Lasers in Medical Science (2020) 35:1179–1184
https://doi.org/10.1007/s10103-020-02958-8

ORIGINAL ARTICLE

A comparative study between intradermal botulinum toxin A and fractional microneedle radiofrequency (FMR) for the treatment of primary axillary hyperhidrosis

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Received: 8 May 2019 / Accepted: 8 January 2020 / Published online: 14 January 2020

Abstract

Microneedle radiofrequency (FMR) for the treatment of primary axillary hyperhidrosis radiofrequency (RF) technology is a new modality that applied deep heat energy directly affecting the epidermis and dermis. Limiting data about FMR for axillary hyperhidrosis is concerning. To compare clinical efficacy between fractional microneedle radiofrequency and intradermal botulinum toxin type A injection. This study was a randomized, intraindividual split-side comparative study. Twenty female subjects clinically diagnosed of primary axillary hyperhidrosis were enrolled. All subjects randomly assigned to receive either FMR device on one side of axilla or 50 units of intradermal botulinum toxin A on contralateral side of axilla. Treatment with FMR device was scheduled for 2 sessions for 4 weeks apart. After treatment, mean Hyperhidrosis Disease Severity Score (HDSS) of both groups revealed remarkably better reduction from the baseline ($p < 000.1$). By comparing between the two groups at the endpoint visit (12th week), the botulinum toxin A group had significantly better reduction of mean HDSS score than the microneedle RF group with 1.60 (0.59) versus 2.05 (0.68), respectively ($p = 0.0332$). At the week-12 visit, the botulinum toxin A group had significantly better participant's satisfaction score by quartile rating scale than the microneedle RF group (2.55 + 0.69 versus 1.70 + 1.03, respectively, $p = 0.004$). Therefore, the botulinum toxin A group also demonstrated with significantly better improvement for their quality of life by DLQI score at the 12th week than the microneedle RF group ($p = 0.013$). Intradermal botulinum toxin A had better efficacy than fractional microneedle radiofrequency for the treatment of primary axillary hyperhidrosis.

Keywords Fractional microneedle radiofrequency · Intradermal botulinum toxin A · Primary axillary hyperhidrosis

Introduction

Primary axillary hyperhidrosis (PAH) is abnormal excessive sweating in the axillary area caused by overstimulation of eccrine sweat glands due to cholinergic innervations [1]. Use of antiperspirant, avoidance of hot weather, or application of topical aluminum chloride solution are the main treatments. However, these treatments usually have temporary effects and have adverse effects such as skin itching, burning sensation, and skin rashes [2]. Intradermal injection of botulinum toxin type A is a new alternative, which was approved by the US FDA for standard treatment of primary axillary hyperhidrosis [3–5]. Radiofrequency (RF) technology is a non-invasive modality which typically applies deep heat energy, directly to the skin at the depth of deep dermis and subcutaneous tissue without epidermal damage [6]. However, there is a lack of evidence regarding clinical efficacy of fractional radiofrequency for PAH treatment. The main mechanism of non-invasive radiofrequency device for PAH treatment is to destroy eccrine sweat glands that mainly contain high components of water molecules which lead to a frictional heating effect [7]. The objective of this study was (1) to compare the clinical efficacy of fractional microneedle radiofrequency device (FMR) and intradermal botulinum toxin type A injection for PAH treatment, (2) to compare total amount of sweat production by transepidermal water loss (TEWL), and (3) to examine patient's satisfaction score and patient's quality of life by Dermatology Life Quality Index (DLQI) and side effects between the 2 groups.

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Patients and methods

This study was a prospective, randomized, assessor-blinded, intraindividual split-side comparative study. This study was approved by the independent Ethics Committee (IEC)/ Institutional Review Board (IRB) of Mae Fah Luang University on August 1, 2016, and registered with ClinicalTrials.gov (identification number: NCT03054480). This study was conducted at Mae Fah Luang University Hospital, Asoke Bangkok. Twenty male and female subjects, age range between 18 and 60 years, were clinically diagnosed with primary axillary hyperhidrosis and confirmed by positive iodine starch test at screening visit.

Inclusion criteria

1. Male or female subjects, age between 18 and 60 years
2. Healthy volunteers
3. Subjects who have experienced excessive sweating on both sides of axillary areas and have a positive result for iodine starch test on the screening day
4. Willing to participant in the study and voluntary sign the informed consent form

Exclusion criteria

1. Active bacterial or fungal infection over tested area, axillae
2. Pregnancy and breast feeding
3. Previously underwent surgical treatment such as radical resection of sweat glands for primary axillary hyperhidrosis
4. Currently being treated with intradermal botulinum toxin type A injection at the axillary area for less than 12 months
5. Currently have implanted devices such as the cardiac pacemaker or any other internal electronic devices
6. Secondary hyperhidrosis caused by hyperthyroidism, drug induced, abnormal autonomic, or neurological disorder that affect sweat gland
7. Allergy to botulinum toxin type A
8. Known contact allergy to iodine
9. Unable to follow and comply to the study protocol

For subjects who meet the study criteria, they will be randomly assigned to receive either FMR device on one side of axilla or intradermal botulinum toxin A on contralateral side of axilla as a control group. Subjects who meet the study criteria receive FMR device on one side of axilla and intradermal botulinum toxin A on contralateral side of axilla as a control group. Treatment with FMR device will be scheduled for 2 sessions for 4 weeks apart. Subjects underwent 2 sessions of treatment with FMR device 4 weeks apart. The control group was given 50 units of intradermal botulinum toxin A injection for only a single treatment on the first visit. The study protocol was followed for 12 weeks duration for a total of 3 visits (at baseline, 4th week, and at 12th week). Efficacy evaluations include Hyperhidrosis Disease Severity Score, iodine starch test, total amount of sweat production by TEWL measurement, patient's satisfaction, quality of life by DLQI questionnaire, and adverse effects. The blinding was assigned to clinical assessors who will evaluate the study outcomes to prevent the study bias.

Study flow

The subject who meets the criteria and has a positive result for iodine starch test will follow the study protocol:

1. Assessment for disease severity score using Hyperhidrosis Disease Severity Score (HDSS) questionnaire.
2. The measurement of transepidermal water loss (TEWL) by using TEWA-meter to determine total amount of sweat production on both sides of axillae.
3. Prior to the treatment, subjects will be informed of the study protocol and the possible adverse effects.
4. Each side of axilla of study subjects will be randomly assigned to receive either FMR device or intradermal botulinum toxin type A by randomization log using one by one randomization allocation basis. "A" will be considered to represent the "Left side" and "B" represents the "Right side" of axillae.
5. Photographic assessment of both sides of the axillae will be taken at baseline visit.
6. To numb the tested skin, local anesthesia with 2.5% lidocaine and 2.5% prilocaine (Emla® cream) with occlusive technique will be applied at both tested sides of axillae for 45 min and then washed off.
7. On the intervention group, each patient will be treated with an FMR DeAge EX® applicator device (Daeshin Enterprise Co., Ltd., Guro-Gu, and Seoul, South Korea) at 4-week intervals for 2 sessions of the treatment. This applicator consists of rows of 36 (6 × 6 needles) insulated microneedles that form an array of positively and negatively charged electrodes. The microneedles will deliver bipolar radiofrequency energy in a fractional manner that extends from 0.1 to 4.0 mm below the surface of the skin. The bipolar electrode pins form a closed circuit through the affected skin and deliver 1 MHz of radiofrequency current conducted to the skin. Energy levels of up from 3 mJ to 3.5 J can be delivered with a 5–10% coverage rate, according to program selection, through a 200-μm-diameter pin, and the energy deposition occurs and accumulates in 1–100 ms. The targeted axillary side will be treated with a total of 4 passes. The treatment protocol

includes the following parameters: (1) the first 2 passes will be delivered at a depth of 3.5 mm for 10 to 40 ms, at energy level 10 to 40, and (2) the second 2 passes will be delivered at a depth of 3.0 mm for 10 to 40 ms, at energy level 10. The study investigator will start with the lowest dose at energy level 10 to 20; if the subject can tolerate the starting dose, the investigator will escalate the RF parameter until the maximal tolerate dose of below level 40 (40 ms of pulse duration). Ice packs will be applied during treatment and within 10 min after FMR therapy to reduce heat damage to the epidermis.

On the contralateral axillary side, 50 units of botulinum toxin type A (Neuronox®, neu-BoNT/A) will be intradermally injected over the axillary area. According to the protocol, 1–2 units will be used per 1 injection area of 1×1 cm^2. Ice packing will be applied during the procedure to minimize the painful symptom. Study subjects will assess the pain score using the visual analog scale.

8. The safety and adverse effects of the study will be closely monitored during the study period. The study volunteers will be advised to observe any adverse effects such as persistent pain, skin overlying redness and inflammation, and an itching or burning sensation. In presence of any adverse effects, the study volunteers can directly contact study investigator or/and visit study site to determine the side effect and will be provided with prompt treatment.

Follow-up visits (4th and 12th week for 2 visits)

All subjects will be advised to follow the clinical outcomes at the 4th- and 12th-week visit after the enrollment. On each visit, the investigator will perform the following:

1. History taking and physical examination (4th and 12th week)
2. To evaluate disease severity using Hyperhidrosis Disease Severity Score (HDSS) questionnaire assessed by study volunteer (4th and 12th week)
3. Satisfaction determination will be evaluated using satisfaction score with quartile rating scale and assessed by study volunteer (4th and 12th week)
4. An evaluation of transepidermal water loss (TEWL) using TEWA-meter to determine total amount of sweat production will be obtained on both sides (4th and 12th week)
5. At the 4th-week visit, on axillary side of intervention, local anesthesia, 2.5% lidocaine and 2.5% prilocaine (Emla® cream), will be applied with occlusive technique at tested sites for 45 min and then washed off. Study subjects will undergo a second session of FMR treatment. Each patient will be treated with DeAge® FMR applicator device with the same parameter as the baseline protocol. Ice packs will be applied during treatment and within 10 min after FMR therapy to reduce heat damage to the epidermis.
6. The study volunteers will be interviewed about any adverse effects occurred during the study period. Signs and symptoms of adverse effects will be recorded with grading of severity (4th and 12th week).

Hyperhidrosis Disease Severity Score will be assessed by studying the subjects at baseline, 4th week, and at 12th week and is categorized to 4 levels: (1) my axillary sweating is never noticeable and never interferes with my daily activities, (2) my axillary sweating is tolerable but sometimes interferes with my daily activities, (3) my axillary sweating is barely tolerable and frequently interferes with my daily activities, (4) my axillary sweating is intolerable and always interferes with my daily activities. Participants' satisfaction assessment will be determined at the endpoint visit (4th–12th week) after the treatment using quartile rating scale on each side of axilla. Quartile rating scale by comparing with the baseline that is categorized to 4 levels: (3) greatly satisfy with treatment result, (2) moderately satisfy with treatment result, (1) slightly satisfy with treatment result, (0) no different with treatment result.

Statistical analysis

Descriptive analysis will report as average mean and standard deviation if the data is continuous data with normal distribution but with median and inter-quartile range if it contains non-distributed data. Frequency and the percentage will be reported for categorical data.

For inferential analysis, independent Student's t test and repeated analysis of variance (ANOVA) test will be used to compare different time point between the 2 groups for continuous data if the data are normal distribution. In the case of non-distributed data, Mann-Whitney U test will be used and reported with median and inter-quartile range. Clinical outcomes for continuous data include iodine starch test score, Hyperhidrosis Disease Severity Score, transepidermal water loss, and satisfaction score. Pearson's chi-square test and Fisher's exact test will be used to compare categorical data. Significance level with $p < 0.05$ will be used. A threshold for significance of 0.05 was used for all analyses. Statistical Package for the Social Sciences (SPSS) version 22.0 was used for data analysis. GraphPad Prism version 7.0 for Windows, GraphPad Software, La Jolla, CA, USA, was used for digital figure preparation.

This study was conducted according to the International Conference of Harmonization (ICH) Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. The study

protocol was submitted to the Mae Fah Luang University IRB for approval prior to participant enrolment.

Result

The study was enrolled and conducted at Mae Fah Luang University Hospital Bangkok, Thailand during 15 August 2016–30 March 2017.

Demographics data

Twenty female subjects were diagnosed with axillary hyperhidrosis by positive iodine starch test at screening visit. All study subjects were randomized and completed study protocol. Mean age (standard deviation, SD) was 36.8 (9.8) years, range between 20 and 54 years.

Primary outcomes

-Hyperhidrosis Disease Severity Score

At baseline, average mean (SD) of Hyperhidrosis Disease Severity Score (HDSS) of the botulinum toxin A group was 3.10 (0.44) and the microneedle RF group was 3.10 (0.44) with equal balance ($p = 1.00$). After receiving the treatment on both sides, mean HDSS score of both groups revealed remarkably better reduction from the baseline ($p < 000.1$). Comparing between the two groups at the endpoint visit (week 12), the botulinum toxin A group had significantly lower reduction of mean HDSS score than the microneedle RF group with 1.60 (0.59) versus 2.05 (0.68), respectively ($p = 0.0332$) (Fig. 1).

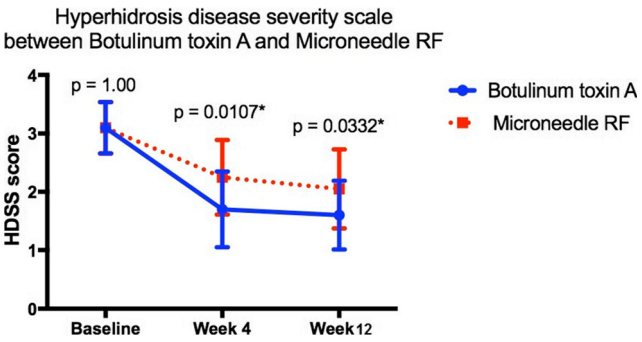

Fig. 1 To compare the changes of Hyperhidrosis Disease Severity Score (HDSS) at different time-point between the 2 groups. An asterisk indicates that analysis of variance (ANOVA) test was used by adjusted covariate data at baseline visit

Secondary outcomes

-Transepidermal water loss measurement

There was a slight reduction of transepidermal water loss (TEWL) in the botulinum toxin A group on week 4 but increased gradually in the week-12 visit. There was no difference for mean TEWL measurement at the 12th-week visit ($p = 0.1037$) as shown in Fig. 2.

-Patient's satisfaction score by quartile rating scale

At the week-12th visit, the botulinum toxin A group had significantly better participant's satisfaction score by quartile rating scale than the microneedle RF group (2.55 (0.69) versus 1.70 (1.03), respectively, $p = 0.004$) (Fig. 3).

-Quality of life by Dermatology's Living Quality of Life Index

Both groups had better improvement in terms of their quality of life at week 4 and week 12 than the baseline. At week 12, the botulinum toxin A group demonstrated with significantly better improvement for their quality of life by Dermatology's Living Quality of Life Index (DLQI) score than the microneedle RF group ($p = 0.013$) (Figs. 4 and 5).

-Adverse effects

Mild prolonged erythema ($n = 2$, 10%), mild skin desquamation ($n = 1$, 5%), and mild burning sensation ($n = 1$, 5%) were reported on the microneedle RF group. Skin dryness ($n = 1$, 5%) was found in the botulinum toxin A group. Pain score assessment by visual analog scale (VAS) of the microneedle RF group was slightly higher than botulinum toxin A (mean (SD); 3.45 (2.11) versus 2.65 (1.98), respectively) but did not differ between the 2 groups (Wilcoxon rank-sum test, $p = 0.19$).

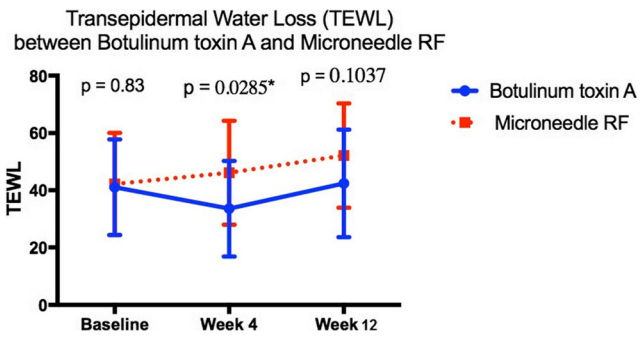

Fig. 2 Transepidermal water loss (TEWL) measurement at baseline, weeks 4 and 12. An asterisk indicates analysis using the analysis of variance (ANOVA) test with adjusted covariate data based on the baseline visit

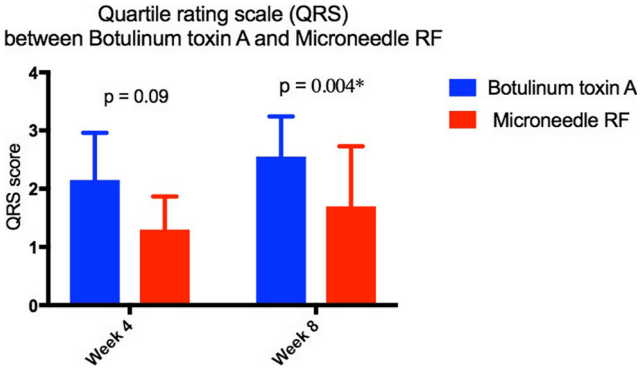

Fig. 3 Participant's satisfaction score by quartile rating scale (QRS). An asterisk indicates that independent Student's *t* test was used

Discussion

Primary axillary hyperhidrosis involves about 1–3% of general population and directly affects their quality of life [1, 2]. Our study enrolled twenty female subjects with mean age of 36.8 years old. After receiving each treatment on both axillae, mean HDSS score of both groups showed remarkably reduced from the baseline ($p < 000.1$). By comparing between the two groups at the endpoint visit (12th week), the intradermal botulinum toxin A group had significantly better reduction of mean HDSS score than the microneedle RF group with 1.60 (0.59) versus 2.05 (0.68), respectively ($p = 0.0332$). At the week-12th visit, the intradermal botulinum toxin A group also had a significantly better participant's satisfaction score and improvement for their quality of life by DLQI score than the microneedle RF group. Nevertheless, there was no difference for transepidermal water loss (TEWL) measurement at the 12th-week visit between the 2 groups. Mild prolonged erythema ($n = 2$, 10%), mild skin desquamation ($n = 1$, 5%), and mild burning sensation ($n = 1$, 5%) were reported on the microneedle RF group. Skin dryness ($n = 1$, 5%) was found in the botulinum toxin A group. A study by evidence-based review by Neumann et al. (2013), from total of 923 patients enrolled, supported the evidences to recommend for using botulinum toxin A injection for both A/Abo and A/ Ona

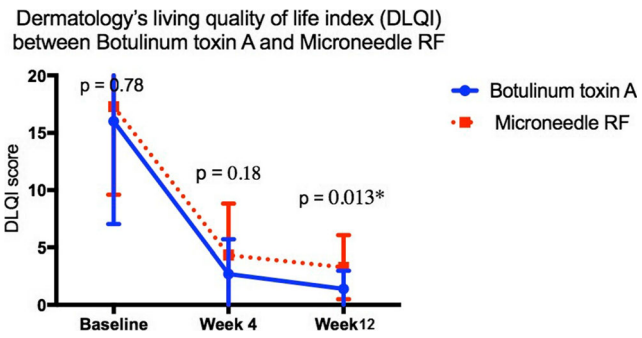

Fig. 4 Self-report participant's quality of life by Dermatology's Living Quality of Life Index (DLQI) at weeks 4 and 12. An asterisk indicates that analysis of variance (ANOVA) test was used by adjusted covariate data at baseline visit

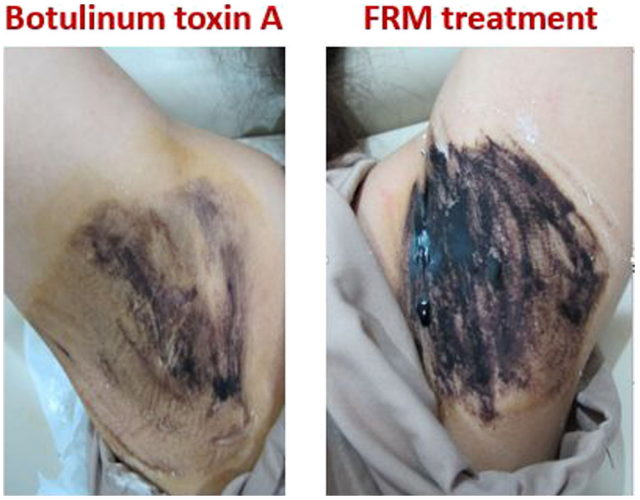

Fig. 5 Minor's starch iodine test to compare botulinum toxin A and FMR at week-12 visit

subtype for the treatment of primary axillary hyperhidrosis [8]. A study by Heckmann et al. (2001) that conducted a randomized controlled study to compare between 200 units of botulinum toxin A (A/Abo) by comparing with the placebo and follow-up duration of 26 weeks concluded sweat production reduction by gravimetric measurement [3]. A study by Neumann et al. (2001) enrolled 320 patients with PAH, to compare between 50 units (A/Ona) of botulinum toxin with the placebo for 16 weeks follow-up time, and botulinum toxin showed significantly better sweat gland production reduction by gravimetric measurement than the placebo ($p < 0.001$). A common side effect of botulinum toxin included dry eye and dry skin [4]. A study by Lowe et al. (2007) was conducted for 322 PAH patients, to compare 3 arms comparison between 50 units of A/Ona, 75 units of A/Abo per axilla, and placebo and follow-up about 1-year duration. This study reported percent change at least 2 levels of HDSS of both botulinum toxin groups and were significantly better (75%) than the placebo with only 25% ($p < 0.001$). Botulinum toxin had longer duration of clinical effect than the placebo [5].

A study by Bahareh Abtahi-Naeni et al. (2016) enrolled twenty-five patients with axillary hyperhidrosis, to determine an efficacy and safety of fractional microneedle radiofrequency device compared with the same protocol as the controls. This study showed significant improvement for hyperhidrosis severity score to favor FMR than the controls at 1-year follow-up ($p < 0.001$). There were 10 patients (42%) without clinical relapse at 1-year follow-up [9]. Another study demonstrated that a treatment with fractional microneedle RF for severe PAH significantly improved patient's quality of life after treatment [10]. A pilot study by Miri Kim et al. enrolled twenty patients with PAH treated with two sessions of bipolar fractional needle RF at 4 weeks apart. The results showed significant reduction of HDSS score after 8 weeks from the completion of FMR treatment comparing with the baseline. There

were 75% of patients self-report with at least 50% symptoms improvement from the baseline prior to enrollment [11]. Another study was conducted to determine histopathological change of PAH who were treated with FMR. This study demonstrated the reduction in number and size of eccrine sweat gland with mild lymphocytic infiltration occurring after the completion with FMR which can confirm RF thermolysis targeting to sweat gland [12]. However, even the FMR treatment could confirm the efficacy in clinical trial as previous studies mentioned elsewhere, but our study showed that FMR had significantly lower clinical efficacy in PAH than botulinum toxin A.

In conclusion, intradermal botulinum toxin A had better efficacy than fractional microneedle radiofrequency for the treatment of primary axillary hyperhidrosis.

Acknowledgments We are very grateful for research participants and would like to thank The Thai Aesthetics Physicians and School of Anti-aging and Regenerative Medicine, Mae Fah Luang University, Bangkok, Thailand.

Compliance with ethical standards

This study was conducted according to the International Conference of Harmonization (ICH) Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. This study was approved by the independent Ethics Committee (IEC)/Institutional Review Board (IRB) of Mae Fah Luang University on August 1, 2016, and registered with ClinicalTrials.gov (identification number: NCT03054480).

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Atkins JL, Butler PE (2002) Hyperhidrosis: a review of current management. Plast Reconstr Surg 110:222–228
2. Cohen JL, Cohen G, Solish N, Murray CA (2007) Diagnosis, impact, and management of focal hyperhidrosis: treatment review including botulinum toxin therapy. Facial Plast Surg Clin North Am 15:17–30 **v-vi**
3. Heckmann M, Ceballos-Baumann AO, Plewig G, Hyperhidrosis Study G (2001) Botulinum toxin A for axillary hyperhidrosis (excessive sweating). N Engl J Med 344:488–493
4. Naumann M, Lowe NJ (2001) Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial. Bmj 323:596–599
5. Lowe NJ, Glaser DA, Eadie N et al (2007) Botulinum toxin type A in the treatment of primary axillary hyperhidrosis: a 52-week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety. J Am Acad Dermatol 56:604–611
6. Lolis MS, Goldberg DJ (2012) Radiofrequency in cosmetic dermatology: a review. Dermatol Surg 38:1765–1776
7. Hong HC, Lupin M, O'Shaughnessy KF (2012) Clinical evaluation of a microwave device for treating axillary hyperhidrosis. Dermatol Surg 38:728–735
8. Naumann M, Dressler D, Hallett M et al (2013) Evidence-based review and assessment of botulinum neurotoxin for the treatment of secretory disorders. Toxicon 67:141–152
9. Abtahi-Naeini B, Naeini FF, Saffaei A et al (2016) Treatment of primary axillary hyperhidrosis by fractional microneedle radiofrequency: is it still effective after long-term follow-up? Indian J Dermatol 61:234
10. Abtahi-Naeini B, Naeini FF, Adibi N, Pourazizi M (2015) Quality of life in patients with primary axillary hyperhidrosis before and after treatment with fractionated microneedle radiofrequency. J Res Med Sci 20:631–635
11. Kim M, Shin JY, Lee J, Kim JY, Oh SH (2013) Efficacy of fractional microneedle radiofrequency device in the treatment of primary axillary hyperhidrosis: a pilot study. Dermatology 227:243–249
12. Naeini FF, Saffaei A, Pourazizi M, Abtahi-Naeini B (2015) Histopathological evidence of efficacy of microneedle radiofrequency for treatment of axillary hyperhidrosis. Indian J Dermatol Venereol Leprol 81:288–290