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Pulsed dye laser treatment of capillary malformations in infants at 2 weekly versus 3 monthly intervals, reducing the need for general anaesthesia

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Summary

Background

Capillary malformations (CMs) cause significant psychosocial complications. Pulsed dye laser (PDL) treatment at 6-12 weekly intervals in childhood remains standard care, with treatment of children aged 6 months or older requiring general anaesthesia (GA). The safety of repeated GA in children is controversial. Shortening PDL treatment intervals enables multiple treatments prior to 6 months of age, which may reduce the need for GA.

Objectives

To investigate the safety and effectiveness of more frequent PDL treatment of CMs in infants.

Methods

We performed a pilot prospective patient-controlled study of 10 infants with CMs. Using 595nm (Vbeam) PDL, the entire CM was treated initially, then half of the CM randomly allocated to 2 weekly and half to 3 monthly intervals for 2 further treatments. Photographs of the CMs taken 3 months after treatment completion were evaluated by an independent blinded dermatologist.

Results

Nine infants completed the study. Three infants (33%) had more improvement on the 2 weekly treated side and 4 infants (44%) had more improvement on the 3 monthly treated side. Two patients (22%) showed no difference between sides. Treatments were well tolerated without complications.

Conclusions

Two weekly PDL treatment of CMs in infants under 6 months is well tolerated without adverse effects. Our preliminary data suggests possible superior efficacy with 3 monthly treatment intervals, however larger studies are warranted for stronger evidence. More frequent non-GA treatment of CMs in infants should be further investigated to decrease the risk of repeated GA exposure in young children.

Introduction

A capillary malformation (CM), also known as a port wine stain, is a birthmark comprised of anomalous dilatations of capillaries and venules within the skin dermis. It is the most common type of vascular malformation, typically noted at birth in 0.3% of newborns with no sex predilection and commonly affects the head and neck but can involve any area of the body.[1]

CMs present at birth as well demarcated pink patches and if left untreated, will grow proportionally with the child. In adulthood they can progressively darken, hypertrophy and develop nodules which are at risk of bleeding.[2] CMs also have a significant psychosocial impact on the patient with 85% of patients believing that their CM influences their life in a negative way.[3] Patients with CMs suffer from higher rates of anxiety[4] and lack of self esteem, causing social difficulties in interpersonal relationships and school life.[3] This impact increases with age and has been shown to significantly improve with treatment.[3]

The gold standard of treatment for CMs remains pulsed dye laser (PDL) at 6 to 12 weekly intervals under general anaesthetic (GA) in early life. Treatment during infancy and early childhood allows improvement of the CM before starting school and may also confer a better result.[5-8] The safety of repeated GA in children under 4 years of age is controversial

with possible long term neurodevelopmental consequences reported.[9,10] Experience at our hospital indicates that PDL treatment is well tolerated without GA in infants prior to 6 months of age and this practice is well established as the international standard of care.[8,11,12] Shortening the PDL treatment intervals could shorten the length of time needed to complete treatment and may reduce the need for GA. In addition, there is early evidence emerging that more frequent treatment intervals may improve PDL outcomes.[13]

The optimal PDL treatment interval for CM treatment in infancy has not been established. In order to determine the safety and feasibility for further definitive studies in this area, we designed a prospective patient-controlled pilot study of 10 infants to investigate the efficacy and safety of PDL treatment without GA at 2 weekly compared to 3 monthly intervals.

Materials and Methods

Subjects

Ten infants less than 8 weeks old with a CM who were referred to our laser clinic were prospectively recruited into this pilot study. Exclusion criteria included the following: CMs greater than 50cm^2 that could not be entirely treated at one visit, CMs that crossed the midline, CMs that were not visible at all times, and CMs that were variable in colour. Infants with Fitzpatrick skin type V and VI were excluded due to the higher likelihood of post treatment pigment changes caused by PDL. Infants that could not attend frequent appointments due to geographical reasons were also excluded.

Laser

All laser treatments were performed with the Candela Vbeam Perfecta flashlamp-pumped pulsed dye laser (Candela Corp, Wayland, MA, USA) which emits a wavelength of 595nm. Treatments were at 7-8.5 J/cm2, 1.5ms and spot size 10mm. The desired endpoint was mild persisting purpura. Dynamic cooling was used with tetrafluoroethane spray 30 ms before each laser pulse followed by 20ms laser pulse delay. Pulses were delivered to the

entire treatment area overlapping 10 to 20%. Standard safety precautions for use of lasers were employed including eye protection.

Treatment protocol

The study design and treatment protocol were reviewed and approved by Human Research Ethics Committee at our hospital and informed consent was obtained from parents or guardians of all participating infants. All patients received initial treatment to the whole CM before 8 weeks of age. The CM was then divided into halves that were randomly allocated by sealed envelopes to 2 weekly or 3 monthly intervals for a further 2 treatments, such that both sides of the CM received 3 treatments each. Where practical, the CMs were divided radially on the basis that the central face area tends to respond less well that the peripheral face[14]. Radial division enabled both treatment areas to contain areas of central and peripheral face.

For all PDL treatments without GA (infants under 6 months of age), 24% sucrose syrup 0.5 to 1mL was given orally prior to the procedure with repeated aliquots given as required during the treatment. Infants were also given a pacifier if accustomed and were swaddled and cradled by their parents during the procedure. When treatment was complete, the infants were comforted by their parents and feeding was encouraged. Infants settled within seconds following the procedure and did not show distress on return visits. When the infants were 6 months of age or older, GA was undertaken for the remaining treatments to complete the study.

Digital photography was performed before and after each PDL treatment as well as 3 months after the final treatment. All photography was performed by a departmental professional medical photographer, using similar light conditions for each episode.

Information on age, sex, anatomic location and colour of the CM and adverse events was recorded for each study participant. Efficacy was assessed by an independent blinded staff dermatologist with experience in laser, who studied the final post treatment photograph to compare the two differently treated sides of the CM. One side of the CM was noted as either mildly improved, greatly improved or no difference when compared to the other side.

The participants continued to be reviewed and treated as needed following completion of the study.

Results

Infants were recruited into the study between 2010 and 2012. Of the 9 infants who completed the study, 6 (66%) were male and 3 (33%) were female (Table 1). All infants had a CM affecting the face which was unilateral. All CMs were uniform pink to red in colour on a background of Fitzpatrick skin type I to III. Age at first treatment ranged from 1 to 6 weeks with a mean of 3.2 weeks of age. One patient withdrew from the study due to a non-study related medical condition.

When the two differently treated sides of the CM were compared to each other, 3 infants (33%) were more improved on the 2 weekly treated side. Whereas, 4 infants (44%) were more improved on the 3 monthly treated side, 3 of which were greatly improved. Two infants (22%) showed no difference between the treatment sides of the CM (Table 1). Representative photos shown in Fig. 1. All 9 infants who completed the study appeared to show response of the CM to laser treatment (subjective reports from parents and clinicians). The treatments were well tolerated by all patients and there were no significant adverse reactions documented for the duration of the study.

Discussion

Current literature suggests that embarking on PDL treatment for CMs at an early age should improve outcomes. There have been varying hypotheses to explain this phenomenon including CMs being smaller, more superficial, containing fewer and smaller diameter vessels, and infants have more erythrocytes in circulation and less melanin in the skin.[15] There is also a physiological lightening of CMs in early infancy even without treatment due to changes in haematocrit.[15] A large study by Namba et al.[8] of 644 patients of age 3 months to 93 years showed significantly more “excellent” and “good” outcomes in patients who started treatment before 10 years old.[8] This trend has been confirmed in many other studies[16-18] with

only a single smaller study failing to show the trend.[19] In addition to improved efficacy, there may be a lower CM recurrence rate if treatment is performed before 10 years of age.[20]

Further studies have narrowed the optimal age for PDL treatment to infancy as compared to older children.[5-7] Morelli et al.[6] studied 85 patients with facial CMs from 0 to 18 years of age and showed that infants under 1 year old had highest mean clearing of CM (65%), and this trended down with increasing age. Smaller studies[11,21] have investigated PDL for CM in infants less than six and twelve months of age with frequent interval PDL treatments of 3 or 4 to 6 weekly. These studies show such treatment to be effective and safe but do not allow conclusions to be made regarding frequent versus standard longer treatment intervals in this age group. A retrospective study by Anolik et al.[11] studied 2, 3 and 4 week treatment intervals in 24 infants with facial CMs less than 12 months of age and concluded that shorter treatment intervals were trending to a better response although did not achieve statistical significance.[11]

In adults rather than infants, Tomson et al.[13] prospectively studied 13 patients with CM using a half of the CM as self-controls to compare 2 weekly versus 6 weekly PDL treatment intervals.[13] They concluded that the more frequent 2 weekly treatment interval had a statistically significant greater reduction in reflectance measurements compared with 6 weekly treatment intervals.[13]

We are the first group to prospectively study infants as self-controls to compare 2 weekly to 3 monthly PDL treatment of CMs in early infancy. We have been able to demonstrate that 2 weekly PDL treatment of CMs in infants under 6 months without GA is well tolerated and safe. While there were similar numbers of patients with more improvement on the 2 weekly treated side of CM (3 infants) when compared to the 3 monthly treated side of CM (4 infants), our limited data suggested superior efficacy on the 3 monthly treated side.

The major limitation of our pilot study was the small patient cohort, which limited our ability to draw conclusions with statistical significance. PDL treatment of CM is known to be most effective on the midline forehead, followed by peripheral face and relatively treatment resistant on the centrofacial region including medial cheek, nose and upper cutaneous lip.[7,14] In recognition of this variable, we halved the CM in a radial direction from the central face to allow equal representation of central and peripheral face in each treatment side. We designed the study using patients as self-controls as it is well recognised that response to PDL differs

between patients with age, skin type, CM size and colour.[7,16,21] We did not have access to reproducible, controlled, colour intensity measurement, so for assessment of results, the comparison of the 2 treatment sides of the CM was made based on a single photograph, showing the whole CM in order to reduce potential effects of variability of photo conditions over time. We recognise that there may be inherent subjectiveness in the assessment of the 2 treated sides of the CM for mild versus greater improvement. Additionally, this study design did not allow us to quantitatively assess the degree of improvement of the CM at the end of the study compared to the pre-treatment baseline. If we were to perform this study again, we would ideally use a more quantitative method for objective assessment of response such as reflectance spectrometry.[13] Future larger studies need to be designed with these limitations in mind.

By showing that there is equal safety and perhaps only mildly reduced efficacy in treating CM with PDL at 2 weekly intervals in infants, we postulate that the treatment course could be accelerated such that more treatments may be achieved under the age of 6 months, potentially reducing the need for GA and its associated risks. PDL treatment for CM in infants less than 6 months of age in our experience is well tolerated without GA. Both oral sucrose[22] and pacifier[23] have been shown to be safe and significantly reduce infant crying time with painful stimuli including heel lancing and venepuncture, and we have used these techniques successfully for our infants needing PDL treatments. PDL treatment is usually tolerated in adults without GA, however it can be a distressing or anxiety provoking procedure in a child so GA is required for infants over 6 months of age. Infants have the highest rate of anaesthetic adverse events in the paediatric population[24] and require subspecialty-skilled anaesthetic staff. There has also been growing evidence in animal models that anaesthetic agents cause apoptosis of neurons and glia cells and impair neurogenesis with the peak vulnerability during the period of rapid synaptogenesis, which for humans would be the first few years of life.[25] A study in nonhuman primates by Paule et al.[26] demonstrated that exposure to ketamine can result in long lasting cognitive deficits.[26] The differences in an animal model make this difficult to apply to humans[9] and unfortunately human studies are limited. Retrospective human studies have shown a correlation of anaesthetic exposure in infants less than 4 years old with neurodevelopmental disturbances.[27,28] This relationship is particularly prevalent with multiple anaesthetic exposures and longer duration of exposure.[27,28] The controversy thus remains as to the safety and long-term effects of GA in children less than 4 years of age and as such, the current recommendations are that GA

should be minimised in this patient group while studies in this area continue.[10] Controversy also exists regarding the long term effects of neonatal pain responses. There have been some reports of subsequent increased pain sensitivity, however it is unclear whether this is prevented by adequate analgesia or anaesthesia, furthermore these effects seem to wear off after 12 or 16 years of age.[29,30]

PDL treatment of CMs should ideally be completed before school age to avoid psychosocial complications. Ideally this should be done without GA due to its associated anaesthetic risks and the as yet unproven possibility of long term neurodevelopmental effects. We believe that shortening the PDL treatment interval to maximise the number of treatments completed prior to the time when a GA is required should be further investigated in a larger study with participants as self-controls as this may be a safer alternative with only mildly reduced efficacy compared to the current standard of care.

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Table 1.

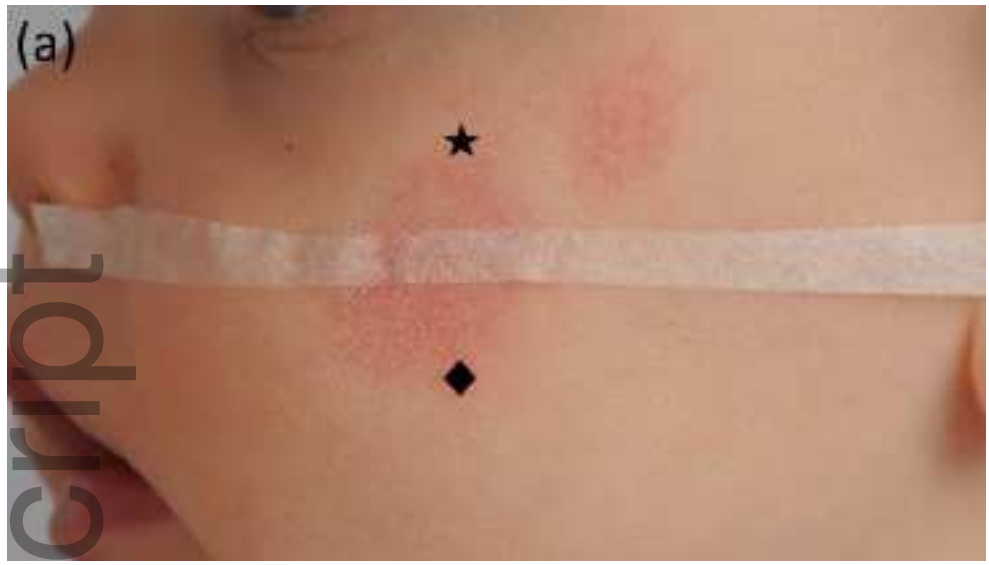
Case	Gender	Age at first treatment	2 weekly treated side of CM	3 monthly treated side of CM

1	F	1 week		++
2	M	3 weeks	-	-
3	M	1 week	+	
4	F	5 weeks	+	
5	F	4 weeks	+	
6	F	withdrawn		
7	M	2 weeks		++
8	M	3 weeks		+
9	M	6 weeks	-	-
10	M	4 weeks		++

Patient characteristics and results after 3 PDL treatments at 2 weekly and 3 monthly intervals. CM Capillary Malformation, F Female, M Male, + mildy improved compared to other side CM, ++ greatly improved compared to other side CM, - no difference compared to other side.

Figure legend

Figure 1. Representative photos of capillary malformations treated with Pulsed Dye Laser. (a) Case 4 with mild improvement on 2 weekly PDL treated side compared with the 3 monthly treated side, (b) Case 9 with no difference between both treated sides and (c) Case 10 with great improvement on 3 monthly treated side compared with the 2 weekly treated side. 2 weekly treated side, 3 monthly treated side.



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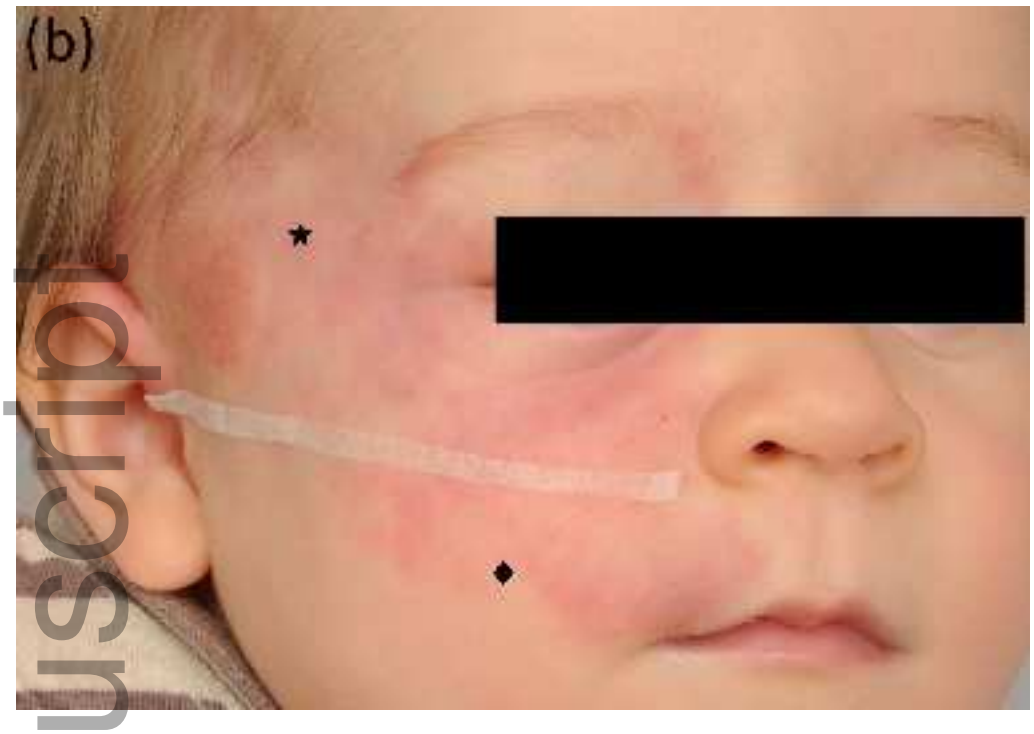

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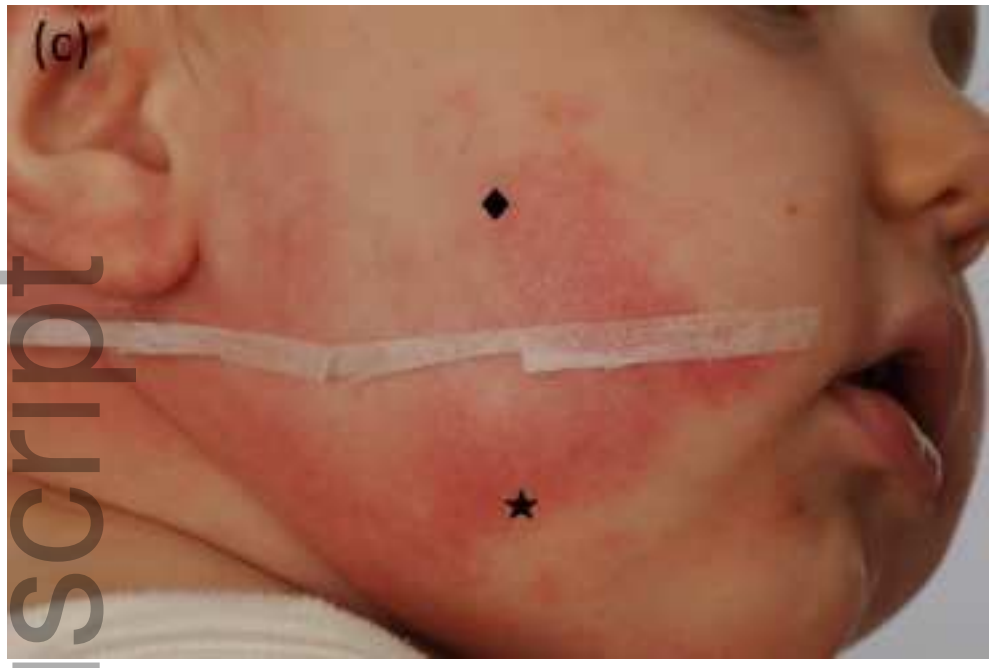

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