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Systematic Review

Comparative Outcomes of Propranolol and Corticosteroids in Infantile Haemangiomas: A Systematic Review and Meta-Analysis

Alma Sato[1,2], James W.F. Burns[3], Kesavan Sivanesan[4], Robyn Haysom[5], David Riese[6], Ebaney Ghotra[1], Kangjie R. Chua[7], Sum-Yu C. Lee[8], Hayato Nakanishi[9], Christian A. Than[4,10], Kai Yuen Wong[4,*]

[1]School of Medicine, University of Nicosia, 2417 Nicosia, Cyprus
[2]Department of Orthopedic Surgery, Mayo Clinic, Rochester, MN 55905, USA
[3]Bolton NHS Foundation Trust, BL4 0JR Bolton, UK
[4]Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, CB2 0QQ Cambridge, UK
[5]University Hospitals of North Midlands, ST4 6QG Stoke-on-Trent, UK
[6]Medical School, European University Cyprus, 2404 Nicosia, Cyprus
[7]Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia
[8]Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, LE1 5WW Leicester, UK
[9]Department of Surgery, Mayo Clinic, Rochester, MN 55905, USA
[10]School of Biomedical Sciences, The University of Queensland, Brisbane, QLD 4072, Australia
*Correspondence: kaiyuen.wong@cantab.net (Kai Yuen Wong)

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Abstract

Aims/Background: Infantile haemangiomas (IH) are the most common benign vascular tumours of infancy. Oral propranolol has become the first-line treatment, while corticosteroids remain second-line or adjunctive options when propranolol is contraindicated or insufficient. This meta-analysis provides updated comparative evidence on the efficacy and safety of oral propranolol versus oral and intralesional corticosteroids in paediatric IH. **Methods:** A systematic search of Ovid MEDLINE, Embase, Cochrane Library, CINAHL, and other databases was conducted on April 15, 2025, following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Data were synthesised using a random-effects model. **Results:** Fifteen studies met inclusion criteria (n = 1841). Propranolol demonstrated a significantly higher overall treatment effectiveness compared to corticosteroids (odds ratio [OR]: 4.96, 95% confidence interval [CI]: 2.19–11.26; $p = 0.0001$). In subgroup analyses by route, propranolol was superior to oral corticosteroids (OR: 6.56, 95% CI: 1.98–21.73; $p = 0.002$), but showed no difference compared to intralesional corticosteroids. Overall adverse event odds were lower with propranolol (OR: 0.27, 95% CI: 0.10–0.71; $p = 0.008$), specifically when compared against oral corticosteroids (OR: 0.17, 95% CI: 0.03–0.88; $p = 0.03$) and in treatment-related ulceration rates (OR: 0.18, 95% CI: 0.08–0.42; $p < 0.0001$). No significant differences were observed between treatment groups regarding overall treatment duration, recurrence rate, or surgical resection rate. **Conclusion:** Propranolol was associated with greater overall treatment effectiveness and a lower incidence of adverse events than corticosteroids. Greater effectiveness was observed compared with oral corticosteroids, but not intralesional corticosteroids. Intralesional corticosteroids may remain appropriate for selected patients, highlighting the importance of considering corticosteroid route and individual lesion characteristics when selecting treatment. **Systematic Review Registration:** PROSPERO (CRD420251025754).

Keywords: propranolol; corticosteroids; treatment outcome; safety; vascular anomalies; haemangioma; capillary; systematic review

1. Introduction

Infantile haemangiomas (IH) are a common, benign vascular tumour of infancy with a reported incidence rate of 4.5% [1]. Typically, IHs develop with a proliferation phase of rapid growth in infancy followed by an involutional phase that can extend throughout childhood. Resolution can occur without obvious scarring, with regression around 5–9 years of age [2]. Up to 15% can be associated with complications such as ulceration, bleeding, infection, and adverse scarring, as well as site-specific risks such as visual obstruction, auditory impairment, or airway compromise [3,4]. It is therefore important to understand the outcomes and management of different treatment modalities [3,5].

Since the 1960s, oral corticosteroids have been used to treat IH, offering reasonable efficacy but are often associated with a substantial side effect burden [6]. This may include risk of systemic adverse reactions such as secondary Cushing's syndrome, behavioural change and gastrointestinal side effects [3,6]. While intralesional treatment has shown efficacy to mitigate oral side effect profiles, this modality also incurs its own risks such as ulceration, infection and necrosis [6]. Although delivery routes differ, the overall risk of adverse events appears comparable between oral and intralesional corticosteroids [7].

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In 2008, the therapeutic landscape for IH shifted with discovery of oral propranolol efficacy. Propranolol, a non-selective beta-blocker, was found to induce rapid haemangioma regression in an infant treated for cardiomyopathy [8]. Since then, propranolol has gained widespread adoption, supported by growing evidence of faster response rates and fewer complications compared to corticosteroids [7]. The most common adverse events associated with propranolol are sleep disturbance, peripheral coldness and agitation. There is also risk of more serious reactions such as bronchospasm, heart block, and hypotension [6]. Initially reserved as second-line therapy, beta-blockers are showcasing traction as first-line agents, including as monotherapy [3,9]. In 2019, the American Academy of Pediatrics (AAP) produced its first clinical practice guideline on IH and recommended oral beta-blockers as the preferred first line therapy with corticosteroids as second-line [10]. Similarly, propranolol is the recommended first line treatment in the United Kingdom [11].

A 2021 meta-analysis by You et al. [3] compared the efficacy of oral propranolol and corticosteroids in treating IH shortly after the AAP guideline release. Given the shift in first-line therapy after nearly five decades of first line use of corticosteroids, a comprehensive re-evaluation of both drug classes is warranted. This updated meta-analysis aims to further evaluate the efficacy and safety of propranolol and corticosteroids for the management of IH. Our updated meta-analysis also provides a subgroup comparison of oral versus intralesional corticosteroids, which has not been addressed in prior reviews. This addition offers further insight into how the route of corticosteroid administration may influence clinical outcomes.

2. Methods

2.1 Data Sources and Search Strategies

A comprehensive literature search was conducted across Ovid MEDLINE (https://www.ovid.com/), Embase (https://www.embase.com/), Cochrane Library (https://www.cochranelibrary.com/), and CINAHL (https://www.ebsco.com/products/research-databases/cinahl-database) from their inception to April 15, 2025. Additional sources were manually identified through Google Scholar and PubMed. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator, using a combination of controlled vocabulary and keywords focused on IH patients who received either propranolol or corticosteroids. The full search strategy, including all terms and combinations used, is detailed in **Supplementary Item 1**. This study was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [12] and was prospectively registered with PROSPERO (CRD420251025754, https://www.crd.york.ac.uk/PROSPERO/view/CRD420251025754). The completed PRISMA 2020 checklist is provided in the **Supplementary Item 2**.

2.2 Eligibility Criteria and Quality Assessment

Studies were considered eligible if they met the following criteria: (1) randomised controlled trials (RCTs), non-RCTs, experimental studies, or cohort studies; (2) included paediatric patients aged ≤18 years with IHs; (3) focused on IHs of any subtype (superficial, deep, or mixed) without any syndromic cause; (4) compared oral propranolol versus corticosteroids (oral or intralesional) as primary treatment; and (5) reported on our primary outcome. Studies were excluded if they (1) were case reports, case series, abstracts, or reviews, or (2) were not published in English. Studies were excluded if they included IH associated with Posterior fossa malformations, Haemangiomas, Arterial anomalies, Cardiac defects, and Eye abnormalities (PHACE) or Perineal haemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, and Skin tag (PELVIS) syndrome or presented data that could not be separately extracted for isolated IHs. Additionally, studies reporting patients with pre-existing ulceration were also excluded. In instances of overlapping datasets, we included only the most recent or comprehensive report to avoid duplicate data inclusion.

All retrieved records were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) for duplicate removal and study screening. Title and abstract screening followed by full-text screening was conducted independently by two assessors. Disagreements were adjudicated by a third author (AS) and discussed with co-authors as necessary. Data extraction was subsequently conducted independently by six assessors (JWFB, KRC, RH, KS, DR, EG). Each article required agreement from at least two different assessors to be included. The quality of each study was independently evaluated by two authors (KRC, RH) using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) [13] and Version 2 of the Cochrane risk-of-bias tool for randomized trials (ROB2) [14]. Disagreements in the determination of quality were resolved by discussion with an adjudicator until a consensus was reached (HN). The methodology and results of the quality assessment of all included studies are shown in **Supplementary Items 3,4**.

2.3 Extracted Primary Outcomes

Baseline and clinical characteristics extracted from the included studies included publication year, country, study design, sample size, age, sex, lesion location, clinical type of IH (superficial, deep, or mixed), treatment duration, and follow-up duration. The primary outcomes were rate of effectiveness, surgical resection, adverse events, and recurrence. Effectiveness was defined as regression >50% in accordance with Achauer et al. [15], which includes Grade I, poor response (0%–25% regression); Grade II, fair response (26%–50% regression); Grade III, good response (51%–75% regression); and Grade IV, excellent response

(76%–100% regression). Grades III and IV were considered responsive to treatment [15]. Adverse events were defined as treatment-related complications reported after initiation of therapy. Because the included studies varied in their reporting of adverse events, we included only events explicitly attributed to treatment by the original study authors. Reported adverse events included hypotension, hypoglycaemia, sleep disturbance, gastrointestinal symptoms, secondary cushingoid features, behavioural changes, developmental delay, and hypertension. Ulceration was included among adverse events when reported as a treatment-related adverse event. Persistent ulceration reported as a distinct safety outcome was analyzed separately. Reported propranolol dosage ranged from 1–3 mg/kg/day in two divided doses. Oral corticosteroids dosage was 2–3 mg/kg/day. Intralesional corticosteroid regimens varied across studies and were reported using different dosing measures, including injection volumes and fixed doses per injection.

2.4 Statistical Analysis

The pooled means and proportions for our data were analysed using a random-effects, generic inverse variance method for continuous data and the Mantel-Haenszel method for dichotomous data. For dichotomous outcomes, odds ratios (ORs) or risk ratios (RRs), as appropriate, with 95% confidence intervals (CIs) were used as effect measures. For continuous outcomes, mean differences (MDs) with 95% CIs were used. This meta-analysis was restricted to studies that reported outcomes for propranolol and oral corticosteroids or intralesional corticosteroids within the same study, enabling a direct comparison between the two techniques (two-arm analysis). The heterogeneity of effect size estimates across the studies was quantified using the Q statistic and I^2. A value of I^2 of 0–40% indicates heterogeneity that may not be important, 30–60% moderate heterogeneity, 50–90% substantial heterogeneity, and 75–100% considerable heterogeneity [16]. A two-sided p-value < 0.05 was considered statistically significant. When the mean was not reported, the median was used as the measure of central tendency when appropriate, and when the standard deviation (SD) was unavailable but the interquartile range (IQR) was reported, the SD was estimated from the IQR, in accordance with the Cochrane Handbook [16]. If the SD was not available or extractable, the reported mean was omitted from the calculation. Additionally, if mean and SD were only depicted in figures, mean and SD were digitized from figures using WebPlotDigitizer version 4.4. (https://automeris.io/WebPlotDigitizer/). Data analysis was performed using RevMan software version 5.4 (Review Manager, The Cochrane Collaboration, 2020, Copenhagen, Denmark). Where sufficient data were available, analyses were additionally stratified by study design to assess whether treatment effects differed between RCTs and observational studies. A separate RCT-only analysis was performed where possible [4,5,17,18]. Study-design-specific analyses were not performed for outcomes with only one contributing RCT. For outcomes demonstrating substantial heterogeneity, leave-one-out sensitivity analyses were performed by sequentially excluding each study and recalculating the pooled effect estimate and I^2 statistic to assess the influence of individual studies on the overall results and heterogeneity. Publication bias was assessed using funnel plot analysis for outcomes with at least 10 included studies.

3. Results

3.1 Study Selection and Patient Characteristics

The initial literature search of the electronic databases yielded 1223 studies, and one additional record was identified through website searching. After removing duplications and applying the inclusion and exclusion criteria, 60 studies were retained for full-text review. Fifteen unique studies involving 1841 patients were included in this meta-analysis and a PRISMA flowchart of the study selection process is depicted in **Supplementary Item 5**. These studies included nine retrospective cohorts [9,19,20,21,22,23,24,25,26], one prospective, parallel-group, non-inferiority study [27], four RCTs [4,5,17,18], and one prospective, open-label, parallel-group study [28]. Among these, three were multicentre studies [5,19,25] and twelve were single-centre studies [4,9,17,18,20,21,22,23,24,26,27,28]. The mean age of participants across studies ranged from 0.1 months to 28.8 months, and 396 (69.4%) patients were female. Follow-up time ranged from 3 to 33 months after the treatments. Among the studies reporting location of IH included head & neck (n = 191, 47.4%), facial (n = 104, 25.8%), lip (n = 52, 12.9%), torso (n = 14, 3.5%), extremities (n = 24, 6.0%), and perineal (n = 18, 4.5%) [5,9,17,22,24,26,27]. Clinical types included superficial (n = 77, 77.8%), deep (n = 9, 9.1%), and mixed (n = 13, 13.1%) [4,5,28]. The baseline characteristics of the included studies are described in Table 1 (Ref. [4,5,9,17,18,19,20,21,22,23,24,25,26,27,28]).

3.2 Risk of Bias

Results of the quality assessment of all included studies are shown in **Supplementary Items 3,4**. Four RCTs were evaluated using the RoB-2 tool. One study was rated as low risk of bias [17], two studies were rated as having some concerns [4,5], and one study was rated as high risk [18]. The high risk was due to lacking features in selection of the reported results. Eleven non-randomised studies were assessed using the ROBINS-I tool. Nine studies [19,21,22,23,24,25,26,27,28] were considered to have a moderate risk of bias. Two studies [9,20] were judged to have a serious risk. Those studies found to be of serious risk were due to missing data, or deviations from intended intervention. Despite these risks of bias, all included studies were considered to have sufficient participant selection

Table 1. Baseline and clinical characteristics of included studies.

Study and publication year	Country	Study type	Total No. of participants, N	No. of participants per group, N	Female sex, N (%)	Age, Mean ± SD (Months)	Adverse events, N (%)	Surgical resection, N	Duration of treatment, Mean ± SD (Months)	Recurrence rate (%)	Effectiveness >50%, N (%)	Follow-up (Months)	Location, N	Clinical subtype, N
Ali et al., 2018 [28]	India	Prospective, Open-Label, Parallel-Group, Single-centre	60	OC: 30 OP: 30	36 (60)	OC: NR OP: NR	OC: 3 (10) OP: 1 (3)	OC: NR OP: NR	OC: NR OP: NR	OC: 0 OP: 0	OC: 12 OP: 21	OC: 6 OP: 18	OC: NR OP: NR	OC: Superficial 30 OP: Superficial 30
Bauman et al., 2014 [5]	USA	RCT, Multicentre	19	OC: 8 OP: 11	14 (74)	OC: 4 ± 0.6 OP: 2.5 ± 0.4	OC: 7 (88) OP: 9 (82)	OC: NR OP: NR	OC: 9.7 ± 5.3 OP: 10.6 ± 1.6	OC: 1 OP: 2	OC: NR OP: NR	OC: NR OP: NR	OC: Facial 8 OP: H&N 1, Facial 6, Lip 2, Torso 1	OC: Superficial 2, Deep 2, Mixed 4 OP: Superficial 3, Deep 2, Mixed 6
Bertrand et al., 2011 [20]	Canada	Retrospective Cohort, Single-centre	24	OC: 12 OP: 12	NR	OC: 3.8 ± 2 OP: 3.7 ± 1.8	OC: 7 (58) OP: 8 (67)	OC: NR OP: NR	OC: 12.7 ± 5.8 OP: 10.6 ± 1.5	OC: NR OP: NR	OC: 0 OP: 12	OC: NR OP: NR	OC: NR OP: NR	OC: NR OP: NR
Chang et al., 2023 [27]	China	Prospective, Parallel-Group, Non-Inferiority, Single-centre	50	IC: 25 OP: 25	35 (70)	IC: 4.2 ± 1.9 OP: 3.7 ± 2.6	IC: 2 (9) OP: 1 (4)	IC: 2 OP: 10	IC: 2.1 ± 1.1 OP: 6.3 ± 1.4	IC: 5 OP: 0	IC: 22 (96) OP: 19 (76)	IC: 14.7 OP: 12.7	IC: Lip 25 OP: Lip 25	IC: NR OP: NR
Hoornweg et al., 2014 [9]	Netherlands	Retrospective Cohort, Single-centre	43	IC: 29 OP: 14	35 (81.4)	IC: 2.9 ± 1.9 OP: 2.7 ± 1.3	IC: 9 (31) OP: 6 (43)	IC: 10 OP: 0	IC: 15.9 ± 7.6 OP: 6.5 ± 3.6	IC: NR OP: NR	IC: NR OP: NR	IC: NR OP: NR	IC: Facial 29 OP: 14	IC: NR OP: NR
Kim et al., 2017 [17]	Republic of Korea	RCT, Non Superiority, Single-centre	34	OC: 17 OP: 17	19 (56)	OC: 3 ± 1.8 OP: 3.6 ± 2.0	OC: 10 (59) OP: 16 (94)	OC: NR OP: NR	OC: 4.2 ± 0.9 OP: 4 ± 0.8	OC: NR OP: NR	OC: NR OP: NR	OC: 13 OP: 4.6	OC: H&N 2, Facial 13, UE 2, LE 1 OP: H&N 1, Facial 10, Torso 3, UE 3	OC: NR OP: NR
Malik et al., 2013 [4]	India	RCT, Single-centre	20	OC: 10 OP: 10	9 (45)	OC: 5.5 ± 1.5 OP: 4.6 ± 1.8	OC: 9 (90) OP: 2 (20)	OC: NR OP: NR	OC: 13.3 ± 2.8 OP: 10.7 ± 5.5	OC: 3 OP: 0	OC: 9 (90) OP: 10 (100)	OC: NR OP: 3	OC: NR OP: NR	OC: Superficial 5, Deep 3, Mixed 2 OP: Superficial 7, Deep 2, Mixed 1

Table 1. Continued.

Study and publication year	Country	Study type	Total No. of participants, N	No. of participants per group, N	Female sex, N (%)	Age, Mean ± SD (Months)	Adverse events, N (%)	Surgical resection, N	Duration of treatment, Mean ± SD (Months)	Recurrence rate (%)	Effectiveness >50%, N (%)	Follow-up (Months)	Location, N	Clinical subtype, N
Mohamed et al., 2020 [19]	Egypt	Retrospective Cohort, Multicentre	52	IC: 26 OP: 26	29 (56)	IC: 22.8 ± 2.4 OP: 28.8 ± 2.1	IC: 2 (8) OP: 1 (4)	IC: NR OP: NR	IC: 4.5 ± 0.8 OP: 4.5 ± 0.8	IC: NR OP: NR	IC: 9 (35) OP: 21 (81)	IC: NR OP: NR	IC: NR OP: NR	IC: NR OP: NR
Polites et al., 2019 [26]	USA	Retrospective Cohort, Single-centre	247	OC: 52 OP: 195	184 (75)	OC: 2.2 ± 1.5 OP: 3.5 ± 2.2	OC: 0 (0) OP: 3 (2)	OC: 14 OP: 18	OC: NR OP: NR	OC: 0 OP: 5	OC: NR OP: NR	OC: NR OP: NR	OC: H&N 35, Torso 1, Combined Extremity 4, Perineal 3 OP: H&N 114, Torso 9, Combined Extremity 14, Perineal 15	OC: NR OP: NR
Price et al., 2011 [25]	USA	Retrospective Cohort, Multicentre	110	OC: 42 OP: 68	NR	OC: NR OP: NR	OC: 42 (100) OP: 7 (10)	OC: 12 OP: 8	OC: 5.2 ± 1.4 OP: 7.9 ± 2.6	OC: NR OP: NR	OC: 12 (29) OP: 56 (82)	OC: NR OP: NR	OC: NR OP: NR	OC: NR OP: NR
Saha et al., 2018 [18]	Bangladesh	RCT, Single-centre	60	OC: 30 OP: 30	NR	OC: NR OP: NR	OC: 23 (77) OP: 8 (27)	OC: NR OP: NR	OC: 6 ± 1.5 OP: 6 ± 1.5	OC: NR OP: NR	OC: NR OP: NR	OC: NR OP: 6	OC: NR OP: NR	OC: NR OP: NR
Sawa et al., 2014 [21]	Canada	Retrospective Cohort, Single-centre	16	OC: 9 OP: 7	NR	OC: NR OP: NR	OC: 0 (0) OP: 0 (0)	OC: NR OP: NR	OC: 4.4 ± 1.4 OP: 12.2 ± 3.2	OC: NR OP: NR	OC: NR OP: NR	OC: 16.8 OP: 12.2	OC: NR OP: NR	OC: NR OP: NR
Theunissen et al., 2015 [22]	Netherlands	Retrospective Cohort, Single-centre	46	OC: 15 OP: 31	35 (76)	OC: 0.1 ± 0.2 OP: 0.6 ± 0.7	OC: 15 (100) OP: 0 (0)	OC: 2 OP: 0	OC: 4 ± 3.3 OP: 6 ± 2.9	OC: NR OP: NR	OC: NR OP: NR	OC: NR OP: NR	OC: H&N 13 OP: H&N 25	OC: NR OP: NR
Yang et al., 2015 [23]	China	Retrospective Cohort, Single-centre	1036	IC: 574 OP: 462	NR	IC: NR OP: NR	IC: 325 (57) OP: 55 (12)	IC: NR OP: NR	IC: 6 ± 1.5 OP: 6 ± 1.5	IC: NR OP: NR	IC: 309 (54) OP: 416 (90)	IC: NR OP: NR	IC: NR OP: NR	IC: NR OP: NR
Yuan et al., 2014 [24]	China	Retrospective Cohort, Single-centre	24	IC: 16 OP: 8	NR	IC: NR OP: NR	IC: 2 (13) OP: 1 (13)	IC: NR OP: NR	IC: NR OP: 6.5 ± 1.3	IC: 5 OP: 0	IC: NR OP: NR	IC: 33 OP: 33	IC: Facial 16 OP: Facial 8	IC: NR OP: NR

Acronyms: H&N, Head and Neck; IC, Intralesional Corticosteroid; LE, Lower Extremity; N, Number of patients; NR, Not reported; OC, Oral Corticosteroids; OP, Propranolol; RCT, Randomised Controlled Trial; SD, Standard deviation; UE, Upper Extremity.

Notes: Persistent ulceration was analyzed separately as an ulceration outcome. In Kim et al. (2017) [17], one patient had lesions in two locations (scalp and upper limb); therefore, the total number of locations exceeds the number of participants. In Chang et al. (2023) [27], 50 patients were enrolled (25 per group); two patients in the intralesional group withdrew, leaving 23 for subsequent outcome analyses. Baseline sex data remain based on the enrolled population (35/50, 70.0%).

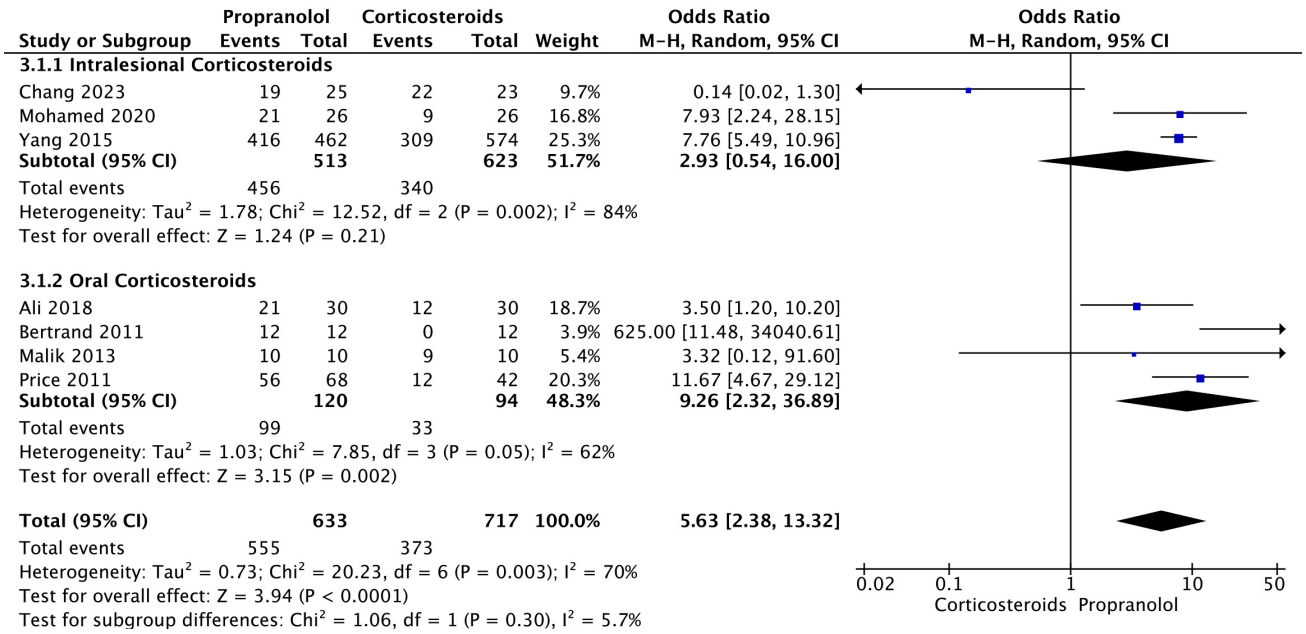


Fig. 1. Pooled estimates of treatment effectiveness [4,19,20,23,25,27,28].

and intergroup comparability to support their inclusion in the meta-analysis.

3.3 Clinical Characteristics

Among the fifteen included studies, a total of 1841 paediatric IH patients received either propranolol (n = 946, 51.4%) or corticosteroids (n = 895, 48.6%). All of the propranolol group received oral administration. Within the corticosteroid group, oral corticosteroids (n = 225, 25.1%) and intralesional corticosteroids (n = 670, 74.9%) were the routes of administration. Treatment duration ranged from 2.1 to 15.9 months. The clinical characteristics of the included studies are summarized in Table 1.

3.4 Outcomes

3.4.1 Treatment Effectiveness

The summary of outcomes is described in Fig. 1 (Ref. [4,19,20,23,25,27,28]). Propranolol was associated with a higher effective treatment rate compared to corticosteroids (OR: 4.96, 95% CI: 2.19 to 11.26; I^2 = 69%, p = 0.0001) [4,19,20,23,25,27,28]. The notably large effect estimate for Bertrand et al. [20] was attributable to the absence of treatment effectiveness events in the oral corticosteroid group (0/12), resulting in an extreme odds ratio with a very wide confidence interval. When comparing propranolol with intralesional corticosteroids, propranolol showed no difference in effectiveness (OR: 2.93, 95% CI: 0.54 to 16.00; I^2 = 84%, p = 0.21) [19,23,27], while propranolol demonstrated a higher effectiveness compared with oral corticosteroids (OR: 6.56, 95% CI: 1.98 to 21.73; I^2 = 53%, p = 0.002) [4,20,25,28]. Test for subgroup differences was not statistically significant (p = 0.30).

3.4.2 Adverse Events and Safety Profile

The odds of experiencing adverse events were lower in the propranolol group (OR: 0.27, 95% CI: 0.10 to 0.71; I^2 = 75%, p = 0.008) [4,5,9,18,19,20,23,24,25,26,27,28] (Fig. 2a). In subgroup analysis, no difference in adverse events was observed between propranolol and intralesional corticosteroids (OR: 0.46, 95% CI: 0.10 to 2.18; I^2 = 81%, p = 0.33) [4,5,18,20,25,26,28], while propranolol was associated with significantly lower odds of adverse events compared with oral corticosteroids (OR: 0.17, 95% CI: 0.03 to 0.88; I^2 = 76%, p = 0.03) [9,19,23,24,27]. In the RCT-only analysis, propranolol was also associated with significantly lower odds of adverse events (OR: 0.12, 95% CI: 0.03 to 0.46; I^2 = 30%, p = 0.002) [4,5,18] (Fig. 2b). Treatment-related ulceration was less frequent with propranolol (OR: 0.18, 95% CI: 0.08 to 0.42; I^2 = 0%, $p < 0.0001$) [9,19,22,24,25] (Fig. 3).

3.4.3 Treatment Duration and Recurrence

There was no difference in treatment duration between the propranolol and corticosteroids groups (MD: 0.39 months, 95% CI: –1.15 to 1.94; I^2 = 95%, p = 0.62) [4,5,9,17,18,19,20,21,22,27] (Fig. 4a). Similarly, subgroup analyses showed no significant differences between groups. Likewise, there was no difference in treatment duration in the RCT-only analysis (MD: –0.20 months, 95% CI: –0.65 to 0.24; I^2 = 0%, p = 0.38) [4,5,17,18] (Fig. 4b). Recurrence rates were similar between groups (OR: 0.36, 95% CI: 0.08 to 1.70; I^2 = 29%, p = 0.20) [4,5,24,26,27] (Fig. 5).

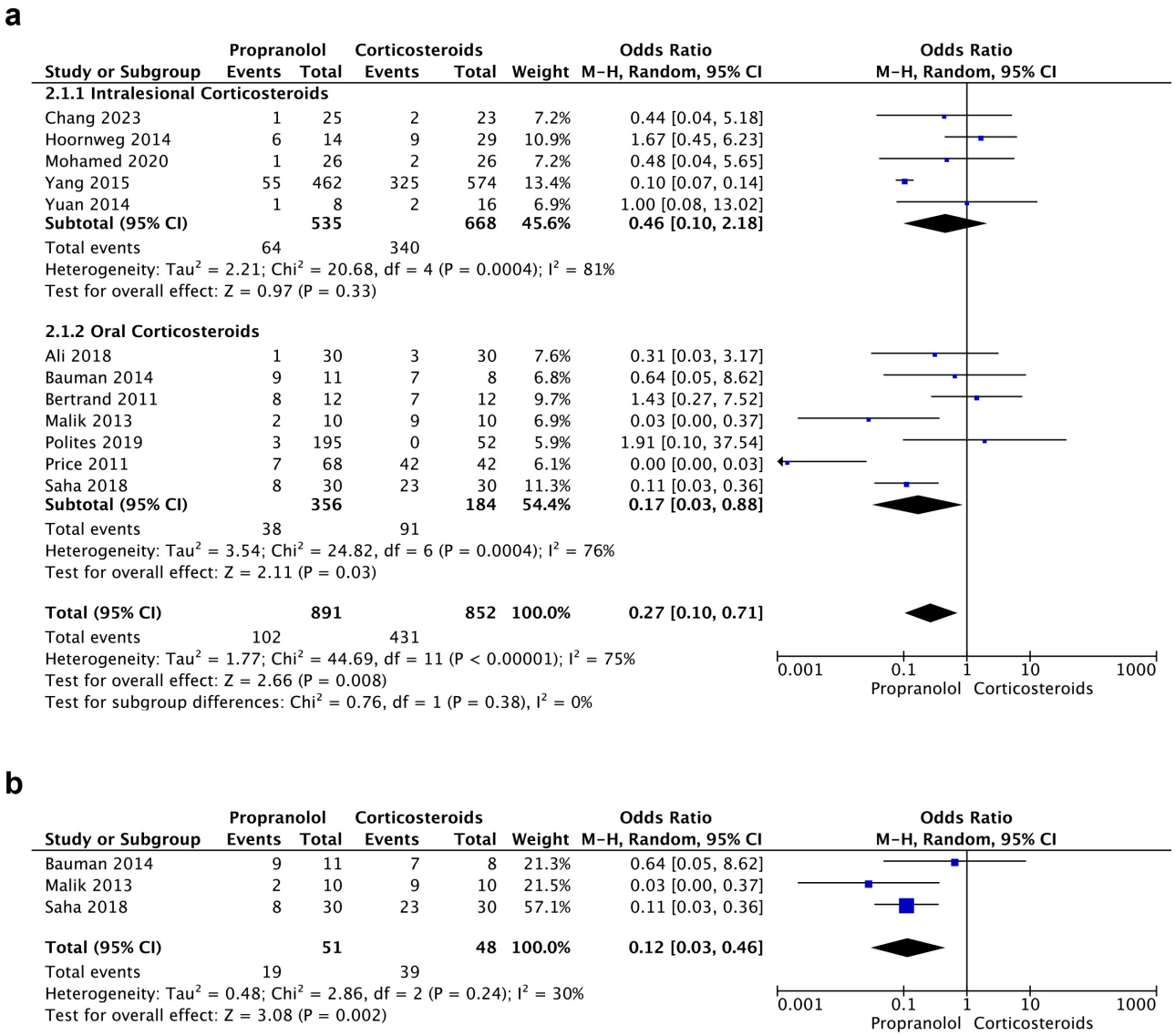


Fig. 2. Pooled estimates of adverse events for (a) all study designs [4,5,9,18,19,20,23,24,25,26,27,28] and (b) randomised controlled trials (RCTs) only [4,5,18].

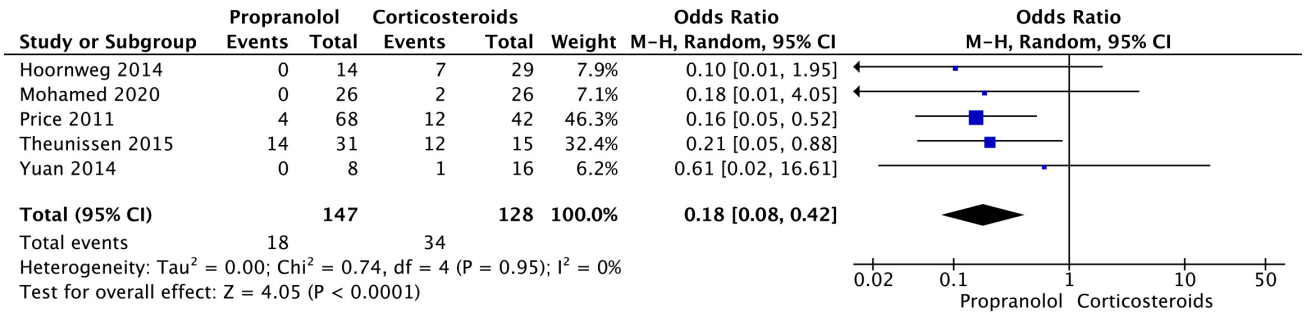


Fig. 3. Pooled estimates of ulceration rate [9,19,22,24,25].

3.4.4 Surgical Intervention Rates

No difference was observed in surgical resection rates between the propranolol and corticosteroids treatments (RR: 0.59, 95% CI: 0.19 to 1.88; I^2 = 76%, p = 0.37) [22,25,26,27] (Fig. 6). Notably, Chang et al. [27] showed an effect estimate in the opposite direction to the other contributing studies and appeared to be a major contributor to the observed heterogeneity. Across individual studies, the

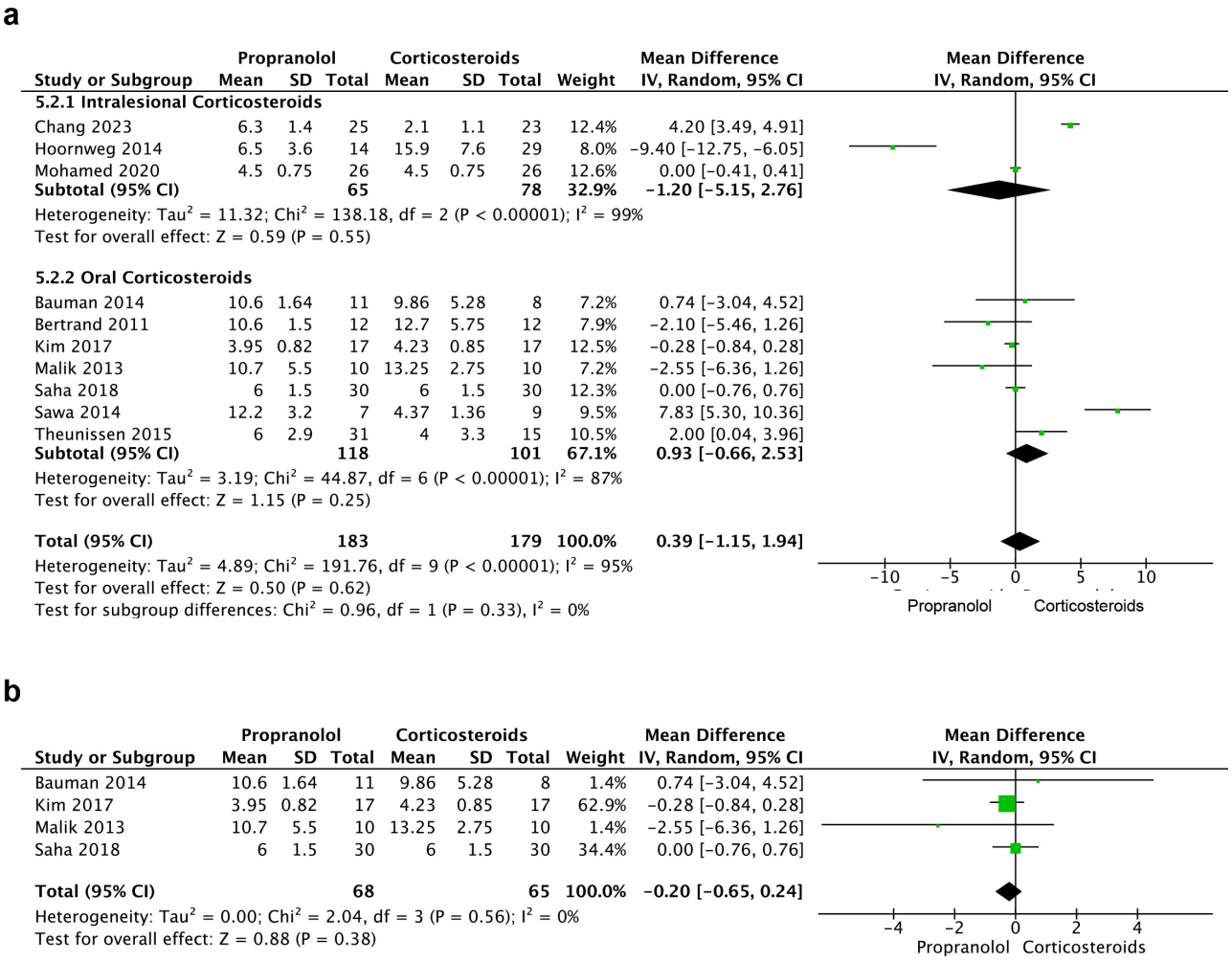


Fig. 4. Pooled estimates of treatment duration comparing propranolol and corticosteroids for (a) all study designs [4,5,9,17,18,19,20,21,22,27] and (b) randomised controlled trials (RCTs) only [4,5,17,18].

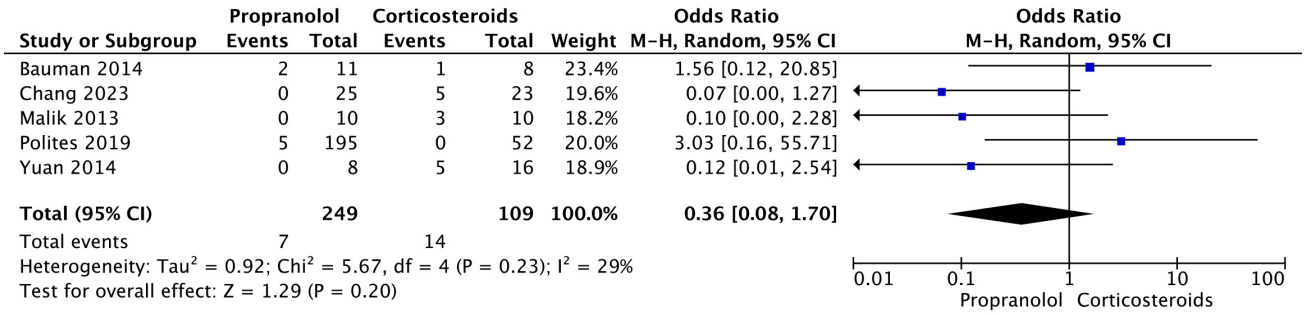


Fig. 5. Pooled estimates of recurrence rate [4,5,24,26,27].

most common indications for surgery included lesions refractory to medical therapy, functional risk, and cosmetically unacceptable outcomes in critical locations such as the nasal tip or lip [22,25,26,27].

3.5 Sensitivity Analyses

Leave-one-out sensitivity analyses were performed for outcomes with substantial heterogeneity. For treatment effectiveness, exclusion of individual studies reduced overall heterogeneity from $I^2 = 69\%$ to 30% following exclusion of Chang et al. [27]. Other individual study exclusions did not substantially reduce heterogeneity. For surgical resection, exclusion of Chang et al. [27] reduced heterogeneity from $I^2 = 76\%$ to 0% and resulted in a statistically significant pooled effect (RR: 0.35, 95% CI: 0.22 to 0.58; $I^2 = 0\%$, $p < 0.0001$), compared with the non-significant pri-

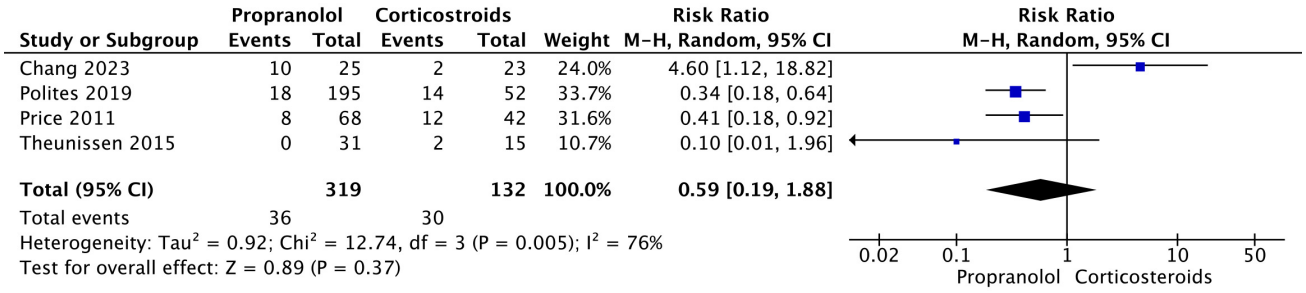


Fig. 6. Pooled estimates of surgical resection rate [22,25,26,27].

mary analysis (RR: 0.59, 95% CI: 0.19 to 1.88; I^2 = 76%, p = 0.37). For treatment duration, exclusion of individual studies did not meaningfully reduce heterogeneity, which remained high (I^2 = 89–96%). Similarly, adverse events did not meaningfully reduce heterogeneity, which remained substantial (I^2 = 66–77%). Outcomes with low heterogeneity (I^2 < 50%), including recurrence rate and ulceration, were not subjected to sensitivity analysis. A funnel plot was generated to assess potential publication bias for the adverse-event and treatment duration outcome (Fig. 7). Visual inspection of the funnel plots showed asymmetry for both adverse events and treatment duration, without a clear or consistent pattern in the distribution of studies. These findings suggest possible small-study effects or publication bias; however, the plots should be interpreted cautiously given the limited number of contributing studies and substantial between-study heterogeneity.

4. Discussion

The management of non-resolving IH continues to evolve, with propranolol widely used as first-line therapy, yet corticosteroids remain an important alternative treatment option. This meta-analysis evaluated the comparative effectiveness and safety of propranolol and corticosteroid therapies for IH. Our findings demonstrated that propranolol was associated with greater overall treatment response and fewer adverse events compared with corticosteroids, while no difference was observed in surgical intervention rates. Notably, stratification by corticosteroid route of administration further revealed differing patterns of outcomes, with propranolol showing greater effectiveness than oral corticosteroids but similar effectiveness to intralesional corticosteroids. These findings highlight the continuing relevance of corticosteroids as alternative or second-line therapies when propranolol is contraindicated or insufficient and emphasize the importance of considering administration route and lesion characteristics in IH management.

Propranolol is often selected as a first-line therapy for IH due to its tendency to produce early visible improvements, such as softening and fading of lesion color, often within days to weeks of initiation [18,25]. In contrast, both intralesional and oral corticosteroids tend to exert their effects more slowly, with visible changes often not evident until 6 months or longer into therapy [4,28]. Our meta-analysis found a higher effectiveness of >50% regression among patients treated with propranolol compared to those treated with corticosteroids, reinforcing its reputation for better regression response than corticosteroids [25,29]. Consistent with this, several included studies observed that lesions treated with propranolol became not only lighter in color but also flat and non-palpable within the first weeks of therapy, highlighting its rapid clinical effect

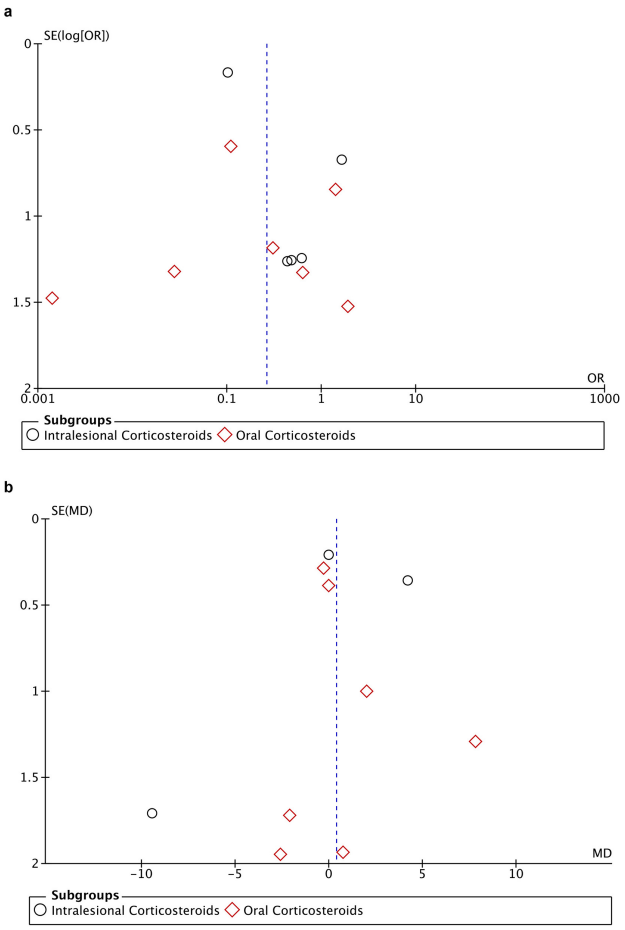


Fig. 7. Funnel plots assessing potential publication bias for (a) adverse events and (b) treatment duration.

[4,18,24]. There was no difference in treatment duration between propranolol and corticosteroids. Recent evidence has also highlighted the importance of treatment duration in relation to rebound growth following propranolol discontinuation [30]. Comparison of regression rates between treatment modalities was not possible because most studies did not report this outcome. For patients and families, early visible improvement with propranolol may be particularly meaningful given the psychosocial impact of IH, especially for disfiguring facial lesions. Studies have reported reduced parental worry and improved parental quality of life following propranolol treatment [29]. With respect to subtype, only a few studies provided details, though Malik et al. [4] reported faster responses in mixed lesions compared with superficial or deep types. Anatomical site and lesion subtype may influence treatment selection and early response, underscoring the need for more specific reporting in future studies. Future research should therefore explore whether this early response varies across IH subtypes, as tailoring treatment to lesion characteristics may further optimise outcomes.

Our subgroup analysis provides additional insight beyond prior meta-analyses by distinguishing outcomes according to the route of corticosteroid administration. When corticosteroids were separated into intralesional and oral regimens, propranolol showed similar effectiveness to intralesional corticosteroids, whereas propranolol demonstrated greater effectiveness than oral corticosteroids. For safety outcomes, propranolol was associated with fewer adverse events than oral corticosteroids, while no statistically significant difference was observed when compared with intralesional corticosteroids. This subgroup finding should be interpreted separately from the overall corticosteroid analysis, in which propranolol was associated with fewer adverse events. These findings suggest that the route of corticosteroid administration may influence observed treatment outcomes and should be considered when interpreting comparisons between corticosteroids and propranolol. The clinical context in which each corticosteroid route is used may partly explain these differences. The substantial heterogeneity observed in the comparison of propranolol with intralesional corticosteroids for treatment effectiveness (I^2 = 69%) may reflect differences in lesion characteristics, anatomical location, and treatment selection across studies. Sensitivity analysis showed that heterogeneity was reduced to 0% following exclusion of Chang et al. [27] and Bertrand et al. [20], suggesting that these studies may have contributed substantially to the observed variability. However, exclusion of Chang et al. [27] also reduced overall heterogeneity from I^2 = 69% to 30%, indicating that the influence of this study extended beyond the intralesional corticosteroid subgroup. However, the limited number of studies and inconsistent reporting of these characteristics precluded further quantitative exploration of the specific sources of heterogeneity. Intralesional corticosteroids were generally used for localised lesions in anatomically sensitive areas such as the periorbital region, cheek, nasal tip, and lip [5,9,24,27], whereas oral corticosteroids were more commonly used for larger or more extensive lesions involving the head and neck, perineum, extremities, and trunk [17,20,22,26,28]. Taken together, the comparable effectiveness observed between intralesional corticosteroids and propranolol may reflect differences in lesion characteristics and treatment selection rather than equivalent efficacy across all IH presentations. Similarly, the lower effectiveness observed with oral corticosteroids should be interpreted in the context of potential differences in baseline lesion burden and severity. Because most included studies did not provide sufficient patient-level data to adjust for lesion size, depth, anatomical location, or severity, our findings cannot establish that one treatment route is preferable for a specific lesion type. Nevertheless, intralesional corticosteroid monotherapy may remain appropriate for carefully selected patients with relatively small, focal, and well-localised IHs, particularly when the lesion is bulky and localised proliferation threatens anatomic landmarks such as the lip or nose [10]. Treatment selection should therefore consider lesion characteristics, anatomical location, severity, and potential functional or cosmetic consequences rather than comparative efficacy alone.

Surgical resection remains an important option for lesions in functionally or cosmetically sensitive sites where pharmacological treatment alone may not achieve sufficient regression or when rapid intervention is required, such as for periorbital lesions to prevent amblyopia [9,19,26,27]. Although earlier studies suggested propranolol could reduce the need for surgical excision, our analysis found no difference between propranolol and corticosteroids (oral or intralesional) [2,26,31]. The decision to proceed with surgery is influenced by lesion behaviour, treatment response, and parental preference, rather than solely reflecting medical failure [4,28,30]. The discrepancy between our findings and previous cohort studies may partly reflect differences in patient selection and indications for treatment. Lesion characteristics such as size, depth, anatomical location, and severity may influence both the choice of medical therapy and the likelihood of subsequent surgery [10,26]. Surgical intervention may also be undertaken for persistent or residual tissue, functional impairment, cosmetic concerns, ulceration, or late presentation, rather than treatment failure alone [10,26,29]. Confounding by indication may therefore contribute to differences between treatment groups, as patients with more extensive or clinically challenging lesions may have been more likely to receive corticosteroid therapy or surgery [26,32]. In addition, differences in treatment era and institutional thresholds for surgical intervention may contribute to variation across studies [26,29]. Therefore, the absence of a significant difference in surgical resection rates in our pooled analysis should be interpreted in the context of these clinical

and methodological differences. Leave-one-out sensitivity analyses indicated that individual studies contributed substantially to heterogeneity, particularly for treatment effectiveness. Therefore, these pooled estimates should be interpreted with caution.

Adverse events are a crucial consideration when selecting treatments for IH patients, particularly those vulnerable to pharmacological side effects. In the overall analysis, corticosteroids were associated with more treatment-related adverse events than propranolol. Ulceration can cause pain, increase infection risk, and lead to adverse scarring [26]. It can interrupt treatment, requiring pauses, dosage changes, or a switch to alternative treatments, ultimately delaying haemangioma resolution and prolong discomfort, especially in cases involving cosmetically or functionally sensitive areas [4,22,30]. Ulceration rates were lower with propranolol, although the mechanism underlying this effect is likely multifactorial. The early vasoconstrictive effect of propranolol is followed by inhibition of proangiogenic signalling, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), which may promote growth arrest and subsequent involution through effects on proliferating endothelial cells [8,18]. These mechanisms may contribute to the lower ulceration rates observed with propranolol, although a direct causal relationship between these pharmacological effects and ulceration prevention has not been established. This finding aligns with prior reports and reinforces propranolol's clinical advantage, particularly for lesions in sensitive or visible areas, where ulceration can cause long-term cosmetic or functional harm [21,24,31,33]. This dual benefit of effective lesion control and ulceration prevention supports a smoother and more continuous treatment course, underscoring propranolol's advantages as a frontline therapy. The findings should be interpreted separately from the management of IHs with pre-existing ulceration, which were not represented in our analysis. In a retrospective study specifically evaluating ulcerated IHs, Polites et al. [26] reported no significant difference between propranolol and steroids in the proportion of lesions healed, time to healing, or overall complication rates. Further studies are warranted to determine whether baseline ulceration modifies treatment response, healing time, or subsequent complications and should be considered when evaluating the safety of IH therapies.

5. Limitation

Despite the strengths of this meta-analysis, several important limitations should be acknowledged. Firstly, most included studies were retrospective and often lacked control over confounding variables, introducing potential selection and reporting biases. Many were conducted in single-centre settings, limiting the generalisability of findings across diverse healthcare contexts. Although treatment regimens were broadly similar, other potential confounding factors such as variation in patient age at treatment initiation, haemangioma phase (proliferative versus involuting), lesion size, depth, and haemangioma location may have influenced treatment response and safety outcomes. Inclusion of more multicentre, standardised studies could enhance the robustness and external validity of future analyses.

Secondly, substantial heterogeneity was observed across several pooled outcomes, with I^2 values ranging from 0% to 95%. Heterogeneity in outcome reporting was evident. While most studies assessed treatment effectiveness, definitions and response criteria varied, with some using institution-specific or subjective measures. Additional sources of heterogeneity may include differences in patient age at treatment initiation, haemangioma phase, lesion size, depth, anatomical location, corticosteroid administration route, treatment dosage and duration, and study design. However, the available data did not permit reliable meta-regression or sufficiently powered subgroup analyses to determine the independent contribution of these factors to the observed heterogeneity. This variability may have reduced the precision of pooled estimates. Overall, the risk of bias across studies ranged from moderate to high, largely due to confounding, heterogeneous study populations, and inconsistent follow-up. Therefore, pooled estimates with substantial heterogeneity should be interpreted with caution. Furthermore, the study-design-stratified analysis of adverse events showed differing results between randomised and observational studies, suggesting that study design may have influenced the observed treatment effect.

Thirdly, baseline patient characteristics were often poorly described, limiting subgroup comparisons. Although our eligibility criteria excluded syndromic IH, some included studies did not explicitly report syndromic status. Studies in which syndromic patients comprised less than 10% of the study population were considered acceptable, as their contribution was considered unlikely to materially influence the pooled estimates. Where syndromic and non-syndromic patients could not be separated, studies were retained only when the proportion of syndromic patients was below this prespecified threshold. Nevertheless, the inability to completely exclude syndromic patients from all included datasets may have introduced some clinical heterogeneity. The lack of detailed and consistent reporting of haemangioma subtype, anatomical location, and severity also prevented reliable subgroup analyses examining whether these factors modified treatment efficacy or adverse event profiles.

Lastly, relatively short follow-up durations in many studies may have limited the assessment of long-term outcomes such as recurrence and rebound growth, which remain clinically relevant following discontinuation of propranolol [34]. Recent studies have further investigated clinical factors associated with relapse following propranolol discontinuation [34,35]. Incomplete outcome reporting and inconsistent definitions of treatment response may have in-

troduced further uncertainty. Future prospective multicentre studies with standardised reporting, well-defined confounder adjustment, and extended follow-up will be crucial to clarifying long-term comparative outcomes in infantile haemangioma management.

6. Conclusion

This meta-analysis found that propranolol was associated with greater overall effectiveness and fewer adverse events compared with corticosteroids. Subgroup analysis highlights that the route of corticosteroid administration may influence outcomes, supporting their continued selective use when propranolol is contraindicated. These findings reinforce a tailored approach to IH management, while future research should explore long-term outcomes and optimise strategies across subtypes and anatomical sites.

Key Points

• This systematic review and meta-analysis compared the effectiveness and safety of propranolol with oral and intralesional corticosteroids for the treatment of infantile haemangiomas across 15 studies including 1841 patients.

• Propranolol was associated with significantly greater overall treatment effectiveness than corticosteroids, with a significant advantage over oral corticosteroids but no significant difference compared with intralesional corticosteroids.

• Propranolol was associated with significantly fewer adverse events overall and a lower rate of ulceration compared with corticosteroids, and this difference remained statistically significant in the RCT-only analysis.

• No significant differences were observed between propranolol and corticosteroids in treatment duration, surgical resection rates, or recurrence.

• These findings support a tailored approach to infantile haemangioma management that considers the route of corticosteroid administration and individual lesion characteristics when selecting treatment.

Availability of Data and Materials

All data generated or analysed during this study are included in this published article and its supplementary information.

Author Contributions

AS, HN, CAT, and KYW contributed to the conception and design of the study. KS, RH, DR, EG, JWFB, SYCL, AS and KRC contributed to data screening and data acquisition. HN, AS, KYW, and CAT contributed to analysis and interpretation. AS, KS, RH, DR, EG, JWFB, and KRC drafted the manuscript. AS, HN, CAT, SYCL, and KYW critically revised the manuscript for important intellectual content. All authors approved the final version for submission. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflicts of Interest

Given his role as Editorial Board Member, Kai Yuen Wong had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Jian Yang. The other authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM54357.

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