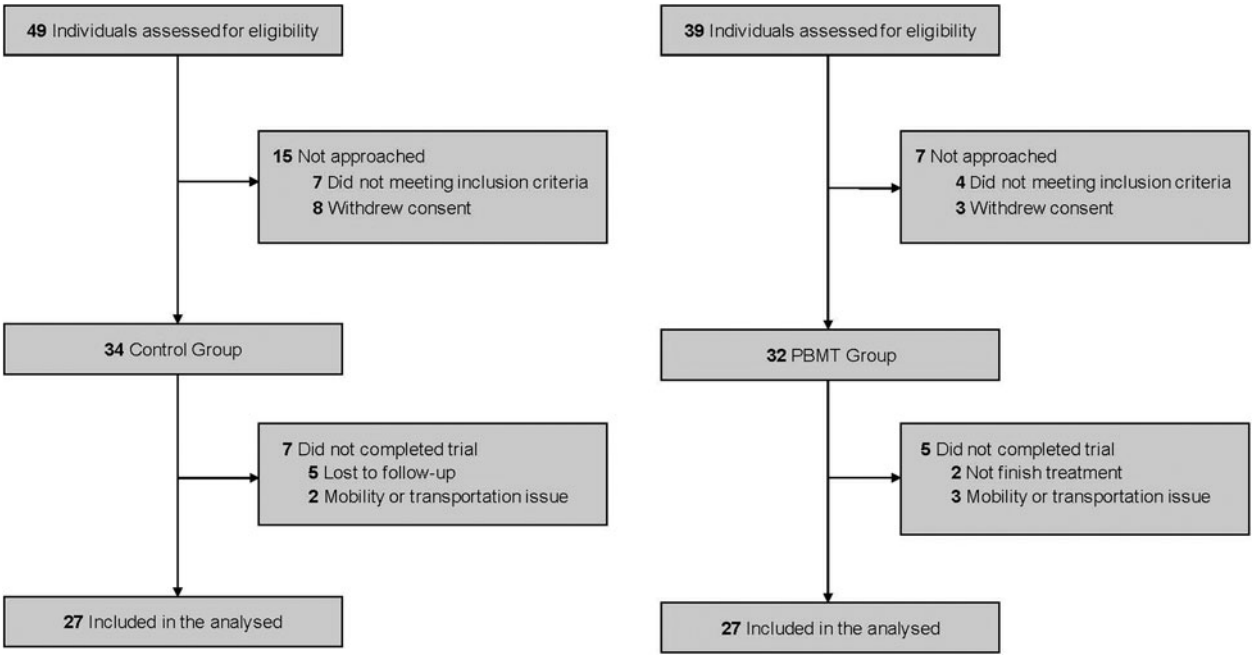

FIG. 1. Study flow diagram.

Primary outcome

Table 4 shows that 6 were abnormal HB results in PBMT group and 22 in control group. It was statistically different between the two groups (RD, –0.59, 95% CI, –0.81 to –0.38, RR, 0.27, 95% CI, 0.13–0.56, $p < 0.001$) after treatment. The numbers of abnormal HB in PBMT group were statistically significantly lower than the numbers in baseline (RD, 0.78, 95% CI, 0.62–0.93, RR, 4.50, 95% CI, 2.22–9.11, $p < 0.001$) (Fig. 2).

Compared with baseline, Table 3 shows that SB grading was 30.70 points higher (95% CI, 24.33–37.08; $p < 0.001$) at 12 weeks in PBMT group and 9.33 points higher in the control group (95% CI, 3.58–15.09; $p < 0.01$). Participants in PBMT group had statistically significant higher scores compared with those in the control group after treatment (19.78, 95% CI, 12.31–27.24; $p < 0.001$) (Fig. 3).

Compared with baseline, Table 3 shows that FaCE was 16.05 points higher (95% CI, 11.49–20.61; $p < 0.001$) at 12 weeks in PBMT group and 5.19 points higher in the control group (95% CI, 0.49–9.89; $p = 0.03$). Participants in PBMT group had statistically significant higher scores compared with those in the control group after treatment (10.92, 95% CI, 5.58–16.27; $p < 0.001$) (Fig. 3).

Table 2. Baseline Demographic Patient Characteristics

Characteristic	*PBMT group*	*Control group*
Age, mean (SD), years	40 (33–48)	42 (34–52)
Gender, No. (%)		
Female	12 (44.44)	15 (55.56)
Male	15 (55.56)	12 (44.44)
Affected side of facial paralysis, No. (%)		
Right	11 (40.74)	17 (62.96)
Left	16 (59.26)	10 (37.04)
Duration of facial paralysis, median (IQR), month	4 (4–5)	4 (3–5)

PBMT, photobiomodulation therapy.

Secondary outcomes

Compared with baseline, Table 3 shows the amplitude of CMAPs and latency by ENoG, and a statistically significant difference compared with those in the control group, orbicularis oculi (amplitude of CMAPs, 0.84, 95% CI, 0.62–1.05; $p < 0.001$; latency, –0.30, 95% CI, –0.58 to –0.02; $p = 0.04$), frontalis muscle (amplitude of CMAPs, 0.36, 95% CI, 0.22–0.45; $p < 0.001$; latency, –0.37, 95% CI, –0.71 to –0.03; $p = 0.03$), orbicularis oris (amplitude of CMAPs, 1.49, 95% CI, 1.41–1.57; $p < 0.001$; latency, –0.33, 95% CI, –0.50 to –0.17; $p < 0.001$), ala nasi muscle (amplitude of CMAPs, 0.23, 95% CI, 0.19–0.28; $p < 0.001$) after treatment, except latency of ala nasi muscle (–0.20, 95% CI, –0.41 to 0.02; $p = 0.07$) (Fig. 3).

Table 4 shows that all the pathologic numbers of ENoG in PBMT group are statistically significantly lower than the numbers in control group after treatment, orbicularis oculi (RD, –0.48, 95% CI, –0.68 to –0.28, RR, 0.50, 95% CI, 0.34–0.74, $p = 0.01$), frontalis muscle (RD, –0.51, 95% CI, –0.74 to –0.30, RR, 0.22, 95% CI, 0.09–0.57, $p = 0.01$), orbicularis oris (RD, –0.33, 95% CI, –0.54 to –0.12, RR, 0.22, 95% CI, 0.04–0.74, $p = 0.01$), and ala nasi muscle (RD, –0.44, 95% CI, –0.68 to –0.20, RR, 0.37, 95% CI, 0.19–0.74, $p = 0.01$) (Fig. 3).

All the amplitude of MUAPs and duration by EMG had statistically significant difference compared with those in the control group after treatment, frontalis muscle (amplitude of MUAPs, –34.22, 95% CI, –56.57 to –14.50; $p = 0.01$; duration, –1.13, 95% CI, –1.62 to –0.65; $p < 0.001$),

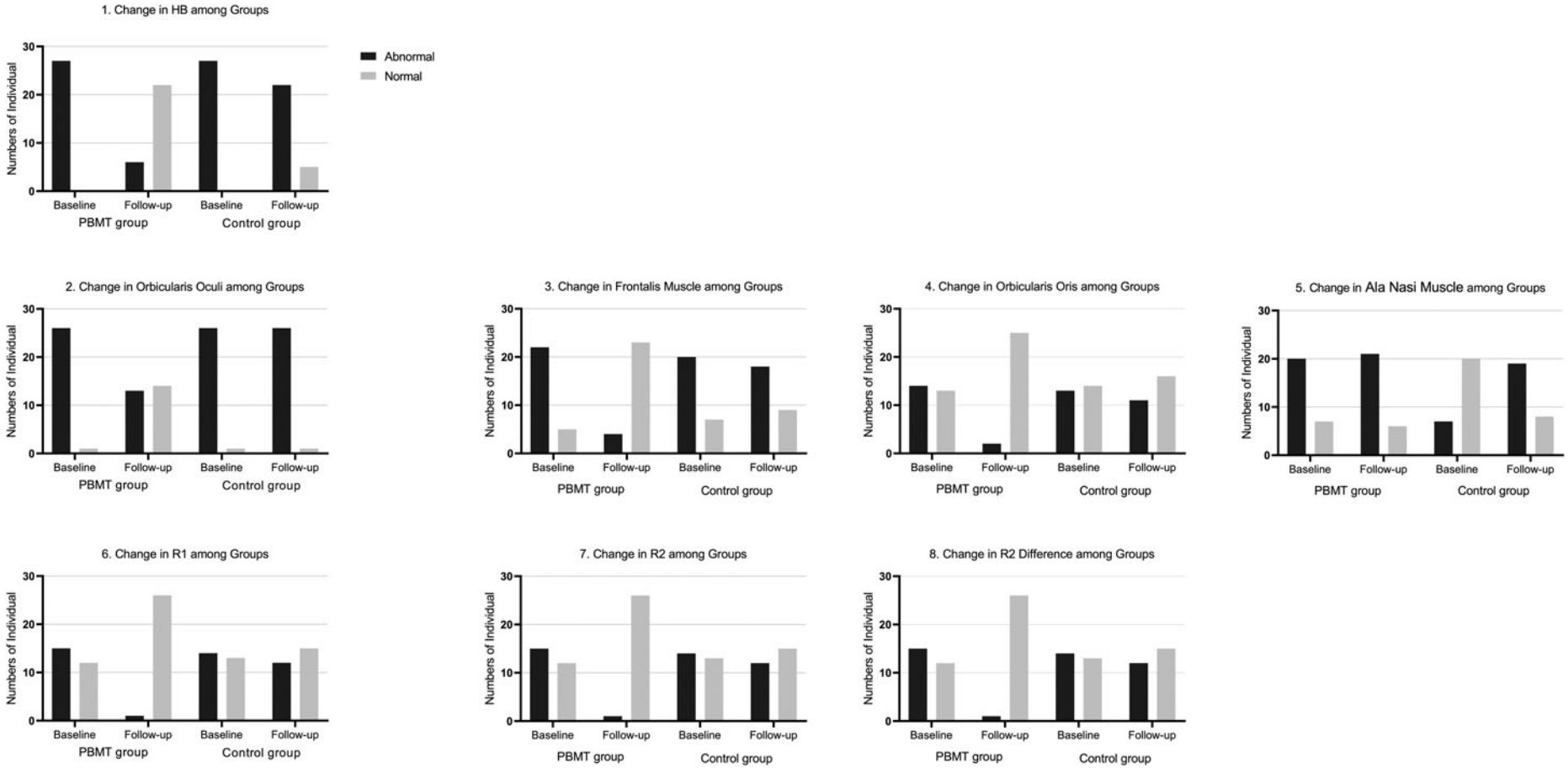

FIG. 2. Categorical outcome measures over time in the PBMT group and control groups. HB, House–Brackmann facial nerve grading system; ENoG, electroneuronography.

Table 3. Comparison of Continuous Variable Outcome Measure

	Baseline				*Follow-up*				*Change from baseline*			
									PBMT group		*Control group*	
	PBMT group, mean (SD) or median (IQR)	*Control, mean (SD) or median (IQR)*	*Estimated difference (95% CI)*	p[a]	*PBMT group, mean (SD) or median (IQR)*	*Control, mean (SD) or median (IQR)*	*Estimated difference (95% CI)*	p[a]	*Estimated difference (95% CI)*	p[a]	*Estimated difference (95% CI)*	p[a]
SB grading[b]	31.56 (8.75)[c]	33.15 (13.39)[c]	−1.59 (−7.77 to 4.58)	0.61	62.26 (15.07)[c]	42.48 (12.11)[c]	19.78 (12.31 to 27.24)	<0.001	30.70 (24.33 to 37.08)	<0.001	9.33 (3.58 to 15.09)	<0.01
FaCE												
Total scores[d]	50.12 (10.06)[c]	51.05 (9.08)[c]	−0.93 (−6.16 to 4.31)	0.72	66.17 (8.27)[c]	56.23 (10.56)[c]	10.92 (5.58 to 16.27)	<0.001	16.05 (11.49 to 20.61)	<0.001	5.19 (0.49 to 9.89)	0.03
Latency (ms) of ENoG[e]												
Orbicularis oculi	3.22 (0.44)[c]	3.34 (0.53)[c]	−0.12 (−0.38 to 0.15)	0.39	2.99 (0.53)[c]	3.28 (0.50)[c]	−0.30 (−0.58 to −0.02)	0.04	−0.23 (−0.46 to −0.01)	0.04	−0.05 (−0.37 to 0.27)	0.74
Frontalis muscle	3.12 (0.41)[c]	3.20 (0.40)[c]	−0.08 (−0.30 to 0.15)	0.49	2.68 (0.76)[c]	3.05 (0.42)[c]	−0.37 (−0.71 to −0.03)	0.03	−0.44 (−0.82 to −0.07)	0.023	−0.15 (−0.41 to 0.12)	0.26
Orbicularis oris	3.00 (0.34)[c]	2.97 (0.25)[c]	0.03 (−0.13 to 0.20)	0.69	2.64 (0.31)[c]	2.97 (0.30)[c]	−0.33 (−0.50 to -0.17)	<0.001	−0.36 (−0.57 to −0.16)	<0.01	0.00 (−0.13 to 0.13)	1
Musculus levator superioris alaeque nasi	3.23 (0.43)[c]	3.24 (0.54)[c]	−0.00 (−0.27 to 0.26)	0.98	2.86 (0.38)[c]	3.05 (0.39)[c]	−0.20 (−0.41 to 0.02)	0.07	−0.38 (−0.59 to −0.16)	<0.01	−0.18 (−0.43 to 0.06)	0.14
Amplitude of the MUAPs (mv)[e]												
Orbicularis oris	502.17 (46.08)[c]	495.62 (37.40)[c]	−6.55 (−29.47 to 16.37)	0.57	465.12 (50.07)[c]	495.09 (34.49)[c]	−29.97 (−53.45 to −6.49)	0.01	−30.50 (−58.56 to −2.45)	0.03	−7.08 (−28.16 to 14.01)	0.50
Depressor anguli oris	557.97 (503.19–631.05)[f]	555.75 (513.92–583.24)[f]	16.31 (−30.55 to 56.02)	0.49	519.53 (480.20–539.48)[f]	549.50 (509.73–590.87)[f]	−35.55 (−61.90 to −7.73)	0.02	−40.65 (−78.42 to −2.88)	0.04	3.96 (−21.71 to 29.62)	0.75
Frontalis muscle	402.29 (378.14–430.77)[f]	405.64 (375.59–426.40)[f]	−3.35 (−24.11 to 18.90)	0.80	366.97 (345.66–398.64)[f]	423.04 (379.66–431.17)[f]	−34.22 (−56.57 to −14.50)	0.001	−28.48 (−50.28 to −6.68)	0.01	1.10 (−19.04 to 21.24)	0.91
Duration (ms) of EMG[e]												
Orbicularis oris	8.03 (0.86)[c]	7.97 (1.05)[c]	0.06 (−0.46to 0.58)	0.82	6.42 (1.02)[c]	7.54 (0.97)[c]	−1.12 (−1.67 to −0.58)	<0.001	−1.61 (−2.17 to −1.06)	<0.001	−0.42 (−0.89 to 0.04)	0.07
Depressor anguli oris	8.46 (0.60)[c]	8.41 (0.94)[c]	0.05 (−0.38 to 0.48)	0.80	6.43 (0.83)[c]	8.07 (1.67)[c]	−1.64 (−2.36 to −0.92)	0.01	−2.03 (−2.43 to −1.64)	<0.001	−0.34 (−1.11 to 0.44)	0.38
Frontalis muscle	6.91 (0.58)[c]	6.86 (0.70)[c]	0.04 (−0.30 to 0.40)	0.73	5.42 (0.82)[c]	6.56 (0.95)[c]	−1.13 (−1.62 to −0.65)	<0.001	−1.48 (−1.86 to −1.10)	<0.001	−0.30 (−0.83 to 0.30)	0.25

[a]Statistical significance was calculated with *t* test or Wilcoxon rank-sum test, as appropriate. All tests were two-sided. $p < 0.05$ was considered significant.
[b]Facial paralysis symptoms were measured using SB grading (range, 0–100; lower scores are equivalent to greater severity of facial paralysis symptoms).
[c]Data are presented as mean (SD).
[d]Facial impairment and disability after facial paralysis were measured using FaCE (range, 0–100; lower scores are equivalent to greater severity of facial impairment and disability).
[e]Electrophysiological examinations were measured using electroneurography and electromyography. The testing of ENoG involves recording the CMAP of muscles, and EMG measures that facial nerve function by recording MUAPs.
[f]Data are presented as median (IQR).

CMAPs, compound muscle action potentials; EMG, electromyography; ENoG, electroneuronography; FaCE, Facial Clinimetric Evaluation Scale; IQR, interquartile range; MUAPs, motor unit action potentials; PBMT, photobiomodulation therapy; SB, Sunnybrook facial grading system; SD, standard deviation.

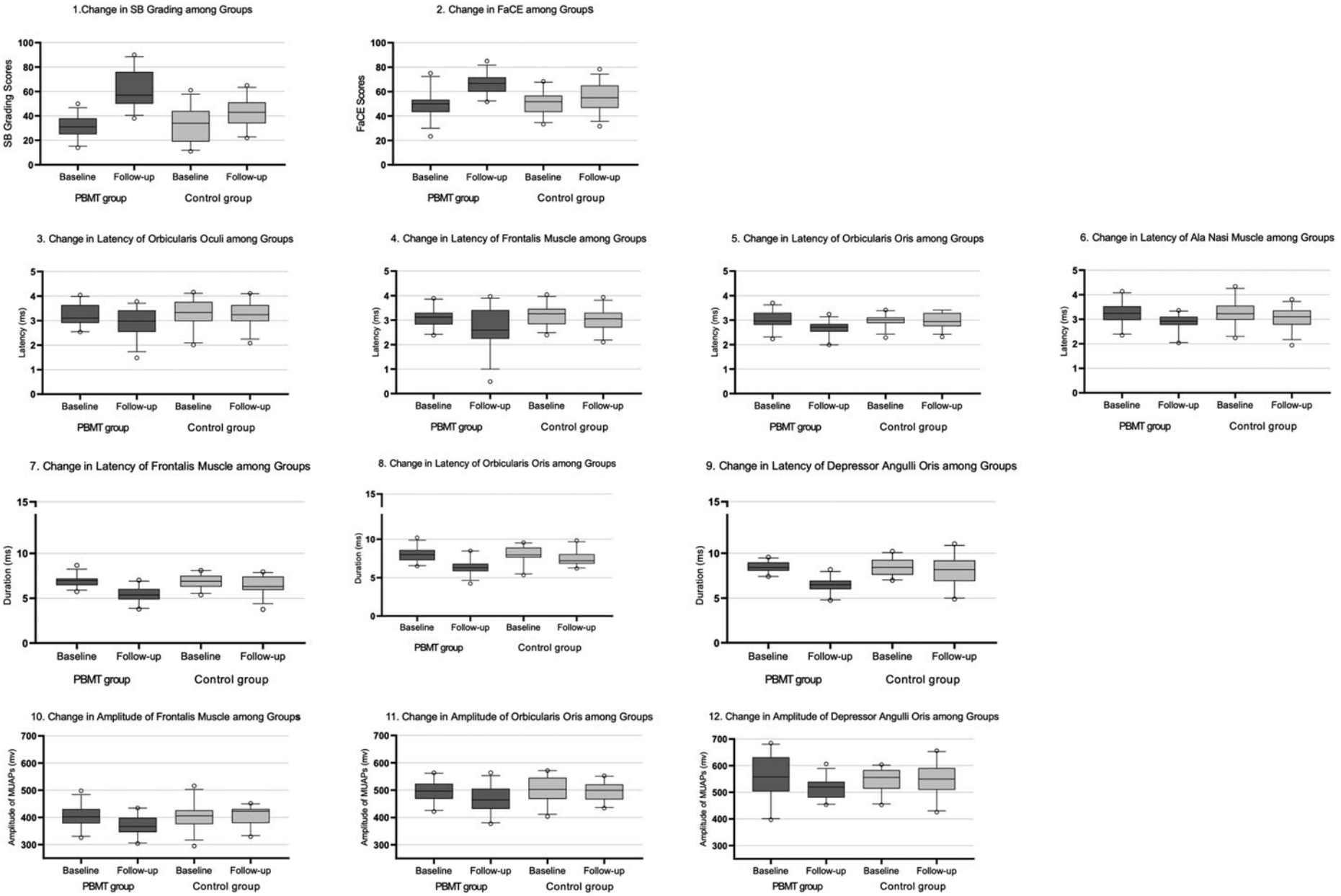

FIG. 3. Continuous outcome measures over time in the PBMT group and control groups. FaCE, Facial Clinimetric Evaluation Scale; MUAPs, motor unit action potentials; PBMT, photobiomodulation therapy; SB grading, Sunnybrook facial grading system.

Table 4. Comparison of Categorical Variable Outcome Measures

	Baseline					*Follow-up*					*Value of pairwise comparison*					
											PBMT group			*Control group*		
	PBMT No./ total No. (%)	*Control No./ total No. (%)*	*Risk difference, % (95% CI)*	*Relative risk, (95% CI)*	p[a]	*PBMT No./ total No. (%)*	*Control No./ total No. (%)*	*Risk difference, % (95% CI)*	*Relative risk, % (95% CI)*	p[a]	*Risk difference, % (95% CI)*	*Relative risk, % (95% CI)*	p[a]	*Risk difference, % (95% CI)*	*Relative risk, % (95% CI)*	p[a]
HB[b]	100 (27/27)	100 (27/27)	NA	NA	1	22.22 (6/27)	81.48 (22/27)	–0.59 (–0.81 to –0.38)	0.27 (0.13 to 0.56)	<0.001	0.78 (0.62 to 0.93)	4.50 (2.22 to 9.11)	<0.001	0.19 (0.04 to 0.33)	1.22 (1.03 to 1.47)	0.03
ENoG[c]																
Orbicularis oculi[c,d]	96.30 (26/27)	96.30 (26/27)	NA	NA	1	48.15 (13/27)	96.30 (26/27)	–0.48 (–0.68 to –0.28)	0.50 (0.34 to 0.74)	<0.001	0.48 (0.28 to 0.68)	2.00 (1.34 to 2.98)	<0.001	NA	NA	1
Frontalis muscle	22.22 (6/27)	74.07 (20/27)	0.07 (–0.15 to 0.30)	1.10 (0.83 to 1.47)	0.51	14.81 (4/27)	66.67 (18/27)	–0.51 (–0.74 to –0.30)	0.22 (0.09 to 0.57)	<0.001	0.67 (0.47 to 0.87)	5.50 (2.19 to 13.83)	<0.001	–0.13 (–0.37 to 0.11)	0.81 (0.54 to 1.21)	0.31
Orbicularis oris	51.85 (14/27)	48.15 (13/27)	0.04 (–0.23 to 0.30)	1.08 (0.63 to 1.84)	0.79	7.41 (2/27)	40.74 (11/27)	–0.33 (–0.54 to –0.12)	0.22 (0.04 to 0.74)	<0.01	0.44 (0.23 to 0.66)	7.00 (1.76 to 27.89)	0.001	0.07 (–0.19 to 0.33)	1.18 (0.65 to 2.15)	0.58
Musculus levator superioris alaeque nasi	74.07 (20/27)	77.78 (21/27)	–0.03 (–0.26 to 0.19)	0.95 (0.71 to 1.29)	0.75	25.93 (7/27)	70.37 (19/27)	–0.44 (–0.68 to –0.20)	0.37 (0.19 to 0.74)	0.001	0.48 (0.25 to 0.71)	2.86 (1.45 to 5.61)	<0.001	0.07 (–0.16 to 0.30)	1.10 (0.80 to 1.51)	0.53
Blink reflex[d]																
R1	55.56 (15/27)	51.85 (14/27)	0.03 (–0.23 to 0.30)	1.07 (0.65 to 1.76)	0.78	3.70 (1/27)	44.44 (12/27)	–0.41 (–0.60 to –0.21)	0.08 (0.01 to 0.60)	<0.01	0.51 (0.32 to 0.72)	15.00 (2.12 to 105.71)	<0.001	0.07 (–0.19 to 0.34)	1.17 (0.67 to 2.04)	0.59
R2	51.85 (14/27)	59.26 (16/27)	–0.07 (–0.34 to 0.19)	0.88 (0.54 to 1.41)	0.58	0 (0/27)	55.56 (15/27)	0.56 (0.39 to 0.74)		<0.001	0.52 (0.33 to 0.71)		<0.001	0.03 (–0.23 to 0.30)	1.07 (0.67 to 1.69)	0.78
R2 latency differences	51.85 (14/27)	48.15 (13/27)	0.04 (–0.23 to 0.30)	1.08 (0.63 to 1.84)	0.79	7.41 (2/27)	40.74 (11/27)	–0.33 (–0.54 to –0.12)	0.18 (0.04 to 0.74)	0.01	0.44 (0.23 to 0.66)	7.00 (1.76 to 27.89)	0.001	0.07 (–0.19 to 0.34)	1.18 (0.64 to 2.15)	0.58

[a]Statistical significance was calculated with chi-square tests or Fisher's exact tests, as appropriate. All tests were two-sided. $p < 0.05$ was considered significant.

[b]The HB is based on a 6-grade score that offers a gross evaluation of facial motor function. The prognoses of patients with grade 3 or higher were considered poor. All the HB grading was assessed by the same medical chief physician.

[c]The testing of ENoG involves recording the CMAPs of the mimetic muscles, including orbicularis oculi, frontalis muscle, orbicularis oris, and musculus levator superioris alaeque nasi, the amplitude of the CMAPs obtained was measured, and the affected side and the normal side were compared. The percentage of degenerated nerve fibers is calculated. A side difference of 30% or bigger is considered pathologic in our study.

[d]In blink reflex testing, two responses, R1 and R2, are analyzed. R1 is the fast ipsilateral response of the orbicularis oculi muscle with a latency of about 10–12 ms. The second bilateral response R2 has a latency of about 30–41 ms. The R1 latency higher than 12 ms or the R2 latency higher than 41 ms is considered pathologic. The R2 latency differences between both sides higher than 8 ms are considered pathologic.

HB, House–Brackmann grading system; NA, not available.

orbicularis oris (amplitude of MUAPs, −29.97, 95% CI, −53.45 to −6.49; $p = 0.02$; duration, −1.12, 95% CI, −1.67 to −0.58; $p = 0.01$), and depressor anguli oris (amplitude of MUAPs, −35.55, 95% CI, −61.90 to −7.73; $p = 0.001$; duration, −1.64, 95% CI, −2.36 to −0.92; $p < 0.001$) (Fig. 2).

Table 4 shows that all the items of blink reflex in PBMT group were statistically significantly lower than the numbers in control group after treatment, R1 (RD, −0.41, 95% CI, −0.60 to −0.21, RR, 0.08, 95% CI, 0.01–0.60, $p < 0.01$), R2 (RD, −0.56, 95% CI, −0.74 to −0.39, $p < 0.001$), and R2 latency differences (RD, −0.33, 95% CI, −0.54 to −0.12, RR, 0.18, 95% CI, 0.04–0.74, $p = 0.01$) (Fig. 2).

Discussion

This nonrandomized controlled trial, single-center study, to our knowledge, is the first study to evaluate the efficacy of PBMT in the treatment of facial paralysis symptoms lasting beyond 8 weeks. The class IV MLS laser device is commercially available and built in compliance with EC/EU and FDA, and certificated in the National Medical Products Administration of China in December 2020. Before January 2021, we could not use this laser device for the participants in control group. Currently, there is no established treatment for Bell's palsy over 8 weeks, with natural recovery being the only option. The implementation of class IV MLS laser therapy effectively regulates the laser's peak power, avoiding potential thermal damage such as scalding.

Based on our prior clinical experience, it was challenging to achieve clinical efficacy in patients with complete facial paralysis or those exhibiting a prolonged course of facial paralysis lasting over 1 year. Therefore, we recruited patients who did not have HB VI, greater than 90% denervation on ENoG, no voluntary EMG activity, or no latency in blink reflex. Our study has not used a contemporaneous control group, because the placebo PBMT may have been undertreated and led to lifetime dysfunction.

Some studies believed that electrical stimulation or facial exercise is the most used treatment in facial paralysis, however, many patients struggle to adhere to this treatment.[1,45–47] Our previous clinical experience suggests that beyond 6 months, PBM treatment has no statistically significant difference than a 6-month treatment based on electrophysiological tests. Therefore, the time of treatment lasted 6 months in our study. We found that the recurrence symptoms of facial paralysis had not occurred after 6 months of PBMT, and therefore, we did not collect the follow-up data.

The evaluation of facial nerve damage and prediction of the prognosis are important to patients with facial paralysis. We used objective and subjective facial nerve damage measures to provide a comprehensive assessment. After 6 months of therapy, the results of SB grading and FaCE indicated that PBMT can improve the symptoms and quality of life. We found that six patients were still considered to be HB grading III, indicating that the prognosis of Bell's palsy over 8 weeks is poor and treating is difficulty. Starting PBMT as early as possible may increase the probability of complete recovery.

Considering that most of the studies did not used objective measures as a reliable and accurate tool for assessment,[48] our study used electrophysiological evaluation to assess the symptoms of facial paralysis.

The amplitude and latency of CMAPs reflect the degree of facial nerve degeneration on the affected side. In patients with facial palsy, the amplitude of CMAPs decreased and the latency increased. After treatment, the amplitude of CMAPs of orbicularis oculi, frontalis muscle, orbicularis oris, and ala nasi muscle increased. Also, the latency of orbicularis oculi, frontalis muscle, and orbicularis oris decreased after treatment. The latency of ala nasi muscle was not statistically significant after treatment compared with the control group, however, it tended to decrease after treatment in PBMT group. EMG analyzes the facial MUAPs, which are the spikes in electrical activity generated when a motor unit fires. A motor unit consists of a motor neuron and the corresponding muscle fibers. The duration of MUAPs is increased in patients with axonotmesis or neurotmesis.

In our study, the amplitude of and duration of MUAPs decreased after treatment. Blink reflex occurs via the trigeminal nerve, the trigeminal nucleus, and then to the facial nerve nucleus and facial nerve. After treatment, the numbers of pathologic R1, R2, and R2 differences between both sides are decreased. Combined with subjective rating scales and electrophysiological examinations, we suggest that PBMT can improve the facial nerve function and promote rehabilitation.

The therapeutic mechanism of PBMT is proposed to be that photons of laser accelerate mitochondrial respiration, then create adenosine triphosphate and increase additional transportation of intracellular Ca^{2+}, and induce the pathways of reactive oxygen species, cyclic adenosine monophosphate (cAMP), and nitric oxide.[49–52] These effects lead to stimulation of various transcription factors related to migration and cell proliferation, promoting tissue repair and regeneration.[53]

Limitation

Some limitations in our study should be noted. For example, the number of participants was small, only 27 participants enrolled in each group. Further investigations will expand sample sizes, and multi-center trials are necessary to confirm these positive results in a larger patient population with a broader range and at different clinical centers. This will increase the general applicability of PBMT in the treatment of facial paralysis duration longer than 8 weeks.

In addition, we did not include iatrogenic facial paralysis, trauma, or bilateral facial paralysis. In the future, we will recruit facial paralysis with multi-factorial etiology.

Conclusions

The findings of this nonrandomized controlled trial, single-center study suggest that PBMT relieved symptoms and improved the quality of life for patients with Bell's palsy with duration greater than 8 weeks. PBMT by class IV MLS laser treatment can be considered a therapy in treatment of Bell's palsy with duration greater than 8 weeks.

Authors' Contributions

Concept and design: D.W. Administrative, technical, or material support: D.W., Y.-L.Z., and R.-J.D. Acquisition, analysis, or interpretation of data: R.-K.Q. and Y.-Q.W. Data collection: J.-Y.S. and Y.-Q.W. Statistical analysis:

K.C. Drafting of the article: D.W. Guidance and intervention: D.W. Critical revision of the article for important intellectual content: Y.W. Administrative, technical, or material support: Y.-L.Z. and R.-J.D.

State of Human Rights

The intervention conformed to the ethical criteria.

Author Disclosure Statement

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Supplementary Material

Supplementary Data

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