A Direct Comparison of Pulsed Dye, Alexandrite, KTP and Nd:YAG Lasers and IPL in Patients With Previously Treated Capillary Malformations

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Introduction: Several studies have reported laser treatment of Capillary Malformations (CMs) using systems other than pulsed dye lasers (PDL). Few, however, have compared different systems in the same patients. This study aimed to directly compare CM fading using five different systems.

Methods: Eighteen previously PDL-treated patients were test-patched using the alexandrite, KTP, and Nd:YAG lasers and intense pulsed light (IPL) with additional PDL patches as a control. Pre- and post-treatment videomicroscopy, and colour measurements using Munsell colour charts were carried out.

Results: Four patients failed to respond to any test patches. The alexandrite laser test patches had the largest mean improvement in Munsell colour following treatment \(P = 0.023\) and resulted in CM fading in 10 patients, although 4 patients developed hyperpigmentation, and 1 patient scarring, following treatment. In addition, the alexandrite laser caused a significant decrease in mean post-treatment capillary diameter \(P = 0.007\), which was not mirrored by the other systems. The KTP and Nd:YAG lasers were least effective, with fading seen in two patients for both systems, whilst IPL patches resulted in CM fading in six patients. In addition, five patients had further CM fading using double-passed PDL treatment. Mean pre-treatment capillary diameter measurements were predictive of those patients likely to respond to laser treatment.

Conclusions: Alexandrite laser treatment was the most effective, but resulted in hyperpigmentation and scarring in four patients, probably due to its deeper penetration and lower specificity for oxyhaemoglobin causing non-specific dermal damage. Double passing of the PDL can result in further CM fading even in previously treated patients. Videomicroscopy measurements of capillary diameter before treatment may be predictive of the likelihood for patient’s to respond to laser treatment. Lasers Surg. Med. 40:390–398, 2008. © 2008 Wiley-Liss, Inc.

Key words: port wine stains; videomicroscopy

INTRODUCTION

Oxyhaemoglobin has three main peaks of light absorption at 418, 542 and 577 nm. Over the past two decades, the treatment of Capillary Malformations (CMs) has focused mainly on using the pulsed dye laser (PDL) that emits light around the 577 nm absorption peak, since that provides good oxyhaemoglobin absorption whilst reducing competitive melanin absorption. However, complete CM clearance rates have remained around 15% despite the use of later generation PDL’s with longer wavelengths and deeper penetration [1]. Therefore other laser and non-laser systems have been used in an attempt to improve CM clearance, including intense pulsed light (IPL) [2–6], the KTP laser [7,8], and the long-pulsed Nd:YAG laser [9].

From the reports in the literature, it appears that each of these systems may be capable of causing further fading of PDL-treated CMs in certain patients. However, there is little evidence to suggest which patients are likely to benefit from further treatment with one of these systems, and, in addition, few studies have directly compared these alternative lasers/IPL systems with further treatment using the PDL. Therefore, it is difficult to predict whether some of the improvement would have been achieved with further treatment using the PDL alone.

In this study of previously PDL-treated patients, using the PDL as a control, we set out to directly compare test patches with an IPL system and a combined KTP and long-pulsed Nd:YAG laser. We also included an alexandrite laser in the study to investigate whether there would be any benefit from routinely using this laser for treating CM’S. Alexandrite lasers are primarily used for hair removal, however they have been used for treating leg thread veins [10–14], and small venous malformations [15]. In addition to comparing treatment efficacy, we set out to investigate if

The Lumina Intense Pulsed Light system used in this study was initially on loan from Lynton Lasers Ltd. (Chapelcross, Cheshire, UK). The Laser suite at Glasgow Royal Infirmary has since purchased the IPL system. The Gemini combined Nd:YAG and KTP laser was also loaned by Laserscope (Laserscope UK Ltd., Cwmbran, Gwent, Wales) for the purposes of the study. The authors declare no other conflicts of interest.

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measuring vessel morphology using videomicroscopy can help to predict which patients are likely to benefit from alternative laser/IPL treatment.

METHODS

Subjects

Twenty patients were randomly selected from a database of 250 patients with resistant CMs. All the patients on this database had received at least five PDL treatments. They were assessed using standardised photography and treatment stopped once they were no longer achieving improvement. Inclusion criteria were: a CM located on the head or neck that had stopped responding to PDL treatment and was large enough to allow a 5 cm × 3 cm test patch grid to be placed on an area of uniform colour. CMs were restricted to the head and neck to ensure that the patients included were as comparable as possible, since response to laser treatment tends to vary with location.

Two patients were excluded since their CM was too small to allow grid placement, leaving 18 patients in the study. All of the included patients had Fitzpatrick skin type’s I–II. This group included 13 females and 5 males, average age 43 years (range 19–63). These patients had undergone an average of 20 (range 12–33) previous PDL treatments using the 585 nm, 0.45 ms SLS Chromos PDL (SLS Biophile, Wales, UK). The time since previous treatment varied between 2 and 76 months, average 32 months.

Measurements

Capillary depth and diameter were measured with a compact videomicroscope attached to a 200 × Cy-scope lens (PW Allen, Tewkesbury, UK), using the depth and diameter measuring videomicroscopy (DMV) technique as previously described [16,17]. CM colour changes were assessed using Munsell colour charts (GretagMacbeth, New Windsor, NY) [16,18–20]. Colour measurements using the colour charts were carried out by a single observer in standardised lighting conditions and following 20 minutes acclimatisation to room temperature, to exclude potential sources of error and allow detection of genuine changes in CM colour following treatment.

Lasers and IPL System Used

Table 1 lists the systems and parameters used. The PDL used was the 585 nm, 0.45 ms SLS Chromos (SLS Biophile, Wales, UK), which was included as a control treatment. A second PDL test patch, which was double-passed with a 30 seconds delay, was also carried out. The alexandrite laser was a 755 nm, 3 ms pulse duration GentleLase (Candela Corp., Wayland, Maryland), with accompanying Dynamic Cooling Device (DCD) set at 30 ms spray and 30 ms delay. The IPL used was the Lumina (Lynton Lasers, Cheshire, England) with a 550–1,100 nm filter and a 1 cm × 1 cm quartz block. This system delivers pulse trains and in this case was set to deliver 2 pulses with a 10 ms delay. Finally, a Gemini combined long-pulsed Nd:YAG 1,064 nm and KTP 532 nm laser, incorporating a Cooltouch handpiece, was used (Laserscope UK Ltd., Cwmbran, Gwent, Wales). In addition to the separate test patches with the 532 and 1,064 nm wavelengths, further combined test patches were carried out, alternating which laser was fired first and with a 15 seconds gap between shots.

Study Protocol

On attending for treatment, each patient was initially photographed and then rested for 20 minutes in a temperature-controlled room at 28°C to allow a standard starting point and induce capillary vasodilatation. An area of uniform colour within the CM was identified and the test patch treatment grid taped onto the skin. A digital photograph was taken to record the grid position, to allow accurate re-positioning of the grid at the follow-up appointment.

Once acclimatised, five DMV measurements of capillary depth and diameter were taken from the area of the CM to be treated, and a further three measurements taken from an adjacent control area. Following this, the colour of the CM was measured using Munsell colour charts. Treatment was then carried out, with test patches from each of the lasers and the IPL placed according to the treatment grid. Purpuric response was assessed for each test patch.

Two months later the patients were brought back for a further assessment. A follow-up photograph was taken using the same camera settings and views as in the pre-

<table>
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<th>Laser</th>
<th>Wavelength (nm)</th>
<th>Fluence (J/cm²)</th>
<th>Spot size (mm)</th>
<th>Pulse duration (milliseconds)</th>
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<td>Combined 2: Nd:YAG/KTP</td>
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treatment photograph. The patients were again acclimated for 20 minutes at 28°C, prior to examination of the CM for any areas of fading. Munsell colour assessment was repeated, followed by DMV measurements taken from each test site to assess any changes in vessel morphology.

**Statistical Analysis**

The capillary depth and diameter measurements were analysed using Analysis of Variance (ANOVA) and paired t-tests, after fulfilling the Anderson–Darling tests of normality. In the case of the capillary diameter data, one patient’s values were markedly larger and were excluded for the purposes of statistical analysis to avoid undue influence on the results. The values did fail Box’s test of compound-symmetry for the variance–covariance matrix and therefore the more conservative Greenhouse–Geisser correction factor was used. In contrast, the values for Munsell colour failed tests of normality and were therefore analysed using the non-parametric Friedman and Wilcoxon signed ranks tests. For the purposes of analysis, the Munsell colour chart scores were converted into a numerical scale and the numerical values used to determine changes between pre- and post-treatment. Spearman’s rank correlation coefficient was also calculated to assess whether there was any correlation between the time since previous treatment and the number and type of test patches showing a colour response.

**RESULTS**

The results for 16 patients are included here since 2 patients failed to attend for follow-up and were therefore excluded from analysis.

**Effect of Treatment on CM Colour**

Figure 1 displays the number of patients responding to each test patch. Five patients failed to show improvement in CM colour in response to any of the systems tested in the study. In contrast, one patient responded to all of the test patches (including the PDL) despite having previously had 22 treatments with the PDL. In total, 3 out of 16 patients demonstrated an improvement in CM colour to the single pass (SP) PDL test patches and 5/16 responded to double pass (DP) PDL test patches. Despite the fact that more test patches responded to the DP patches than the SP patches, the difference in the mean post-treatment Munsell colour results failed to reach statistical significance between the two groups.

The alexandrite laser generated the most responses out of all the systems tested. 18 out of 32 (57%) test patches with the alexandrite laser had measurable CM colour fading: 8/16 at the 50 J/cm² setting and 10/16 at the higher fluence setting of 70 J/cm². Comparison of colour improvements obtained by all 12 systems using Friedman’s test was statistically significant (P = 0.016), with the alexandrite laser at 70 J/cm² resulting in the largest mean improvement in Munsell colour scores (2.6 ± 0.7, see Fig. 2). Comparison of the overall effect of each laser and IPL (excluding the PDL) using Friedman’s test was statistically significant (P = 0.023), with the alexandrite laser generating a larger mean improvement in Munsell colour than found for the other systems.

The Lumina IPL produced an improvement in colour in 4/16 patients at the 28 J/cm² and 6/16 patients at the higher fluence setting of 34 J/cm². The IPL at the higher fluence setting of 34 J/cm² resulted in the next highest mean changes in Munsell colour after the alexandrite laser 1.6 ± 0.5. However, this improvement in colour was not statistically different from the lower IPL fluence setting, nor from the PDL, KTP or Nd:YAG lasers tested in the study.

The KTP and Nd:YAG lasers fared less well: in each case only 2/16 patients demonstrated an improvement in CM colour. Therefore, the KTP and Nd:YAG lasers were outperformed by the PDL. Likewise for the combined KTP/Nd:YAG patches, only 2/16 patients demonstrated any improvement. One of these patients responded to all 12 test patches, whilst the other responded to the KTP alone at the higher fluence setting.

Time since previous treatment was compared to the total number of test patches responding to treatment, and also to the number of test patches showing a response for each laser or IPL, using Spearman’s rank correlation coefficient.
There was no significant correlation found for either the total number of responses seen or for any individual system.

The difference in Munsell colour between the two fluence settings for the non-PDL systems tested (IPL, alexandrite, KTP and Nd:YAG) was not statistically significant although it did approach significance ($P = 0.051$, Wilcoxon Signed Rank test). Likewise, the interaction between each of the systems tested and energy level employed was not statistically significant for ($P = 0.277$, Friedman’s test).

**Effect of Treatment on Capillary Depth**

When the post-treatment mean capillary depth measurements for all of the test patches combined were compared with the pre-treatment values it was clear that there was an overall effect of laser treatment resulting in an increase in mean depth following treatment, from $115 \mu m \pm 13$ ($\pm$ SEM) to $135 \mu m \pm 13$ ($P = 0.013$, paired $t$-test). However, when the different laser/IPL systems were compared with each other, there was no statistically significant difference between the post-treatment mean capillary depths ($P = 0.617$, ANOVA) (see Table 2). Post-treatment depth values for the interaction between each of the laser/IPL systems and the energy settings used failed to identify any marked difference between the type of treatment and fluence level ($P = 0.292$, ANOVA). In addition, there was no detectable separate effect of higher fluences on capillary depth ($P = 0.389$, paired $t$-test) for any of the systems. Nor was there any difference between the post-treatment capillary depths between the IPL system and alexandrite, KTP and Nd:YAG lasers when averaged for energy ($P = 0.630$, ANOVA).

To investigate whether the pre-treatment capillary depth values were capable of predicting a patient’s probable response to treatment, the pre-treatment values were organised into three groups: first, a superficial group with...
a depth less than 85 μm, containing four patients; secondly, a intermediate group with a depth between 85 and 120 μm, containing six patients; thirdly, a deep group with a depth greater than 120 μm, also containing six patients. For each group, the mean pre-treatment capillary depth and combined post-treatment depth for all the test patches was as follows: 61 μm ± 12 increasing to 73 μm ± 4 for the superficial group (P = 0.318, paired t-test); 96 μm ± 4 increasing to 130 μm ± 3 for the intermediate group (P = 0.097, paired t-test); and 170 μm ± 14 increasing to 181 μm ± 4 for the deep group (P = 0.120, paired t-test). Therefore, there was no statistically significant difference between pre-treatment mean capillary depth and combined post-treatment values for the superficial, intermediate or deep groups. For all three groups, the differences between post-treatment mean capillary depth for each of the 12 test patches was not statistically significant (P = 0.448, P = 0.615, and P = 0.457 for the superficial, intermediate and deep groups respectively; ANOVA).

**Effect of Treatment on Capillary Diameter**

The results for capillary diameter exclude one patient whose diameter results lay far outside the distribution of the remaining patients and therefore would potentially have unduly influenced the results. The mean pre-treatment capillary diameter for all the laser/IPL systems combined was 60 μm ± 9, decreasing to a mean of 42 μm ± 3 post-treatment (P = 0.021, paired t-test). In contrast to the capillary depth results, there was a statistically significant difference between the post-treatment mean capillary diameters (P = 0.009, ANOVA), with the alexandrite laser at 70 J/cm² having the smallest post-treatment mean diameters followed by the alexandrite laser at 50 J/cm² and the IPL at 34 J/cm² (see Table 2). When the lasers and IPL were compared (averaged for energy) the alexandrite laser had the smallest post-treatment mean capillary diameter (P = 0.007, ANOVA). However, there was no significant difference between the interaction of the lasers and IPL and energy level used (P = 0.382, ANOVA), suggesting that there was no detectable effect of increasing the fluence on capillary diameter for any of the systems tested.

In a similar fashion to that carried out for capillary depth, the patients were split into three groups to investigate whether it was possible to predict the response to treatment based upon the pre-treatment capillary diameter (see Fig. 3). These groups were: a small diameter group, with mean capillary diameter less than 40 μm and containing five patients; an intermediate diameter group with diameter between 40 and 65 μm containing six patients; and a large diameter group, with diameter greater than 65 μm, containing four patients (excluding the patient whose values lay out with the normal distribution). For each group, the mean pre-treatment capillary diameter and combined post-treatment diameter for all the test patches was as follows: 32 μm ± 2 pre-treatment and 37 μm ± 0.2 post-treatment for the small group (P = 0.100, paired t-test); 53 μm ± 4 decreasing to 39 μm ± 2 for the intermediate group (P = 0.023, paired t-test); and 104 μm ± 18 decreasing to 51 μm ± 4 for the large group (P = 0.021, paired t-test). Therefore, there was a statistically significant effect of treatment upon mean capillary diameter for the intermediate and large groups, but not the small group. It is worth noting that all four of the patients who failed to respond to any of the test patches were in the small group. Within all three groups, there was no detectable difference between the post-treatment capillary diameters for the 12 test patches. However, the results for the large diameter group did approach statistical significance (P = 0.058, ANOVA). When the alexandrite, KTP and Nd:YAG lasers and IPL system are compared (averaged for energy) the mean capillary diameters within the alexandrite laser test patches were significantly lower than those for the other systems in the large diameter group (P = 0.04, ANOVA) and approached statistical significance in the intermediate group (P = 0.078, ANOVA).
Side Effects of Treatment

Overall the test patches were well tolerated by all of the study participants. Purpuric responses were seen for the PDL and also in those patients who went on to respond to treatment for each of the other systems tested. This purpuric response was most marked with the alexandrite laser at the higher fluence setting. There were no side effects for any of the test patches from the PDL, KTP or Nd:YAG lasers or the IPL. However for the alexandrite laser, four patients sustained hyperpigmentation at the higher fluence level of 70 J/cm². One of these patients also had evidence of atrophic scarring. There were no side effects, other than purpura, resulting from treatment with the lower fluence (50 J/cm²) used for the alexandrite laser.

DISCUSSION

Response of CM Colour to Test Patches

The patients included in the study were deemed to have stopped responding to treatment with the 585 nm 0.45 milliseconds SL Chromos PDL, after undergoing an average of 20 treatments. Despite this, five patients demonstrated fading of their CM in response to further PDL treatment. The most likely reasons for this are: first, all five patients had a mean capillary diameter greater than 40 μm, meaning that they had capillaries within the ideal target range for PDL treatment; secondly, that four out of five patients had not had any laser treatment for at least 37 months (although there was no statistical correlation between time since previous treatment and subsequent response), during which time there may have been progressive capillary ectasia that would increase the chances of a response to treatment. Although the fifth patient had last undergone laser treatment 5 months previously, he still had capillaries within a treatable range, most likely because he has a large facial and neck CM that had received multiple partial treatments.

Double passing with the PDL did result in two additional patients demonstrating CM fading when compared to single passing, although there was no detectable difference between the amount of improvement in CM colour seen between the two groups. This finding is in keeping with those of Tanghetti et al. where double passing was found to be more effective than single passing at clearing CMs [21]. In that study, which used a 0.5 milliseconds pulse duration PhotoGenica V-star PDL, Tanghetti et al. found that with a fluence of 7 J/cm² the depth of vascular injury increased with the time delay between pulses, up to the maximum of 30 minutes employed in the study. This suggests that using a longer time delay between pulses in this study may have improved the CM clearance achieved.

Out of all the systems tested, the largest response to treatment occurred in the test patches treated with the alexandrite laser. This was both in terms of the number of test patches fading in response to treatment and the amount of fading seen per test patch. In addition, the alexandrite laser was found to have a significantly larger effect on post-treatment capillary diameter—the diameter values were measurably smaller after alexandrite laser treatment, suggesting that it was more effectively destroying the larger capillaries than the other systems tested.

This is initially somewhat surprising since the alexandrite laser is more commonly used for targeting melanin for the purposes of hair removal and, according to the principles of selective photothermolysis [22], the 755 nm near-infrared wavelength utilised by this system should be less specific for oxyhaemoglobin absorption than the PDL and KTP lasers and IPL system. However, the alexandrite laser has been used for the treatment of vascular conditions such as leg thread veins [10–14], and small venous malformations [15]. Therefore, it is clear that the alexandrite laser is capable of successfully targeting vascular conditions, although these have tended to include larger vessel sizes than commonly found within CMs. A potential reason for the CM fading seen with the alexandrite laser is the deeper penetration provided by the 755 nm wavelength, when compared to PDL treatment, combined with the 3 milliseconds pulse duration. This pulse duration is longer than the PDL but is still within the 1–10 milliseconds range that has been shown to match up with the thermal relaxation time of CM vessels [23]. In previously laser-treated CM patients, who tend to have smaller and deeper capillaries [16,24,25], this will give the alexandrite laser an advantage over the PDL since these deeper capillaries can be reached by the longer wavelength and longer pulse duration. Clearly, despite the lower specificity of 755 nm light for oxyhaemoglobin, the alexandrite laser is still being selectively absorbed by blood in the aberrant capillaries within the dermis leading to capillary destruction and, ultimately, CM fading. The alexandrite laser did lead to a notable purpuric response, especially at the higher fluence setting (75 J/cm²). In conjunction with this, the test patches treated with the higher fluence setting did have an unacceptably high level of side effects—4 out of the 10 patients responding to this setting developed hyperpigmentation after treatment, with one patient having evidence of atrophic scarring in addition to the hyperpigmentation. This is most likely due to non-selective dermal heating and peri-vascular damage at the higher fluence level, since the complications were not seen at the 50 J/cm² setting, which still had a higher response rate than any of the other systems tested. These complications were seen in patients with skin types I–II. It is probable that the complication rate in patients with skin types IV–VI would be significantly higher with the alexandrite laser due to the specificity for melanin of the 755 nm wavelength resulting in an increase in non-specific dermal heating.

The Lumina IPL system test patches did result in an improvement in CM colour in 6 out of the 16 patients and was, in that respect, the next most successful system tested after the alexandrite laser. However, the Munsell colour scores for the IPL test patches were not detectably different from the PDL, KTP or Nd:YAG lasers. In addition, the IPL did not have a statistically different effect on post-treatment vessel morphology than the other systems tested, although the mean capillary diameter did decrease to a similar level as that found for the alexandrite laser at 50 J/cm². In its favour, the IPL treatment did not result in
any notable side effects, even at the higher fluence setting (34 J/cm²), which is a potential advantage over the alexandrite laser. The level of improvement seen here is in keeping with previous studies, which have found that up to 50% of previously treated CM patients will respond to IPL treatment, although complete clearance was rare [2–5]. This was also the case in previously untreated patients [6]. Theoretically, IPL systems do have a potential advantage over the alexandrite laser and PDL since they incorporate both the highly oxyhaemoglobin selective wavelengths around 577–600 nm and also emit longer wavelengths that will allow deeper penetration into the dermis and deeper capillary destruction. It is most likely this factor that explains why more patients responded to this system than to the PDL, KTP or Nd:YAG lasers. However, in practice, the energy emitted from the IPL is spread across the available wavelengths with the peak energy tending to be distributed towards the centre of the light spectrum, falling away towards the ends of the spectrum. Therefore, the energy available at the most useful part of the spectrum (the region between 570 and 600 nm and possibly extending into the near infrared) is only part of the total emitted energy. Combined with this, the IPL delivers its energy in two pulses separated by a 10 milliseconds delay, whilst the pulse on time varies with the fluence used, meaning that the overall pulse duration is greater than 10 milliseconds and therefore longer than the calculated thermal relaxation time of CM vessels. This may explain why the IPL is less effective than the alexandrite laser, despite the latter’s less selective wavelength.

The other laser tested in the study was the Gemini combined KTP and Nd:YAG laser. The KTP laser emits green light, wavelength 532 nm, which is shorter than the PDL and will therefore penetrate less deeply into the dermis. It does however have relatively high specificity for oxyhaemoglobin absorption. Previous studies using a KTP laser to treat CMs have similarly focused upon patients who have previously been treated with the PDL [7,8]. These have indicated a varying degree of response to treatment, with one study reporting a 14% response rate [7], whilst the other reported a 53% response rate [8]. Neither study reported any patients having complete clearance of their CM with KTP treatment. The results in this study were more in keeping with those reported in the former study [7], with only 2 out of 16 patients showing CM fading, one of which responded to all 12 test patches. Similarly, the results for the long-pulsed Nd:YAG were also poorer than the other systems tested here. Again only 2 out of 16 patients had CM fading in their Nd:YAG test patches and again one of these was the patient who responded to all 12 test patches. One previous study did compare 595 nm PDL and long-pulsed Nd:YAG treatment of CMs and found that, unlike the results of this study, both achieved a similar level of fading in 17 patients [9]. Their rationale for treating patients with the Nd:YAG was that although the absorption coefficient for oxyhaemoglobin is much lower at 1,064 nm than at 595 nm, it is still significantly higher than that of the surrounding dermis, and is combined with less optical scattering that allows deeper dermal penetration [9]. However, they did find that there was a high rate of complications with the Nd:YAG at higher fluences, which reduced its usefulness for clinical use. It may be that the fluences used for the Gemini laser in this study were too low to generate a higher level of response, particularly given the long pulse durations utilised by this system—at lower fluences, insufficient intravascular heating will be generated over the 30–60 milliseconds pulse duration employed by the Gemini laser since the thermal relaxation time of the CM vessels should be less than 10 milliseconds resulting in diffusion of heat to the surrounding dermis. This is potentially borne out by the lack of side effects seen with the Nd:YAG test patches and the overall lack of purpuric response in most of the patients studied. However, the settings used were those suggested by the laser manufacturer as within the standard range for vascular lesion treatment. In particular, the higher fluence test patches were at the high end of those suggested settings. Overall, the response of the Nd:YAG and KTP lasers was disappointing, as it was less than previous studies have suggested is possible and also less than that of the 585 nm PDL.

The lack of response to either of the KTP and Nd:YAG settings alone explains the equally poor response to the lasers combined. The basis for combining the test patches was that the cumulative wavelengths might have an additive effect. One possibility was that initial treatment with the Nd:YAG followed by the KTP would allow the deeper vessels to be cleared first followed by the more superficial vessels. Alternatively, it has been suggested that the Nd:YAG is more effective when targeting methaemoglobin [9], which is produced after reversible heating of the red blood cells at temperatures between 50 and 54°C. Therefore the other possibility was that initial KTP treatment would result in some capillary destruction and methaemoglobin production that could potentiate the secondary Nd:YAG treatment. In the end though, the only combined test patches to respond to treatment were those where an individual test patch with either the KTP or Nd:YAG lasers had responded, suggesting that it was more likely to be a reaction to the individual laser than a combined effect of the two wavelengths. Given the possibility that the fluences used were on the low side, it would perhaps make sense to repeat the combined treatments after calibrating the response to each individual laser so that the fluences used were high enough to generate a purpuric response.

**Predictive Effect of Vessel Morphology**

The mean pre-treatment capillary diameter and depth values are consistent with those of previously treated patients in preceding studies [16,20,24,25]. These are smaller and deeper than those described for untreated patients, demonstrating that the prior PDL treatment had had a measurable effect upon vessel morphology. In addition, there was a detectable overall effect of further CM treatment in this study since the combined post-treatment diameter and depth values for all 12 test patches were smaller and deeper respectively than the
pre-treatment values. This supports the findings of Sivarajan and Mackay [16,20], and previous studies [24–27].

Apart from the overall treatment effect, capillary depth was not predictive of the outcome of treatment for any of the systems tested in the study. Even when the patients were analysed, based upon mean pre-treatment depth values, into superficial, intermediate and deep groups, there was no detectable difference between groups for either the overall response to treatment for all 12 test patches or for individual systems. This mirrors the findings of Sivarajan et al. in their comparison of test patches with different PDL settings [26]. The most probable reason for this is that DMV measures the depth of the most superficial visible capillaries, not the total malformation depth. For each of the patients studied, the most superficial visible vessels were all less than 300 µm from the epidermal surface. Since this depth is within the reach of all of the systems tested in the study, it is probable that the differences in DMV measured depth do not significantly affect the outcome of treatment. However, it is likely that overall CM depth is still one of the most important factors for determining the outcome after laser treatment.

In contrast to the capillary depth findings, there was a detectable difference in post-treatment capillary diameter between the systems tested, with the alexandrite laser at its higher fluence setting causing the largest reductions in diameter following treatment. When the patients were split into groups based upon pre-treatment diameter, there was again a statistically significant effect of treatment, but only for those in the intermediate and large diameter groups (those with a pre-treatment capillary diameter greater than 40 µm). The alexandrite laser treatment caused the biggest reduction in post-treatment diameters for those in the large diameter pre-treatment group and this effect approached statistical significance for the intermediate group. These findings, combined with the fact that the four patients who failed to respond to any of the test patches all had pre-treatment capillary diameters within the small group (pre-treatment capillary diameters less than 40 µm), suggest that the pre-treatment capillary diameter does have a predictive effect on treatment outcome in this study. This contrasts with the previous findings of Sivarajan et al. in their study comparing different PDL settings [26], which failed to identify any predictive effect of pre-treatment capillary diameter or depth on treatment, possibly because the differences between parameters in the PDL study were insufficient to identify post-treatment trends in vessel morphology. The systems in this study had a much greater variance in terms of wavelength, fluences and pulse durations used than in this previous study and this may have helped to uncover differences post-treatment.

Overall, based upon these findings, it does seem that pre-treatment capillary diameter measurements have the potential to have a predictive effect for the outcome of treatment, particularly for the alexandrite laser, where patients with mean pre-treatment diameters greater than 40 µm are more likely to respond to treatment than those with a mean diameter less than this. Given that capillary diameter is so important in determining the outcome of laser treatment, it is interesting to note the results of recent studies that have aimed to locally increase capillary diameter and blood volume fraction, either through the local application of suction [28,29] or by causing venous stasis [30], where reduced purpuric thresholds and improved CM blanching were demonstrated in a small group of patients. It is possible that, by incorporating these techniques with alexandrite laser or IPL therapy, that further CM clearance could be achieved. In particular, with regards to the alexandrite laser, it may be possible to reduce the fluences required for effective treatment and therefore limit the high side-effect profile in CM treatment since increasing capillary diameter improves blood volume fraction absorption and reduces the transmission of energy to the surrounding tissues. This is an area that would merit further exploration.

CONCLUSIONS

The alexandrite laser clearly outperformed each of the other lasers and the IPL system used in this study in terms of the number of test patches demonstrating an improvement CM colour and the amount of improvement seen. These results suggest that the alexandrite laser is worth considering for further treatment of patients who have stopped responding to PDL treatment, although care needs to be taken since at higher fluences there was a significant rate of hyperpigmentation due to the reduced specificity for the target chromophore. It is interesting to note the poor response rate to both KTP and Nd:YAG laser treatment, which were outperformed by the PDL and is in contrast to the findings of previous studies. This may be due to the settings used in this study, and further studies at higher fluences resulting in a purpuric response may be appropriate. Finally, double passing with the PDL proved to be a useful technique that may allow further improvement in CM colour in previously laser-treated patients and does not appear to increase the risk of side effects.

REFERENCES

8. Woo WK, Jasim ZF, Handley JM. Evaluating the efficacy of treatment of resistant port-wine stains with variable-pulse