

Q-switched ruby laser alone or in combination with topical flutamide for the treatment of Becker's nevus syndrome; a randomized clinical trial

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Background: Becker's nevus syndrome (BNS) is a benign hamartoma that is aesthetically bothersome and usually appears during puberty. Various modalities of laser therapy alone or in combination with other medications can be used for the treatment of BNS, but no unified approach with an acceptable response is yet available. The current study aimed to compare the outcomes of Q-switched ruby 694 nm laser (QSRL) alone and in combination with 4% topical flutamide for the management of BNS.

Methods: The current randomized clinical trial was conducted on twenty-two BNS patients between 2016-2018. The patients were randomly allocated to treatment with QSRL 694 nm alone (group A) versus in combination with 4% topical flutamide (group B). The QSRL was administered twice with four-week intervals for both groups, while group B was also administered topical flutamide 4% twice a day for eight weeks. The treatment outcomes were assessed and compared at baseline and then within 4 and 8 weeks of commencing the interventions.

Results: The evaluation of the two groups in terms of lesion size alterations, response to treatment, and patients' satisfaction showed insignificant differences between the two groups ($P > 0.05$). In addition, neither approach A ($P = 0.33$) nor approach B ($P = 0.46$) led to remarkable changes in lesion color.

Conclusion: Based on the findings of the current study, the use of QSRL alone or even in combination with topical 4% flutamide was not suitable for the management of BNS lesions.

Keywords: Becker's nevus, Q-switched ruby laser, hamartoma, flutamide

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INTRODUCTION

Becker melanosis or Becker's nevus syndrome (BNS) is a type of epidermal nevus and relatively benign cutaneous hamartoma that appears as a light brown-to-dark lesion with an irregular and bizarre border. BNS poses cosmetically distressing effects on patients ^{1,2}. This hyperpigmented, hypertrichotic

patchy lesion is rare at birth and commonly appears in the first and second decades of life, progressing during adolescence; it is two-fold more common among males and typically involves the trunk unilaterally ³. Histopathologically, BNS lesions show acanthosis, hyperkeratosis, and infiltration of melanophages into the dermis ⁴.

There is evidence in favor of an association

between BNS and other anatomical malformations such as skeletal defects and hypoplasia of the breasts, areolae, muscles, and nipples⁵. The exact etiology of BNS is unknown; however, there are two theories in this regard. The first insists on postzygotic autosomal mutations, and the second one gives a hormonal etiology for the pathogenesis. Accordingly, the supporters of the latter theory believe in an increased level of androgenic receptors in the area near the lesion. Therefore, the progression of the lesions during puberty is assumed to be due to elevation in the androgenic hormones, particularly in men^{6,7}.

Therapeutic approaches for BNS are limited, among which electrolysis, makeup, and lasers are the most common ones. In this regard, long-pulsed lasers are helpful for hypertrichosis, and Q-switched lasers are effective in treating hyperpigmentation⁸. Nevertheless, the data regarding the use of Q-switched lasers for the treatment of BNS are controversial; in addition, patients have reported several relapses and even disappointment⁹.

Flutamide is a non-steroidal anti-androgenic agent that competitively binds to androgenic receptors¹⁰. Therefore, due to the hypothesis regarding the androgenic hormonal basis of BNS, scientists have turned to the use of flutamide for the treatment of BNS. However, information about the use of flutamide, particularly for the treatment of BNS, is in its early stages and requires further investigations¹¹.

In addition, considering the diversity in the responses toward various approaches for BNS, some researchers have recommended combination therapies^{12,13}. Due to the points mentioned, we aimed to investigate the efficacy of the Q-switched ruby (694 nm) laser alone and in combination with 4% topical flutamide in the treatment of BNS.

PARTICIPANTS AND METHODS

Subjects

The current randomized clinical trial was conducted on twenty-two BNS patients referred to the outpatient dermatology clinics affiliated to Isfahan University of Medical Sciences (Isfahan, Iran) from May 2016 to May 2018.

The Ethics Committee of Isfahan University of Medical Sciences approved the study proposal.

After that, the study protocol was explained to the participants; they were informed about the advantages and disadvantages of the therapeutic approaches and reassured about the confidentiality of their personal information. Eventually, the participants provided written consent.

Patients with the clinical manifestations of BNS were included; while pregnancy, breastfeeding, a previous history of BNS treatment (e.g., topical or laser therapy), hypersensitivity to flutamide, and photosensitivity were considered as the unmet criteria. Failure to refer for follow-up visits and withdrawal from the study at any stage were considered as the exclusion criteria (Figure 1).

As this study was a census report, all of the patients who met the inclusion criteria were selected through convenience sampling. After that, using Random Allocation software, they were randomly allocated to one of the therapeutic approaches, namely Q-switched ruby (694 nm) laser alone (group A) or in combination with 4% topical flutamide (group B). Each patient was provided with a particular number; she/he was allocated to group A if even and to group B if odd.

In order to minimize the inter-observer bias, two skilled target dermatologists presented their assessments of the therapeutic approaches in each stage of the study. These dermatologists were blinded to the type of treatment done for each patient.

Ethical approval for this study was obtained from Isfahan University of Medical Sciences (IRCT code: (IRCT20190208042657N1). Written informed consent was obtained from all subjects before the study.

Therapeutic approaches

Q-switched ruby (694 nm) laser. Both groups were treated with Q-switched ruby (694 nm) 5Jh(Q1 laser, Quanta System company) twice with fluence at the study initiation and after four weeks.

Topical flutamide. Group B, in addition to the treatment with Q-switched ruby (694 nm) laser has a similar pattern to group A, were treated with topical 4% flutamide cream (Faculty of Pharmacology, Isfahan University of Medical Sciences, Iran) a day after cleaning of the lesion for eight weeks. Both groups were recommended to use SPF 30% sunscreen during the period of the study.

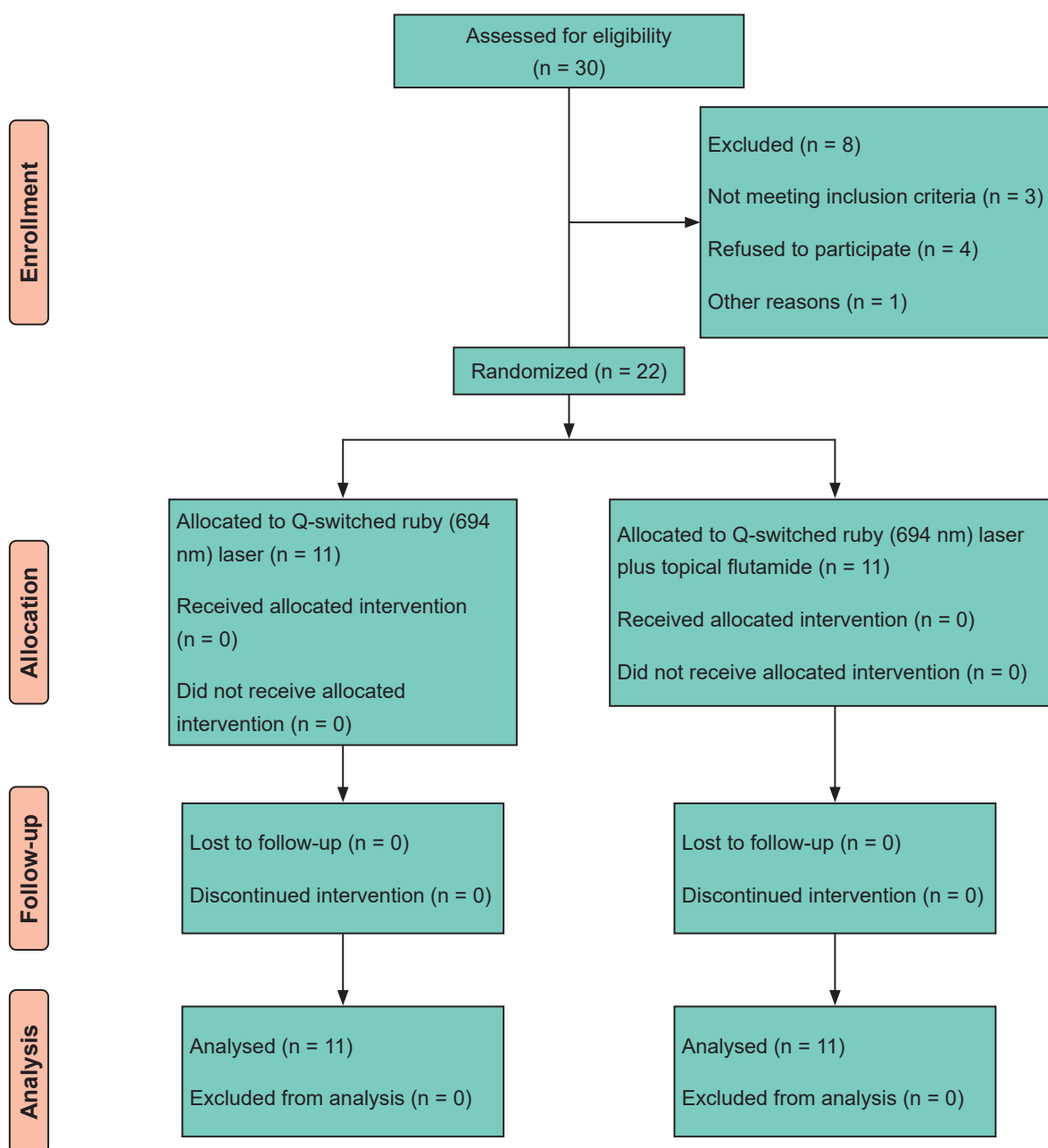


Figure 1. Consort diagram of the studied population.

Outcomes

All assessments were performed before the interventions and within four and eight weeks following the interventions. The assessments are detailed in the following sections.

Response to the treatment. Photographs were taken from the patients in standard views; the environmental light, patients' position, and patients' viewing angle were simulated in each assessment. In

order to minimize bias, all photographs were taken using an 18-megapixel digital camera (Fotofinder, Germany). The camera had the ability of 180 degrees' rotation with a resolution of 18 megapixels. Two blinded dermatologists evaluated the alterations in the nevi in terms of hyperpigmentation based on a Likert scale scoring from 1-5 as no change, little, fair, moderate, and excellent.

Size of the lesions. The size of each lesion was measured from the outermost territories bilaterally

and vertically. After that, the area of the lesion was measured and compared across the mentioned intervals.

Satisfaction. By the end of the study, the patients were requested to present their satisfaction from the intervention using a Visual Analog Scale (VAS) ranging from zero as the worst to 10 as the best satisfactory condition.

Color assessment. For color assessment, we categorized the lesions into four groups of black, dark brown, brown, and light brown.

Statistical analysis

The obtained data were entered into the Statistical Package for Social Sciences (SPSS) version 23. The descriptive data were presented in mean, standard deviation, absolute numbers, and percentages. For analytics, the chi-squared test and Fisher's exact test were used. A P-value of less than 0.05 was considered significant.

RESULTS

In the current study, 22 patients consisting of 7 (31.81%) males and 15 (68.18%) females were randomly allocated to the two treatment approaches.

The participants of the two groups were similar in terms of the distribution of gender ($P = 0.5$) and age ($P = 0.33$), as well as the lesions' location ($P = 0.53$), size ($P = 0.19$), and color ($P = 0.95$). The detailed comparison of the demographic information of the studied groups is demonstrated in Table 1.

The comparison of the lesion size between group A and B revealed an insignificant difference between the groups by the fourth ($P = 0.2$) and eighth week ($P = 0.19$) of treatment. Similar outcomes were presented in the assessment of response to the therapeutic approaches done by the blinded dermatologists within the fourth ($P = 0.6$) and eighth weeks ($P = 0.56$) of treatment. Besides, the comparison of the patients' satisfaction about the type of treatment also showed an insignificant

Table 1. The comparison of demographic characteristics of the studied groups

Characteristics	Q-switched ruby (694 nm) laser (n = 11)	Q-switched ruby (694 nm) laser + flutamide (n = 11)	P-value
Sex, n (%)			
Male	4 (36.4)	3 (27.3)	0.5
Female	7 (63.6)	8 (72.7)	
Age (years), mean \pm standard deviation	21.27 \pm 3.22	22.81. 27 \pm 3.86	0.33
Location, n (%)			
Head and neck	1 (9.1)	1 (9.1)	0.53
Trunk	9 (81.8)	9 (81.8)	
Extremities	1 (9.1)	1 (9.1)	
Size of lesions (mm), mean \pm standard deviation	131.09 \pm 40.51	140.72 \pm 53	0.19
Color of lesions, n (%)			
Black	2 (18.2)	2 (18.2)	0.95
Dark brown	5 (45.5)	4 (36.4)	
Brown	2 (18.2)	2 (18.2)	
Light brown	2 (18.2)	3 (27.3)	

Table 2. The comparison of lesion size, response to treatment, and satisfaction between the study groups

Variables	Q-switched ruby (694 nm) laser (n = 11)	Q-switched ruby (694 nm) laser + flutamide (n = 11)	P-value
Size of the lesion (mm), mean \pm standard deviation			
Baseline	131.09 \pm 40.51	140.72 \pm 53.09	0.63
Fourth week	130.81 \pm 40.35	140.27 \pm 52.62	0.2
Eighth week	128.27 \pm 39.95	136.81 \pm 51.86	0.19
Response to the treatment, mean \pm standard deviation			
Fourth week	2.9 \pm 0.83	3.18 \pm 1.07	0.6
Eighth week	3.72 \pm 0.46	3.9 \pm 0.53	0.56
Satisfaction, mean \pm standard deviation	6 \pm 1.8	5.7 \pm 1.48	0.69

Table 3. Lesion color alterations following eight weeks of therapy in the isolated Q-switched ruby (694 nm) laser therapeutic approach

	Final color					Total	P-value
	Black	Dark brown	Brown	Light brown	Skin color		
Baseline color							
Black	0	0	0	2	0	2	0.33
Dark brown	0	0	2	3	0	5	
Brown	0	0	1	1	0	2	
Light brown	0	0	0	2	0	2	
Total	0	0	3	8	0	11	

Table 4. Lesion color alterations following 8 weeks in the Q-switched ruby (694 nm) laser plus 4% topical flutamide therapeutic approach

	Final color					Total	P-value
	Black	Dark brown	Brown	Light brown	Skin color		
Baseline color							
Black	0	0	1	1	0	2	0.46
Dark brown	0	0	1	3	0	4	
Brown	0	0	0	2	0	2	
Light brown	0	0	0	2	1	3	
Total	0	0	2	8	1	11	

difference ($P = 0.69$) (Table 2).

The alterations in the lesion color at the end of the interventions are demonstrated in Tables 3 and 4. Based on these Tables, neither group A ($P = 0.33$) nor group B ($P = 0.46$) featured remarkable changes in lesion color.

DISCUSSION

To the best of our knowledge, the current study is the first one assessing the efficacy of Q-switched ruby 694 nm laser plus topical flutamide combination therapy for the treatment of BNS in comparison with isolated Q-switched ruby 694 nm laser. Besides, another strength of the current study is its assessment of 11 cases in each of the intervention groups, a population that is remarkably larger than most of the other studies assessing the use of different approaches for the treatment of BNS.

The participants of the two groups were similar in terms of demographic characteristics; therefore, all of the findings are merely attributed to the therapeutic approaches. We found that neither the use of Q-switched ruby (694 nm) laser alone or in combination with topical flutamide could properly affect Becker's nevi. These disappointing results were achieved by the comparison of the treatments in terms of size and response to the treatment (assessed by two blinded dermatologists) as well

as the patients' satisfaction. Even the evaluation of skin colors by the end of the interventions revealed negligible alterations.

The Q-switched laser provides a rapid, short-duration, pulsed burst of energy in a period equal or even shorter than the relaxation time of melanin particles¹⁴. This wave is appropriately absorbed by the superficial melanin and induces hypopigmentation/depigmentation at the site of the lesions¹⁵. The use of Q-switched lasers for the treatment of BNS has been proposed since the 1990s; however, data in this regard is not enough and controversial¹⁶⁻¹⁸. Studies assessing the use of the Q-switched ruby (694 nm) laser have demonstrated temporary effects due to the induction of selective damage limited to superficial melanocytes¹⁰. Besides, this treatment only can improve hyperpigmentation and does not affect hypertrichosis¹⁹.

Tse *et al.* performed a comparative study in order to compare the efficacy of Q-switched ruby (694 nm) laser vs. QS Nd:YAG (1064 nm) for the treatment of pigmented lesions and reported the superiority of the former by evaluation of the lesions in terms of patients' satisfaction and post-procedural complications¹⁸.

In the study of Nelson and colleagues, the influence of Q-switched ruby (694 nm) laser was evaluated on 35 pigmented lesions, among which four were Becker nevus. They represented

satisfactory results in all types of studied lesions. The number of laser therapy sessions required was dependent on the size of the lesions for all types; Becker nevus required 6-8 sessions. As well as satisfactory outcomes, they eventually concluded good toleration of Q-switched ruby (694 nm) laser without skin scar formation or alteration in skin texture¹⁶.

Kopera *et al.* assessed a patient with Becker nevus histopathologically following treatment with Q-switched ruby (694 nm) laser and described significant damage to the superficial pigmented cells, while the deeper layers were preserved²⁰. In addition, Hafezi and colleagues evaluated a patient with rheumatoid arthritis who was referred with the complaint of Becker nevus. They administered Q-switched ruby (694 nm) laser for the patient, who had undergone ten years of treatment with immunosuppressive agents (prednisolone and methotrexate). Remarkable pigmentation improvement was seen in their patient without recurrence within 18 months of follow-up. Although they reported a successful therapeutic effect by the use of Q-switched ruby (694 nm) laser without recurrence, they proposed a theory about the role of immunosuppressive agents in the response of their patient to the treatment and its perseverance²¹.

Therefore, due to the temporary effect of Q-switched laser and also its inefficacy on hypertrichosis and in order to achieve better clearance of the lesions, some scientists have recommended combination therapy instead of mere use of lasers.

A review of the literature showed no report in terms of concurrent treatment with Q-switched laser and topical flutamide; however, information about the use of topical flutamide alone is also restricted to some case presentations. This anti-androgenic agent is absorbed from the skin appropriately as well as systematically, a feature that convinced Taheri *et al.* to use it for the treatment of Becker nevus in a 22-year-old patient. They described a noticeable improvement in the nevus lesion in terms of both pigmentation and hypertrichosis¹¹. However, further evaluations on larger numbers of patients are required to achieve generalizable outcomes.

Oral flutamide also can be used for treating other conditions in dermatology, such as an androgenic pattern of hair loss. In 2011, Yazdabadi *et al.* reported

a woman whose hair loss progressed while using spironolactone and topical minoxidil in combination but reversed with oral use of flutamide (250 mg daily), a potent androgen receptor antagonist. This report documents the therapeutic response of the female pattern of hair loss to oral flutamide through the blockage of androgenic receptors²².

In 2015, Adalatkah *et al.* investigated the efficacy of 1% flutamide cream vs. 4% hydroquinone cream on melasma. A hormonal role seems to exist in the pathogenesis of melasma, and sex-hormone-related drugs may affect this condition²³. Topical flutamide appeared as effective as topical hydroquinone in treating melasma with higher patient satisfaction in flutamide treatment vs. topical hydroquinone.

In 2010, Meesters *et al.* sought to assess the efficacy and safety of ablative 10,600-nm fractional laser therapy (FLT) in the treatment of BNS²⁴. Eleven patients with BN, older than 18 years, were included in a prospective randomized controlled, observer-blinded, split-lesion trial. The conclusion was that ablative FLT was moderately effective in some patients with BN. However, postinflammatory hyperpigmentation and relatively negative patient-reported outcomes still preclude ablative FLT from being a standard therapy.

In summary, we found no significant influence using Q-switched ruby laser (694 nm) alone or even in combination with topical 4% flutamide. These findings may be due to the short period of treatment; however, evidence in this regard is limited and requires further investigations.

CONCLUSION

Based on the findings of the current study, the use of Q-switched ruby (694 nm) laser alone or even in combination with topical 4% flutamide is not effective for the management of Becker nevus lesions. In future studies, it is recommended to test the Becker nevus lesions' response to treatment with either different laser types or flutamide in higher concentrations and even in different vehicles.

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