Port-wine stain and infantile hemangioma treatment

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Policy contains: Infantile hemangiomas, laser treatment for port-wine stains, propranolol.

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Coverage policy

Laser treatment for port-wine stains and infantile hemangiomas is clinically proven and, therefore, medically necessary when one of the following criteria is met:

- Emergency therapy due to life-threatening complications.
- Urgent therapy of existing or imminent functional impairment, pain, or bleeding.
- Evaluation to identify structural anomalies potentially associated with the disorder.
- Elective treatment to reduce likelihood of long-term or permanent disfigurement (Brightman, 2015; Darrow, 2015; Randel, 2016).

Only pulsed dye laser therapy should be used for port-wine stains (Brightman, 2015), and it should be used for infantile hemangiomas only in refractory cases (Darrow, 2015; Krowchuk, 2019). Propranolol should be used for systemic therapy for infantile hemangiomas, at 2 – 3 mg/kg daily, for at least six months to as many as 12 months (Krowchuk, 2019).

Note: Depending on the extent of the port-wine stains, several laser treatments may be required, spaced at two- to three-month intervals.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Consultation with dermatologist.

Background

A port-wine stain (nevus flammeus) is a red or purple mark, often on the face. Port-wine stains represent the most common vascular malformation and are commonly known as firemarks. They are caused by a localized area of abnormal blood vessels (capillaries). About three in 1,000 babies are born with port-wine stains (Nguyen, 2019). Most occur on the face, but any area of the skin can be affected. Although the vast majority of port-wine stains are present at birth, they can occasionally develop later on (Cunliffe, 2012).

A modest percentage of port-wine stains located over the eye and central forehead can be associated with glaucoma and/or complications in the brain resulting in seizures or developmental disabilities. This association of facial port-wine stains and glaucoma and/or seizures is called the Sturge-Weber Syndrome. The location and the extent of the port-wine stains on one extremity can lead to enlargement of the extremity relative to an unaffected limb (Klippel-Trenaunay-Weber Syndrome).

In 2013, the cause of port-wine stains and Sturge-Weber Syndrome was discovered. A somatic activating mutation in the guanine nucleotide-binding protein was identified in 12 of 13 cases of port-wine stains and 23 of 26 cases of Sturge-Weber Syndrome, confirming a long-standing hypothesis (Shirley, 2013).

There are several types of laser systems available for port-wine stain treatments. The flashlamp-pulsed dye laser is the gold standard for treatment of port-wine stains. It emits a yellow light wave length of 595 to 600 nanometers, which allows deeper penetration than the original 577 nanometer models introduced in the 1980s (Brightman, 2015). Pulsed dye lasers target oxyhemoglobin and deoxyhemoglobin. The pulsed dye laser penetrates up to two millimeters of skin with a duration of just milliseconds. The procedure is delivered in outpatient settings, over multiple sessions, with or without anesthesia (Cunliffe, 2012).

Infantile hemangiomas are the most common benign childhood tumors. They develop within four to six weeks of birth, and are present in 1% to 3% of newborns, and in 10% to 20% of infants under age one (Darrow, 2015). In newborns weighing less than 1,000 grams, the rate can be as high as 22% to 30% (Zheng, 2013). Up to 70% of cases lead to residual skin changes. Complications include ulceration, bleeding, feeding problems, and visual impairment (Randel, 2016).

A Mayo Clinic study of Olmsted County, Minnesota, demonstrated that the rate of infantile hemangiomas more than doubled from 1976 – 1980 to 2006 – 2010, increasing from 0.97 to 1.97 cases per 100 person-years. A total of 999 cases were identified in the 35-year period, and the increase was correlated with declines in average gestation period (39.2 weeks to 38.3 weeks, $P < .001$) and average birth weight (3,383 grams to 3,185 grams, $P = .003$) (Anderson, 2016).

Infantile hemangiomas can also be associated with a constellation of congenital anomalies:

- Posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities,

sternal cleft, and supraumbilical raphe.

- Perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag.
- Lower-body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies.

A distant subset of infantile hemangioma consists of multiple small lesions varying in size from a few millimeters to one to two centimeters. This form of infantile hemangioma (so-called multiple neonatal hemangiomatosis) has a higher risk of visceral involvement, particularly in the liver and gastrointestinal tract; however, the prognosis for the skin lesions is usually good, as they often involute by two years of age.

After laser therapy for infantile hemangioma, the area will often turn off-white within seven to 14 days. An evaluation should be made every two to four weeks after treatment until the condition is resolved, or another treatment is needed (Zheng, 2013).

The Food and Drug Administration has approved a variety of lasers for marketing, through the 510(k) process, for a variety of dermatologic indications, including treatment of port-wine stains and infantile hemangiomas. \

Findings

No specific professional guidelines exist for treating port-wine stains, although experts maintain that pulsed dye laser is the gold standard for treatment (Chen, 2012). An American Academy of Pediatrics guideline notes that after 2008, systemic corticosteroids — in particular, propranolol — have been used to treat infantile hemangioma.

The guideline recommends the drug, with cardiovascular monitoring every hour for two hours, with repeat monitoring for any dose increase over five mg/kg. If propranolol cannot be used or is ineffective, corticosteroids (usually daily oral prednisone or prednisolone) can be an alternative therapy. Laser therapy may be useful in treating early lesions (Randel, 2016).

A 2015 report from the American Academy of Pediatrics provided updates on the pathogenesis, treatment, and clinical associations of infantile hemangiomas, including the use of pulsed dye laser for refractory cases (Darrow, 2015). A summary of recommended therapies for infantile hemangioma includes lasers, along with chemotherapy, interferon alfa-2a, systemic or intralesional steroids, radiation or cryotherapy, therapeutic embolization, and surgery (Fette, 2013). Another guideline states that laser therapy for infantile hemangioma should be repeated every two to four weeks, and that it is not suitable for deep-seated hemangiomas (Zheng, 2013).

The most recent American Academy of Pediatrics guideline on infantile hemangiomas declares that pulsed dye laser is safe and effective, and evidence has demonstrated that pulsed dye is more effective than other laser therapies, although acknowledging there is controversy over using the technique in infants. The guideline also recommends using propranolol for systemic treatment of infantile hemangiomas (Krowchuk, 2019).

Port-wine stains results:

A systematic review found 81 of 85 studies (n = 3,310) of patients treated for port wine stains assessed efficacy using measures of improvement/appearance. However, multiple other scoring systems were used, and only 44% of studies could be compared. Just 13 of the 85 studies were of good quality (van Raath, 2020).

Another systematic review of 77 studies (by the above research team) reviewed outcomes measurement instruments for port wine stain treatment, finding 93% of studies had low or very low quality of evidence. Authors

state it is not possible to recommend a particular instrument(s); even terms such as “improvement,” “blanching,” “clearance,” and “lightening,” cannot be presumed to be interchangeable (van Raath, 2021).

A systematic review of 34 studies (n = 3,777, only one of which was randomized) found interval time between pulsed dye laser treatments for port wine stains had no effect on patient outcomes (Snast, 2021).

A 2015 review of the literature finds that lasers, and in particular, pulsed dye lasers, are effective modes of treatment for port-wine stains, asserting that 80% to 90% improvements are common in early and optimal treatments (Brightman, 2015).

One large non-randomized study on pulsed dye laser for port-wine stains included 848 cases, using a 595 nanometer laser. The response rate was 69.9%, and the cure rate among respondents was 6.3%. The response for infants under age one was 93.3%, significantly greater than for patients over age 50. The temporal region had the highest clearance rate (75.5%), while the rate for extremities was just 44.5%. Patients with lesion size of less than 20 centimeters had a higher rate of clearance than those with lesions greater than 80 centimeters — 73.8% versus 53.2%. Finally, early intervention was associated with higher clearance rates (Shi, 2014).

A literature review determined that no topical treatment currently in use is helpful as an adjunct to pulsed dye laser to treat port-wine stains (Lipner, 2018).

Pain is a common side effect after laser therapy for dermatological procedures for conditions such as port-wine stains. A review of 32 randomized and nonrandomized controlled studies showed that noninvasive techniques, including pulsed dye laser, resulted in less pain than placebo, and topical anesthesia had better outcomes than skin cooling (Greveling, 2017).

A large randomized controlled trial compared outcomes for adults and adolescents with port-wine stain treated with hemoporfin photodynamic therapy (n = 330) or irradiation with placebo (n = 110). After eight weeks, the proportion reporting at least some improvement in the treatment group was significantly greater than the placebo (89.7% versus 24.5%, $P < .0001$) (Zhao, 2016).

A review of 65 studies (n = 6,207) revealed that just 21% of patients with port-wine stains treated with pulsed dye laser achieved 75% to 100% clearance, and observed no improvement over time, indicating the need for further research of novel therapies (van Raath, 2019).

Infantile hemangioma results:

A systematic review and network meta-analysis of 30 randomized trials assessing treatment for infantile hemangioma showed laser with topical beta blockers showed greatest efficiency, and long-pulsed dye laser to be most effective. A higher dose and a longer treatment duration of propranolol orally achieved a higher success rate and increased side effects, while plus pulse dye laser with propranolol had the lowest incidence of adverse reactions (Fei, 2020).

A meta-analysis analyzed efficacy of combined therapy with adrenergic beta-antagonist and lasers for infantile hemangiomas. Combined therapy with oral propranolol and lasers was superior to propranolol or lasers alone (both $P < 0.00001$). Combined therapy with topical timolol and lasers was superior to topical timolol ($P < .00001$) or lasers ($P = .007$) alone. Authors observed no differences in adverse effects (Chen, 2020).A meta-

analysis of eight randomized trials (n = 759) documented that combined treatment of infantile hemangiomas with topical timolol and oral propranolol may be more effective than either treatment alone. Topical timolol alone was equally effective as oral propranolol, but with fewer adverse events (Qiao, 2020).

A meta-analysis of 13 studies (n = 1,580) showed an 89.1% resolution rate and a 6.28% adverse effect rate of pulsed dye laser on infantile hemangioma (Shen, 2015). A systematic review of 76 studies (n = 1,239) showed no significant advantages in outcomes between various treatment modes for ulcerated infantile hemangiomas; oral propranolol was associated with a 97.0% complete ulcer healing in 197 cases (Wang, 2018).

An Agency for Healthcare Quality and Research review of 148 studies of infantile hemangioma outcomes indicated that longer-pulse pulsed dye laser was generally more effective than observation (Chinnadurai, 2016a). This finding was consistent with a review of 29 studies, which also concluded that pulsed dye laser worked better than other laser therapies (Chinnadurai, 2016b).

A systematic review of 41 studies (n = 1,264) showed propranolol administration for infantile hemangiomas resulted in a 98% response rate, with rebound growth of 17%. A total of 371 adverse events (over half of which were changes in sleep and acrocyanosis) plus 10 serious adverse events were observed (Marqueling, 2013).

A systematic review and meta-analysis of 16 studies (n = 2,629) of patients with infantile hemangiomas showed response to propranolol therapy was significantly greater than response to corticosteroid therapy (99% versus 90%) after 12 months of follow-up (Izadpanah, 2013).

A meta-analysis of 61 studies (n = 5,130) found propranolol was more effective in treating infantile hemangioma than other modalities (odds ratio = 0.92), and was especially effective at daily doses greater than 2 mg/kg. Propranolol also had significantly fewer complications than systemic steroids (odds ratio = 0.68), laser ablation (0.55), other beta-adrenergic blockers (0.56), and surgery (0.55) (Liu, 2015).

A meta-analysis of 35 studies (n = 572) of infantile hemangioma patients revealed that propranolol (n = 324) was significantly more effective than other therapies ($P < .001$). Propranolol effectiveness was greater versus steroids ($P < .001$), vincristine ($P = .003$), and laser treatment ($P = .02$) in treating cutaneous ($P < .001$), periocular ($P < .001$), infantile airway ($P < .001$), and hepatic ($P = .033$) hemangioma (Lou, 2014).

A systematic review of periorbital infantile hemangiomas of 31 studies (n = 425) compared outcomes after propranolol and corticosteroid treatment. Propranolol had significantly better outcomes for response rate (94.0% versus 82.3%, $P = .001$), reduction in spherical power ($P = .005$), and postoperative amblyopia (16.7% versus 31.1%, $P = .04$). Corticosteroids were associated with significantly fewer temporary adverse events (9.5% versus 24.0%, $P = .006$) (Xu, 2014).

A systematic review of 83 studies, three pooled clinical trials, and one compassionate use program (n = 5,862) of infantile hemangioma patients treated with propranolol documented an adverse event in about one third of patients (1,945 of 5,862). The most frequent adverse events were sleep disturbances, peripheral coldness, and agitation. The most serious events (atrioventricular block, bradycardia, hypotension, bronchospasm/bronchial hyper reactivity, and hypoglycemia-related seizures) were controlled by decreasing doses or discontinuing propranolol, temporarily or permanently (Leaute-Labreze, 2016).

A Cochrane review of 28 studies (n = 1,728) found that compared with placebo, oral propranolol (three mg/kg daily) for infantile hemangiomas probably improves clinician-assessed clearance with no difference in rates of

serious adverse events, including no instances of bradycardia or hypotension (Novoa, 2019).

References

On June 1, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “port wine stain,” “propranolol,” “infantile hemangioma,” and “laser treatment.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

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