EDITORIAL

Early Use of Laser for Port-Wine Stains
Timing, Efficacy, and Shared Decision Making

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In this issue of *JAMA Dermatology*, Jeon and colleagues[1] report on the safety and efficacy of pulsed dye laser (PDL) use in the treatment of port-wine stains (PWS) in a cohort of nearly 200 infants treated without the use of general anesthesia. The authors retrospectively analyzed photographs from short-term follow-up and found a high rate of excellent clearance and no major cutaneous adverse events. They emphasize the feasibility of treating young infants without general anesthesia, an approach that is increasingly relevant because of recent concerns raised about possible developmental effects of general anesthesia in children younger than 3 years. Although the authors' treatment approach is similar to ours in many respects, there are several aspects of their study that are worthy of further discussion. We base our comments on published literature on this topic as well our experiences as pediatric dermatologists with a busy laser practice that has used PDL for PWS treatment since 1989 (in the case of the senior author).

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Concerns regarding associations of general anesthesia use with brain and neurocognitive development in young infants have recently been emphasized.[2] In 2014, the US Food and Drug Administration and the International Anesthesia Research Society convened a diverse group of experts and issued a consensus statement on the use of anesthetic and sedative drugs in infants and toddlers.[3] This statement emphasized avoidance of elective and repeated general anesthesia in young infants, a caution that is highly relevant for the treatment of PWS with PDL.

There is broad consensus that PDL is a painful procedure and increases in pain as PWS size increases because more pulses are required. Although Jeon and colleagues acknowledge this as an issue, they also note that dynamic cooling devices, which spray a cryogen prior to the laser pulse, "significantly diminish pain during PWS treatment."[1] We agree that dynamic cooling devices may reduce pain, but they certainly do not eliminate it. Pain experienced during infancy has been shown to have both short-term and potentially long-term effects, including possible effects on the developing neural circuitry that result in long-lasting differences in pain perception.[4,5] For example, higher numbers of same-day preschool vaccines have recently been shown to contribute to "needle phobia" in school-aged children and adolescents.[6] Even though the short-term or long-term effects of repeated PDL treatment on emotions and pain perception have not been studied systematically, we cannot assume that there is no effect. The patients in the study by Jeon and colleagues[1] received an average of 10 treatments. Although all patients started treatments before 1 year of age, the mean age at initiation was 3.38 months, so some of these patients continued treatment into the second year after birth. Our own experience is that by age 12 to 15 months, many infants show signs of fear and struggle more with laser treatments, particularly if multiple treatment sessions have already occurred.

In considering infant reactions to PDL, the total number of treatments is also worthy of discussion. Some authors have found that the degree of PWS improvement with PDL treatment diminishes after an average of 5 treatments,[7] whereas the mean number of treatments in the study by Jeon and colleagues[1] was 10. It would be helpful to know, either in this cohort or in future studies, how much additional benefit accrues with each additional treatment, particularly in infants receiving more than 5 to 10 treatments. Of note, the authors treated eyelid PWS in awake infants after inserting metal eye shields. A supplementary video shows this being done fairly easily in a young infant for a very brief period of time. We question whether this insertion and removal would be as easily done for a vigorously crying infant during multiple subsequent treatments.

A striking aspect of this study is the rate of PWS clearance. The authors report 100% clearance in 27.4% of patients and a rate of excellent clearance (76%-99%) in 39.1% of patients. This degree of clearance is higher than in our experience and in other reports.[8-10] Although not an explanation for complete resolution, higher rates of excellent responses could be partly explained by the rapid decrease in hemoglobin concentrations from neonatal levels (range, 14-16 g/dL) to a nadir of 9 to 9.5 g/dL by 3 months of age. This physiologic anemia could potentially contribute to an overestimation of the percent clearance in patients treated in the first 3 to 4 months of life with limited follow-up. In addition to factors such as age of initiation, frequency and number of treatments, differences in population skin types, and short follow-up time, the laser settings used by the authors might contribute to the high rate of clearance. The authors used a 10-mm spot to treat the face, whereas we typically use a 7-mm spot size, which we find useful for the finer contours of infants' faces. Owing to the variability of different approaches in clinical practice and lack of a comparison group in this study, it is difficult to say if the results reported are superior to others. Further studies are needed to determine if specific laser settings are truly uniformly superior.

Even if we accept that approximately 25% of patients treated with early and frequent laser treatment cleared completely, albeit with short-term outcomes, the fact remains that 75% did not. A major breakthrough in our understanding of the pathogenesis of PWS came in 2013, when Shirley and colleagues[11] demonstrated that activating somatic mutations in *GNAQ*, specifically codon 209, cause Sturge-Weber syndrome and the cutaneous PWS in that condition. We now know that the majority of PWS is caused by activating somatic mutations in *GNAQ* or its paralog (twin) gene, *GNA11*, and less commonly in other genes, including *PIK3CA*.[12,13] Our understanding that PWS is caused by activating mutations in genes involved in controlling tissue growth and development helps explain why PWS can redarken, even after effective laser treatments, and why some patients develop soft-tissue overgrowth despite laser treatment. Redarkening of PWS after PDL treatment is relatively common and may be delayed by years.[9,14] Thus, although the short-term outcomes reported by Jeon and colleagues[1] are impressive, it would be of great interest to evaluate this same cohort for longer-term outcomes. In PWS, both superficial nodularity and deeper, full-thickness tissue overgrowth may develop. This latter form of overgrowth is likely not, as was often thought in the past, due to too much nourishment of tissues from increased capillary blood vessels, but rather the activating nature of these mutations that favor growth over inhibitory signaling pathways. Patients with PWS and overgrowth, particularly when noted during early childhood, are a distinct subset who may not benefit as much from laser treatment and should be counselled as such.[15] Going forward, these patients could potentially benefit from adjunctive treatments that decrease the activating signaling in the mTOR (mechanistic target of rapamycin) or Ras pathways.[16]

We thank Jeon and colleagues[1] for contributing to our understanding of the safety, efficacy, and logistics of laser treatment for PWS in infancy. In the face of imperfect evidence, we feel it is important to engage in a process of shared decision making with parents (and children, if age appropriate) about the treatment of the child's PWS on initial presentation for consultation and throughout the treatment course. In this process, we emphasize an approach that considers not just the PWS, but also the psychosocial consequences of treatment, nontreatment, pain control, and the risks and benefits of general anesthesia. Based on concerns about general anesthesia use in infants, our approach in facial PWS is similar to the authors' in offering families the option of undergoing as many treatments as are needed and feasible before 12 to 18 months of age without general anesthesia. In larger and more persistent facial PWS, we then consider the use of general anesthesia depending on family preferences and our assessment of whether further treatments will result in substantial clinical benefit. However, with rare exceptions, we defer PDL treatments with general anesthesia until after 3 years of age. For nonfacial PWS, we often defer treatment until the child is older and can help decide whether to proceed. We inform parents that PDL in young infants is safe and that although our experience suggests that most infants younger than 1 year seem to tolerate PDL treatments of small- and medium-sized PWS without obvious signs of posttreatment emotional trauma, they often become increasingly distressed by treatments after 12 to 18 months of age. Moreover, we do not know for sure whether numerous treatments might result in longer-term effects, such as altered perception of pain or fear of procedures. We discuss that although there is inconsistent evidence from primarily retrospective case series that earlier treatment is better, there is compelling evidence to suggest that long-term outcomes are better predicted by the size and site of the PWS. Parents must also be informed that even with numerous PDL treatments, the majority of PWS will not resolve completely. We discuss the issue of redarkening and potential need for another (often shorter) series of treatments if this occurs. We and our patients hope that new insights into the causes of PWS offer hope for new treatment options and even better outcomes.

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