REVIEW

Paediatrics: how to manage infantile haemangioma

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Abstract

Infantile haemangiomas (IHs) are relatively common benign vascular tumours found in the paediatric population. They have varying sizes and involve different depths in the skin leading to various colours, shapes and textures. Although considered harmless in most cases, they may lead to life-threatening complications or cause permanent disfigurations and organ dysfunction. For problematic IHs, the treatment options include oral and topical beta-blockers, systemic corticosteroids, laser treatment, and surgery. In this narrative review, the treatment options for problematic IH are compared and delivered concisely to facilitate the clinical decisions from practitioners, including those in primary care settings. Oral propranolol is currently considered the first-line intervention for problematic IHs. For superficial lesions, there is robust evidence for the use of topical timolol maleate. Systemic corticosteroids are sometimes used in specific situations such as resistance or contraindications to beta-blockers. Surgical excision can be considered in cases requiring urgent intervention such as airway obstruction; this can be done alongside laser therapies for the removal of residual tissue or when reconstructing areas of deformity. The combination of multiple treatment modalities may lead to a more rapid clinical response.

Keywords: dermatology, haemangioma, paediatrics.

Introduction

Infantile haemangiomas (IHs) are benign vascular tumours commonly encountered in paediatric dermatology practice. They occur in about 4–5% of children and affect girls more than boys.[1,2] IHs are usually absent at birth but appear early in life. Most IHs proliferate quickly for the first 5 months of age and achieve complete growth by 9 months of age.[3] However, deep and segmental IHs may have a prolonged proliferative stage. Soon after the proliferative stage, the lesions undergo involution and typically resolve by approximately 4 years of age.[4] Most IHs do not lead to complications and do not require treatment. However, some IHs may have serious adverse effects such as permanent disfigurement, ulceration, obstruction of vital organs and visual disturbance.[3,5]

Multiple treatment options have been developed over the years including oral, topical and intralesional (IL) corticosteroids, systemic IFNα, oral and topical beta-blockers, laser treatment, and surgical excision.[6] Most often, medical intervention is not necessary as the lesions resolve spontaneously. However, it is important to recognize high-risk patients who will benefit from surgery or medications that will prevent permanent disfigurement, scarring, or organ dysfunction.[6]

Current guidelines provide comprehensive information on IH management but may not be ideal for some practitioners seeking a concise resource to aid clinical decisions, for example, for appropriate referrals or treatment initiations in primary care settings. This narrative review aims to deliver concise information to help facilitate clinical decisions and supplement the recommendations with up-to-date evidence.

Methods

This study is a narrative review on IH with a primary focus on disease management. Using the keywords "infantile hemangioma" and "management", Ovid Medline, PubMed and Google Scholar were used for the search. Multiple searches were conducted, each with different filters to narrow the results, for example, by year of publication to discover recent studies or by study type to isolate randomized controlled trials (RCTs). The Strength of Recommendation Taxonomy (SORT) grading system was used herein.[7]

Review

Epidemiology

The prevalence of IH is of ~4–5% and is more prevalent in white female infants with a history of prematurity or chorionic villus sampling.[1,2] There is a clear predominance of females in this condition, with a sex ratio of 2.4:1 (female to male ratio).[1] This number has been shown to increase to 9:1 in patients with Posterior fossa brain malformations, Hemangiomas, Arterial anomalies, Coarctation of the aorta and cardiac defects, and Eye abnormalities (PHACE) syndrome.[8] IHs are quite common in infants with low birth weight (<2500 g) and the risk increases by 40% with each 500 g decrease in birth weight.[1,9] Preterm birth was also associated with a higher incidence of developing IH compared to term infants.[9] The risk of developing IH was tripled if there was a history of chorionic villus sampling.[1,10] One study suggested that having a sibling with an IH may increase the risk in subsequent siblings.[11] Advanced maternal age, multiple gestation and pre-eclampsia appear to increase the risk of developing an IH though these may also be confounding factors.[1]

Pathophysiology

Hypoxic exposure during foetal development is associated with the vasculogenesis and angiogenesis of IHs.[12–15] This hypothesis is supported by the epidemiological data showing the prevalence of low birth weight and prematurity, both associated with foetal hypoxia.[1] Tissue ischaemia increases the expression of hypoxia-inducible factor 1α (HIF1α) in the endothelial cells of IH, which is a transcription factor that induces the activity of vascular endothelial growth factor A, stromal cell-derived factor 1α, GLUT1, matrix metalloproteinase 9 and IGF2, all of which are associated with IH.[13,16,17] An increase in vascular endothelial growth factor A and HIF1α levels leads to the mobilization and trafficking of endothelial progenitor cells that is crucial for vasculogenesis.[12] These angiogenic factors are also found to be upregulated by oestrogen, as suggested by elevated serum levels of estradiol-17-beta and oestrogen receptors in children with IH.[18] The female predominance seen in IH may be explained by the relatively higher oestrogen levels compared to a male baby.[18]

The renin-angiotensin system has been shown to be a hypoxia-independent factor that promotes the production of HIF1α and the downstream upregulation of angiogenic cytokines. High levels of renin in preterm or low birth weight neonates lead to increased angiotensin II, which promotes HIF1α.[15,19–21]

Clinical manifestations

IHs present with variable morphologies, from small benign growths to functionally disabling masses.[3,22] Typically, these lesions measure less than 3 cm and can be found mostly on the face, neck and trunk.[1,14,22] Based on their soft-tissue involvement, IHs are classified as superficial, deep or mixed. Superficial IHs often have a bright red colour early in their proliferative phase and do not involve deeper structures of the skin. Deep IHs present as a soft mass with a bluish hue. The mixed type combines both superficial and deep IHs and can resemble a 'poached egg'.[14,22,23] Compared to IHs with a flat or smooth appearance, IHs with abrupt borders or rough surfaces are more likely to have permanent residual skin changes.[24] IHs can also be categorized as localized, segmental, indeterminate or multifocal based on spatial involvement. Segmental IHs are the most likely to cause complications.[1,14,25] A rare variant of IH with minimal or arrested growth may be mistaken for port-wine stains but can be differentiated based on the presence of fine or coarse telangiectasias with occasional papules populating the periphery of the IH.[26]

The two main stages of growth in IH are proliferation and involution. Although IHs are usually not congenital, some newborns may be born with premonitory skin changes such as pale or telangiectatic macules prior to the proliferation of the IH.[5,14,22] Typically, IHs appear within weeks of birth and undergo rapid proliferation for the first 5 months of age. Some continue to grow at a slower rate up to about 1 year of age.[3,22] Following the proliferative stage, the tumour undergoes spontaneous involution that usually resolves by about 4 years of age.[4] Although most IHs resolve without treatment, 55–69% of cases can have residual lesions (e.g. telangiectasia, fibrofatty tissue, anetoderma, pigmentation changes, erythema, scars), which may cause a significant impact on a child's self-esteem.[6,24,27]

According to a study in 2007, complications may occur in 24% of IH cases, prompting treatment.[1] Ulceration is the most common complication but airway obstruction, ocular dysfunction and hypothyroidism can also occur though infrequently.[28–32] IHs may also present with other systemic features as in PHACE syndrome and Lower body haemangioma and other cutaneous defects, Urogenital anomalies, Ulceration, Myelopathy, Bony deformities, Anorectal malformations, Arterial anomalies, and Renal anomalies (LUMBAR) syndrome.[33,34]

Treatment

For the past few decades, numerous pharmacological and surgical management approaches for IHs have been suggested.[6,23] As IHs naturally enter a phase of involution and regress without further management, the mainstay of the treatment of IHs has been 'watchful waiting'. However, more than one-third of the cases may be associated with functional impairment or a significant impact on the quality of life and require medical intervention.[1,23] The initial step to managing IHs should include risk stratification, as reinforced in the recent Clinical Practice Guideline from the American Academy of Pediatrics (AAP) published in 2019.[6] This is important considering that most of the IH growth occurs early in life and a delay in treatment may lead to relatively poor outcomes.[3] Key points to consider are whether the lesion is causing obstruction, ulceration, functional impairment, has potential for permanent disfigurement, or has any associated structural abnormalities. An infant presenting with lesions involving the tip of the nose,

perioral, periocular, cheeks or perineal areas requires further evaluation. If there is a history of bleeding from the lesion, feeding impairment, stridor, hypothyroidism, congestive heart failure, or auditory or visual disturbance, the infant would require an urgent referral to a specialist and may benefit from treatment.[6,23,35] A recent publication by Léauté-Labrèze et al. offers a referral assessment tool consisting of 12 questions with a sensitivity of 96.9% that may assist in the decision to refer early.[36]

The following subsections discuss each treatment modality separately. A summary of their indications, advantages, disadvantages and strength of recommendations is available in Table 1.

Oral beta-blockers

Currently, oral propranolol is the first-line therapy in the management of problematic IHs.[6,23] A proprietary oral propranolol solution has been approved by Health Canada, the FDA and the European Medicines Agency for this use.[37]

The precise mechanism of action is unknown, but it is thought to be mediated through vasoconstriction, inhibition of vasculogenesis and angiogenesis, and induction of apoptosis.[6,38–40] To date, numerous studies support the effectiveness of oral propranolol.[41–44] A meta-analysis in 2019 reviewed the efficacy and safety of oral propranolol in the treatment of IHs.[45] A total of 18 studies including 10 RCTs demonstrated a superior response rate of IHs to oral propranolol therapy compared to other treatments, including oral atenolol, topical timolol maleate (TTM), oral prednisolone, IL triamcinolone acetate, Nd:YAG laser, oral captopril and IL bleomycin (RR 1.40, 95% CI 1.13–1.75).[45] However, the subgroup analysis revealed that low-dose propranolol (1 mg/kg/day) was not superior to the control whilst medium-dose (2 mg/kg/day) and high-dose (3 mg/kg/day) treatments showed superior efficacy.[45] According to a small prospective study in 2019, IHs not responding to 1–1.5 mg/kg/day of oral propranolol were unlikely to respond to higher doses at 3–4 mg/kg/day.[46] The effectiveness of propranolol also varied between individuals

Table 1.   Comparison of different treatment modalities for infantile haemangioma.

Drug	Indication	Pros	Cons	Strength of Recommendation[a]
Oral propranolol	- Treatment of choice	- Superior outcomes - Well tolerated - Easy to administer	- Limited evidence for <5 weeks of age or post-conceptional age <48 weeks - Potential risk with known asthma or reactive airway disease - ADRs of beta-receptor blockade (sleep disturbance, bradycardia, hypotension and bronchial irritation)	A
Topical timolol maleate	- Thin or superficial IH	- Easy to administer - Minimal systemic exposure, lower risk of ADRs than oral propranolol - Non-inferiority to oral propranolol in superficial IH	- Limited efficacy in bulky or deep IH - Risk of local irritation and ulceration, particularly in preterm infants	A
Oral prednisone/ prednisolone	- Contraindication to propranolol or inadequate response	- No risk of hypotension or bradycardia	- Not safe for long duration - ADRs (cushingoid appearance, delayed growth, infection, hypertension, mood changes)	B

(Continued)

Table 1. *(Continued)*

Drug	Indication	Pros	Cons	Strength of Recommendation[a]
IL corticosteroid (triamcinolone with/without betamethasone)	- Focal, bulky IH during proliferation or critical anatomic locations such as lips	- Localized - Low risk of systemic ADR - Less frequent administration - Administered by physician - Protects anatomic landmarks	- Fear of injections - Frequent appointments - Not ideal for large lesions - Lower rate of clearance - Rare risk of central retinal artery embolization	B
Surgery	- Severe cosmetic deformity or life-threatening complications (e.g. airway obstruction, profuse bleeding from ulceration, high-output cardiac failure) - Removal of residual deformities - Contraindications to pharmacotherapy - Treatment failure with pharmacotherapy - High probability of resection in the future	- Early intervention before child develops body image and self-esteem - Immediate results - Avoids chronic exposure to drugs - Less caregiver burden	- Risks associated with anaesthesia - Inferior outcome - Bleeding risk - Iatrogenic injuries - Residual scar formation	C
Laser	- Removal of residual erythema and superficial telangiectasias	- Improves physical appearance of the lesions - Reduces psychological stress on the child - May be combined with other therapies	- Risk of skin atrophy, pigmentary changes, bleeding and ulceration - Weak evidence to support use as primary treatment - PDL may not penetrate to deep tissues - Requires multiple treatments	C

[a]Strength of recommendations based on Strength of Recommendation Taxonomy (SORT).
ADR, adverse drug reaction; IH, infantile haemangioma; IL, intralesional; PDL, pulsed dye laser.

based on their cytochrome P450 2D6 (CYP2D6) genotype, possibly explaining the difference in treatment response between individuals.[47] A comparison of different treatment durations revealed a better response when oral propranolol was taken for more than 6 months.[45] As to the timing of initiation, ages of 5 weeks to 5 months are suggested, with an exception of premature infants, who would require a corrected age greater than 5 weeks.[43]

With regard to safety, there was no statistical difference in the adverse reactions between patients receiving oral propranolol and the control group (RR 0.78, 95% CI 0.45–1.34).[45] When comparing the different doses, high-dose propranolol therapy had a higher risk of adverse events compared with medium-dose therapy. A systematic review by Léaute-Labrèze et al. confirmed the tolerability of oral propranolol up to 3 mg/kg/day for 7 months.[48] The most common adverse

reactions were sleep disturbance, peripheral coldness and agitation. There were small numbers of serious adverse reactions (e.g. heart block, bradycardia, hypotension, bronchospasm, hyperglycaemia-associated seizure) reported and these were managed through dose adjustments and/or discontinuation.[48] Absolute and relative contraindications for the use of oral propranolol include prior hypoglycaemic episodes, second- and third-degree heart block, hypersensitivity to propranolol, weight under 2 kg, prematurity under 5 weeks of corrected age, a history of asthma or bronchospasm, severe hypotension, and pheochromocytoma.[35,49]

Several accounts of hyperkalaemia have been reported with oral propranolol at doses of 2 mg/kg per day, with serum potassium levels reaching 7.3 mmol/L in one case that resolved with a switch of therapy from oral propranolol to oral atenolol.[50–52] Atenolol is unlikely to cause hyperkalaemia due to its beta-1 selectivity, avoiding the blockade of beta-2 receptors associated with potassium uptake into the cells. In addition, propranolol has been linked to abrupt cell lysis leading to the release of intracellular potassium.[50,52] Several early studies have also raised concerns regarding the negative impact of propranolol on central nervous system development in children.[53,54] However, more recent studies have demonstrated that the risk of central nervous system development impairment was not increased with the use of oral propranolol.[55–57]

Various recommendations are available regarding the in-office monitoring of vitals at initiation or dose adjustment of propranolol.[37,49,58,59] A recent study in 2020 found that in-office vital monitoring is unlikely to be useful in infants older than 5-week gestational corrected age with normal birth weight.[60]

There have been attempts to investigate the use of other oral beta-blockers in the treatment of IHs. Atenolol, metoprolol, acebutolol and nadolol are the most common alternate oral beta-blockers that have been used.[61–65] A systematic review and meta-analysis comparing atenolol 0.5–1 mg/kg/day to propranolol 2 mg/kg/day showed that atenolol was non-inferior to propranolol in treating IHs and possibly has a lower risk of adverse reactions.[62] In theory, atenolol's specificity for the beta-1 receptor and its hydrophilic property preventing the penetration of the blood–brain barrier are thought to have advantages over propranolol in terms of safety.[62,66] In a retrospective study, metoprolol was compared to propranolol at 2 mg/kg/day dose and showed comparable effectiveness with a potentially better safety profile.[63] Acebutolol at 8–10 mg/kg/day has successfully been used to treat IHs without complications in two case series.[64,65] In a cohort study, nadolol was taken at a mean dose of 2.19±1.1 mg/kg for 6 months and showed better effectiveness than propranolol on the visual analogue scale of the appearance of the IH with minor adverse reactions.[67] A small retrospective study reported less sleep disturbance in nadolol compared to propranolol.[68] An alarming case report of a case of nadolol-associated death attributed to the accumulation of nadolol to toxic levels suggests caution

when used in children with irregular bowel movements. Compared to propranolol, nadolol has a longer half-life and is excreted into the faeces through the biliary system, which may theoretically be reabsorbed via the enterohepatic circulation and accumulate in the blood.[69]

Topical beta-blockers

In the 2019 clinical practice guideline by the AAP, TTM is suggested as a treatment option for thin or superficial IHs.[6] To date, there is an appreciable number of studies that support the efficacy and safety of TTM in term infants with IHs.[70–76] A meta-analysis in 2020 showed that TTM is likely non-inferior to oral propranolol (OR 0.955, 95% CI 0.700–1.302, p=0.769) in treating superficial IHs. In addition, it was superior to topical imiquimod (OR 2.561, 95% CI 1.182–5.550, p=0.017) and conservative management (OR 18.458, 95% CI 5.660-60.191, p<0.001). In patients aged 1–13 months, TTM solution, gel or ointment at concentrations of 0.25–0.5% were applied once to three times daily for a duration ranging from 1 to 7 months. The risk of adverse reactions was lower compared to oral propranolol (OR 0.191, 95% CI 0.043–0.858, p=0.031). Some examples of adverse reactions include desquamation, nocturnal crying, erythema and diarrhoea, all of which occurred in around 1% of cases.[76] According to Drolet et al., one drop of 0.5% TTM twice daily has the potential of reaching a plasma concentration known to have systemic beta-blocking activity in adults, especially with increasing IH thickness. In thick IHs, doses exceeding two drops of 0.5% TTM per day are not recommended and may not have the safety advantage over oral beta-blockers.[77]

TTM may have benefits as an adjunctive therapy following oral propranolol to reduce the duration of therapy. However, the timings of initiating TTM and discontinuation of oral propranolol were unclear in the study, limiting the application of the findings.[78]

There are relatively less robust data regarding the use of topical propranolol for IHs.[6] However, a meta-analysis in 2020 including 4 studies with 91 superficial IH cases and 89 controls suggests possible non-inferiority of topical 0.5–1.0% propranolol compared to oral propranolol (OR 0.486, 95% CI 0.165–1.426, p=0.189). Similarly, there was no difference in the risk of adverse reactions (OR 1.258, 95% CI 0.471–3.358, p=0.647).[76]

Oral and IL corticosteroids

Oral and IL corticosteroids were used in the treatment of IH since the 1960s until the introduction of beta-blockers, which had a more favourable efficacy and safety profile.[79–81] Nevertheless, both prednisone and prednisolone have shown success in treating IHs.[23,82,83] In a systematic review, the response rate with oral prednisone was 84% with a rebound rate of 36%.[84] Likewise, there is a considerable number of studies supporting the use of IL corticosteroid therapy.[85–87] Out of 749 cases treated with triamcinolone alone or combined with betamethasone or dexamethasone, 71% had excellent responses, defined as tumour regression of greater than 75% in size.[86] Rebound growth occurred in 0.6% of the cases

treated with IL injections.[86] Compared to other treatment options, a network meta-analysis in 2016 showed that oral corticosteroids had a relative expected clearance rate of 43% (95% Bayesian credible interval (BCI) 21–66%) compared to 6% (95% BCI 1–11%) of controls, 58% (95% BCI 22–99%) with IL triamcinolone, 62% (95% BCI 39–83%) with TTM and 95% (BCI 88–99%) with oral propranolol.[88] A second network meta-analysis in 2020 showed a similar hierarchy of effectiveness between the common treatment options.[41]

The use of oral corticosteroid treatments was associated with systemic adverse reactions, which occurred at a rate of 35% (95% CI 27–44) and included transient growth delay, behavioural changes, adrenal suppression, secondary infections and gastric irritation.[84,89,90] When comparing the different oral doses, the risk was significantly higher with daily doses greater than 3 mg/kg compared to lower doses.[84] Local adverse reactions following IL injections occurred in 3.8% of the cases and consisted of ulceration, atrophy, calcification, infection, scarring and necrosis, in order of frequency.[86] The risk of retinal artery embolization was reported following administration into IHs near the ocular orbit and is thought to be related to high injection pressure.[91–93] IL injections have also resulted in systematic adverse reactions similar to oral treatments (e.g. adrenal suppression) at a rate of 2.7%.[86] In the network meta-analysis, the risk of adverse events was increased in the oral glucocorticoid group *versus* the observation or placebo (OR 28.69, 95% credible intervals (CrI) 1.82–1263) and oral propranolol (OR 4.33, CrI 0.40–43.06) groups.[41] There was no difference between the IL and oral groups (OR 1.12, CrI 0.03–46.58).[41]

Oral systemic corticosteroid is currently recommended as a second-line option in cases with contraindications or resistance to oral propranolol therapy.[6,94] Most literature, including the AAP guideline, mention systemic corticosteroids when referring to an oral formulation.[6,94] Previously, an RCT compared monthly IV methylprednisolone to daily oral prednisolone and showed better clinical outcomes with oral prednisolone, albeit with an increased risk of adverse effects such as delayed growth.[95] IL formulation can be considered as a second-line agent for well-localized, small and bulky lesions affecting the lip, nose or other important anatomic landmarks.[6,94] The doses reported in previous studies ranged from 1 to 5 mg/kg/day of oral prednisone or prednisolone and 2–3 mg/kg/day was recommended to maximize the efficacy whilst minimizing the adverse effects.[6,84] The duration of 4–12 weeks with gradual taper until the age of 9–12 months has been recommended by clinical guidelines, with high variability in treatment duration between the studies cited.[6,23] For IL injections, no clear recommendation on the regimen has been suggested in the literature.[6,23,86] Prasetyono and Djoenaedi suggest a 3–5 mg/kg total equivalent triamcinolone dose (maximum 60 mg per treatment) with or without 6 mg/mL betamethasone sodium acetonide (or phosphate) per 40 mg/mL triamcinolone, at an interval of 3–4 weeks repeated 1–7 times.[86] However, the use of oral beta-blockers has largely supplanted the need for IL corticosteroid therapy.

Surgical and laser treatment

Oral propranolol therapy has also significantly decreased the need for surgical procedures and laser therapies.[6,96] Nevertheless, the benefits may overweigh the risks on certain occasions. Despite the risks associated with anaesthesia and the risk of bleeding, surgical intervention may be performed to remove non-healing ulcerated, obstructive or aesthetically sensitive lesions.[6,23,97] For example, in a retrospective review, 214 lip haemangioma cases were managed with surgical excision with clinical improvements and minimal complications.[98] Typically, surgery can be considered during the involution phase if the prognosis is clear (e.g. extent of post-op scar unlikely to change) or after involution for the removal of residual fibrofatty tissues, scars and reconstructing areas of deformity.[6,23,99] Due to reduced bulk and vascularity in involuted IHs, the risks of bleeding from the procedures are likely lower.[99]

Pulsed dye laser (PDL) is the most commonly studied laser and can be used for the treatment of residual macular erythema or superficial telangiectasias. In a systematic review, PDL appeared to show better outcomes compared to conservative management, although the heterogeneity in the included studies limited the overall analysis. Compared with TTM, PDL was half as effective in achieving complete or near-complete resolution in one of the studies included in the review. Instead, when PDL was combined with oral propranolol, a higher proportion of the patients attained clinical improvement compared to oral propranolol alone. Other lasers were also reviewed, including Nd:YAG, argon and CO_2, but no clear conclusions were made due to the heterogeneity of the studies included. Side-effects of laser therapy include pigmentary changes, ulceration, atrophy, bleeding and scarring.[97,100]

Combination

An RCT comparing 2–3 mg/kg/day oral propranolol with 1–4 mg/kg/day prednisolone *versus* a combination of the two has shown that there was no benefit in using combination therapy compared to oral propranolol monotherapy.[101] In a different study, combination therapy initially showed an earlier rapid clinical response compared to propranolol alone. However, this difference was lost once the treatment duration reached 6 months.[102] As mentioned earlier, a combination of topical and oral beta-blockers (i.e. oral propranolol and TTM) with lasers (e.g. PDL, Nd:YAG) have shown superior effectiveness as well as safety.[103]

Multiple network meta-analyses have been published in recent years, providing insight into the relative effectiveness and safety of numerous IH treatment options.[41,42,88] Based on cluster analyses, oral propranolol was most effective, followed by IL corticosteroids and topical beta-blockers. On the other hand, topical beta-blockers were the safest, followed by IL propranolol and oral propranolol.[41] Applying the same analytic method, combination therapies were analysed in a different study.[42] Topical beta-blockers with laser therapy were more effective than oral propranolol combined with laser therapy. Both combinations were more effective than monotherapy

with 3 mg/kg/day oral propranolol or other therapies. This study did not specify the type of laser used, unlike its analysis of safety. Topical beta-blockers were safer than Nd:YAG whether given alone or in combination.[42]

Others

Over the years, some treatments have fallen out of favour due to safety concerns.[23] Vincristine, IFNα and topical imiquimod have shown positive outcomes in treating IH and may be viable options in severe and recalcitrant IH.[23,104–106] However, the risks of neurotoxicity (e.g. cranial nerve palsy, spastic diplegia) are associated with vincristine and IFNα and local inflammatory changes (e.g. ulceration) with imiquimod should be weighed against the benefit.[23,106–108] Other treatments (e.g. itraconazole, captopril, pingyangmycin, lauromacrogol/polidocanol, bleomycin, bevacizumab, brimonidine, sirolimus/rapamycin, deoxycholic acid) have also been mentioned in the literature but the recommendation for their use is limited due to relatively inferior efficacy, product availability or a lack of high-quality studies.[109–115]

Involuting or involuted IH

Based on the literature and clinical practices, oral propranolol has been used beyond the proliferative phase with proven clinical outcomes. For this reason, oral propranolol is still recommended for the management of IHs during involution. Considering the reduced volume of IHs during the involution,

TTM may play some role in resolving residual IHs as well.[116] In comparison to the proliferative phase, treatments of involuting/involuted IHs may involve non-pharmacological therapies such as surgeries and lasers. As mentioned above, surgical management may be considered for certain involuted IHs to improve aesthetic outcomes with relatively less bleeding risk.[99] Similarly, PDL has been effective in resolving residual macular erythema or telangiectasias.[97,100]

Conclusion

IHs are a common benign tumour of infancy that occasionally require treatment to prevent permanent sequelae. The management of IHs has evolved over the past decades, favouring more effective and safe treatments. To date, oral propranolol therapy is a good first-line option that is minimally invasive and effective. There is robust evidence for TTM as an alternative for superficial IHs, which carries a lower risk of adverse events. Oral corticosteroid therapy is reserved for children who cannot tolerate or are unresponsive to beta-blocker therapy. Surgical procedures are helpful when managing life-threatening IHs and for the reconstruction of disfigurement or to remove residual fibrofatty tissue. Vascular lasers are useful to treat ulceration acutely and to treat residual telangiectasia. Given the advances in IH treatment, future research in prevention may reduce the burden on healthcare resources.

Key practice points

- Oral propranolol is the treatment of choice for infantile haemangioma (IH) (Strength of Recommendation: A).
  - This is administered 2–3 mg/kg/day and initiated between ages 5 weeks and 5 months.
  - Common adverse drug reactions (ADRs) were sleep disturbance, peripheral coldness and agitation.
  - Severe ADRs are rare and include heart block, bradycardia, hypotension, bronchospasm and hyperglycaemia-associated seizure requiring dose adjustments or discontinuation.
  - Propranolol is contraindicated in patients with prior history of hypoglycaemic episodes, second-degree and third-degree heart block, hypersensitivity, weight <2 kg, or prematurity under 5 weeks of corrected age.
- Topical timolol maleate for thin or superficial IH appears non-inferior to oral propranolol with a lower risk of ADRs (Strength of Recommendation: A).
  - Concentrations used range from 0.25% to 0.5% once to three times daily (not exceeding two drops of 0.5% per day).
  - ADRs include local irritation, ulceration, nocturnal crying and diarrhoea.
- Oral prednisone/prednisolone may be considered for patients with contraindications to propranolol or inadequate response to other treatments (Strength of Recommendation: B).
  - 2–3 mg/kg/day is recommended to maximize the effectiveness whilst minimizing the adverse effects.
  - The risks of growth delay, behavioural changes, adrenal suppression, secondary infections and gastric irritation must be considered prior to starting therapy.
- Surgical management is an option in cases involving severe cosmetic deformity or life-threatening complications (Strength of Recommendation: C).
- Laser therapy may be used for residual erythema and superficial telangiectasias (Strength of Recommendation: C).
  - Pulsed dye laser is currently the most studied laser for use in IH.
- There is insufficient evidence to recommend the use of other oral or topical beta-blockers besides propranolol and timolol.
- There is limited evidence to recommend combinations of pharmacological therapies.

Strength of recommendations is based on Strength of Recommendation Taxonomy (SORT).[7]

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