

# Incidence and treatment of infantile haemangioma in preterm infants

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## ABSTRACT

Infantile haemangioma (IH) are vascular tumours with a unique growth dynamic, mostly absent at birth, growth in the first months followed by involution over several years, often resulting in residual skin changes. Immunohistologically, IH cells are exclusively glucose transporter protein-1 positive. The incidence of IH is increasing with decreasing gestational age, from 1–4% in term infants to 23% in those of <1000 g birth weight, with a female and Caucasian predominance. Discovery of systemic and topical beta blockers as an effective treatment option resulted in a rapid shift away from systemic steroids towards these drugs. For preterm infants, however, data on efficacy, pharmacokinetics and long-term safety are sparse or absent. Topical treatment without systemic side effects like cryotherapy may thus be an attractive alternative at an early growth stage (<10 mm). Indications for treatment with beta blockers, mostly propranolol systemically and timolol maleate 0.5% topically, are currently extrapolated from studies in older infants. Both seem effective, but adverse effects on sleep, circulation and metabolism are well described for propranolol. Long-term outcome data for either drug are missing. In conclusion, evidence on optimal IH treatment in preterms is lacking despite their high incidence; pharmacokinetic and clinical studies are warranted.

## DEFINITION

Infantile haemangioma (IH) or haemangioma of infancy consists of proliferating vascular tumours. IH is typically absent at birth and has a characteristic growth pattern with rapid enlargement during the first 5–9 postnatal months, a period of most rapid growth at 5–8 weeks,<sup>1</sup> and a slower regression or involution phase taking up to 5 years to complete, with residual deformities like skin atrophy, scarring, destroyed anatomical structures, a fibrofatty mass, redundant skin and telangiectasia in some cases.<sup>2–6</sup>

A landmark in defining IH was the differentiation between haemangiomas and vascular malformations introduced by Mulliken and Glowatzki.<sup>7–9</sup> Based on a large case series, IHs were subsequently further classified as localised, representing the majority with 67% (1022/1530), segmental (13%), indeterminate (17%) and multifocal (4%),<sup>10</sup> and additionally subdivided into superficial, mixed and deep<sup>11–13</sup> resulting in a distinction by the pattern of distribution on the body surface and anatomic depth of involvement.<sup>14</sup> Recently found histochemical markers like glucose transporter protein-1 are characteristic of IH and differentiate them from other vascular tumours or birthmarks, especially congenital haemangioma (CH).<sup>15–18</sup>

Differential diagnosis of IH includes CH, comprising rapidly involuting CH (RICH) and non-involuting CH (NICH), kaposiform haemangioendothelioma, tufted angioma, pyogenic angioma and multifocal lymphangioendotheliomatosis.<sup>17</sup> Older nomenclature like capillary or strawberry haemangioma has been discouraged in recent years.<sup>2</sup>

## EPIDEMIOLOGY

The incidence of IH in preterm infants is probably higher than in term infants, but exact incidence data are missing, not least due to the inconsistent nomenclature used prior to the widespread acceptance of the above classification system.<sup>7–9</sup> Data from existing studies are summarised in table 1 and indicate an increasing IH incidence with decreasing gestational age (GA) and birth weight, with up to 23% for those born at <1000 g compared with 1–4% for term infants, a female predominance and a higher rate in Caucasian infants compared with other ethnicities.<sup>19–21</sup> Facial involvement seems to be less common in preterm infants.<sup>22</sup>

## INDICATION FOR TREATMENT

Despite the high frequency of IH in preterm infants, there are no studies tailored especially to this high-risk group except for one small study using nitrogen-cooled cryocontact therapy (NCCT) exclusively in preterm infants.<sup>30</sup> Thus, decisions can only be made in analogy to term infants, and therefore indications for treatment are mainly based on individual considerations. A Cochrane review on interventions for IH identified only four randomised controlled trials (RCTs) until March 2011 and concluded that evidence from RCTs is too limited to support any of the interventions existing at that time (pulsed dye laser and corticosteroids).<sup>31</sup> For infants, there is agreement that haemangioma with life-threatening or function-threatening properties, ulcerations or a risk thereof, rapid growth or a risk for acute or chronic disfigurement must be treated. This applies to those in the face, scalp, neck, hands, feet and intertriginous and anogenital regions.<sup>5 32–36</sup>

A series of recent publications, however, emphasised the high proportion of residual deformity found in 69–88% of IHs.<sup>6 37</sup> The characteristic growth pattern with a peak at 5–8 weeks suggests that therapy should be started before reaching this age.<sup>1</sup> Moreover, the introduction of beta blockers since 2008 as a very effective therapy with less severe adverse events lowered the threshold for intervention.<sup>38</sup> Thus, a paradigm shift can be observed in the timing of referral and initiation of IH treatment.<sup>1</sup> A rapid increase in beta blocker and decrease in steroid use have already been reported.<sup>39</sup>



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**Table 1** Incidences of IH in preterm infants reported in the literature

Study (Ref.)	Survey period/source	Age range covered for IH occurrence	Target population	N infants included	IH incidence N (%)	Comment
Holmdahl <sup>23</sup>	1951–1954 hospital based	Birth to 20 weeks	BW ≤2000 g BW 2010–2500 BW ≥2500	293 347 186	20 (6.8) 16 (4.6) 15 (8.1)	Inconsistencies in text and tables. Results potentially questionable.
Powell <i>et al</i> <sup>24</sup>	1980–1981 Epidemiologic, regional based, retrospective, registers and charts	Survivors, birth to 1 year	BW ≤2000 g GA 25–29 wk GA 30–34 wk GA 35+ wk	615 85 300 230	68 (11.1) 16 (18.8) 33 (11.0) 19 (8.3)	Incidence increases with decreasing GA, p=0.015 Boys vs girls: 9% vs 13% p=0.02 No selection bias
Amir <i>et al</i> <sup>25</sup>	1977–1984 retrospective hospital based charts and clinic reports	Survivors, birth to 1 year	BW <2000 g BW 500–1000 g BW 1001–1500 BW 1501–2000	973 96 418 459	78 (12.7) 22 (22.9) 58 (13.9) 44 (9.6)	Male to female ratio 1:1.4. Frequency increases with decreasing BW
Queisser-Luft <i>et al</i> <sup>26</sup>	1990–1991 Register of congenital Malformations	First 10 days	All newborns	8332	225 (2.7)	Type of haemangioma and GA or BW not indicated
Haggstrom <i>et al</i> <sup>19</sup>	Sept 2002–Oct 2003	Not defined	Infants referred to seven paediatric dermatology clinics <12 years	1058 to compare with US National Vital Statistics System		Infants with IH more likely: female p<0.00 001; white p<0.0001; preterm/very preterm p<0.0001; LBW/VLBW p<0.0001; to have mother >30 years
Garzon <i>et al</i> <sup>22</sup>	Sept 2002–Oct 2003 Prospective. Practices based	Not defined	Infants referred to seven paediatric dermatology practices		833 term; 214 preterm	Female to male ratio 2.62; female to male ratio 1.85 p=0.04; mean no. of IH/patients: term vs GA<32 wk=1.4:1.8 p<0.001 IH in face: less in preterms p<0.005. Relevant referral bias
Drolet BA <sup>24</sup>	Sept 2002–Oct 2003 Prospective	Not defined	Infants referred to two paediatric hospitals		420 IH; 353 controls	Infant with IH are more likely to be preterm p<0.0001; female p<0.0001; LBW p<0.0001; white p<0.0001. Every 500 g decrease=IH increase by 40%. Relevant referral bias
Praveen <i>et al</i> <sup>27</sup>	2000–2005 Retrospective evaluation of neonatal database	Birth to discharge	BW ≤1250 g	351	49 (14)	Recruitment stopped at discharge
Dickison <i>et al</i> <sup>28</sup>	2007–2011 Prospective. Hospital based	Birth to 24 wk	Newborns with maternal consent	1065; term 933; pret 132	19 (2.0) 9 (6.8)	Female to male ratio 5:1; not all infants <32 wk included. Relevant recruitment bias
Kanada <i>et al</i> <sup>20</sup>	Not reported; hospital based; prospective	Birth to 3 m	All newborns	594 term; 523 pret 71	22 (4.3) 7 (9.8)	Relevant recruitment bias
Doege <i>et al</i> <sup>29</sup>	1999–2005 hospital based charts; retrospective	During neonatal period	GA <37 wk GA 23–26 GA 27–30 GA 31–34 GA 35–36	2563 155 346 1038 1024	110 (4.3) 24 (15) 41 (12) 40 (4) 5 (0.5)	Result potentially underestimating true incidence: incomplete chart documentation, recruitment stopped at discharge

BW, birth weight; GA, gestational age; IH, infantile haemangioma; pret, preterm; (V)LBW, (very) low birth weight; vs, versus; wk, weeks.

**Table 2** Randomised controlled studies using beta blockers for treatment of IH

Study (Ref.)	Type	Inclusion criteria	Intervention Duration	Age at start Preterm inf.	Sample size	Primary outcome time	Result	Comment
Abarzua-Araya <i>et al</i> <sup>45</sup>	RCT dbl Non-inferiority	Functional impairment Aesth. disfigurement Ulcerated or loc. on folds	<i>Atenolol</i> 1 mg/kg SD vs <i>Propr.</i> 2 mg/kg 6 m	1–15 m No preterms mentioned	13:10 Not calculated	Complete response Partial response 6 m	54%:60% ns 46%:40% ns	Small sample size. Atenolol less side effects?
Bauman <i>et al</i> <sup>46</sup>	RCT bl Phase II	Sympt. IH: impaired function Ulcerating Pain Cosmetically sensitive	<i>Propr.</i> 2 mg/kg/d vs <i>Predn.</i> 2 mg/kg/d At least 4 m	2 w to 6 m No preterms mentioned	11:8 calculated 55	Surface area 4 m	64%:41% ns	Stopped prior due to SAE in predn. group
Malik <i>et al</i> <sup>47</sup>	RCT Not bl	Functionally threatening Potentially disfiguring	<i>Propr.</i> vs <i>predn.</i> vs both <i>propr.</i> and <i>predn.</i> <i>Combined</i> Mean 11/13/10 m	1–8 m No preterms mentioned	10:10:10	Size Visual Analogue Scale Satisfaction After 18 m observation	Geom. red.: 36:22:32%, ns VAS size reduction 90:67:83% p<0.05	<i>Propr.</i> favoured, combined not superior
Zaher <i>et al</i> <sup>48</sup>	RCT bl	Rapidly progressive Function threatening Cosmetic disfigurement	<i>Propr. Oral</i> 2 mg/kg/d vs topical 1% twice/d vs. intrales. 1 mg/wk Mean 5.1/7.5/7.9 m	1–18 m No preterms mentioned	15:15:15	Efficacy Safety 6 m after end of treatment	Excellent result 60:20:13% Treatment time shortest for <i>propr.</i> (p=0.002)	Intralesional application not recommended
Chan <i>et al</i> <sup>49</sup>	RCT dbl Placebo controlled	IH superficial not requiring systemic therapy	<i>Timolol</i> topic. 0.5% vs placebo 1 drop rub in twice/d 24 wk	5–24 wk No preterms mentioned	19:22	Colour Volume 24 wk	p=0.003 p=0.002	Treatment favoured
Leaute-Labreze <i>et al</i> <sup>50</sup>	RCT dbl Pilot Placebo controlled	IH>1 cm Non-threatening, no steroids required	<i>Propr.</i> 3 mg/kg/d for 15 d and 4 mg/kg/d for add. 15 d vs placebo 30 d	<16 wk No preterms mentioned	7:7	Thickness Size After 30 d treatment	–45% vs +11% p=0.004 –16% vs +9% p=0.041	Early treatment favoured
Hogeling <i>et al</i> <sup>51</sup>	RCT bl Placebo controlled	Pediatric Dermatol. Clinic Age 9 wk–5 years IH with deep component, could impair function, too late for corticosteroids	<i>Propr.</i> 2 mg/kg/d vs placebo 6 m	11 wk–4 years No preterms mentioned	20:20	Volume Redness Blueness Elevation After 24 wk therapy	–60% vs –14% p=0.01 p=0.04 p=0.17 p=0.01	Treatment favoured. Limitations: heterogeneous, small numbers, age at incl. >6 m

add, additional; bl, blind; d, day; dbl, double blind; geom. red., geometric reduction; IH, infantile haemangioma; incl., inclusion; loc., location; m, month; ns, not significant; predn., prednisolone; propr., propranolol; RCT, randomised controlled trial; SAE severe adverse event; sympt., symptomatic; topic., topical; VAS, Visual Analogue Scale; vs, versus; wk, weeks.

## THERAPY

Pharmacological therapy of IH has been revolutionised by the observation of Léauté-Labrèze that propranolol resulted in a dramatic shrinking of large haemangiomas.<sup>38</sup> It is now considered by most experts to be the first line drug if systemic therapy is indicated.<sup>5 16 40</sup> The same is true for topical application of another beta blocker, timolol maleate 0.5%, following its first description by Guo.<sup>41</sup>

Therefore, only therapeutic studies published after 2008 are considered in the following. Traditionally used drugs like corticosteroids, interferon-alpha and vincristine<sup>13</sup> are now regarded second or third line agents, mainly due to their severe side effects, including spastic diplegia and other neurological abnormalities.<sup>42–44</sup> Additional therapeutic options include cryocontact, laser and surgical therapy, as well as topical and intralesional drug application.

A PubMed search to assess the effects of interventions for IH in preterm infants using the keywords ‘hemangioma, infantile, (therapy or treatment), (study or trial), controlled, preterm’ identified only a single study which used NCCT (see below). Thus, treatment for the patient group with the highest incidence (and the highest risk of side effects) is the one least well studied, as also reflected in national guidelines that exclude preterm infants from their recommendations<sup>34</sup> or do not mention them at all.<sup>36</sup>

Repeating the above PubMed search after omitting ‘preterm’ brought 29 hits for studies published after 2008, seven of them being RCTs comparing propranolol versus steroids (two studies), propranolol versus atenolol,<sup>1</sup> propranolol versus placebo<sup>3</sup> or different application modes<sup>1</sup> (table 2), but again none of these RCTs referred to preterm infants.

## Treatment options for preterm infants

For topical therapy, data from preterm infants exist for cryocontact, laser and timolol maleate,<sup>16</sup> while for systemic therapy, studies on propranolol and, as a second line drug, steroids (prednisolone), the former standard therapy, are available.

## Cryocontact therapy

One prospective controlled study (quasi-randomised) could be identified,<sup>30</sup> using NCCT (−196°C, 2–6 s application time) of IH (<10 mm in diameter) in infants ≤34 weeks GA compared with untreated intraindividual control-IH. NCCT led to fast regression with good cosmetic results. Limitations include the premature termination of the study, a follow-up period of only 2 years and mild scarring as a side effect in four of 17 infants (compared with residual IH in 14 of 17 controls). Further data on NCCT, with good results and rare scarring, are reported from other centres<sup>52 53</sup>; this treatment is also recommended in current German guidelines.<sup>34</sup> The method is fast, easy to apply, well tolerated, cheap, available at the bedside and, most

important, without systemic side effects. It is yet, however, limited to superficial IH of ≤10 mm in diameter.

## Laser

There are no data on laser therapy from preterm infants. A single RCT compared pulsed dye laser in early childhood with no treatment. When evaluated at 1 year of age, there was no group difference in the number of children with complete regression or minimal residual signs.<sup>54</sup> At present, there are insufficient data to recommend this treatment for preterm infants.<sup>2 55</sup>

## Propranolol

Six RCTs have been published in the last 6 years (table 2), two comparing propranolol with prednisolone, of which one was stopped early due to severe adverse events in the steroid group.<sup>46</sup> A combination of both propranolol and prednisolone was not superior to propranolol only.<sup>47</sup> Two trials were placebo controlled and favoured treatment.<sup>50 51</sup> Propranolol and atenolol were compared in one trial with similar results for complete and partial response, but atenolol had fewer side effects, possibly because of its higher beta-1 receptor selectivity.<sup>45</sup> One study compared oral propranolol with topical and intralesional application and found best results for oral administration.<sup>48</sup> None of these studies reported the inclusion of preterm infants. One large RCT, double blind and placebo controlled, finished recruitment in May 2014; first results are available and show better cosmetic results with propranolol at 3 mg/kg/d for 24 weeks. Preterm infants, however, could only be included after reaching term equivalent age (TEA) (*Study to Demonstrate the Efficacy and Safety of Propranolol Oral Solution in Infants With Proliferating Infantile Hemangiomas Requiring Systemic Therapy*. Trial Identifier: NCT01056341). Details can be seen in the release of the Committee for Medicinal Products for Human Use (CHMP) Assessment Report of the European Medicines Agency (EMA) for this drug ([http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Public\\_assessment\\_report/human/002621/WC500166912.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002621/WC500166912.pdf)).

Additionally, numerous reports evaluated the efficacy of propranolol. In a systematic review of all studies reporting on >10 patients published between June 2008 and June 2012, the average response rate for treatment with propranolol was 98%. Most common adverse effects were changes in sleep (like insomnia, nightmares, restlessness and sleep disturbances), acrocyanosis, hypotension, bradycardia, hypoglycaemia and respiratory as well as gastrointestinal symptoms. Rebound growth was reported in 17% after stopping initial treatment.<sup>56</sup> A second large systematic review and meta-analysis compared the data available from 1965 through March 2012 to compare propranolol and corticosteroids in the treatment of IH. Again, only studies with >10 patients and systemic application were included. There was only one RCT in each group. The difference concerning any improvement was 97.3% for

**Table 3** Systematic reviews on the treatment of IH

Systematic review	Studies included. Therapy	Patients (n)	Age at treatment initiation	Dose	Duration of therapy	Any improvement	Adverse events
Marqueling <i>et al</i> <sup>56</sup>	N=41 2008–2012 Propranolol	1264	6.6 m (3d to 10 y)	Mean: 2.1 mg/kg/d	Mean 6.4 m Range 1 wk to 15 m	98% Range 82–100%	See text
Izadpanah <i>et al</i> <sup>57</sup>	N total=41 N Propr=25 N Cortic. 16	795 2629	12±6 m Not reported	2 mg/kg/d 3SD 2–3 mg/kg/d	4 wk –12 m 4–8 wk	97.3% 71% p<0.0001	See text

Cortic, corticosteroids; d, day; IH, infantile haemangioma; m, months; propr., propranolol; wk, weeks; y, years.

**Table 4** Clinical studies with >10 study participants using topical timolol maleate

Publication (Ref.)	Type	Inclusion criteria	Intervention	Age at start Preterm infants	Sample size	Primary outcome	Result	Comment	AE tim.
Yu <i>et al</i> <sup>63</sup>	Prospective	Superficial IH, No prior treatm. Thickness ≤3 mm	Timolol 0.5% solution 3× daily	≤12 mo n.r.	101 tim. top. 23 observations	Growth	Efficacy 92% Treated vs untreated: p<0.05	Erythr. ointm. for prevent. of leakage	No AE
Qiu <i>et al</i> <sup>64</sup>	Retrospect. matched pairs	Superficial IH	Tim. 0.5% sol. or Imiquimod 5% cream	1–8 m n.r.	20:20	VAS	No difference	AE only in Imiquimod group	No AE
Berk <i>et al</i> <sup>65</sup>	n.r.	n.r.	Timolol 7% Gel	n.r.	125	n.r.	n.r.	No side effect. Tim.conc. n.r.	No AE
Xue <i>et al</i> <sup>66</sup>	n.r.	Infantile H	Tim. 7%	n.r.	93	n.r.	98% good to moderate response	2 deep IH: poor response	1 sl.di.
Semkova and Kazandjieva <sup>67</sup>	Prospective, preliminary results	IH, superficial, non-ulcerated	Tim. 0.1% gel 5× daily	30 wk (12–68) n.r.	25	Clinical score	85% improvement from baseline		No AE
Ye <i>et al</i> <sup>68</sup>	Prospective Abstract only	Periocular haemangioma only	Tim. 7% 2× daily	n.r.	12	Clinically after 4 weeks	4 perfect, 2 moderate, 4 stable, 2 continuing growth	Article in Chinese	No AE
Moehrle <i>et al</i> <sup>61</sup>	Prospective	IH >8 mm, growing	Tim. 0.5% 0.05 mL in Finn Chamber 1× daily	9–25 wk, 6 of 11 preterm 29–35 wk GA	11	Colour, thickness (semiquantitatively)	Reduction 7/11 >80% 4/11 50–80% 2/11 relapse	Dose and application standardised relapse: tim. again with succ.	n.r.
Chambers <i>et al</i> <sup>69</sup>	Retrospective, single-masked	Periocular IH	Tim 0.25% gel 2× daily vs observation	4.8 m: 3.7 m n.r.	13:10	Clinical 2 m later (semiquantitatively)	Good 62%; moderate 31%; poor 8%	1 deep IH: poor response	No AE
Oranje <i>et al</i> <sup>70</sup>	Prospective	IH, max. 100×50 mm	Tim. 0.5% sol. 3–4× daily	2–10 m n.r.	20	Clinical score, HAS	Good or excellent 85%; poor 15%	Mixed or deep IH: poor response	No AE
Chakkittakandiyil <i>et al</i> <sup>71</sup>	Retrospective, multicentre, comparative	IH, treated with tim. maleate 0.1% or 0.5%	Tim. maleate 0.1% vs 0.5% 2× daily	median 4.3 m, n.r.	62 tim. 0.5% 11 tim. 0.1%	VAS	Tim. 0.5% better p<0.001	Treatm.>3 m better, deep IH worse	1 sl.di.
Blatt <i>et al</i> <sup>72</sup>	Retrospective	IH	Tim. 0.5% or propranolol oral	1–2× daily 1– 4 mg/kg/d	17 47	Clinical	Not clear	Preterms not reported	No AE
Guo and Ni <sup>41</sup>	Case report	IH upper eyelid	Tim. 0.5% Sol 2× daily	4 m	1	Clinical, photo	Good result	First report on topical timolol	No AE
Ma <i>et al</i> <sup>62</sup>	Prospective	Deep IH only	Ablative fractional laser-assisted drug delivery and timolol 0.5% gel	1–6 m, preterms excluded	9	HAS	8 good or excellent	Might improve results for deep IH, plasma tim. <20 pg/mL	No AE

AE, adverse event; conc., concentration; d, day; erythr., erythromycin; GA, gestational age; HAS, Haemangioma Activity Score; IH, infantile haemangioma; m, month; n.r., not reported; ointm., ointment; retrospect., retrospectively; succ., success; tim., timolol; treatm, treatment; VAS, Visual Analogue Scale; wk, weeks.



propranolol versus 71.0% for corticosteroids ( $p < 0.0001$ ).<sup>57</sup> Both publications did not mention preterm infants (table 3).

In a case series, nine very low birthweight (VLBW) infants were treated with propranolol (2 or 3 mg/kg/d) at a corrected age of  $-5$  to  $+15$  weeks. Growth was not impaired and no relevant side effects were reported.<sup>58</sup> A larger case series of 99 infants treated with propranolol included 7% preterm infants. IH improved in 99%, but no additional information on the preterm group was given.<sup>59</sup> A unique severe side effect, hyperkalaemia, has been reported in a girl of 28 weeks gestation with a large and ulcerating IH 72 h after starting propranolol at TEA. No electrocardiographic changes were noted; maximum  $K^+$  concentration was 6.5 mmol/L with therapy.<sup>60</sup>

In summary, currently available data for IH treatment of preterm infants are scarce, both for treatment in the first postnatal weeks or beyond reaching TEA. There is also no information about long-term neurocognitive outcomes. Therefore, systemic propranolol, a vasoactive drug, should be indicated cautiously in immature infants. That former preterms having passed their TEA can be considered similar to term infants may seem plausible, but needs to be confirmed in clinical studies.

### Topical timolol maleate solution or gel

There is one double-blind placebo-controlled RCT comparing topical timolol 0.5% solution with placebo. After 24 weeks of therapy twice daily, the endpoints colour and volume of IH favoured treatment ( $p < 0.003$  and  $p < 0.002$ , respectively) (table 2).<sup>49</sup> A PubMed search to assess the efficacy of topical application of timolol solution or gel-forming solution revealed 11 hits reporting study results for  $>10$  enrolled infants/study (table 4). Most studies used either drug, applied 2–4 times/day by gently rubbing in with a fingertip. One study used a standardised dose of 0.05 mL timolol 0.5% gel with occlusive dressing through Finn Chambers.<sup>61</sup> The duration of therapy was variable, in the only RCT it was 24 weeks. In all studies, good or excellent improvement in the majority of superficial IH was reported. While results were worse for deep IH (table 4), results improved using a combination of a special laser technique and topical timolol.<sup>62</sup> A double-blind RCT currently recruiting patients compares topical timolol 0.5% and placebo, inclusion criteria are VLBW and diagnosis of IH; estimated completion date is September 2015 (<https://clinicaltrials.gov/ct2/show/record/NCT01434849>).

No pharmacokinetic (PK) data are available on the transdermal absorption of timolol. Systemic adverse effects rarely appear (see table 4). However, the skin of preterm infants has much less barrier function than that of older children; therefore, timolol absorption might increase considerably. Important to know, timolol is about six times more potent than propranolol.<sup>73</sup> Up to now, no safety data are available for either preterm or term infants. PK of topical timolol should be evaluated urgently in these age groups.

Summarising currently available RCT data for topical timolol application to preterm infants is limited to one small study,<sup>61</sup> both for treatment in the first postnatal weeks or beyond reaching TEA. There are neither PK data available nor data on long-term outcomes. However, it seems reasonable to consider treatment with topical timolol as a method with a considerably lower risk profile than systemic propranolol.

### CONCLUSION

For preterm infants, evidence for IH treatment is lacking despite their high incidence. PK and clinical studies are warranted. Given the unknown long-term cognitive outcome of systemically

used vasoactive beta blockers, local treatment like NCCT should be revisited as an alternative early intervention before the rapid growth phase starts. At present, most treatment decisions must be extrapolated from studies in older infants.

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