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# Treatment of Café-Au-Lait Spots Using Q-Switched Alexandrite Laser: Analysis of Clinical Characteristics of 471 Children in Mainland China

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**Background and Objectives:** Café-au-lait spots, also known as café-au-lait macules (CALMs), are a common pigmentary disorder. Although various laser modalities have been used to treat CALMs, the efficacy of laser treatment in children differs from that in adults. We investigated the efficacy, safety, and clinical factors of the treatment of CALMs using Q-switched alexandrite laser (755 nm) therapy in children.

**Methods:** In total, 471 children with CALMs underwent Q-switched alexandrite laser therapy at a treatment interval of 3–12 months. The safety and efficacy of the laser treatment were evaluated by reviewing clinical records and photographs before and after treatments.

**Results:** Of the 471 patients, 140 (29.72%) were cured completely, 124 (26.33%) showed substantial improvement, 110 (23.35%) showed improvement, and 97 (20.60%) showed no improvement after one to nine treatments. The overall treatment success rate was 79.41%, and the treatment efficacy was positively correlated with the number of laser treatments ($rs = 0.26$, $P < 0.0001$). Sex and the interval of laser treatments were also associated with significant differences in treatment outcomes ($P < 0.05$). No obvious adverse effects were observed. Multivariate logistic regression analysis showed that the number of treatments influenced the treatment efficacy (odds ratio, 2.130; 95% confidence interval, 1.561–2.908).

**Conclusions:** Q-switched alexandrite laser (755 nm) therapy is safe and highly effective for CALMs in children, and the number of treatments affects the treatment efficacy. © 2019 The Authors. *Lasers in Surgery and Medicine* Published by Wiley Periodicals, Inc.

**Key words:** Q-switched alexandrite laser; café-au-lait spot; children

## INTRODUCTION

Café-au-lait spots, also known as café-au-lait macules (CALMs), are common hyperpigmented skin lesions in children. Most are congenital and appear on the face. These lesions affect the children's appearance, often decreasing their self-esteem and thus adversely affecting their learning and social interaction [1]. Parents of affected children tend to prefer early treatment to avoid these adverse consequences. However, the treatment efficacy of CALMs by laser therapy is variable. We treated 471 children with CALMs at the laser clinic of Beijing Children's Hospital from January 2004 to December 2015. These children were treated by Q-switched alexandrite laser (755 nm) therapy and had good clinical improvement. We analyzed the efficacy, safety, and clinical factors of this treatment technique for CALMs.

## Patients and Methods

### Patients

In total, 471 children were recruited in our outpatient clinic, including 190 boys (40.34%) and 281 girls (59.56%). The male:female ratio was 1.00:1.48. The average age at onset age was 0.2 years (range, 0–7 years). CALMs were noted at birth in 326 patients (69.2%), within 1 year of age in 126 (26.7%), from 1 to 3 years of age in 13 (2.7%), and from 3 to 7 years of age in 6 (1.2%). The average age at diagnosis was 3.5 years (range, 0.08–14.3 years), and the average time duration of the CALMs was 3.4 years (range, 0.0–14.3 years).

### Intervention

The patients were treated with an alexandrite laser machine (Cynosure, Inc., Westford, MA) with a wavelength of 755 nm. The first-generation machine used a pulse width of 60 ns, spot diameter of 3 mm,



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frequency of 2–5 Hz, and energy of 7.6–15 J/cm$^2$. The second-generation machine used a pulse width of 50 ns, spot diameter of 3 mm, frequency of 2–5 Hz, and energy of 5–10 J/cm$^2$.

### Questionnaire

We retrospectively analyzed the patients' demographic and basic clinical information (sex, age at onset, and age at diagnosis) by reviewing the medical records. Descriptive statistical analysis was used to evaluate the epidemiological information (potential triggering factors, family history, aggravating factors, and disease association), clinical characteristics (affected areas, color, size, and shape), and treatment parameters and responses (treatment age, times, interval, energy intensity, efficacy, and relapse). The work presented here was reviewed and approved by Beijing Children's Hospital, Capital Medical University (National Center for Children's Health, China), and informed consent was acquired from the parents of each child included in the study.

### Measurement Method

The demographic and clinical data of the patients were recorded, including name, sex, age at diagnosis, date of diagnosis, age at onset, and lesion site and size. A consent form was signed and clinical photographs were taken before each laser treatment, and the treatment parameters were recorded after each treatment.

Before each laser treatment, a clinical examination was performed to assess the color and size of the lesions as well as any pigmentary abnormalities and the presence of scars. For children aged > 3 months, compound lidocaine cream (Beijing Purple Light Pharmaceutical Co., Ltd., Beijing, China) was applied to the skin and covered by plastic film to enhance absorption. The skin was cleaned after 60–90 minutes, and laser treatment was performed. The clinician using the laser wore protective goggles and placed wet gauze or an eye mask over the patients' eyes. Appropriate treatment parameters were chosen according to the children's age, the color and size of the lesion, and the experience of the clinician. The laser handpiece was held vertically to the skin at a distance of 4 cm, and laser therapy was delivered to the skin evenly without overlap or omission. Test spots were performed to the treatment endpoint to achieve a gray-white "frost change." The laser energy was reduced if the skin reacted with wounding or blister formation. Ice compression was immediately provided for 15 minutes after laser treatment. The parents were requested to keep the skin dry, avoid contact with water and scratching, and apply barrier creams to prevent infection and enhance skin recovery for 1 week. Exposure to strong sunshine was avoided for 1–3 months, and wide-brim hats and sunscreen were advised during outdoor activities [2,3]. If blisters occurred, they were punctured by sterile needles to release the blister fluid. If significant edema developed, a topical corticosteroid cream was applied twice per day to reduce inflammation. The treatment interval was adjusted based on the patients' age and treatment reaction, which ranged from 3 to 12 months.

### Assessment of Treatment Effect

The treatment efficacy was evaluated by two attending physicians using pre- and post-treatment clinical photographs of each patient. The treatment efficacy was classified into four levels: Level 1, the lesion improved by ≥75% (curative); Level 2, the lesion improved by 50%–74% (significant improvement); Level 3, the lesion improved by 25%–49% (improved); and Level 4, the lesion improved by <25% (inadequate improvement). Effective treatment was obtained for Levels 1–3 clinical results, and significantly effective treatment was obtained for Levels 1 and 2 clinical results.

### Statistical Analysis

SPSS 19.0 statistical analysis software (IBM Corp., Armonk, NY) was used to analyze the clinical data. The treatment efficacy was analyzed using the Kruskal–Wallis $H$ rank test. Spearman's rank correlation was used to analyze the treatment effect and number of treatments. The dependent variable was effective treatment (combined cases of complete cure, significant improvement, and improvement), and the independent variables were nine items including treatment times, sex, age, lesion characteristics, and laser treatment situation. Multifactor logistic regression analysis was used to analyze the effective influencing factors. The odds ratio was calculated to estimate the relative risk and significance level of the maximum likelihood ratio test ($P < 0.05$).

## RESULTS

### Distribution Characteristics of Damaged Skin

Among the 471 patients, 351 (74.52%) had CALMs on the cheek, 45 (9.55%) on the forehead, 51 (10.83%) on the temple, 8 (16.99%) under the jaw, 13 (2.76%) in the perioral area, 30 (6.37%) on the nose, 19 (4.03%) on the neck, 12 (2.55%) on the trunk, and 15 (3.18%) on the limbs. A total of 407 (86.41%) patients had a single lesion and 64 (13.59%) had multiple lesions.

### Morphologic Characteristics of Damaged Skin

The CALMs were generally round and irregular in shape, and the boundary was clear. The lesional skin color was uniform and consistent in 457 patients (97.03%), among whom 109 patients (23.14%) had sandy beige lesions, 308 (65.39%) had brown lesions, 40 (8.49%) had dark brown lesions, and 14 (2.97%) had heterogeneous lesions. The diameter of the CALMs was ≤2 cm in 271 patients (57.54%), >2–5 cm in 126 (26.75%), >5–10 cm in 52 (11.04%), and >10 cm in 22 (4.67%). One 5-year-old girl had a skin lesion on her right forearm that showed a pattern of linear array; one patient had a traumatic tattoo, two had nevus of Ota, three had freckles, four had neurofibromatosis, and five had nevus spilus.

### Therapeutic Effect

**Comparison of therapeutic effect among different treatment times.** Of the 471 patients, the treatment result was curative in 140 (29.72%) patients,

significantly effective in 124 (26.33%), and effective in 110 (23.35%). The treatment success rate was 79.41%, and 56.05% of patients achieved significantly effective improvement (Table 1). The treatment efficiency was positively correlated with the number of therapy sessions ($rs = 0.26$, $P < 0.0001$); that is, the therapeutic efficacy was statistically different according to the number of treatments ($H = 38.25$, $P < 0.0001$) (Fig. 1).

**Comparison of therapeutic effect among different sex, age, and skin lesions.** The difference in treatment efficacy according to the age at onset, age at treatment and lesion position, color, and size was not statistically significant ($P > 0.05$) (Table 2). The nonparametric rank and inspection results of the treatment effect showed that sex (female vs. male) ($H = 5.04$, $P = 0.0247$) and different treatment intervals ($H = 12.83$, $P = 0.0003$) had statistical significance.

**Logistic regression analysis.** The related value assigned is shown in Supplemental Table S1. Multivariate logistic regression analysis showed that the number of treatments influenced the effectiveness of therapy (odds ratio, 2.130; 95% confidence interval, 1.561–2.908) (Table 3).

**Adverse reactions.** Younger patients cried because of pain during laser treatment. Eight patients developed hyperpigmentation, six developed hypopigmentation, and one developed a superficial punctate scar. These children were advised to use sunscreen, and all of their skin complications resolved within 1 year.

## DISCUSSION

CALMs are a hyperpigmented skin lesions that commonly appear in children. The etiology is not clear, and the morbidity is about 10%–20%, of which 2% appear in newborns [4]. In the present study, most patients developed CALMs within 1 year of age (93.63%, $n = 441$), which is consistent with relevant literature reports. The sex of the patient did not affect the age at onset of CALMs. CALMs appeared mostly on the face and less often on the limbs and trunk; they were circular or irregular in shape with a light brown to dark brown color and clear


Fig. 1. Two-year-old children patient with facial Café-au-lait spots before and after the laser treatment. (**A**) Children patient with facial Café-au-lait spots before laser treatment; (**B**) the spots faded obviously after four-time treatment [Color figure can be viewed at wileyonlinelibrary.com].

**TABLE 1. Comparison of Therapeutic Effect Among Different Treatment Times for Children Patients**

| Treatment times | Cases | Cured completely (%) | Effective significantly (%) | Improved (%) | Invalid (%) | Effective rate (%) | Effective significantly rate (%) |
|---|---|---|---|---|---|---|---|
| 1 | 119 | 21 (17.65) | 24 (20.17) | 24 (20.17) | 50 (42.01) | 57.98 | 37.81 |
| 2 | 178 | 56 (31.46) | 52 (29.21) | 38 (21.35) | 32 (17.98) | 82.02 | 60.67 |
| 3 | 98 | 32 (32.65) | 22 (22.45) | 34 (34.70) | 10 (10.20) | 89.79 | 55.10 |
| 4 | 41 | 18 (43.90) | 14 (34.15) | 6 (14.63) | 3 (7.32) | 92.68 | 78.05 |
| ≥5 | 35 | 13 (37.14) | 12 (34.29) | 8 (22.86) | 2 (5.71) | 94.29 | 71.43 |
| Total | 471 | 140 (29.72) | 124 (26.33) | 110 (23.35) | 97 (20.60) | 79.41 | 56.05 |

Effective rate = cases of (curative + significantly effective + improved)/total cases; significantly effective rate = cases of (curative + effective significantly)/total cases.

**TABLE 2. Comparison of Therapeutic Effect Among Different Patient Groups**

| | Cases | Cured completely (%) | Effective significantly (%) | Improved (%) | Invalid (%) |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male | 190 | 49 (25.79) | 46 (24.21) | 48 (25.26) | 47 (24.74) |
| Female | 281 | 91 (32.38) | 78 (27.76) | 62 (22.06) | 50 (17.80) |
| Onset age | | | | | |
| 0~1 month | 326 | 99 (30.37) | 81 (24.85) | 77 (23.62) | 69 (21.16) |
| 1~12 months | 115 | 31 (26.96) | 34 (29.56) | 27 (23.48) | 23 (20.00) |
| >12 months | 30 | 10 (33.33) | 9 (30.00) | 6 (20.00) | 5 (16.67) |
| Treatment age | | | | | |
| 0~12 months | 112 | 29 (25.89) | 30 (26.79) | 30 (26.79) | 23 (20.53) |
| 12~36 months | 145 | 42 (28.97) | 44 (30.34) | 32 (22.07) | 27 (18.62) |
| >36 months | 214 | 69 (32.24) | 50 (23.37) | 48 (22.43) | 47 (21.96) |
| Position of damaged skin | | | | | |
| Face | 448 | 137 (30.58) | 114 (25.45) | 104 (23.21) | 93 (20.76) |
| Trunk/limbs | 23 | 3 (13.04) | 10 (43.48) | 6 (26.09) | 4 (17.39) |
| Color of damaged skin | | | | | |
| Dark brown | 40 | 12 (30.00) | 10 (25.00) | 11 (27.50) | 7 (17.50) |
| Brown | 308 | 94 (30.52) | 90 (29.22) | 68 (22.08) | 56 (18.18) |
| Sandy beige | 109 | 31 (28.44) | 22 (20.18) | 25 (22.94) | 31 (28.44) |
| Not uniform | 14 | 3 (21.43) | 2 (14.28) | 6 (42.86) | 3 (21.43) |
| Size of damaged skin (diameter, cm) | | | | | |
| ≤2 | 271 | 87 (32.10) | 68 (25.09) | 67 (24.72) | 49 (18.09) |
| >2 and ≤5 | 126 | 37 (29.37) | 34 (26.98) | 28 (22.22) | 27 (21.43) |
| >5 | 74 | 16 (21.62) | 22 (29.73) | 15 (20.27) | 21 (28.38) |
| Energy of laser treatment ($J/cm^2$) | | | | | |
| 5.0~6.5 | 262 | 76 (29.01) | 76 (29.01) | 65 (24.81) | 45 (17.77) |
| 6.5~8.0 | 81 | 21 (25.93) | 26 (32.10) | 18 (22.22) | 16 (19.75) |
| 8.0~10.0 | 63 | 20 (31.75) | 12 (19.04) | 11 (17.46) | 20 (31.75) |
| >10.0 | 65 | 23 (35.38) | 10 (15.38) | 16 (24.62) | 16 (24.62) |
| Interval of laser treatment | | | | | |
| ≤3 months | 333 | 89 (26.73) | 81 (24.32) | 81 (24.32) | 82 (24.63) |
| >3 months | 138 | 51 (36.96) | 43 (31.16) | 29 (21.01) | 15 (10.87) |

boundaries [5]. The size of the CALMs generally increased proportionately with age and development of the body; however, the lesions usually remained <5 cm. There were more female than male patients among all 471 patients. CALMs were seen on the face and neck in 456 patients (96.82%), accounting for the vast majority of cases. Parents tended to pay more attention to the lesion when the patient was a female whose CALMs were present on an exposed part of the body, generally increasing the urgency for treatment. Neurofibromatosis was present in four patients (6.25%) among those with multiple lesions ($n = 64$, 13.59%). Multiple CALMs should alert the

**TABLE 3. Results of Effectiveness by Logistic Regression Analysis**

| Factors | Parameter ($\beta$) | SE ($\beta$) | $\chi^2$ | $P$ | OR | 95%CI | |
|---|---|---|---|---|---|---|---|
| Constant term | −1.5990 | 1.1558 | 1.9138 | 0.1665 | – | – | – |
| Treatment times (×1) | 0.7562 | 0.1588 | 22.6928 | <0.0001 | 2.130 | 1.561 | 2.908 |
| Gender (×2) | 0.4337 | 0.2477 | 3.0659 | 0.0800 | 1.543 | 0.950 | 2.507 |
| Onset age (×3) | 0.3278 | 0.2089 | 2.4632 | 0.1165 | 1.388 | 0.922 | 2.090 |
| Treatment age (×4) | −0.00112 | 0.1517 | 0.0001 | 0.9941 | 0.999 | 0.742 | 1.345 |
| Position of damaged skin (×5) | 0.5359 | 0.6000 | 0.7978 | 0.3718 | 1.709 | 0.527 | 5.539 |
| Color of damaged skin (×6) | −0.0740 | 0.1935 | 0.1463 | 0.7021 | 0.929 | 0.636 | 1.357 |
| Size of damaged skin (×7) | −0.1358 | 0.1573 | 0.7454 | 0.3879 | 0.873 | 0.641 | 1.188 |
| Energy of laser treatment (×8) | 0.2984 | 0.3423 | 0.7601 | 0.3833 | 1.348 | 0.689 | 2.636 |
| Interval of laser treatment (×9) | −0.1457 | 0.1082 | 1.8113 | 0.1784 | 0.864 | 0.699 | 1.069 |

CI, confidence interval; OR, odds ratio; SE, standard error.


Fig. 2. Two-year-old children patient with irregular shape of facial Café-au-lait spots before and after the laser treatment. (**A**) Before laser treatment, irregular facial spots were irregular shape, jagged edge; (**B**) after one-time treatment spots (only the left side of the red line is treated by laser) faded significantly [Color figure can be viewed at wileyonlinelibrary.com].

clinician to the possibility of neurofibromatosis [6–8], Albright syndrome [9], Watson syndrome, and other genetic diseases and solid tumors [10]; relevant genetic investigations are necessary in such cases.

Treatment methods for CALMs include cryotherapy, electrofulguration, chemical peeling, mechanical grinding, and surgical operations. However, these methods commonly cause adverse reactions and trauma to normal tissue as well as an increased risk of permanent pigmentary changes and residual scarring [11]. Laser therapies have been used to treat CALMs [12], including the copper vapor laser [13], 532-nm Q-switched Nd:YAG laser [14,15], Q-switched ruby laser [16], Q-switched alexandrite laser [17,18], erbium-doped yttrium aluminum garnet laser [19–22], pulsed dye laser [23], and dual wavelength picosecond laser [24]. According to the principle of selective photothermolysis proposed by Anderson and Parrish[25], the Q-switched alexandrite laser releases laser beam wavelengths of 755 nm at a pulse width of 100 ns, which is shorter than the thermal relaxation time of 1 ms for melanin granules in melanocytes, keratinocytes, or dermal macrophages. This not only destroys the epidermal melanin but also spares the surrounding tissue to achieve the purpose of noninvasive treatment of CALMs [26,27]. In the present study, the treatment efficacy increased as the number of treatments increased. The total treatment efficacy rate among all 471 patients (79.41%) was higher than that of adult patients reported in the literature [28]. In our study, the treatment efficacy was higher in children at an early stage of treatment (>50% of the treated children in this group were <3 years of age) who had relatively thin skin and lightly colored lesions (children with brown and light brown spots accounted for 88.54%); immature melanocytes have a better response to laser therapy [29]. In younger children, however, we found that with improvement of the primary lesions, new spots appeared around the treatment area or at other sites during treatment. Therefore, although early treatment of CALMs can reduce the number of treatment, especially whether the treatment area lesions rebound or not, new lesions can appear in the treatment region in growing children, and further treatment may be needed in the later stages [30].

In the present study, the treatment effect was not significantly affected by the time of onset, age of the patient, or lesion position, color, or size. However, the nonparametric rank test showed significant differences among different treatment times, sexes, and treatment intervals. According to the results of the multivariate logistic regression analysis after removal of confounding factors, only the number of treatments was a statistically significant factor; this is consistent with previously published reports [28]. The analysis indicated that the treatment interval was related to the number of treatments required in that longer treatment intervals were associated with a requirement for more treatments. Therefore, the reason for the statistically significant difference in the treatment effects according to the treatment interval was the statistically significant difference among the treatment times. According to the abovementioned principle of laser treatment, Q-switched lasers have a selective effect on pigment cells in a very short period of time, destroying the melanin while protecting the surrounding normal skin by the selective photothermal effect. The subsequent inflammatory process removes the pigment granules, which are ingested by macrophages after removal through the lymphatic system [31]. This process is variable but generally takes about 3 months. Therefore, the conclusion is that a longer interval between

laser treatments is associated with more effective transport of the crushed pigment particles in the body. In our observation of the morphology of CALMs and the treatment effect, we found that the treatment effect was higher on lesions with an irregular shape and jagged edge than on those with a regular shape (Fig. 2). This is consistent with the results of Q-switched Alexandrite laser treatments in adults [32,33]. However, because of incomplete data, this study was unable to show any statistical evidence of this association; this is a limitation of the study.

The treatment of CALMs in children differs from that in adult patients. Children generally do not cooperate while the doctor is administering treatment. Therefore, we typically use transcutaneous polidocanol to reduce discomfort and implement some other protective practices, such as covering the eyes and applying physical restraint. For treatment of the eyelid and other sensitive areas, we only administer one treatment during childhood to ensure the patient's safety. We counsel the parents of children with large CALMs, advising initial treatment of a small spot with further treatments if positive outcomes are seen. Adequate communication with the patients' parents is necessary to achieve treatment satisfaction. Early treatment may be effective in not only removing or reducing spots but also reducing the unnecessary psychological burden in nursery or primary school. Additionally, clinicians may consider initial smaller spots treatments is smaller so that the children may experience less pain during the treatment process. Therefore, early treatment for pediatric CALMs is recommended [34]. For children with large spots, some hospitals may also provide intravenous anesthesia to alleviate discomfort. A small number of children may develop hyperpigmentation, hypopigmentation, and superficial scars during the treatment course, but abnormal skin manifestations return to normal with time, and patients do not develop permanent adverse reactions. According to our experience with laser treatment, we choose the most appropriate power setting according to the color of the skin lesion, aiming to cause a gray-white color change; that is, a change into a "frost color." For some more lightly colored spots, high initial power should not be used to avoid subsequent post-inflammatory hyperpigmentation. Conversely, excessive reactions may occur in some children with darker spots. In such cases, pulse overlap should be avoided to decrease the risk of adverse reactions by reducing the pulse frequency and density of the spots.

In summary, Q-switched alexandrite laser therapy may be a safe and effective treatment method for CALMs, and the number of treatments should be considered as a factor that influences the therapeutic effect.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supporting information.