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Original Article

Managing Postmastectomy Lymphedema with Low-Level Laser Therapy

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Abstract

Objective: We aimed to investigate the effects of low-level laser therapy (LLLT) in managing postmastectomy lymphedema. ***Background Data:*** Postmastectomy lymphedema (PML) is a common complication of breast cancer treatment that causes various symptoms, functional impairment, or even psychosocial morbidity. A prospective, single-blinded, controlled clinical trial was conducted to examine the effectiveness of LLLT on managing PML. ***Methods:*** Twenty-one women suffering from unilateral PML were randomly allocated to receive either 12 sessions of LLLT in 4 wk (the laser group) or no laser irradiation (the control group). Volumetry and tonometry were used to monitor arm volume and tissue resistance; the Disabilities of Arm, Shoulder, and Hand (DASH) questionnaire was used for measuring subjective symptoms. Outcome measures were assessed before and after the treatment period and at the 4 wk follow-up. ***Results:*** Reduction in arm volume and increase in tissue softening was found in the laser group only. At the follow-up session, significant between-group differences (all $p < 0.05$) were found in arm volume and tissue resistance at the anterior torso and forearm region. The laser group had a 16% reduction in the arm volume at the end of the treatment period, that dropped to 28% in the follow-up. Moreover, the laser group demonstrated a cumulative increase from 15% to 33% in the tonometry readings over the forearm and anterior torso. The DASH score of the laser group showed progressive improvement over time. ***Conclusion:*** LLLT was effective in the management of PML, and the effects were maintained to the 4 wk follow-up.

Introduction

With the advances of medical technology, more women are surviving breast cancer treatment. Among the two million breast cancer survivors in the United States, approximately 15–20% develop postmastectomy lymphedema (PML) following breast cancer treatment.[1] Tumor resection and radiotherapy may cause insults in the axillary lymphatic system that develop into PML. PML is a chronic edema due to an abnormal accumulation of proteins and interstitial fluid and an increase in capillary filtration. This distressing condition can lead to significant psychosocial problems and poor quality of life.[2–4] Cellulitis, lymphangitis, compartment syndrome, and lymphangiosarcoma are common complications related to PML.[5]

Traditional treatments for PML include massage, manual lymphatic therapy, compression bandaging or garment, extended limb elevation, and intermittent compression devices. These treatments are usually expensive, time consuming, and labor intensive.[6] In the last decade, low-level laser therapy (LLLT) has been suggested to be an effective treatment modality for conditions such as scar formation and disease of immune system, as well as PML management.[7–9]

LLLT has been reported to improve surgical scars by preserving normal tissue architecture[10] and stimulating the proliferation of cultured fibroblasts.[11,12] These effects likely aid management of surgical scars associated with PML and treatment of the brawny lymphedematus limbs.[13] LLLT was speculated to promote lymphangiogenesis[14] and stimulate lymphatic motoricity,[15] which may help remove stagnant tissue fluid and fibrous tissue. LLLT was also found to increase both phagocytic and chemotactic activity of human leukocytes *in vitro*[16] without causing tumor cells to reproduce faster.[17] LLLT may have a role in immunobiological therapy for diseases of the immune system and may activate and boost normal reaction of the immune system components.[17] This possible advantage of LLLT may help reduce the risk of infection.

Although two preliminary studies have shown that LLLT may be an effective treatment in managing PML, the method of delivering LLLT and the dosage used in these studies differed. Moreover, no study has examined if any relief of the

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PML symptoms would lead to an improvement of upper limb function. The present study administered LLLT to the axillary region alone because the lymph nodes at the axillary region are principally responsible for draining the lymphatic system for the upper limb. The insult from the breast cancer operations, radiotherapy and/or chemotherapy is thought to be responsible for the blockage of lymphatic drainage at the axillary region causing PML. Therefore, the application of LLLT to the axillary region can assist in resolving PML by reducing fibrosis caused by breast cancer–related intervention, stimulating the generation of surviving lymphatic drainage pathways, and activating the localized immune response.[13]

A multifrequency scanning laser unit was used in the present study because it can penetrate to both cutaneous and subcutaneous tissues without increasing the tissue temperature. A dose range of 2 to 4 J/cm^2 was used in previous studies, which showed positive effects of LLLT in managing PML. Therefore, the present study aimed to investigate the treatment effectiveness of a scanning LLLT applied to the axillary region as compared to a control group that received no treatment. Outcome measures included reduction in arm volume, tissue resistance, and upper limb disabilities.

Materials and Methods

Subjects

Twenty-one Chinese women were recruited from a local outpatient clinic. They all completed the study and there were no drop-outs. The inclusion criteria were women 18 y or older who had undergone unilateral standard or modified radical mastectomy with subsequent radiotherapy or chemotherapy. All subjects had clinically manifest postmastectomy lymphedema (more than 200 mL difference between arms). Subjects were excluded if they had current metastasis, history of severe trauma or disruptive surgery to the arm, or kidney, heart, or lung disorders, or if they had received medications known to alter body fluid. Subjects having primary lymphedema in the lower limb, restricted shoulder range of motion that prevented elevation or abduction of the affected arm for measuring purposes, or significant changes in treatment regime or the occurrence of cellulitis to the arm in the past 3 months were also excluded.

Treatment procedures

This study was a prospective, single-blinded, controlled clinical trial. The patients were blinded, but the assessor was not. A local university and hospital granted ethical approval of the study, and written consent was obtained from each subject. All subjects attended a 30 min lymphedema education session prior to the study. The session provided information on general skin care of lymphedema, standardized procedures of manual lymphatic drainage, and gentle upper limb mobilization exercises. Demographic data including age, weight at start of trial, dominance of arm, type of surgery received, and previous chemotherapy or radiotherapy received; time since onset of PML and arm volume change were also recorded at the baseline. Subjects were randomly assigned into a laser group ($n = 11$) and control group ($n = 10$) with the Bebbington method. Subjects were blinded to the group allocation. Subjects in the control group received no treatment. They were asked to come back after 4 and 8 wk for reassessment. No concurrent treatment was allowed during the study. Due to ethical reason, the control group was given appropriate intervention after the 8 wk study period. A laser unit (Comby 3 Terza Serie, Model D; ASA S.r.l., Vicenza, Italy) with a scanning head was used. The unit comprises three infrared laser head sources with one emitting at a wavelength of 808 nm and two emitting at a wavelength of 905 nm. The average output of the head source at 905 nm was 24 mW, each with pulsed emission at a frequency varying from 1 to 10,000 Hz. The maximum power of the head source at 808 nm was 500 mW with continuous and emission pulses at a frequency varying from 1 to 1500 Hz. A dose of 2 J/cm^2 was chosen, because it lies within the therapeutic window of laser dose stated by the Arndt–Schultz Law.[7,8]

Subjects in the laser group received a cycle of LLLT three times a week for 4 wk. All subjects were placed in supine positions and LLLT was applied perpendicular to the axillary region of the affected side. The plane of the emission window of the laser head source was parallel to the treatment area. The distance between the plane of laser head and the treatment area was 50 cm. The aiming beam helped to locate the treatment region and to ensure the whole axillary region was covered (estimated area was 144 cm^2). The combined emission mode was used with a dose of 2 J/cm^2 sweeping an area of 144 cm^2; thus the treatment time was about 20 min, as the scanning laser automatically calculated. The pulse frequency of the two head sources was set at the maximum values of 10 kHz and 1500 Hz, respectively. The protocol used for each subject was saved in the laser unit and retrieved in subsequent treatment sessions.

Outcome measures

All outcome measures were assessed at the baseline before the administration of LLLT, at week 4 after the final session of LLLT treatment, then again at the 4 wk follow-up. Arm volume was determined by using a tank volumeter (Sammons-Preston, Model A8612, 7 inches×8 inches×30 inches) with standardized procedures. Volumetry has been shown to be reproducible[18–22] and only a single recording is needed for a valid measurement.[23] A change in arm volume for people with PML acts as a quantitative measurement of their response to the intervention: the arm volume difference between the affected and unaffected arm prior to the treatment minus the arm volume difference between the affected and unaffected arm after treatment.

A mechanical tonometer (BME; Flinder Medical Center, Adelaide, South Australia, Australia) was used to measure tissue resistance to pressure. Tonometry indicates the compliance of the dermis and extent of fibrotic induration in a limb.[24] It has been shown to be a simple, noninvasive, and reliable method to assess tissue hardness in upper extremity lymph edema.[25,26] The softer the tissue, the greater the indentation of the plunger, resulting in a higher reading.[8] Tonometry readings on the affected arm were compared with the readings from the corresponding sites on the unaffected arm. A decrease in the difference of the tonometry readings indicates a reduction in the "hardness" of the tissue. Tonometry of the affected and unaffected arm was measured at four sites: 1) flexor surface of forearm (5 cm proximal to wrist

Table 1. Demographic and Clinical Profiles of Subjects in the Laser and Control Group

	Laser (n = *11*)	*Control* (n = *10*)	p *value*
Age (y)	50.9 ± 8.6	51.3 ± 8.9	0.919
Weight at baseline (kg)	61.6 ± 86.2	62.2 ± 11.9	0.886
Affected arm (%)			
Dominant	63.6	70.0	0.757
Nondominant	36.4	30.0	
Type of surgery (%)			
Simple mastectomy with axillary clearance	27.3	20.0	0.696
Modified radical mastectomy with axillary clearance	72.7	80.0	
Received radiotherapy (%)	90.9	100	0.329
Received chemotherapy (%)	54.6	60	0.801
Onset of postmastectomy lymphedema (months)	43.3 ± 1.0	35.6 ± 9.1	0.082
Arm volume of the affected arm at baseline (mL)	2051.8 ± 559.9	2086.6 ± 535.7	0.886
Arm volume change at baseline (mL)[a]	448.2 ± 145.6	426.0 ± 166.7	0.748

Data are expressed as mean ± standard deviation.
[a]Affected arm volume minus unaffected arm volume.

crease); 2) flexor surface of forearm (5 cm distal to the antecubital fossa); 3) flexor surface of upper arm (5 cm proximal to the antecubital fossa); and 4) anterior torso.

The Chinese version of the Disability of Arm, Shoulder, and Hand (DASH) questionnaire was administered to evaluate the degree of difficulty and severity of pain in performing various activities.[27] The main section of the DASH questionnaire consists of 30 items that evaluate symptoms and physical function. The response option for each item is based on a five-point Likert scale with 1 indicating minimally affected or no effect and 5 indicating maximum difficulty or inability to function. Scoring is calculated by summing up the circled responses, subtracting 30 and then dividing by 1.2 to get a DASH function or symptom score out of 100. A higher score refers to more severe disability. The Chinese version of the DASH questionnaire was shown to be valid, reliable, and acceptably equivalent to the original version.[27] It was proven to produce valid and responsive results across the whole extremity with any upper extremity disorders.[27,28]

Statistical analysis

The Statistical Package for the Social Sciences (SPSS Version 16) was used for data analysis, and it was performed by an independent investigator. The interaction and main effects between the laser group and control group in the three outcome measures were analyzed by general linear model repeated measures analysis of variance (ANOVA). The level of significance (α) was set at 0.05 and Bonferroni correction was used to adjust the inflation of α due to multiple comparisons.

Results

Demographic and clinical profiles

The demographic and clinical profiles of subjects are shown in Table 1. Both the laser and control groups were matched by age and weight at the beginning of the study. The mean of onset of lymphedema in both groups was 39.6 ± 10.1 months, with a range from 22 to 60 months. Over 90% of the subjects received radiotherapy after mastectomy, and about 60% of all subjects received chemotherapy. The baseline measurements in both groups showed no significant difference (all $p > 0.05$).

Cumulative effects on arm volume

In the laser group, the change in arm volume decreased significantly, from 448.2 ± 145.6 mL to 320.9 ± 102.9 mL at 4-wk follow-up ($p = 0.00$). In contrast, the control group showed a significant increase, from 426.0 ± 166.7 mL at baseline, to 447.0 ± 161.7 mL ($p = 0.00$) at the 4 wk follow-up (Table 2). By the follow-up session, the laser group had a 28% cumulative reduction in the arm volume in contrast to a 6% increase in the control group. The between-group difference reached significance level ($p = 0.044$) (Fig. 1). However, due to multiple comparisons, the between-group difference fell short of significance after being adjusted by Bonferroni correction (0.05/3 = 0.017).

Cumulative effects on tissue resistance

Over time, the laser group demonstrated a significant increase in tonometry readings at sites 1, 2, and 4. The mean tonometry readings increased from baseline to follow-up, from 2.61 ± 0.66 to 3.41 ± 0.77 ($p = 0.000$) at site 1; 4.53 ± 0.91

Table 2. The Arm Volume Change over Time

	Laser	*Control*	p *value (between-group)*
Baseline	448.2 ± 145.6 (100.0 ± 0.0%)	426.0 ± 166.7 (100.0 ± 0.0%)	0.748
Week 4	373.6 ± 128.4 (84.2 ± 8.5%)	432.1 ± 164.4 (101.5 ± 2.4%)	0.365
Follow-up	320.9 ± 102.9 (71.9 ± 6.3%)	447.0 ± 161.7 (106.0 ± 4.3%)	0.044
p value (within-group)	0.000	0.000	

Raw data are expressed as mean (mL) ± standard deviation, and normalized data are presented in parentheses.

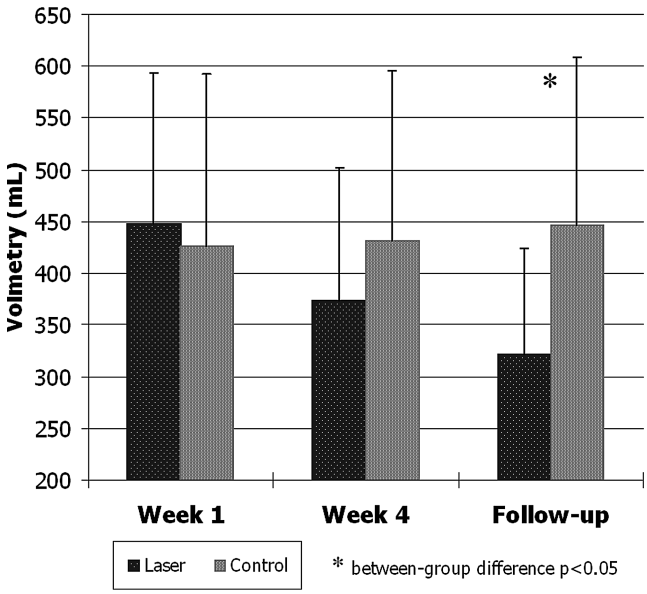

FIG. 1. The arm volume change over time.

to 5.17 ± 0.99 ($p = 0.002$) at site 2; and 3.60 ± 0.98 to 4.55 ± 0.61 ($p = 0.000$) at site 4, respectively (Table 3). This implies a "softening" of the tissue. The control group showed only negligible changes at all sites over time. Upon the follow-up session, there was a 33.2% cumulative increase in tonometry reading at site 1 and a 15.2% cumulative increase at site 2 and 4, with significant between-group difference found at sites 1 and 4 even after adjustment by Bonferroni correction ($p < 0.017$).

Cumulative effects on upper limb disabilities and symptoms

The mean DASH score showed a decreasing trend in the laser group, in contrast to a slight increasing trend in the control group over time. In the laser group, the mean DASH scores decreased significantly from 36.9 ± 25.8 at the baseline to 24.9 ± 18.9 at the follow-up session ($p = 0.040$). The control group showed no significance difference over time ($p = 0.338$) (Table 4). Upon the 4 wk follow-up, the laser group demonstrated a 37% cumulative reduction in DASH scores, compared to a 7% cumulative increase in DASH scores for the control group. Although the laser group tended to show a greater reduction, the between-group differences in the mean DASH scores were not statistically significant.

Discussion

The present study showed that LLLT seems to improve the physical parameters as well as the subjective pain and disability level in various activities of daily living in patients with PML. The observed therapeutic effects could be maintained for at least up to the 4 wk follow-up.

By the end of treatment course (i.e., week 4), the laser group showed a 16% cumulative reduction in arm volume; the effects even showed further improvement after cessation of treatment. There was a 28% cumulative reduction in arm volume by the 4 wk follow-up, and the change reached significant levels over time. This result was consistent with previous studies, which showed a progressive reduction of average arm volume after cessation of LLLT.[7,8,9,13] In contrast, the control group demonstrated a 6% cumulative increase in the arm volume over time. This suggests that

Table 3. The Mean Tonometry Readings at Sites 1, 2, 3, and 4 over Time

	Laser	*Control*	p *value (between-group)*
Site 1			
Week 1	2.61 ± 0.66 ($100.0 \pm 0.0\%$)	2.51 ± 0.43 ($100.0 \pm 0.0\%$)	0.693
Week 4	3.00 ± 0.67[a] ($116.8 \pm 18.8\%$)	2.51 ± 0.43 ($100.0 \pm 4.3\%$)	0.064
Follow-up	3.41 ± 0.77[b] ($133.2 \pm 26.0\%$)	2.53 ± 0.43 ($101.0 \pm 3.8\%$)	0.004
Site 2			
Week 1	4.53 ± 0.91 ($100.0 \pm 0.0\%$)	4.2 ± 0.77 ($100.0 \pm 0.0\%$)	0.379
Week 4	4.96 ± 1.08 ($109.1 \pm 13.8\%$)	4.19 ± 0.81 ($99.6 \pm 3.0\%$)	0.081
Follow-up	5.17 ± 0.99[b] ($115.2 \pm 16.5\%$)	4.21 ± 0.84 ($100.0 \pm 3.7\%$)	0.027
Site 3			
Week 1	5.54 ± 1.13 ($100.0 \pm 0.0\%$)	5.56 ± 0.99 ($100.0 \pm 0.0\%$)	0.961
Week 4	5.37 ± 1.25 ($97.5 \pm 16.6\%$)	5.58 ± 0.99 ($100.4 \pm 3.0\%$)	0.674
Follow-up	5.84 ± 0.95 ($106.7 \pm 12.4\%$)	5.52 ± 0.96 ($99.5 \pm 3.3\%$)	0.452
Site 4			
Week 1	3.60 ± 0.98 ($100.0 \pm 0.0\%$)	3.18 ± 1.21 ($100.0 \pm 0.0\%$)	0.388
Week 4	4.23 ± 0.75[a] ($109.8 \pm 1.4\%$)	3.15 ± 1.23 ($99.6 \pm 3.0\%$)	0.023
Follow-up	4.55 ± 0.61[b] ($115.2 \pm 1.7\%$)	3.14 ± 1.22 ($100.0 \pm 3.7\%$)	0.003

Raw data are expressed as mean (mm) ± standard deviation, and normalized data are presented within the parentheses.
[a]Significant change between week 1 and week 4 within the groups ($p < 0.01$).
[b]Significant change between week 1 and follow-up within the groups ($p < 0.01$).

Table 4. The Mean Disabilities Of Arm, Shoulder, and Hand Scores over Time

	Laser	*Control*	p *value (between-group)*
Week 1	36.9 ± 25.8 ($100.0 \pm 0.0\%$)	30.5 ± 14.8 ($100.0 \pm 0.0\%$)	0.501
Week 4	28.2 ± 22.1 ($70.9 \pm 28.0\%$)	30.9 ± 15.8 ($101.4 \pm 14.0\%$)	0.750
Follow-up	24.9 ± 18.9 ($63.3 \pm 22.2\%$)	32.1 ± 14.5 ($107.0 \pm 12.9\%$)	0.345
p value (within-group)	0.040	0.338	

Raw data are expressed as mean ± standard deviation, and normalized data are presented within the parentheses.

untreated lymphedema can significantly worsen over time and result in an increase in limb volume and/or tissue hardening.[29,30] Our findings of arm volume reduction were corroborated by the improvements in tissue "hardness." The tonometry readings at forearm and anterior torso demonstrated an increasing trend after treatment and upon the follow-up session that suggested a softening of the tissue over the affected arm. Although the change in tonometry readings at the upper arm was not statistically significant, it presented a trend of gradual improvement. The slight hardening of the upper arm after treatment might be due to the ongoing reduction of arm volume and circumference. The underlying deep fascia would then become closer to the skin and produce a potential artifact in the tonometry readings at the upper arm, as suggested by Piller and Thelander.[8]

In the present study, the DASH score was adopted to record the self-perceived upper limb disabilities and symptoms. The laser group showed improvement over time but the between-group difference did not reach a significant level. The DASH questionnaire was proven to be valid, reliable, and responsive in assessing upper limb disorders[28]; however, it is primarily used on musculoskeletal conditions with a predominant symptom of pain. To a certain extent, it may not be a specific tool to monitor the dynamic symptoms associated with PML, including limb heaviness, tension, sensory deficit, and elevated skin temperature. Therefore, caution should be taken when analyzing the results of the DASH questionnaire as a subjective outcome measure for PML. A more reliable, valid, and disease-specific tool should be developed to evaluate the disability and symptoms associated with PML.

Indeed, our findings showed that the LLLT group produced an improvement in arm volume, tonometry, and DASH scores. These improvements were maintained or continued at least up to the 4 wk follow-up, which indicated that the positive effect of LLLT is rather long-lasting. There are several possible mechanisms of LLLT in managing PML. It is thought that LLLT can stimulate new lymphatic pathways and restore lymphatic drainage through the axillary region.[13] LLLT may also produce systemic effects on lymphedematous limb; a localized application of laser therapy to the axillary region produced therapeutic effects in the whole affected limb.[13] The findings on the arm volume reduction and tissue softening after LLLT also provide evidence to support the postulated mechanisms of LLLT on reducing tissue fluid accumulation through changes in blood flow, either by producing a direct effect on blood vessels or by neural regulation of vessels in the limb.[13] As observed in the present study, the gradual tissue softening after LLLT may also suggest the improvement in blood flow and restoration of the drainage system through remodeling of scar tissue and discourage the formation of new scar tissue in the axillary region.

It has been suggested that LLLT interacts with cytochromes of the mitochondrial electron transport chain,[32] and/or may produce local gradients in energy because of laser speckle, resulting in local gradients in cellular heating.[33] LLLT has also been reported to stimulate mitogenic activity, synthetic activity, and viability of fibroblasts under physiological stress or pathological conditions.[11,34–36] LLLT stimulates macrophages to produce factors that increase or decrease fibroblast proliferation at different wavelengths.[37] Moreover, both *in vivo* and *in vitro* studies have found that LLLT activates lymphocytes and stimulates their proliferation.[17,38] It is also believed that lymphocytes become more responsive to natural stimulatory products induced by pathophysiological conditions after LLLT.[39] LLLT stimulates these compromised cell types in order to improve the surgical scarring associated with PML and stimulates the immune system to reduce the risk of infection.

In addition, LLLT has been reported to promote endothelial regeneration after damage *in vitro*. This might be due to the stimulatory effects of LLLT on endothelial cells and vascular endothelium *in situ* at the microcirculatory level.[40] Angiogenic factor production by T lymphocytes associated with endothelial cell proliferation[41] or increased vascular endothelial growth factor (VEGF) production by smooth muscle cells or fibroblasts[42] might also be involved. Although there is no solid evidence of an effect of LLLT on lymphangiogenesis, it is logical to deduce that lymphatic vessels may respond similarly to blood vessels since VEGF-C and VEGF-D (members of the VEGF family) stimulate lymphangiogenesis.[14] LLLT is also reported to have a stimulatory effect on lymphatic vessels[15] and to promote local fluid circulation.[33] Therefore, the increase in lymphatic mobility after receiving LLLT may help remove stagnant tissue fluid in PML and thus reduce the volume of a lymphedematous arm.

The positive findings of this study provided evidence of the effective use of LLLT for PML. LLLT can be used in conjunction with complete decongestive physiotherapy or other conventional physiotherapy to accelerate the benefits and reduce the need for expensive and labor-intensive treatments. The present study employs three commonly used outcome measures that are readily available in the clinical setting to assess the condition of PML. However, PML is a complex condition, with subtle as well as rather pronounced presentations. There is no single measuring parameter that can specifically detect and quantify the dysfunction of PML. The present study is a single-blinded study that included a control group that received no treatment. We were unable to identify the treatment effects contributed by placebo effect. Also, we had a small sample size and a short follow-up period. These are the limitations of the present study. Further study of a larger scale double-blinded controlled study with a group that receives sham laser therapy is indicated.

Conclusion

Our findings suggest that 12 sessions of LLLT at the axillary region with a dosage of $2\,J/cm^2$ for about 20 min is effective in reducing the volume of the affected arm and tissue hardness. Upper limb disabilities and symptoms also showed a trend of improvement as measured by a self-administrated questionnaire. The effects of LLLT can be maintained at least up to a 4 wk follow-up.

Disclosure Statement

No competing financial interests exist.

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