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Editor's Choice

Safety and Efficacy of Blue Light Laser Treatment in Hereditary Hemorrhagic Telangiectasia

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Background and Objectives: Hereditary hemorrhagic telangiectasia (HHT) is a hereditary condition that is associated with arteriovenous malformations. A common site for these malformations is the nasal mucosa, which is associated with severe epistaxis and debilitation for affected patients. We evaluated the efficacy and safety of blue light laser technology in treating these endonasal manifestations in a retrospective chart analysis. Additionally, we compared blue light laser technology to bipolar coagulation in an animal model.

Study Design/Materials and Methods: We performed a retrospective chart analysis of all patients that were diagnosed with HHT and received endonasal blue light laser treatment between 10/2017 and 04/2019. In addition, we performed bipolar or blue light laser coagulation of all macroscopically visible vessels on thyroid gland lobes ($n = 4$) from Dunkin–Hartley Guinea Pigs. Hematoxylin-eosin (HE) staining was then used to visualize depth and area of coagulation surrounding these vessels.

Results: One hundred and fifty-one treatments in 23 patients were analyzed. Under regular blue light laser treatment, quality of life (QOL), indicated on a visual analog scale from 1 to 10, gradually increased significantly from 5.6 ± 0.5 (before the first treatment) to 7.5 ± 0.9 (after the second treatment). Following this, QOL remained steady throughout additional treatments. Adverse effects were not recorded. HE staining showed that coagulation depth (162 ± 56 vs. $586 \pm 192\,\mu m$) and area (74 ± 35 vs. $1015 \pm 449\,\mu m^2$) were significantly lower after laser treatment.

Conclusion: Blue light laser therapy is safe and efficient in treating HHT. Damage to the surrounding tissue is significantly lower compared with bipolar coagulation. © 2020 The Authors. *Lasers in Surgery and Medicine* published by Wiley Periodicals LLC

Key words: blue light laser; laser; HHT; osler; hemorrhagic hereditary teleangiectasis

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is a non-curable autosomal dominant vascular disorder with an estimated prevalence of 1 in 5000 to 10,000 individuals worldwide [1,2]. The disease causes formation of arteriovenous malformations, which may present throughout the human body. The most common clinical manifestation is recurrent epistaxis from dilated blood vessels and arteriovenous malformations (AVM) located in the endonasal mucosa. Epistaxis is considered to be the most frequent clinical characteristic, as has been reported in up to 95% of HHT patients. In addition to epistaxis, affected patients may also develop arteriovenous malformations of the brain, lung, liver, and gastrointestinal tract, from which major, even life-threatening, complications may arise. Nonetheless, epistaxis remains the main clinical symptom and has been shown to have the greatest negative impact on quality of life, even independent of additional systemic HHT manifestations [3].

Chronic epistaxis may already occur in early childhood [4] and symptoms usually increase with age [5]. Unless treated in centers with experience in HHT, treatment is often limited to strategies applied in acute epistaxis [6]. HHT patients experience a mean frequency of 18 epistaxis episodes per month [7]. A variety of treatment modalities are available

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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for management of chronic epistaxis in HHT. However, management is challenging. Conservative methods include regular mucosal care, temporary nasal occlusion with adhesive hypoallergenic tape [8,9], tranexamic acid [10], acetylcystein [11], and estrogen agents [12,13]. Procedural therapies, such as electrical or chemical coagulation techniques show high efficacy in patients with acute epistaxis without HHT. In contrast to patients suffering from common nosebleeds, patients with HHT show a pathologic structure of vessel walls. AVMs represent the final stage of the vascular disease. The chronic nature of the condition dictates the necessity for repeated treatments, which, in turn, may cause complications, for example, cicatrization, dryness of nasal mucosa, and nasal septum perforation [14]. Young's procedure (closure of the nasal cavity), and Saunder's dermoplasty (replacement of the endonasal mucosa by skin or buccal mucosa) are available for the most severe cases [15,16]. Currently, laser therapy systems emitting in near-infrared light (KTP, 532 nm), Nd:YAG (1064 nm), or diode lasers are frequently employed to control chronic epistaxis in HHT [8,17–19]. Laser treatment of nasal manifestations has been shown to be effective in decreasing the number of epistaxis episodes while at the same time showing very little adverse effects on the nasal mucosa. However, laser techniques deployed in the past were not very specific to the chromophore of hemoglobin. Blue light lasers (445 nm) in contrast use hemoglobin as a chromophore and are therefore highly specific to blood vessels and HHT lesions compared with surrounding mucosal tissue (Fig. 1). Due to the chronic nature of HHT, long-term nasal laser treatments should be associated with as little relevant side effects as possible. Taking into account the physical properties of lasers, it can be assumed that lasers emitting blue light are more specific to blood vessels and subsequently exert less thermical damage to the surrounding healthy mucosa. However, to date, there is very limited data on the use of blue light lasers in HHT.

Thus, the aim of this study was to assess the efficacy and safety of blue light lasers in regular treatment of nasal manifestations of HHT. We conducted a retrospective chart analysis of patients treated with blue light lasers in HHT documenting side effects on the one hand as well as efficacy by hemoglobin levels and visual analogue scale on the other hand. In addition to this, we performed animal experiments comparing the coagulation depth and area between blue light lasers and bipolar electrocoagulation.

MATERIALS AND METHODS

Retrospective Chart Analysis

Ethics. This study was registered with the ethics committee of the University of Munich under the ongoing

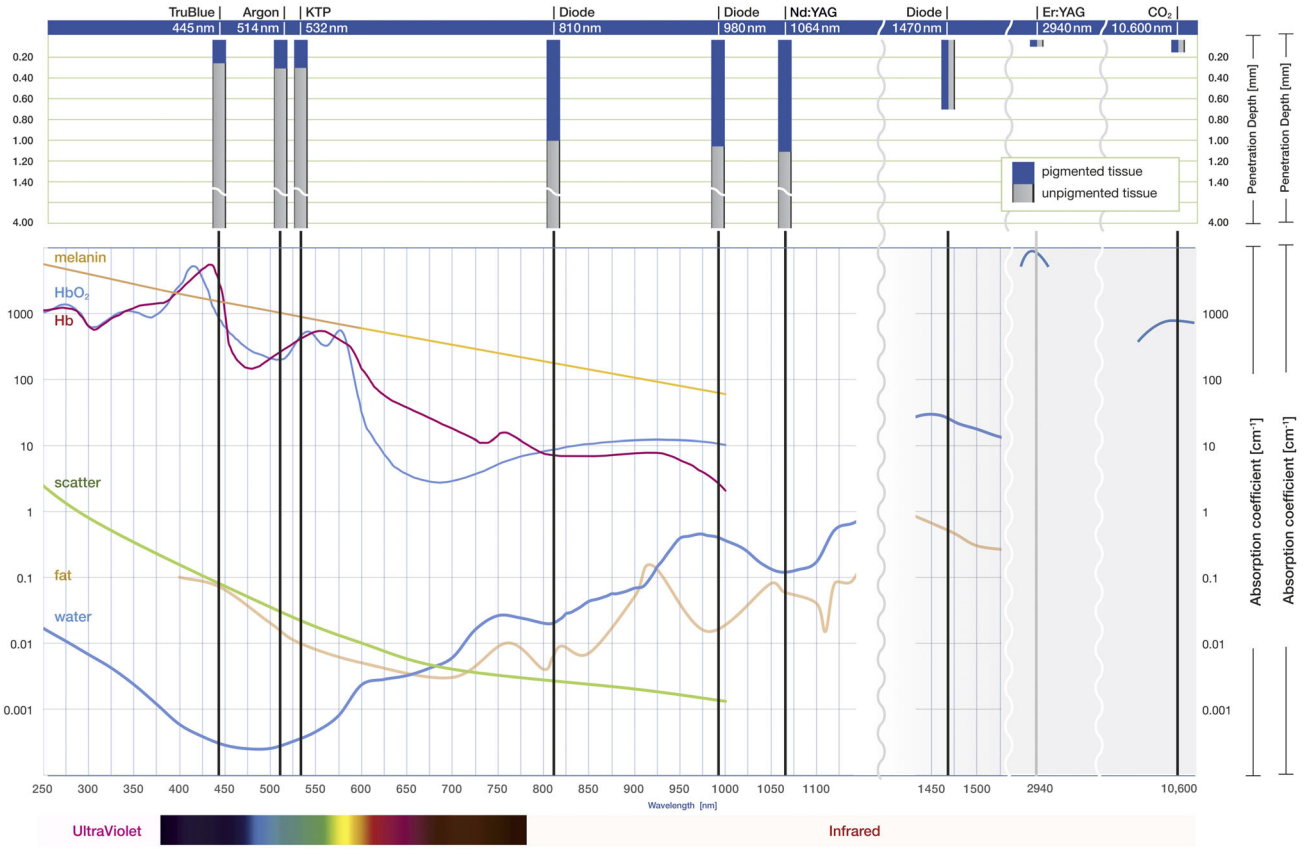

Fig. 1. Wavelengths of different laser systems and corresponding chromophores, kindly provided by ARC Laser Systems.

file number 19-094. The ethics committee waived the need for informed consent since the study was strictly limited to data collection during regular standard practice. There were no changes in treatment caused by this study.

Clinical approach. Patient suspected to suffer from HHT were referred to an in-house specialized consultation desk. If the clinical presentation was consistent with HHT and Curacao-criteria were met or if the diagnosis was confirmed by mutation detection by polymerase chain reaction, patients were considered to have a confirmed diagnosis of HHT. Out of those patients, those that suffered from regular epistaxis were offered laser treatment.

Treatment was performed under local anesthesia (Tetracain 4% solution, applied topically with neurosurgical patties for approximately 10 minutes) in a supine position with the chest elevated at an angle of 40° with an operation microscope (Carl Zeiss Opmi Pico, Carl Zeiss, Oberkochen, Germany). During treatment, all endonasally visible manifestations of HHT were treated with a TruBlue™ laser system (ARC Laser GmbH, D-90411 Nuremberg, Germany), emitting blue light of 445 nm wavelength with a 300 µm bare fiber (1.4 W, 90 milliseconds pulse, 200 milliseconds pause), until the lesions showed macroscopic paling. Exceptions were large turbinate lesions, which were treated by radiofrequency coagulation due to their tendency to cause strong bleeding during laser therapy. Laser settings were established together with the manufacturer with respect to best response of vessel coagulation in terms of paling, without vessel bursting. Figure 2 documents the surgical approach showing the typical paling of HHT lesions after laser treatment.

Before each treatment, every patient was asked to rate his disease related to quality of life on a visual analogue scale, ranging from 1 (very poor quality of life) to 10 (excellent quality of life). A visual analogue scale was chosen since it allowed the patient to include any aspect of the disease that was subjectively relevant.

Most patients had undergone different treatments for HHT prior to TruBlue Laser Treatment, including treatment with KTP, Nd:YAG, and diode lasers. These treatments were discontinued as TruBlue laser treatment was initiated. Additionally, all patients were instructed to regularly use nasal ointment on a daily base.

Data collection. All patients who had been treated in the otorhinolaryngology department of the university hospital in Munich and that had been filed with the ICD-10 diagnosis for hereditary hemorrhagic teleangiectasis (I78.0) from 10/2017 until 04/2019 and who had undergone endonasal procedures to control epistaxis (OPS-codes 5-210.0, 5-210.3, 5-210.x, and 5-210.y) were screened for this study. Only patients who had undergone at least three treatments were included in this study. Only treatments using the TruBlue Laser were included whereas green light or other laser treatments as well medical therapy were omitted from the analysis. Patients having additional treatments including high frequency (4 MHz) coagulation or septal splinting were also excluded. The individual characteristics were collected from the individual electronic patient files and included age, gender, laboratory parameters (in particular hemoglobin), quality of life, number of treatments, amount of energy applied in each individual treatment, time interval between treatments, and side effects of the treatment.

Statistical analysis was carried out using Project R for Mac (Build 3.6.1 for Mac OS X Mojave, the R Project for Statistical Computing, http://www.r-project.org/). To determine whether there was a statistically significant influence of treatments on the Quality of Life, a linear mixed-model was fitted. The model included a random effect for each treated patient. The model was fitted using the lmer function (LME4 package), which relies on a REML fitting. The significance was assessed using Satterthwaite's t test as implemented in the lmerTest package and a significance threshold of 0.05 and 0.20 for α.

Animal Experiments

Ethics. The animal experiments conducted as part of the study at hand were registered with the proper authorities (Regierung von Oberbayern, Maximilianstr. 39, D-80538 Munich, Germany) under the file number ROB-55.2-2532.Vet_02-17-231.

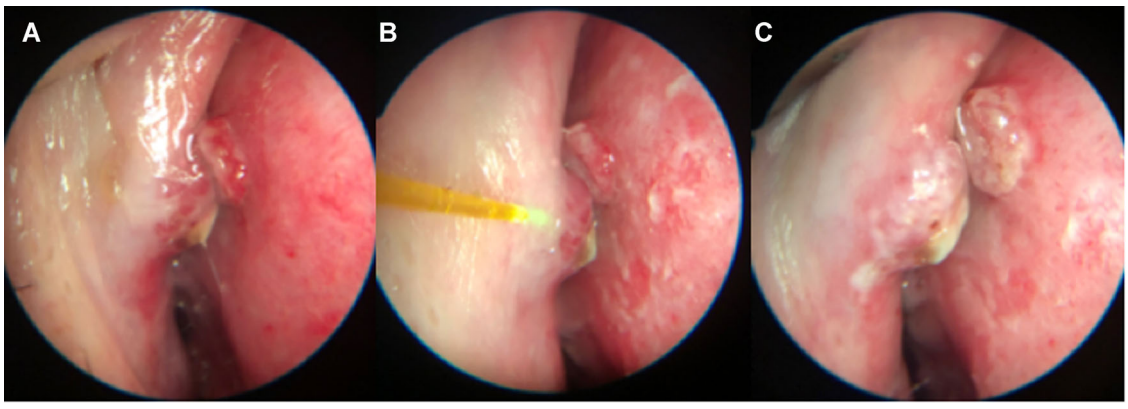

Fig. 2. Endonasal aspect of mucosal hereditary hemorrhagic telangiectasia manifestations before (**A**), during (**B**), and after (**C**) treatment.

Choice of specimens. The thyroid gland was chosen for this experiment since its surgical access is straightforward with little trauma to the organ, easing the subsequent histologic examination. Additionally, it offers—unlike the oral or nasal mucosa in the guinea pig—numerous vessels that serve as targets for bipolar or laser coagulation.

Surgical approach. Dunkin–Hartley Guinea pigs (purchased from Enivgo Laboratories, that weighed from 300 to 450 g were anesthetized using a mixture of ketamine (25 mg/kg bodyweight) and xylazine (2.5 mg/kg bodyweight), applied every 30 minutes intramuscularly. After injection of local anesthetic (lidocaine 2%) in the neck region, the thyroid gland was surgically exposed. Consisting of two lobes, one lobe was treated with bipolar coagulation (Elektrotom B50, KLS Martin Group, Tuttlingen, Germany, output fixed at 10 W) or TruBlue laser, respectively. The settings of the blue light laser were the same as during patient treatment. During treatment, all visible vessels were treated until coagulation was macroscopically visible by paling of the vessel. After explantation, the thyroid gland was embedded in Tissue-Tek (Sakura Finetek Germany, Staufen, Germany) and snap-frozen in liquid nitrogen for later histological preparation. When the experiment was finished, the animals were euthanized.

Histological preparation and analysis. After explantation of the thyroid glands, each gland was frozen and then cross-sections of each lobe with a distance of approximately 1 mm in between slices (slice thickness 5 μm) were made. Following this, routine HE staining was performed. Specimens were then examined under a microscope and images stored digitally. Where vessels were identified, surrounding tissue damage was quantified using ImageJ (Build 1.52e, http://www.imagej.net/).

Statistics. Statistical analysis was carried out using Project R for Mac (Build 3.4.1 for El Capitan, The R Project for Statistical Computing, http://www.r-project.org/). To detect significant differences between the two groups, Student's *t* test was used.

RESULTS

Characteristics of Patients and Individual Treatments

Overall, 23 patients were included in this study. Average age was 63.4 ± 12.3 years. Out of these, 12 were female and 11 were male. These 23 patients had undergone 151 procedures with the TruBlue laser. On average, 99.9 ± 52.8 J were applied endonasally in each procedure. The overall amount of energy applied in each treatment remained steady over the treatments (Fig. 3b). The average time between the treatments was 61.7 ± 45.6 days and remained steady throughout the treatments and patients (Fig. 3c).

Quality of Life

Quality of life gradually increased during initial treatment (Fig. 3a). Before the first treatment session, quality of life was reported at 5.6 ± 0.5 on a visual analogue scale. This increased to 6.8 ± 2.6 before the second treatment and to 7.5 ± 0.9 before the third treatment. From then on, quality of life remained at a

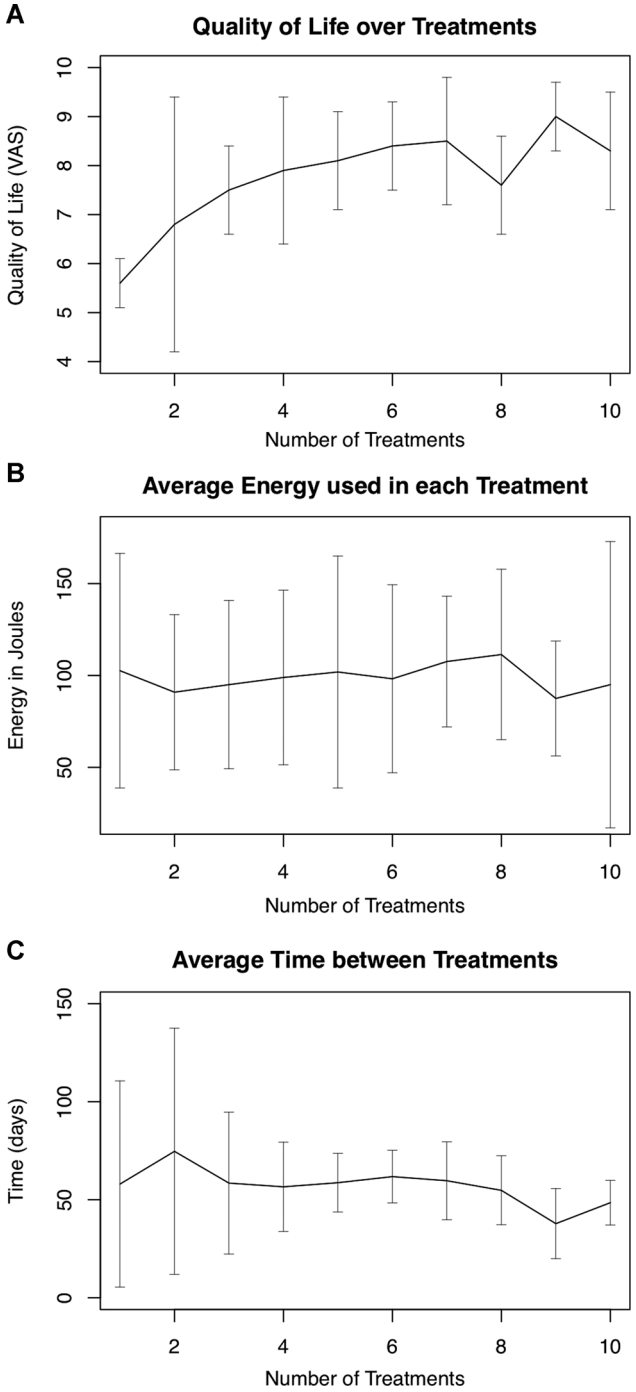

Fig. 3. Average quality of life (**A**), energy used (**B**), and time between (**C**) treatments.

steady level, ranging from 7.9 ± 1.5 before the fourth treatment and 9.0 ± 0.7 before the ninth treatment.

A mixed linear model revealed a significant influence of treatments on quality of life ($P < 0.001$).

Hemoglobin

Overall, 60 hemoglobin values were extracted from patient files that were taken prior to or after treatment. Overall average hemoglobin (g/dl) was 12.2 ± 2.7 g/dl. Average hemoglobin stayed steady during the entire treatment, ranging from 10.9 ± 2.7 to 13.5 ± 2.0 g/dl. Individual hemoglobin levels remained relatively unchanged as well (See Supplemental Table 1 for individual patients' hemoglobin levels).

Side effects

During the period examined, no side effects like infections, ocular damage, or septal perforation were documented. No patient needed additional hemostatic measures during the treatment, no blood transfusions were necessary and no patient was hospitalized during or after treatment. There were no reports of increased crusting after the treatment.

Animal Experiments

Overall four thyroid gland lobes taken from two thyroid glands were used for this study; two lobes were treated with blue light laser and two were treated with bipolar coagulation. Fifteen vessels treated with blue light lasers were identified. The average depth of coagulation after laser treatment was 162 ± 56 µm (Fig. 4a and c). The average area

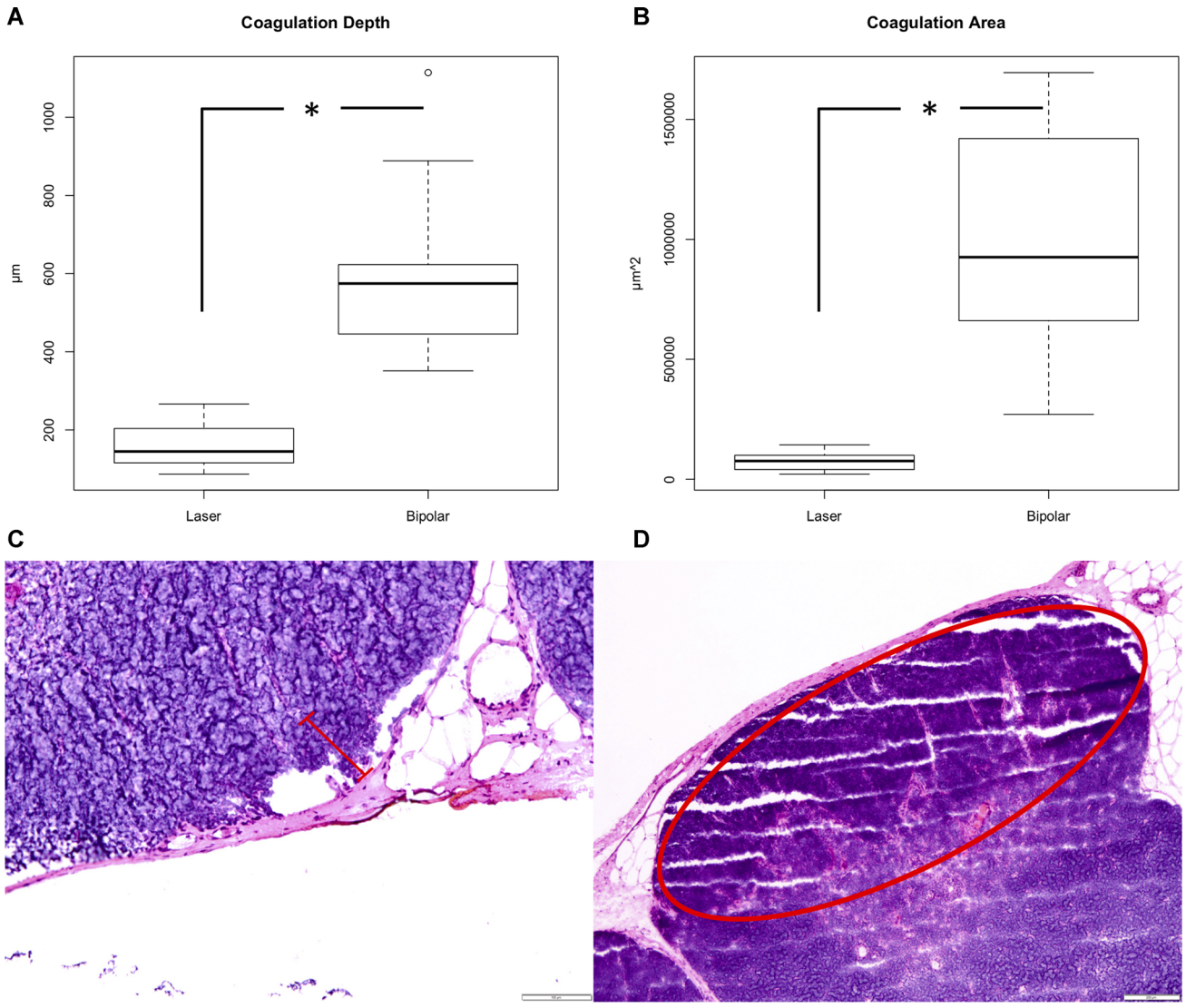

Fig. 4. Average coagulation depth (**A**) and area (**B**) under laser and bipolar coagulation. (**C**) shows a representative hematoxylin and eosin stain of a thyroid gland after TruBlue treatment and how depth of coagulation was measured; (**D**) shows the same after bipolar coagulation treatment and how areas of coagulation were identified.

with coagulation damage surrounding a vessel was $73{,}569 \pm 35{,}346\,\mu m^2$ (Fig. 4b and d). In comparison with this, 16 vessels were identified in lobes treated with bipolar coagulation. The average depth for coagulation damage was $586 \pm 192\,\mu m$, while the average area for coagulation damage was $1{,}014{,}951 \pm 448{,}821\,\mu m^2$. Both the differences in depth and area of coagulation were significantly different from each other ($P < 0.001$, Student's t test).t

DISCUSSION

The aim of the present study was to evaluate the safety and efficacy of a new blue light laser system for the treatment of HHT patients. Most of the patients included had been treated with other lasers in the past. To our best knowledge, no data on the effects of blue light laser in the treatment of HHT patients exist to date.

In the study at hand, we have been able to show that the blue light laser is effective in stabilizing the hemoglobin levels and increase the quality of life in patients suffering from HHT significantly. While it has been repeatedly shown that laser treatment may increase quality of life in HHT patients [19,20], this has not been reported for blue light laser treatment. Although it has not been explicitly addressed in the study at hand, the increase in quality of life is most likely due to the decrease of number and duration of epistaxis episodes, since these are very closely related to quality of life in HHT [21,22]. While the exclusion of patients undergoing additional treatment modalities may cause a selection bias, the data at hand is highly specific for the effects of blue light laser therapy. Additionally, other factors such as decreased postoperative crusting and pain may contribute as to why patients reported an increase in their quality of life over time.

In addition to being effective, we have also been able to show that blue light is not only effective but also safe in treating HHT. We did not observe any relevant side effects, in particular no infections, no crusting, and no nasal septal perforations. This may be due the high specificity of blue light laser to the chromophore hemoglobin, the low intensity, and the little amount of energy applied to mucosal tissue. However, one must bear in mind that laser therapy in HHT is relatively safe in general [18] and that blue light lasers are relatively new and thus the amount of data in the study at hand is limited.

With respect to the biophysical characteristics of the TruBlue™ laser documented in Figure 1 the penetration depth is up to 0.3 mm. This is, in comparison with the penetration of Nd:YAG or green light laser, that reach down more than 1 mm, rather superficial. Previous studies reported about the advantage of a deep tissue penetration of these laser in big lesions and intraoperative bleedings [23]. However, green light laser therapy is regularly associated with postoperative crusting [24], while this was not observed in blue light laser therapy. Additionally, due to relatively high specificity of blue light lasers for hemoglobin, the amount of energy required for adequate therapy and subsequent damage to the surrounding mucosa will show a better ratio in comparison with Nd:YAG or green light lasers. Apart from the risk of septal perforations due to the deeper penetration, other laser types may also cause mucosal atrophy in long-term treatment of the disease. In the present study, we excluded patients who had additional interventions (e.g., high-frequency coagulation, interventions in general anesthesia, or medical treatment). The concept of our institution includes the treatment with 4 MHz coagulation (BM-780 II; Sutter Medical Group, Freiburg, Germany) in acute bleeding and significantly enlarged lesions as described by other authors in the past [8]. Those patients as well as patients having topical and systemical application of immunotherapeutic agents such as bevacizumab [25–27] were excluded to evaluate blue light laser effects only. Our study shows favorable outcomes with short treatment intervals. In contrast to published data on Nd:YAG laser treatments with intervals of 3–4 months [23], the mean time between the TruBlue laser interventions were 2 months.

The fact that hemoglobin did not change during treatment, albeit quality of life increased and therefore severity of epistaxis probably decreased is suprising. This is most likely caused by the fact that almost all patients had received previous treatment (albeit discontinued), including green light or Nd:YAG laser treatment, all of which are efficient in preventing decreases in hemoglobin levels [19,28]. Fittingly, the mean hemoglobin level of 12.2 g/dl of those patients included was already relatively high.

Nonetheless, we have been able to show that blue light laser treatment is safe and efficient in treating HHT in patients suffering from epistaxis. This finding is concludent with the clinical observations made by the authors of this study.

As documented in Figure 2, TruBlue™ laser treatment can be applied very precisely under microscopic view using a small bare fiber. According to our clinical impression, there is very little damage on the mucosa around the treated vessels. In our opinion, this observation is very important in the management of epistaxis patients in general and the repeated treatment of HHT patients particulary. To document the difference between tissue coagulation with a standard bipolar forceps and the specific vessel coagulation using the blue light laser we performed the animal experiments.

In addition to the clinical findings, we have been able to show histologically that laser coagulation with the blue light laser is significantly less invasive than bipolar coagulation. While this observation may be expected it has —to the best of our knowledge—been reported for the first time in the present study.

The very precise coagulation of vessels without relevant impact on the surrounding tissues was documented in all animal specimen. The thyroid glands have been chosen as a model for superficial vessel treatment comparable with the endonasal situation in patients.

We would like to emphasize that the coagulation of perivascular tissue in an acute bleeding situation can be very beneficial. However, this approach is fundamentally different from the treatment needs of HHT patients who suffer from chronic epistaxis. HHT patients profit from the precise vessel coagulation of laser systems to avoid side effects of tissue coagulation on the long term.

CONCLUSION

Blue light laser treatment can be applied very precisely under local anesthesia in HHT patients with superficial lesions. Probably due to the physical properties the perivascular damage is reduced. Quality of life was significantly increased, which is why we prefer this laser therapy as basis of a multimodel therapeutical concept.

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SUPPORTING INFORMATION

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