

# Laser toning e drug delivery: estudo-piloto utilizando laser Q-switched Nd:YAG 1064nm

Laser toning and drug delivery: a pilot study using laser Q-switched laser 1064nm

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## ABSTRACT

**Introduction:** Laser toning technique is performed with the Q-switched Nd:YAG laser 1064 nm, aiming at stimulating neocollagenesis. The technique can also be associated with the application of suitable medicines for drug delivery, increasing its potential for skin permeation.

**Objective:** To evaluate the results of laser toning Q-switched Nd:YAG laser 1064 nm associated with drug delivery through a pilot study.

**Methods:** Four patients underwent four laser sessions with application of a formula for drug delivery or placebo, fortnightly.

**Results:** According to the photographic assessment, laser toning promoted improvement of acne, pores, wrinkles and sensitivity. When associated with the drug delivery, there was superiority in results. In clinical evaluation differences were observed only in the pores analysis (+11%). 75% of patients had acneiform eruption.

**Conclusion:** Results of this pilot study show that laser toning can be enhanced when combined with drug delivery.

**Keywords:** lasers; administration, cutaneous; collagen; hydroxyproline; hyaluronic acid; ascorbic acid

## RESUMO

**Introdução:** A técnica de laser toning é realizada com a modalidade Q-switched Nd:YAG 1064nm, com o objetivo de estimular a neocolagênese. A técnica também pode ser associada à aplicação de medicamentos apropriados para drug delivery, aumentando seu potencial de permeação cutânea.

**Objetivo:** Avaliar os resultados da técnica de laser toning Q-switched Nd:YAG 1064nm associada ao drug delivery por meio de estudo-piloto.

**Métodos:** Quatro pacientes realizaram quatro sessões do laser com aplicação de uma fórmula para drug delivery ou placebo, em intervalos quinzenais.

**Resultados:** Segundo a avaliação fotográfica, o laser toning promoveu melhora da acne, poros, rugas e sensibilidade. Quando associado ao drug delivery, houve superioridade nos resultados. Na avaliação clínica observaram-se diferenças apenas na análise de poros (+11%). 75% dos pacientes apresentaram erupção acneiforme.

**Conclusão:** Os resultados deste estudo-piloto demonstram que o laser toning pode ser potencializado quando associado ao drug delivery.

**Palavras-chave:** lasers; administração cutânea; colágeno; hidroxiprolina; ácido hialurônico; ácido ascórbico

## INTRODUCTION

The transportation of drugs through the skin surface has been receiving increasing attention within various medical specialties, as it is a non-invasive, safe, effective and easy to access method. This administration route avoids first-pass metabolism in the liver and degradation of the drug in the gastrointestinal tract, which is crucial for many medications.<sup>1</sup>

In dermatology, the topical route for delivery of drugs is very important. However, the bioavailability of most drugs varies from 1% to 5%, and many do not reach the depth necessary to act on the target tissue.<sup>2</sup> For this reason, drug delivery techniques via transepidermal route – for instance, facilitated by lasers – are being continuously studied and improved.

The 1,064nm Q-switched Nd:YAG laser was one of the first non-ablative lasers used for rejuvenation and facial resurfacing with clinically and histologically proven results.<sup>3</sup> It can also be used in the treatment of hyperpigmentation, rejuvenation, tattoo removal, hair reduction and in the treatment of scars.<sup>4</sup> The laser toning technique is performed with Q-switched laser, with wave pulses in the magnitude of nanoseconds, aimed at stimulating dermal fibroblasts to engage in neocollagenesis. Multiple passes are performed at a low fluence.<sup>5</sup> The technique provides improved tone and texture of the skin, reducing pores, sebum secretion, rhytids and dyschromias, in addition to promoting drug delivery.<sup>6</sup>

The laser toning technique employing the 1,064nm quality (Q)-switched Neodymium:Yttrium-Aluminum-Garnet (Nd:YAG) laser associated with the application of medications suitable for drug delivery immediately after the procedure, was assessed in the present pilot study.

## METHODS

Four female patients aged between 39 to 54 years, with Glogau aging grades from II to III and Fitzpatrick phototypes II to IV were selected. All ethical principles were observed in the research protocol and all patients signed a free and informed term of consent, agreeing to participate in the study.

In order to evaluate the outcomes of using the laser toning technique as a vector for drug delivery, four sessions were performed at fortnightly intervals, with the application of a specific dispensed formulation immediately after the laser, in two patients. The dispensed formulation contained: 5% Hyaxel<sup>®</sup>, 4% Hidroxiprolisilane C<sup>®</sup>, 5% DMAE Pidolato<sup>®</sup>, 6% Nano Vit C<sup>®</sup>, 4% Matrixyl 3000<sup>®</sup> in anhydrous fluid serum. In the other two patients, only the vehicle was applied as a placebo. The patients continued using the formulations (test or placebo) at home, throughout the duration of the study.

The laser toning technique was performed with the 1,064nm Q-switched Nd:YAG (neodymium-doped yttrium-aluminum-garnet), Ethera<sup>®</sup> platform (Vyndence Medical, São Carlos, São Paulo, Brazil) with the 7mm tip, 5Hz frequency, two passes across the face. The energy used in the first session was 600mJ, being increased to 900mJ in the second, and to 1,200mJ the third and fourth sessions. Roughly 2,500 laser passes were performed in each session.

The following evaluations were carried out: clinical analysis of photographs before and after 15 days of the last session by a blinded dermatologist physician; objective comparison using the Focco<sup>®</sup> device (Focco Fotografias, Fabinject, Taubaté, São Paulo, Brazil) for the parameters *wrinkles, pores, acne lesions, UV index* (photographs with UV lighting, coupled to the device for the analysis of hyperchromia, even when imperceptible to visible light), *sensitivity, spots, and vessels*; subjective evaluation using a patient satisfaction questionnaire. The device allows the progressive comparison of the patient's photographs during the experimental time, including graphs and separate analyzes of all the parameters described above.

## RESULTS

According to the objective evaluation performed with the Focco<sup>®</sup> device, the laser toning procedure associated with the placebo formulation, led to the improvement of acne, pores, wrinkles and sensitivity, as shown in Graph 1. The parameters spots and UV index worsened (16.78% and 68.8% respectively). These results remained for 120 days after the last laser session. The photographs of the patients who underwent the placebo treatment are shown in Figure 1.

When the *laser toning technique + placebo* is compared with the *laser toning technique + drug delivery*, there was superiority of the combined technique in the parameters acne, stains, pores, texture and UV index, according to Graph 2. When comparing the laser toning technique in isolation with associated drug delivery, both showed similar results in the improvement of wrinkles and sensitivity. Photographs of patients who underwent treatment with drug delivery are shown in Figure 2.

The clinical evaluation evidenced improvement in all aspects, in all patients. Nevertheless, the difference between the test-group and placebo-group was observed only in the analysis of pores (+11%).

All patients reported improvement with the procedure in all assessed aspects. There was absence of complaints about the pain caused by the procedure, which was classified as painless for most patients (75%). However, 75% of them – in both groups – showed acneiform eruption, most probably related to the vehicle.

## DISCUSSION

Several chemical and physical methods, such as lasers and microneedling, have been studied aiming at increasing the skin's permeability.<sup>5</sup> Lasers promote the permeation of drugs through three mechanisms: direct ablation; optical breakdown by photomechanical waves that transiently permeabilize the stratum corneum without removing it; and photothermal effect.<sup>7,8</sup> The photomechanical waves promote the expansion of the lacunar spaces in the stratum corneum's lipids, creating pores for the permeation of molecules and also causing changes in cell membranes, thereby facilitating the transcellular route.<sup>7,9</sup>



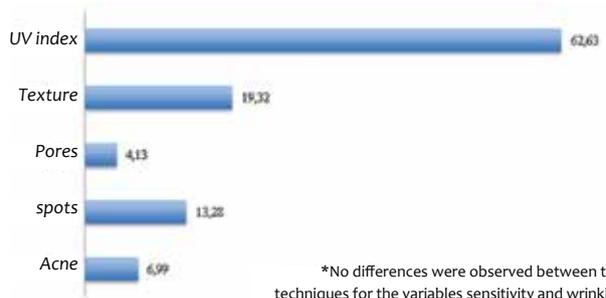
FIGURE 1: Before (left) and after (right) photographs of the two patients in the placebo group (before and 15 days after the last laser session)



FIGURE 2: Before (left) and after (right) photographs of the two patients in the drug delivery group (before and 15 days after the last laser session)



GRAPH 1: Mean value of the improvement in each variable with laser toning + placebo comparing the baseline to 15 days after the end of the treatment



\*No differences were observed between the techniques for the variables sensitivity and wrinkles  
 GRAPH 2: Number of times when the combination laser toning + drug delivery led to better results as compared to the isolated laser toning technique for each variable

Furthermore, there is a possibility of modulating the degree of permeation according to the fluence and number of pulses applied.<sup>7</sup> In general, the fluence required to promote transepidermal delivery is lower than that used for other therapeutic purposes, for once the stratum corneum – which is the main barrier for the drug delivery – is ruptured, there is no additional benefit.<sup>2</sup> Another advantage associated with the use of lasers for the delivery of drugs is the fact that it is a physical method, which reduces the risk of irritating cutaneous reactions and interference with the permeated drug, which can occur when chemical methods are used for drug delivery.<sup>9</sup>

The first lasers studied in connection with the promotion of drug delivery were the fractional and non-fractional ablative. The potential use of non-ablative lasers were analyzed later on.<sup>10</sup> The benefits of the use of non-ablative lasers arise from the shorter recovery time needed, lower risk of adverse effects, preservation of the epidermal integrity, and the potential to achieve many of the results obtained with ablative lasers.<sup>11, 12</sup> In 2014, Lim et al described the use of the fractional non-ablative 1,550nm Erbium:glass laser for drug delivery of aminolevulinic acid (ALA). The results, analyzed by porphyrin fluorescence, showed greater penetration of ALA in the areas treated with the laser and confirmed the drug delivery-promoting effect of the 1,550nm Erbium:glass laser.<sup>11</sup>

The non-ablative 1,064nm Q-switched Nd:YAG laser emits ultra-short waves with duration of nanoseconds and high energy peaks that completely disrupt the keratin and corneocytes, forming micropores in the stratum corneum with minimal increase of the temperature.<sup>7,8</sup> These changes allow increased cutaneous permeation of up to 12 times relative to that of the intact skin, that may last for up to one week after the application of the laser.<sup>2,8</sup> In addition, there is promotion of dermal remodeling without ablation by the laser toning technique, carried out with lasers of the Q-switched type. The neocollagenesis results from the thermal injury caused by the laser in the dermis, and occurs to a lesser degree than that produced by ablative lasers.<sup>12,13</sup>

The laser toning technique comprises the use of Q-switched lasers in multiple passes with low fluence, and has been used for many years in Asian countries for facial rejuvenation and for treatment of melasma.<sup>14</sup>

In 1997, Goldberg performed a pioneering pilot study describing the use of the 1,064nm Q-switched Nd:YAG laser for the treatment of facial rhytids as compared to the treatment using the 10,600nm CO<sub>2</sub> laser.<sup>15</sup> In 1999, Goldberg and Metzler continued studying the 1,064nm Q-switched Nd:YAG laser, observing improvement in the skin's texture and elasticity, and facial rhytids after three monthly treatments.<sup>16</sup> In 2001, the same author carried out a study evaluating histological changes in six patients treated with one session of Q-switched Nd:YAG laser: there was an improvement of the solar elastosis and in the organization of collagen fibers, and an increase in thickness of the papillary dermis observed by histological analysis, three months after treatment.<sup>13</sup> Also in 2001, Trelles described the use of the 1,320nm Q-switched Nd:YAG laser in four sessions for facial rejuvenation with an increase in the epidermal thickness

and density of collagen fibers in all patients.<sup>17</sup> Another study by Berlin et al. in 2008, evaluated ten patients who underwent six fortnightly sessions of 1,064nm Q-switched Nd:YAG laser, with the histological analysis confirming Goldberg's findings.<sup>3</sup> All these studies confirm the effectiveness of the laser toning technique for dermal remodeling and improvement of the cutaneous firmness in facial treatments.

The use of 1,064nm Q-switched Nd:YAG laser for the treatment of periorbital rhytids in six fortnightly sessions in eight patients was described by Karabudak et al.. Fifty percent of them had clinical improvement while all treated patients showed an increase in the average density of collagen fibers ( $p < 0.05$ ), demonstrating the effectiveness and safety of Q-switched lasers also in the treatment of the periorbital area.<sup>5</sup>

The combination of laser toning technique and drug delivery was described for the treatment of melasma in a split-face study. The 1,064nm Q-switched Nd:YAG laser was applied across the face associated with the ultrasonic application of vitamin C in a single hemiface, in four monthly sessions. The evaluation three months after the last session showed superiority of results in the hemiface treated with laser toning associated with drug delivery.<sup>4</sup> Other drugs described in the literature that have had their permeation increased through Q-switched lasers are: ALA and 5-fluorouracil.<sup>18,19</sup>

The results of the present study demonstrate that the laser toning technique can be enhanced when associated with drug delivery and selected active principles. Each of the formulation components had a specific function. As Hyaxel® (an hyaluronic acid of low molecular weight, whose vector is the organic silicon) and Hidroxiprolisilane C® (a source of hydroxyproline) have an effect on neocollagenesis, the authors suggest that the improvement in the skin's texture can be linked to the presence of these two components as well as DMAE Pídelado®, which acts as a surface tensor. Additionally, the Nano Vitamin C® (a nanocoated vitamin C that acts as an antioxidant, whitener, sebum production reducer and neocollagenesis stimulator agent, enabled the improvement in the parameters *acne, texture, stains, and UV index* when observed using the Focco® device. Finally, Matrixyl 3000® (an extracellular matrix re-densifier that stimulates the synthesis of macromolecules which promote increased skin elasticity), being capable of improving texture parameters and reducing pores.<sup>20</sup>

## CONCLUSION

The present pilot study showed promising results arising from the combination of the laser toning technique using Q-switched laser with a drug delivery-specific formulation.

The drug delivery technique deserves attention due to its capacity to optimize the laser toning results, discussing the benefit of the combination of procedures that guarantee more promising results due to increased permeability of the stratum corneum. Due to the fact it is an innovative technology, with a short recovery time, and which does not preclude patients from carrying out their daily activities, in addition to the fact that it can be performed in higher phototypes with minimal risk of

side effects as compared to other laser types, the method evaluated deserves further scrutiny aimed at confirming the findings reported in the present paper.

Studies exploring the use of Q-switched laser for drug delivery are fewer than those related to the use of ablative lasers, either fractional or not. Therefore, further studies are needed to clarify the doubts that persist on the subject matter. ●

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