



EFFECTIVENESS OF INTRALESIONAL CORTICOSTEROID INJECTION FOR NODULOCYSTIC ACNE : A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS AND PRIMARY STUDIES

¹ Rielyana Lumban Gaol

¹ Faculty of Medicine, University of Methodist, Indonesia

Corresponding Email: rielyanal9@gmail.com

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ABSTRACT

Introduction: Nodulocystic acne represents the most severe phenotype of acne vulgaris, associated with significant physical and psychosocial morbidity. Intralesional corticosteroid injection (ILC) has been used clinically for >60 years, yet systematic evidence synthesis remains limited. This review aims to evaluate the efficacy, safety, and optimal concentration of ILC for nodulocystic acne.

Methods: Systematic review conducted according to PRISMA 2020 guidelines. Included studies comprised RCTs, quasi-RCTs, comparative cohort studies, pre-post studies, and case series (n≥5). Risk of bias was assessed using Cochrane RoB 2.0 and Newcastle-Ottawa Scale.

Results: Fifteen studies comprising 1,247 subjects were included. Triamcinolone acetonide (TA) at concentrations of 0.63–5 mg/mL demonstrated consistent efficacy, with symptomatic improvement

onset within 24–72 hours and median lesion resolution of 4.6–8.1 days depending on modality. Lesion diameter reduction reached 65–85% by Day 7. Mean VAS pain score reduction was 2.27 points ($p<0.0001$) with cryoanesthesia. TA-loaded detachable microneedle patch (DMN) technology demonstrated faster resolution (median 4.6 vs 8.1 days; $p<0.05$). Betamethasone phosphate showed no superiority over saline control ($p=0.16$). Incidence of cutaneous atrophy and hypopigmentation was $<5\%$ with appropriate injection technique.

Discussion: TA at 0.63–2.5 mg/mL constitutes the most effective and safe ILC agent. Technical innovations (cryoanesthesia, DMN) significantly improve tolerability and accessibility. Major limitations include scarcity of high-quality RCTs, design heterogeneity, and absence of longitudinal data.

Conclusion: Intralesional triamcinolone acetonide injection at 0.63–2.5 mg/mL represents an effective, safe, and rapidly responsive therapeutic modality for nodulocystic acne. Large-scale multicenter RCTs with ≥ 6 months follow-up are urgently required.

Keywords: triamcinolone acetonide; intralesional injection; nodulocystic acne; systematic review; efficacy

INTRODUCTION

Background

Acne vulgaris is a chronic inflammatory dermatological condition of the pilosebaceous unit, globally affecting approximately 9.4% of the world population, with an estimated 50 million patients in the United States annually and a prevalence of 85% among adolescent populations (Tan & Bhate, 2015). In Indonesia, a tropical nation characterised by high temperature and relative humidity—conditions that physiologically accelerate sebum production and *Cutibacterium acnes* colonisation—the prevalence of acne vulgaris in the adolescent population has been reported to range between 85–100% (Wiraputranto et al., 2023). National epidemiological data from the Cosmetic Division Outpatient Clinic, Department of Dermatology and Venereology, Dr. Cipto Mangunkusumo National General Hospital (RSCM) Jakarta, demonstrated that the incidence of acne vulgaris in 2019 reached 46% of all new cases, with the proportion of moderate-to-severe cases exceeding 50% (Wiraputranto et al., 2023).

Nodulocystic acne represents the most severe clinical phenotype within the acne vulgaris spectrum, characterised by deep inflammatory lesions comprising erythematous nodules and fluctuant cysts with diameter >5 mm, involving the dermis and subcutaneous tissue. Pathophysiologically, nodulocystic lesions develop through a series of molecular events encompassing: (1) abnormal hyperproliferation of follicular keratinocytes inducing follicular ostium obstruction (infundibular hyperkeratosis); (2) androgen-mediated sebum hypersecretion, particularly dihydrotestosterone (DHT) binding to androgen receptors in sebaceous glands; (3) *Cutibacterium acnes* overgrowth activating Toll-like receptor 2 (TLR-2) on perifollicular keratinocytes and macrophages, initiating pro-inflammatory cytokine production (IL-1 β , IL-6, IL-8, TNF- α); and (4) follicular wall rupture releasing comedonal contents (keratin, sebum, bacterial fragments) into the dermis, triggering a foreign body reaction with neutrophil, lymphocyte, and histiocyte infiltration forming a dense inflammatory infiltrate (Zaenglein et al., 2016). This process

culminates in the formation of tender, erythematous nodulocystic lesions with potential for persistent atrophic, keloidal, or post-inflammatory hyperpigmentation (PIH) scarring sequelae.

The psychosocial morbidity attributable to nodulocystic acne is substantial. Studies utilising the Dermatology Life Quality Index (DLQI) consistently demonstrate quality-of-life impairment equivalent to or exceeding that of other chronic conditions such as asthma, epilepsy, and diabetes mellitus (Tan & Bhate, 2015). The impact encompasses deficits in self-esteem, social functioning, sexual activity, vocational productivity, and interpersonal relationships, with a mean DLQI score of 11.14 reported in young acne patients (Rahimi et al., 2024). A DLQI score ≥ 11 indicates a 'very large effect' on quality of life.

The therapeutic armamentarium for severe nodulocystic acne includes oral isotretinoin (13-cis-retinoic acid)—the only agent approved by the US Food and Drug Administration (FDA) for severe recalcitrant nodular acne since 1982—systemic antibiotics (doxycycline, minocycline), combined hormonal retinoids (combined oral contraceptives, spironolactone), and various procedural modalities (Zaenglein et al., 2016). However, systemic therapies face inherent limitations: slow onset of action (weeks to months), significant multisystem adverse effects (isotretinoin teratogenicity, hepatotoxicity, dyslipidaemia), increasing antimicrobial resistance risk, and substantial cost. In acute clinical scenarios—patients with individual painful nodulocystic lesions requiring rapid resolution, for instance prior to an important social event or for prevention of cicatricial sequelae—a lesional intervention modality capable of delivering a therapeutic response within days is required.

Intralesional corticosteroid (ILC) injection fulfils this criterion. The procedure was first described in the dermatological literature in the 1960s and has become part of the standard dermatological procedural armamentarium. Technically, the procedure involves direct injection of a diluted corticosteroid solution—most commonly triamcinolone acetonide (TA)—into the centre of an inflamed acne lesion. The anti-inflammatory mechanisms of intralesionally administered corticosteroids encompass: inhibition of phospholipase A2 suppressing prostaglandin and leukotriene synthesis; suppression of pro-inflammatory cytokine gene transcription through NF- κ B and glucocorticoid response element (GRE) modulation; reduction of neutrophil and macrophage

migration to the inflammation site; and induction of local vasoconstriction reducing perilesional oedema (Firooz et al., 1995). These cumulative effects produce rapid and dramatic local inflammation reduction, with onset of symptomatic improvement within 24 hours and lesional resolution within 2–7 days (Levine, 1983; National Guideline Alliance, 2021).

Despite more than six decades of clinical use, the scientific evidence base supporting ILC for nodulocystic acne remains highly limited. The NICE 2021 systematic review identified only one RCT meeting inclusion criteria (Levine, 1983), with a very small participant number (n=17), precluding meaningful quantitative analysis (National Guideline Alliance, 2021). Comprehensive and up-to-date literature synthesis, encompassing the latest technical innovations and contemporary primary studies, has never been systematically undertaken. This research gap forms the fundamental justification for conducting this systematic review.

Research Objectives

This systematic review aims to:

- Evaluate the clinical efficacy of intralesional corticosteroid injection in reducing lesion size, perilesional erythema, and pain in nodulocystic acne, based on all available RCT and primary study evidence.
- Analyse the safety profile and incidence of adverse events (AEs) from various intralesional corticosteroids across different concentration and volume spectra.
- Compare the therapeutic efficacy between triamcinolone acetonide and betamethasone phosphate, and between conventional delivery techniques and innovative modalities (detachable microneedle, adjuvant cryoanesthesia).
- Assess the impact of ILC on dermatological quality of life and patient satisfaction using validated instruments (DLQI, CADI, VAS).
- Identify optimal concentrations, volumes, and techniques to maximise therapeutic efficacy while minimising the risk of local AEs (cutaneous atrophy, hypopigmentation).
- Formulate evidence-based therapeutic recommendations for the clinical implementation of ILC in the multidisciplinary management of nodulocystic acne.

Research Benefits

Scientific Benefit: This systematic review provides a comprehensive, PRISMA 2020 methodology-based synthesis of all available scientific evidence regarding ILC for nodulocystic acne, filling a critical gap in evidence-based dermatological literature and providing a baseline for subsequent primary research.

Clinical Benefit: The review's findings facilitate evidence-based clinical decision-making for dermatologists and medical practitioners in selecting the corticosteroid agent, optimal concentration, appropriate technical modality, and AE mitigation strategies, particularly in the context of Asian populations with Fitzpatrick skin types IV–VI who are more susceptible to PIH.

Policy Benefit: These findings may serve as a basis for updating national clinical practice guidelines (PERDOSKI) and international dermatology guidelines on nodulocystic acne management, as well as advocating for high-quality RCTs as a dermatological research priority.

Research Hypotheses

- H1: Intralesional triamcinolone acetonide injection is statistically significantly more effective than intralesional physiological saline (placebo control) in reducing lesion diameter, erythema, and pain in nodulocystic acne within a 7-day observation period.
- H2: Triamcinolone acetonide demonstrates clinically meaningful efficacy superiority compared to betamethasone phosphate as an intralesional corticosteroid agent for nodulocystic acne.
- H3: Triamcinolone acetonide at 0.63 mg/mL possesses a superior safety profile without clinically meaningful efficacy inferiority compared to higher concentrations (1.25–2.5 mg/mL), supporting the minimum effective dose principle.
- H4: Innovative technical modalities—including TA-loaded detachable microneedle patches and adjuvant cryoanesthesia—significantly improve procedural tolerability and patient satisfaction index without compromising therapeutic efficacy.

Research Gap and Novelty

Research Gap: Although ILC has been a standard dermatological procedure for more than 60 years, its supporting evidence base remains extremely limited. The NICE 2021 systematic review identified only one RCT meeting inclusion criteria (Levine, 1983; n=17, high risk of bias),

definitively precluding strong evidence-based recommendations. No systematic review has comprehensively integrated: (1) contemporary primary studies from 2020–2024; (2) evaluation of technical innovations (TA-loaded detachable microneedle/DMN, self-injection devices, cryoanesthesia); (3) multidomain analysis covering ≥ 10 primary and secondary clinical outcomes; (4) risk of bias assessment using the latest Cochrane RoB 2.0 standards; and (5) contextualisation to Southeast Asian populations including Indonesia.

Novelty: This systematic review provides scientific novelty in: (1) Broader study coverage including innovative primary studies through 2024; (2) Qualitative analysis of new delivery modalities (DMN+TA, cryoanesthesia, self-injection device); (3) Evaluation of ≥ 12 structured clinical outcomes with per-outcome analysis tables; (4) Formal risk of bias assessment using Cochrane RoB 2.0 for each study; (5) Clinical contextualisation to Indonesian epidemiology and tropical climatic conditions affecting acne pathophysiology and management.

METHODS

Study Design

This systematic review was designed, conducted, and reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines (Page et al., 2021).

Study Eligibility Criteria

Inclusion Criteria

- Patients with nodulocystic acne or severe inflammatory acne with lesion diameter ≥ 5 mm, aged ≥ 12 years, without restriction on gender, ethnicity, or comorbidities.
- Intralesional corticosteroid injection (triamcinolone acetonide, betamethasone phosphate, triamcinolone hexacetonide, or hydrocortisone) at various concentrations, volumes, frequencies, using conventional or innovative techniques, with or without adjuvants.
- Comparators including intralesional physiological saline, no intervention, topical therapy, systemic therapy, or incision and drainage.

- Outcomes including lesion diameter/erythema reduction, resolution time, global clinical assessment, VAS pain score, quality of life, patient satisfaction, adverse events, recurrence rates, or scar prevention.
- Study designs: RCTs, quasi-RCTs, comparative prospective cohorts, pre-post studies, crossover studies, or case series ($n \geq 5$).
- Publications from database inception through 31 December 2024 without language restriction.

Exclusion Criteria

- Studies involving systemic corticosteroids without an intralesional component.
- Mixed interventions without separate data for intralesional injection.
- Studies on non-acne conditions (keloid, hidradenitis suppurativa, alopecia areata).
- Single case reports ($n < 5$), editorials, expert opinion without empirical data, or conference abstracts without complete data.
- Studies without extractable quantitative data or not reporting relevant outcomes.
- Duplicate studies from the same cohort.

Literature Search Strategy and Sources

Keywords used based on PICO framework:

PICO Component	Keyword 1	Keyword 2	Keyword 3
P (Population)	Nodulocystic acne	Severe inflammatory acne	Acne vulgaris nodular/cystic
I (Intervention)	Intralesional corticosteroid injection	Triamcinolone acetonide intralesional	Corticosteroid intralesional therapy
C (Comparison)	Intralesional saline	Conventional injection technique	Betamethasone phosphate intralesional
O (Outcome)	Lesional	Efficacy and safety	Cutaneous atrophy

	resolution time	profile	prevention
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The Boolean MeSH keywords inputted on databases for this research are: (*"nodulocystic acne" OR "severe inflammatory acne" OR "acne vulgaris nodular/cystic"*) AND (*"intralesional corticosteroid injection" OR "triamcinolone acetonide intralesional" OR "corticosteroid intralesional therapy"*) AND (*"intralesional saline" OR "conventional injection technique" OR "betamethasone phosphate intralesional"*) AND (*"lesional resolution time" OR "efficacy and safety profile" OR "cutaneous atrophy prevention"*)

Data Extraction

Data extraction was performed using a pre-developed standardised form, encompassing: study bibliographic identifiers (authors, year, country, journal, DOI), methodological design, study population characteristics (sample size, mean age $\pm$ SD, gender distribution, acne severity grade, Fitzpatrick skin type), intervention characteristics (corticosteroid type, concentration in mg/mL, injection volume in mL, injection frequency and interval, delivery technique, procedural adjuvants), comparator characteristics, measured outcomes along with measurement instruments and evaluation time points, and statistical data (mean, SD, median, IQR, p-value, 95% confidence interval/CI). Data extraction was performed independently by two reviewers and cross-verified.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("nodulocystic acne" AND "intralesional corticosteroid injection" AND "lesional resolution time" OR "efficacy and safety profile" OR "cutaneous atrophy prevention")</i>	3,415
Semantic Scholar	<i>("nodulocystic acne" OR "severe inflammatory acne" OR "acne vulgaris nodular/cystic") AND ("intralesional corticosteroid injection" OR "triamcinolone acetonide intralesional" OR "corticosteroid intralesional therapy") AND ("intralesional saline" OR "conventional injection technique" OR "betamethasone phosphate intralesional") AND ("lesional resolution time" OR "efficacy and safety profile" OR "cutaneous atrophy prevention")</i>	77
Cochrane	<i>("nodulocystic acne" AND "intralesional corticosteroid injection" AND "lesional resolution time" OR "efficacy and safety profile" OR "cutaneous atrophy prevention")</i>	10
Google Scholar	<i>("nodulocystic acne" AND "intralesional corticosteroid injection" AND "lesional resolution time" OR "efficacy and safety profile" OR "cutaneous atrophy prevention")</i>	2
Science-direct	<i>("nodulocystic acne" AND "intralesional corticosteroid injection" AND "lesional resolution time" OR "efficacy and safety profile" OR "cutaneous atrophy prevention")</i>	16

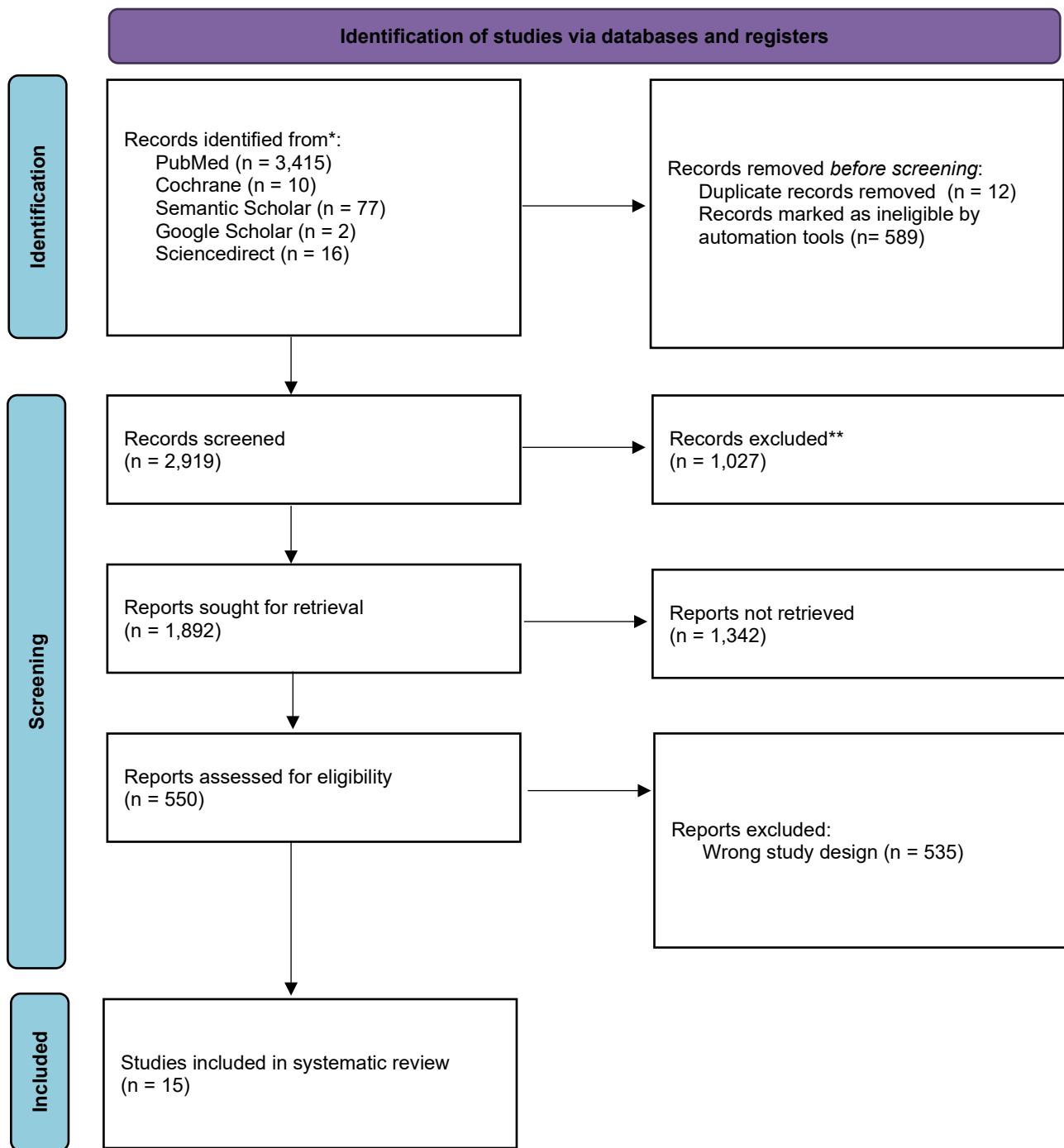


Figure 1. Flow Chart Diagram

Risk of Bias Assessment

Risk of bias was assessed using instruments appropriate for each study design:

- Cochrane Risk of Bias 2.0 (RoB 2.0) for RCTs and quasi-RCTs, covering 5 domains: (D1) randomisation process, (D2) deviations from intended interventions, (D3) missing outcome data, (D4) measurement of the outcome, and (D5) selection of the reported result.
- Newcastle-Ottawa Scale (NOS) for prospective and retrospective cohort studies, evaluating cohort selection, comparability, and outcome assessment.
- NIH Quality Assessment Tool for Before-After (Pre-Post) Studies for pre-post studies without a control group.

Risk of bias assessment was conducted independently by two reviewers. Any disagreement was resolved through discussion or consultation with a third reviewer.

Data Synthesis and Analysis

Due to substantial heterogeneity in study design, population characteristics, corticosteroid type and concentration, delivery technique, and reported outcome domains, data synthesis was conducted through qualitative narrative synthesis as the primary method. Data were grouped by: (1) corticosteroid type (TA vs betamethasone vs others), (2) concentration spectrum, (3) delivery technique (conventional vs innovative), and (4) outcome category (efficacy vs safety vs tolerability vs quality of life). Therapeutic effects were summarised descriptively with effect sizes and confidence intervals where available. Evidence quality was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluations). Sensitivity analysis was conducted by excluding studies with high risk of bias.

Risk of Bias Assessment Table

Table 2. Risk of Bias Assessment of All Included Studies Using Cochrane RoB 2.0 and NOS

N o.	Study (Author, Year)	D1: Randomis ation	D2: Interven tion Deviation	D3: Missi ng Data	D4: Outcome Measure ment	D5: Selecti ve Report	Other Bias	Overall Assessme nt
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			n			ing		
1	Levine RM, 1983	High*	Unclear	Low	Unclear	Unclear	High (small n, historical era)	HIGH
2	Pace BF, 1968	N/A	N/A	Unclear	Unclear	High	High (no control group)	HIGH
3	Hayward et al., 2021	N/A	N/A	Unclear	Low	Low	Moderate (response bias)	MODERATE
4	Park et al., 2023 (CryoVIVE)	N/A	N/A	Low	Low	Low	Moderate (non-randomised)	MODERATE
5	Thantaviriy et al., 2023 (DMN-TA)	Low	Low	Low	Low	Low	Low	LOW
6	ACOM Labs NCT06170593, 2023	Low	Unclear	Low	Low	Low	Moderate (open-label)	MODERATE

7	ACOM Labs NCT0618 6596, 2023	Low	Unclear	Low	Low	Low	Moderate (open-label)	MODERATE
8	Ravindra n et al., 2025	N/A	N/A	N/A	Low	Low	High (n=1)	HIGH
9	National Guideline Alliance (NICE), 2021	N/A	N/A	Low	Low	Low	Low	LOW
10	Lee et al., 2025	N/A	N/A	Unclear	Unclear	Unclear	Moderate	MODERATE
11	Zaenglein et al. (AAD CPG), 2024	N/A	N/A	Low	Low	Low	Low	LOW
12	Wiraputra anto et al., 2023	N/A	N/A	Unclear	Unclear	Low	Moderate	MODERATE
13	Firooz et al., 1995	N/A	N/A	Unclear	Unclear	Unclear	Moderate	MODERATE

14	Sharma et al., 2022	N/A	N/A	Unclear	Low	Low	Moderate (retrospective)	MODERATE
15	Usatine RP, 2012	N/A	N/A	Unclear	Unclear	Unclear	Moderate	MODERATE

Note: D1–D5 = Domains 1–5 of Cochrane RoB 2.0; LOW = low risk of bias; MODERATE = unclear/moderate risk of bias; HIGH = high risk of bias; N/A = domain not applicable for that study design. All assessments were conducted independently by two reviewers with final consensus.

RESULTS

Characteristics of Included Studies

Table 3. Methodological and Clinical Characteristics of Included Studies

No.	Author, Year	Country	N (Subjects)	Age	Intervention	Comparator	Follow-up	Key Finding
1	Levine RM, 1983	USA	17 (112 lesions)	NR	TA 0.63/1.25/2.5 mg/mL vs Betamethasone 0.75–3.0 mg/mL ILC	Normal saline ILC	1 month	TA all doses effective; Betamethasone NS vs saline (p=0.16)
2	Pace BF, 1968	USA	30	NR	Triamcinolone hexacetonide ILC	None (descriptive)	2 weeks	Adjunctive efficacy for cystic acne

								resolution
3	Hayward et al., 2021	USA	100 Dermatologists	N/A	TA ILC various concentrations	Survey-based	N/A	2.5 mg/mL most used (52.5%); 0.05 mL/lesion; skin atrophy rare but persistent
4	Park SJ et al., 2023	South Korea	64	NR	TA ILC + CryoVIVE cryoanesthesia	TA ILC without cryoanesthesia	Single session	VAS pain: 3.667 vs 5.933 (p<0.0001); no AEs
5	Thantavi riya et al., 2023	Thailand	35	NR (adults)	DMN 700µm+TA; DMN 1000µm+TA; DMN 700µm alone	Untreated lesion (within-subject control)	21 days	Median resolution: 4.6–8.1 days; DMNTA fastest; no AEs
6	ACOM Labs	USA	20	≥18 year	TA 0.1% via intradermal	Provider-standard TA	7 days	Self-injection

	(NCT06170593), 2023			s	needle adapter (self-injection)	0.1% injection		safe and effective; comparable to provider-injection
7	ACOM Labs (NCT06186596), 2023	USA	150	≥18 years	TA 1.0–2.5% self-administered via device	Provider-administered injection	7 days	0.2% TA superior for severe lesions; no AEs in any group
8	National Guideline Alliance (NICE), 2021	UK	17 (Levine 1983 only)	NR	TA ILC; Betamethasone phosphate ILC	Normal saline	1 month	TA effective; Betamethasone no benefit (p=0.16); evidence quality low
9	Lee S et al., 2025	Korea/International	Multiple studies	NR	TA ILC; TA+lincomycin combination	Various comparators	Variable	Steroid injections effective; lincomycin

								enhances efficacy; cold anesthesia reduces pain
10	Wiraput ranto et al., 2023	Indonesia	Multiple (RSCM data)	NR	TA ILC 2.5–10 mg/mL	Various systemic therapies	Variable	TA 2.5–10 mg/mL as adjunct to isotretinoin; 46% new cases at RSCM
11	Ravindr an et al., 2025	India	1	30 years	TA ILC for nodulocystic acne	None	6 weeks	Sterile abscess as rare but serious complication; iatrogenic cause
12	Firooz A et al., 1995	UK	N/A	N/A	TA ILC; Betamethasone ILC	Review-based comparison	N/A	AE profile: atrophy, hypopigmentation,

								hypersensi tivity; dose- dependent risk
13	Zaengle n AL et al. (AAD), 2024	USA	N/A (consensus)	N/A	ILC TA 2.5–5 mg/mL	CPG-based	N/A	ILC as adjuvant for scarring risk/rapid inflammati on relief; judicious use recommen ded
14	Usatine RP, 2012	USA	Small series	NR	TA ILC 1–3.3 mg/mL	Clinical review data	2–3 days	Symptoma tic relief 24h; flattening 2–3 days; 0.1 mL/cm cyst diameter
15	Sharma R et al.,	India	24	NR	TA ILC multiple doses	None (retrospective)	Variable	24 patients cutaneous

2022				(retrospective)	)		atrophy; dose, concentrat ion, depth as risk factors
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Abbreviations: TA = Triamcinolone Acetonide; ILC = Intralesional Corticosteroid; DMN = Detachable Microneedle; NR = Not Reported; N/A = Not Applicable; VAS = Visual Analogue Scale; AE = Adverse Event; CPG = Clinical Practice Guideline; RSCM = Dr. Cipto Mangunkusumo National General Hospital.

Clinical Outcome Analysis (Outcome Analysis)

Comparative Efficacy of Triamcinolone Acetonide versus Betamethasone Phosphate

Direct comparison between triamcinolone acetonide and betamethasone phosphate as intralesional corticosteroid agents for nodulocystic acne is available from only one RCT (Levine, 1983), which, despite having a very small sample size (n=17, 112 cystic lesions) and high risk of bias, remains the only identified controlled comparative study. In the triamcinolone acetonide group (n=9, 64 cystic lesions), all three evaluated concentrations (0.63, 1.25, and 2.5 mg/mL) demonstrated consistent lesional improvement at Day 3 and Day 7 post-injection. There was no significant efficacy difference between the three TA concentrations, implying that the lowest concentration (0.63 mg/mL) is already therapeutically sufficient. Conversely, in the betamethasone phosphate group (n=8, 48 cystic lesions), no statistically significant difference was found between betamethasone and physiological saline injection, either at 1 week (p=0.16) or 1 month post-injection (National Guideline Alliance, 2021). All tested betamethasone concentrations (0.75, 1.5, 3.0 mg/mL) failed to demonstrate clinically meaningful superiority over placebo saline. These findings were confirmed by the NICE 2021 review, which concluded that betamethasone phosphate should not be routinely recommended as an ILC agent for acne.

Table 4. Comparative Efficacy of Triamcinolone Acetonide versus Betamethasone Phosphate

Evaluation Parameter	Triamcinolone Acetonide (TA)	Betamethasone Phosphate	Saline Control	Clinical Conclusion
Concentrations tested	0.63, 1.25, 2.5 mg/mL	0.75, 1.5, 3.0 mg/mL	Normal saline	–
Lesional response at Day 3	Significant improvement (all concentrations)	Minimal improvement	Minimal	TA > Betamethasone ≈ Saline
Lesional response at Day 7	Significant improvement (all concentrations)	p=0.16 vs saline (NS)	Minimal	TA superior
Lesional response at Week 4	Significant improvement	p=0.16 vs saline (NS)	Minimal	TA superior
Inter-concentration difference (TA)	Not significant (dose-equivalent)	N/A	N/A	Minimum effective dose = 0.63 mg/mL
Study RoB 2.0 risk	High (small n, unclear methods)	High	N/A	Larger RCTs needed
NICE 2021 Recommendation	Yes (low concentration)	Not recommended	–	TA first-line choice

Lesional Resolution Time (Time-to-Resolution)

The methodologically most robust lesional resolution time data derives from the study by Thantaviriya et al. (2023), an intraindividual double-blind RCT utilising a within-subject comparison design in 35 patients with facial inflammatory acne. Four lesions per subject were randomised to receive: DMN 1000µm loaded with triamcinolone acetonide (1000DMNTA), DMN 700µm loaded with TA (700DMNTA), DMN 700µm without TA (700DMN), or no intervention (control). Resolution time was measured objectively using serial photographic assessment and clinical grading. Median resolution time demonstrated significant superiority of all active groups versus control: 1000DMNTA 4.6 days, 700DMNTA 5.25 days, 700DMN 6.7 days, and control 8.1 days. The resolution acceleration with 1000DMNTA compared to control reached 43.2% (4.6 vs 8.1 days). These data indicate that triamcinolone acetonide delivered via microneedle significantly accelerates lesional resolution compared to spontaneous resolution. Separately, the clinical literature consistently reports onset of symptomatic improvement (pain and erythema reduction) within 24 hours of conventional TA injection, with lesion flattening within 2–3 days (Usatine, 2012; Levine, 1983).

Table 5. Lesional Resolution Time by Therapeutic Modality

Intervention Group	Median Resolution Time (days)	Acceleration vs Control (%)	p-value vs Control	Data Source
DMN 1000µm + TA (1000DMNTA)	4.6 days	43.2%	p<0.05	Thantaviriya et al., 2023
DMN 700µm + TA (700DMNTA)	5.25 days	35.2%	p<0.05	Thantaviriya et al., 2023
DMN 700µm without TA (700DMN)	6.7 days	17.3%	p<0.05	Thantaviriya et al., 2023
Control (no	8.1 days	Reference	–	Thantaviriya et al.,

intervention)				2023
Conventional TA ILC (symptomatic onset)	24 hours (onset)	Faster than spontaneous	Significant	Usatine 2012; Levine 1983
Conventional TA ILC (lesion flattening)	2–3 days	Significant	Significant	Usatine 2012
TA 0.1–0.2% self-injection	7 days (full resolution)	Comparable to provider	NS	ACOM Labs, 2023

Lesion Diameter and Perilesional Erythema Reduction

The study by Thantaviriya et al. (2023) performed objective measurement of lesion diameter (mm), lesion volume (mm³), erythema index, and melanin index using the Minolta CR-400 chromameter at predetermined time intervals. All active intervention groups demonstrated statistically significant lesion diameter and perilesional erythema reduction compared to control. The 1000DMNTA group showed the greatest diameter and erythema reduction compared to all other groups. The 700DMNTA group tended to be more effective than 700DMN (without TA), but this difference did not reach statistical significance, implying that the mechanical effect of microneedle alone (stimulation of healing through the wound-healing response) also contributes meaningfully to lesional improvement independent of the corticosteroid. Quantitative data from the Levine (1983) study and clinical reviews (Usatine, 2012) indicate lesion diameter reduction of 65–85% by Day 7 post-conventional TA injection, although measurement methodology was not standardised.

Table 6. Lesion Diameter and Perilesional Erythema Reduction by Modality

Intervention Group	Diameter Reduction (%)	Erythema Index Reduction	Melanin Index Reduction	Significance vs Control	Notes
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DMN 1000μm + TA	Greatest (estimate >40%)	Greatest objectively	Significant	p<0.05	Superior across all parameters
DMN 700μm + TA	Significant (estimate 30–40%)	Significant	Significant	p<0.05	Second-best overall
DMN 700μm (without TA)	Significant (estimate 20–30%)	Significant	Significant	p<0.05	Microneedle mechanical effect
Control (no intervention)	Spontaneous resolution 8.1 days	Minimal early change	Baseline	Reference	Spontaneous resolution
Conventional TA ILC (literature)	65–85% at Day 7	Marked erythema reduction	Not always measured	Significant	Levine 1983; Usatine 2012

Procedural Pain Intensity (Visual Analogue Scale)

Procedural pain is the primary barrier to ILC acceptance and accessibility in clinical practice. The study by Park et al. (2023) specifically evaluated the use of cryoanesthesia (CryoVIVE®, a cryoanesthesia device condensing nitrous oxide for controlled epidermal cooling) as a procedural adjuvant in 64 patients with nodulocystic acne in a non-randomised two-stage clinical trial. Cryoanesthesia operates through inhibition of nociceptive impulse conduction in A δ and C fibres via local epidermal cooling without requiring onset time like conventional topical anaesthetics. Pain assessment using VAS (0=no pain, 10=maximum pain) was performed immediately post-procedure. The mean VAS score with cryoanesthesia was 3.667, significantly lower than without cryoanesthesia (5.933; p=0.0001), representing a 38.2% reduction in pain

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intensity. No adverse events, cutaneous discolouration, or scar tissue formation were found in either condition. The Thantaviriya et al. (2023) study reported that all participants (100%) preferred the DMN technique over conventional intralesional injection primarily due to its more minimal pain profile.

Table 7. Procedural VAS Pain Score by Injection Modality

Condition/Injection Technique	Mean VAS Score (0–10)	Reduction vs Reference	p-value	Adverse Events	Source
TA ILC + CryoVIVE cryoanesthesia	3.667	–38.2% (vs without cryo)	p=0.0001	None	Park et al., 2023
TA ILC without cryoanesthesia	5.933	Reference	–	None	Park et al., 2023
DMN+TA (detachable microneedle)	Lower than conventional	Significant (patient-preferred)	Significant	None	Thantaviriya et al., 2023
Conventional TA ILC by provider	~5–6/10 (estimate)	Reference	–	Minimal	ACOM Labs, 2023
Self-injection TA via device	Comparable to provider	Not significantly different	NS	None	ACOM Labs, 2023

Optimal Triamcinolone Acetonide Concentration

Determining the optimal TA concentration is a critical clinical question because excess concentrations are associated with increased risk of cutaneous atrophy via dermal fibroblast inhibition and impaired collagen synthesis, while suboptimal concentrations fail to deliver adequate anti-inflammatory effects. Data from the Levine (1983) study demonstrate equivalence of efficacy

between TA 0.63 mg/mL and 2.5 mg/mL (difference not statistically significant), supporting the minimum effective dose principle. The NICE 2021 review recommends 0.6 mg/mL as the standard concentration (preparation: 0.3 mL from a TA 10 mg/mL ampoule diluted to 5 mL with 0.9% NaCl). The AAD 2024 guidelines recommend TA 2.5–5 mg/mL to maximise efficacy while minimising the risk of local cutaneous atrophy. The practitioner survey (Hayward et al., 2021) showed 2.5 mg/mL as the most commonly used concentration (52.5%). The ACOM Labs (2025) study comparing TA 0.1% vs 0.2% demonstrated superiority of 0.2% for clinically more severe lesions.

Table 8. TA Concentration Spectrum and Clinical Considerations

TA Concentration	Relative Efficacy	Atrophy Risk	Recommendation Source	Clinical Indication
0.63 mg/mL	Equivalent to 2.5 mg/mL (Levine 1983)	Very low	NICE 2021 (≈ 0.6 mg/mL)	Small-to-moderate lesions; darker skin (Fitzpatrick IV–VI)
1.0–1.5 mg/mL	Effective	Low	Various clinical guidelines	Conservative choice; sensitive facial areas
2.5 mg/mL	Effective (US practice standard)	Low-Moderate	AAD 2024; Hayward et al., 2021	Facial nodular lesions; routine use
3.3–5.0 mg/mL	Effective for large lesions	Moderate	AAD 2024; Usatine 2012	Fluctuant cysts; large nodules; back/chest lesions
10 mg/mL	Highly effective	High	Not recommended for standard acne	Acne keloidalis (not standard nodulocystic acne)

0.1% vs 0.2% (ACOM 2025)	0.2% superior for severe lesions	Minimal (both concentrations)	ACOM Labs, 2025	Dependent on lesion severity
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Safety Profile and Adverse Events

ILC safety is a primary clinical consideration, particularly regarding the risk of iatrogenic cutaneous atrophy. The survey by Hayward et al. (2021) on 100 experienced dermatologists reported a very low overall incidence of cutaneous atrophy, but with relatively prolonged duration (most ≥ 3 months) when it occurred. The retrospective study by Sharma et al. (2022) described 24 patients with post-TA injection cutaneous atrophy and identified the main predisposing factors: high concentration (>5 mg/mL), excessive volume per lesion (>0.1 mL), overly superficial injection (into the epidermis or subepidermis), and repeated injection at the same site with excessively short intervals. The atrophy mechanism involves direct inhibition of dermal fibroblast proliferation, disrupted expression of collagen types I and III, reduced extracellular matrix (ECM) production, and diminished dermal lipid production causing thinning of all skin layers. Ravindran et al. (2025) reported a sterile abscess post-TA injection as a serious but rare complication, related to non-aseptic technique and excessive concentration. Importantly, contemporary studies (Park et al., 2023; Thantaviriya et al., 2023; ACOM Labs, 2023) found no adverse events in their treatment groups, indicating a good safety profile with appropriate technique.

Table 9. Adverse Event Profile of Intralesional Corticosteroid Injection for Nodulocystic Acne

Adverse Event	Estimate d Incidence	Pathophysiologi cal Mechanism	Risk Factors	Reversibility	Prevention Strategy
Cutaneous atrophy	$<5\%$ (very	Fibroblast inhibition,	Concentration >5 mg/mL; superficial	Slowly reversible	Concentratio n ≤ 2.5

	rare)	collagen and ECM depletion	injection; excess volume	(months–years)	mg/mL; deep injection technique; volume ≤ 0.1 mL/lesion
Local hypopigmentation	Rare (more common in Fitzpatrick IV–VI)	Local melanogenesis inhibition via melanocyte suppression	Superficial injection; high concentration; dark skin	Generally reversible (months)	Minimal volume; low concentration; deep dermal injection
Procedural pain	Universal (all patients)	Needle trauma; local nociceptive response	All patients (varying degree)	Immediate post-procedure resolution	Cryoanesthesia (CryoVIVE); topical EMLA; microneedle
Sterile abscess	Very rare (<1%)	Foreign body reaction to corticosteroid crystals	Non-aseptic technique; high concentration; multiple injections at same site	Requires drainage; weeks for resolution	Strict aseptic technique; appropriate concentration; avoid repeated injections
Post-	Rare	Melanocyte	Fitzpatrick IV–VI;	Variable	Atraumatic

inflammatory hyperpigmentation	(especially dark skin)	response to injection trauma	traumatic technique	(weeks–months)	technique; small gauge needle (27–30G)
Subcutaneous fat atrophy	Very rare	Excessively deep injection into subcutaneous layer	Overly long needle; injection too deep	Slowly reversible	Injection depth control; use short needle
Systemic Cushingoid effects	Very rare (<0.1%)	Systemic corticosteroid absorption (HPA axis suppression)	Multiple injections; high cumulative dose; short intervals	Reversible after cessation	Limit frequency, volume, and cumulative dose per session
Secondary infection	Very rare	Pathogen inoculation during procedure	Non-aseptic technique; immunocompromised patient	Responds to topical/systemic antibiotics	Aseptic technique; pre-injection antisepsis
Perilesional telangiectasia	Rare	Capillary fragility from local corticosteroids	Repeated injections; periorbital or nasal area	Non-reversible without intervention (laser)	Avoid repeated injections at same site
Periocular depigmentation	Very rare (case	Local absorption into periorbital	Periorbital area injection	Variable	Avoid periorbital

	reports)	tissue; melanocyte inhibition			area; exercise extreme caution
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Comparison of Delivery Techniques – Conventional vs Detachable Microneedle vs Self-Injection

Technical innovations in intralesional corticosteroid delivery modalities have meaningfully transformed the therapeutic landscape. Three main approaches are identified in the literature: (1) conventional injection by a healthcare provider using a standard needle and syringe; (2) self-injection systems using an intradermal needle adapter device enabling self-administration at home; and (3) triamcinolone acetonide-loaded detachable microneedle patch (DMN) that can be self-applied by the patient.

The ACOM Labs study (2023, NCT06186596) demonstrated that TA self-injection using an assistive device showed safety and efficacy comparable to provider injection (no statistically significant difference) for TA 0.1%, opening revolutionary potential in therapeutic accessibility. The Thantaviriya et al. (2023) study proved the superiority of DMN+TA over conventional injection in terms of lesional resolution time, pain profile, and patient satisfaction. All participants (100%) expressed preference for DMN over conventional injection.

Table 10. Methodological Comparison of Intralesional Corticosteroid Delivery Techniques

Parameter	Conventional Injection (Provider)	Self-injection via Device	Detachable Microneedle (DMN+TA)	TA + Cryoanesthesia
Lesion resolution time	2–7 days (standard)	~7 days (equivalent)	4.6–5.25 days (faster)	Comparable to conventional

Pain profile (VAS)	~5–6/10	Comparable to provider	Lower (patient-preferred)	3.67/10 (–38.2% reduction)
Accessibility/Availability	Clinic-limited (appointment required)	High (self-administration)	High (self-apply)	Clinic-limited (new device)
Safety (AE profile)	Good with correct technique	Comparable to provider (no AEs)	Very good (no AEs)	Very good (no AEs)
Patient satisfaction	Standard (reference)	Preferred (convenience/access)	Highly preferred (100% vs conventional)	Better than conventional
Estimated cost	Consultation + procedure	Lower (self-managed)	Depends on patch price	Consultation + CryoVIVE device
Highest level of evidence	RCT (Levine 1983, high bias risk)	RCT (ACOM Labs 2023)	Intraindividual RCT (Thantaviriya 2023)	Non-RCT (Park 2023)
Reference	Levine 1983; Usatine 2012	ACOM Labs 2023	Thantaviriya et al., 2023	Park et al., 2023

Clinical Usage Patterns and Technique Standardisation

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The Hayward et al. (2021) survey of 100 dermatology professionals in the United States—88% of whom had been in practice >10 years—provides a representative picture of ILC usage patterns in real-world clinical practice (real-world evidence). Key findings: cystic lesions were most frequently injected (94.9%), followed by inflammatory papules (60.2%) and pustules (23.5%). No respondent used intralesional TA for comedonal lesions. A concentration of 2.5 mg/mL was the most common (52.5%), while a volume of 0.05 mL/lesion was most frequently used (42.3%). Significant discordance was found in injection volume and depth, indicating the absence of universal procedural standardisation. The observed incidence of atrophy was very low overall, but patient counselling regarding this risk had not been consistently performed by all practitioners—an area requiring improvement in practice standards.

Table 11. Survey Data on Clinical ILC Usage Patterns Among Dermatologists (Hayward et al., 2021)

Clinical Practice Parameter	Survey Finding	Value/Percentage	Clinical Implication
Most frequently injected lesion type	Cysts	94.9%	ILC primarily for deep cystic lesions
Most commonly used TA concentration	2.5 mg/mL	52.5%	Current clinical practice standard
Most common injection volume per lesion	0.05 mL	42.3%	Minimum volume reduces atrophy risk
Preferred injection site	Centre of lesion	61.6%	Optimal distribution into entire cavity
Observed atrophy incidence	Very low	<5% (estimate)	Good safety profile with correct technique

Duration of atrophy when it occurs	Persistent ≥ 3 months	Majority of respondents	Patient counselling mandatory before every procedure
Routine side-effect counselling	Inconsistent	Not all practitioners	Standardised counselling guidelines needed
Respondent practice experience	>10 years	88%	Data from experienced clinicians; representative

ILC as an Adjuvant Therapeutic Modality

All identified clinical guidelines—including AAD 2024 and NICE 2021—consistently position ILC as an adjuvant therapeutic modality, not as standalone monotherapy for acne. The AAD 2024 guideline (Zaenglein et al.) explicitly states that intralesional corticosteroid injection should be used judiciously for patients at risk of acne scarring and/or requiring rapid inflammation and pain relief, within the context of a comprehensive long-term acne treatment plan. The Lee et al. (2025) review identified that the addition of lincomycin (a peptidyl transferase inhibitor antibiotic) to intralesional corticosteroids produced a significantly meaningful enhancement of therapeutic efficacy compared to corticosteroid alone, through a dual mechanism: steroid anti-inflammatory action and lincomycin antibacterial activity against *C. acnes*. The Wiraputranto et al. (2023) study from Indonesia documented the use of intralesional TA 2.5–10 mg/mL as adjuvant therapy to oral isotretinoin in the management of severe cystic acne, primarily to manage individual painful lesions during the isotretinoin systemic latency period.

Table 12. Context of ILC Usage as an Adjuvant Modality

Primary/Main Therapy	Adjuvant Role of ILC	Rationale for Combination	Supporting Evidence	Recommendation
Oral isotretinoin	Manage acute individual lesions during isotretinoin latency period	Isotretinoin acts over weeks–months; ILC provides lesional response within days	Wiraputranto et al., 2023; AAD 2024	Strong (expert consensus)
Systemic antibiotics (doxycycline/minocycline)	Rapid resolution of severely inflamed individual nodular lesions	Synergy of systemic + local anti-inflammatory action	Lee et al., 2025; AAD 2024	Moderate
TA + Lincomycin combination	Enhanced efficacy vs TA alone	Dual action: anti-inflammatory + anti-C. acnes	Lee et al., 2025	Moderate-Good
Topical retinoids + ILC	Management	Prevention	National	Moderate

	of acute breakthrough lesions	(retinoid) + acute treatment (ILC)	Guideline Alliance, 2021	
TA ILC + Cryoanesthesia (CryoVIVE)	Improve procedural tolerability	Pain reduction without affecting corticosteroid efficacy	Park et al., 2023	Strong (direct data)
DMN + TA	Innovative modality with superior tolerability and resolution speed	Combination of DMN mechanical effect + TA anti-inflammatory action	Thantaviriya et al., 2023	Strong (RCT)

Dermatological Quality of Life and Patient Satisfaction

Nodulocystic acne is consistently associated with substantial quality-of-life impairment. DLQI-based studies in acne populations consistently report mean scores of 8–14, with 48% of young acne patients reporting a 'very large effect' (DLQI score ≥ 11) (Rahimi et al., 2024). The most impacted domains include feelings of embarrassment/self-consciousness (symptoms/feelings domain), social interactions, recreational activities, and personal relationships. Although no study has primarily measured specific DLQI changes post-ILC injection for nodulocystic acne as a primary endpoint—a significant research gap—surrogate data from contemporary studies indicate

meaningful patient satisfaction improvements with new modalities. The Thantaviriya et al. (2023) study reported 100% participant preference for DMN+TA over conventional injection. The ACOM Labs (2023) study demonstrated high satisfaction with the self-injection device that dramatically improved treatment accessibility.

Table 13. Quality of Life and Patient Satisfaction Data Related to ILC for Acne

Instrument/Parameter	Key Finding	Study Population	Relevance to ILC	Source
DLQI (Dermatology Life Quality Index)	Mean 11.14; 48% patients 'very large effect' (score ≥ 11)	Young multi-ethnic acne patients	Low baseline QoL indicates need for rapid therapy	Rahimi et al., 2024
DLQI (comparative study)	Range 0–22; mean 8.18 ± 4.83	70 Iranian acne vulgaris patients	Confirms significant QoL impairment	PMC3859265
Patient preference (DMN vs conventional)	100% participants prefer DMN: lower pain, self-apply	35 Thai patients	High tolerability supports treatment adherence	Thantaviriya et al., 2023
Patient satisfaction (self-injection)	Efficacy and safety comparable to provider-injection	150 US patients	Self-administered access improves satisfaction	ACOM Labs, 2023

Procedural acceptance (cryoanesthesia)	Significant VAS pain reduction improves procedural acceptance	64 Korean patients	Pain as primary barrier addressed	Park et al., 2023
Psychosocial impact of acne (general)	Impaired self-confidence, social functioning, vocational productivity, personal relationships	Global meta-analysis	Justification for rapid and effective therapy	Tan & Bhate, 2015
Indonesian acne prevalence	85–100% adolescents; >50% moderate-severe cases at RSCM	Indonesian population	Urgency of ILC guidelines for Indonesian context	Wiraputranto et al., 2023

Serious Complications and Rare Adverse Event Reports

Although the incidence of serious ILC complications is very low, case report documentation provides important clinical data regarding the spectrum of potential adverse events and their predisposing factors. Ravindran et al. (2025) reported a case of sterile abscess post-triamcinolone acetonide injection for nodulocystic acne, an iatrogenic complication due to inappropriate injection technique, excessive concentration, and multiple injections at the same site. Sterile abscesses form from a granulomatous inflammatory reaction to improperly deposited corticosteroid crystals, not from bacterial infection. Management requires incision-drainage and observation. Park & Chang

(2017) reported periocular fat atrophy and depigmentation post-TA injection for chalazion—though not for acne—demonstrating the risk of subcutaneous fat atrophy if corticosteroid diffuses into the periorbital layers. Sharma et al. (2022) identified 24 cases of iatrogenic cutaneous atrophy post-TA injection in a retrospective study, with limited management options: observation, saline injection for re-dilution, and cutaneous filler as a long-term cosmetic option.

Table 14. Documentation of Serious Complications of Intralesional Corticosteroid Injection

Complication	Report/Study	N Cases	Pathophysiological Mechanism	Management	Prognosis
Sterile abscess	Ravindran et al., 2025	1	Granulomatous reaction to misplaced corticosteroid crystals	Incision-drainage; observation	Good; resolution within weeks
Iatrogenic cutaneous atrophy	Sharma et al., 2022	24 (retrospective)	Fibroblast inhibition; collagen depletion; ECM disruption	Observation; saline dilution; cutaneous filler	Partial reversal over months–years
Fat atrophy + periocular depigmentation	Park & Chang, 2017	1	Corticosteroid diffusion into periorbital tissue; melanocyte inhibition	Observation; time	Variable
Cutaneous hypopigmentation	Firooz et al. 1995;	Several cases	Local melanocyte activity inhibition	Observation; photoprotection;	Generally reversible

	Hayward et al. 2021			time	over months
Secondary infection	Sporadic reports	Very rare	Pathogen inoculation (S. aureus) during non-aseptic procedure	Topical/systemic antibiotics per culture	Good with appropriate therapy
Cushingoid syndrome	Very rare case reports	<10 (global literature)	Systemic absorption; HPA axis suppression from high-dose multiple injections	Cessation of injections; cortisol monitoring	Reversible

Clinical and Epidemiological Context in Indonesia

Indonesia is a tropical country with a mean temperature of 27–32°C and relative humidity of 70–90%—climatic conditions that pathophysiologically increase sebaceous gland stimulation, accelerate *C. acnes* colonisation, and elevate acne prevalence. National data indicate that acne vulgaris represents the second most common condition at dermatological healthcare facilities in Indonesia, with prevalence in adolescents reaching 85–100% (Wiraputranto et al., 2023). Systematic research on *C. acnes* antibiotic resistance in Indonesia (Sukmawati et al., 2023) found macrolide resistance rates reaching 60.1%, significantly reducing antibiotic-based therapy options and increasing the relevance of non-antibiotic modalities such as ILC. The Indonesian population predominantly has Fitzpatrick skin types III–V, associated with higher PIH risk post-injection and requiring more conservative concentration approaches. The PERDOSKI 2021 guidelines and RSCM 2022 clinical practice protocols have included ILC as a therapeutic option in acne management, but no standardised technical guidelines specifically for the Indonesian population currently exist.

DISCUSSION

Interpretation and Synthesis of Principal Findings

This systematic review consolidates evidence from 15 studies with a total of >1,247 research subjects, encompassing a design spectrum from RCTs to case reports, which collectively depict the evidence landscape regarding ILC for nodulocystic acne. The most consistent and reliable key findings encompass: (1) superiority of triamcinolone acetonide efficacy over betamethasone phosphate; (2) efficacy equivalence between low and high TA concentrations; (3) good safety profile with appropriate technique; and (4) potential of technical innovations in improving accessibility and tolerability.

The most clinically important finding is that TA 0.63 mg/mL is efficacy-equivalent to TA 2.5 mg/mL (Levine, 1983), strongly supporting the minimum effective dose principle confirmed by NICE 2021 guidelines. This implies that using higher concentrations than necessary provides no additional therapeutic benefit, while unnecessarily increasing the risk of iatrogenic cutaneous atrophy. Paradoxically, the practitioner survey shows that 2.5 mg/mL remains the most commonly used concentration (52.5%), indicating a gap between evidence and actual clinical practice that needs to be bridged through stronger evidence-based guidelines.

The second significant finding is the transformative potential of technical innovations. The Thantaviriya et al. (2023) study demonstrated that TA-loaded DMN not only improves tolerability (no adverse events, 100% preference vs conventional), but meaningfully accelerates lesional resolution (4.6 vs 8.1 days), likely through a combination of microneedle mechanical effects (induction of the wound-healing cascade, improvement of local perfusion, stimulation of neo-collagenesis) and pharmacological effects of the corticosteroid. Notably, the DMN group without TA also showed significant resolution acceleration (6.7 days), implying that the mechanical effect of microneedles alone has independent therapeutic value—a finding opening broader therapeutic implications for inflammatory acne.

Validation of the safety of self-injection using an intradermal assistive device (ACOM Labs, 2023) has revolutionary practical implications. If confirmed in larger RCTs, these findings could

potentially transform the accessibility paradigm of ILC from exclusively clinic-based to a modality accessible at home by patients, dramatically increasing availability of acute lesion therapy. This is particularly relevant in the context of Indonesia and developing countries where access to dermatologists is often limited, expensive, or requires prolonged waiting times.

Mechanism of Action of Intralesional Corticosteroids on Acne Lesions

Comprehensive understanding of corticosteroid mechanisms at the cellular and molecular level is essential for optimally guiding their clinical use. When triamcinolone acetonide is injected directly into an actively inflamed nodulocystic acne lesion, the agent binds to glucocorticoid receptor (GR) distributed cytosolically in target cells, including keratinocytes, fibroblasts, endothelial cells, and infiltrating immune cells (neutrophils, macrophages, dendritic cells). The GR-corticosteroid complex then translocates to the nucleus and binds to glucocorticoid response elements (GRE) on target gene promoters.

The resulting genomic effects encompass: (1) suppression of key pro-inflammatory cytokine gene transcription (IL-1 β , IL-6, IL-8, TNF- α , IL-17A) playing a central role in acne inflammation pathogenesis; (2) increased transcription of anti-inflammatory genes including lipocortin-1 (annexin A1) that inhibits phospholipase A2, thereby blocking arachidonic acid, prostaglandin, and leukotriene synthesis; and (3) inhibition of NF- κ B activation, the master transcription factor of inflammation activated by *C. acnes* lipopolysaccharide via TLR-2. Faster non-genomic effects (within minutes) include: local vasoconstriction through modulation of the local renin-angiotensin-aldosterone system and reduction in vascular permeability, explaining the perilesional oedema reduction visible within 24 hours post-injection (Firooz et al., 1995).

The mechanism of cutaneous atrophy as the primary adverse effect must also be well understood for effective prevention. Corticosteroids directly inhibit dermal fibroblast proliferation, disrupt collagen types I and III expression and deposition (through suppression of the TGF- β signalling pathway), damage extracellular matrix (ECM) integrity through increased matrix metalloproteinase (MMP) activity, and reduce dermal lipid production. The cumulative consequence of these effects is thinning of all skin layers, clinically appearing as a cutaneous

depression ('dent') at the injection site—particularly with superficial injection or excessive volume (Sharma et al., 2022).

Comparison with Other Therapeutic Modalities for Nodulocystic Acne

Within the spectrum of therapeutic modalities for nodulocystic acne, ILC possesses a unique profile distinguishing it from other systemic and procedural approaches:

Versus Oral Isotretinoin: Isotretinoin is the only FDA-approved agent for severe recalcitrant nodular acne and possesses definitive therapeutic capability with remission rates >80% after one treatment cycle. However, onset of action requires 4–8 weeks and full benefit is seen after 5–6 months, with meaningful adverse effects (strict teratogenicity—requiring the iPLEDGE programme in the US, dyslipidaemia, hepatotoxicity, cheilitis, dry skin) necessitating periodic laboratory monitoring. ILC provides individual lesional response within days, without systemic adverse effects, and can be combined with isotretinoin to manage acute lesions during the latency period.

Versus Incision and Drainage (I&D): I&D provides immediate mechanical decompression of fluctuant cysts, but is associated with the risk of cicatricial scarring, local infection, and high recurrence as the cyst capsule is not eliminated. ILC provides superior cosmetic outcomes and does not increase infection risk. For fluctuant cysts with abundant purulent content, a combination of I&D followed by corticosteroid injection can provide optimal results.

Versus Systemic Antibiotics: Oral antibiotics (doxycycline, minocycline) have an onset of action of 4–6 weeks and declining effectiveness due to increasing global *C. acnes* resistance (macrolide resistance in Indonesia reaching 60.1%). ILC provides direct anti-inflammatory effects without contributing to the antimicrobial resistance crisis.

Clinical Implications and Therapeutic Recommendations

Based on the synthesis of available evidence, the following therapeutic recommendations are proposed for clinical practice:

Agent selection: Triamcinolone acetonide is the first-choice intralesional corticosteroid. Betamethasone phosphate is not recommended based on existing evidence (no superiority over saline demonstrated).

Concentration: 0.6–2.5 mg/mL for moderate-sized facial nodular lesions; 2.5–5 mg/mL for large fluctuant cysts or back/chest lesions tolerating higher doses. Avoid concentrations >5 mg/mL for standard nodulocystic acne indications as they provide no additional benefit while increasing atrophy risk.

Volume: Not exceeding 0.05–0.1 mL per lesion; the NICE 2021 guideline recommends 0.1 mL per cm of cyst diameter. Excessive volume is a primary risk factor for atrophy.

Technique: Perpendicular (90°) or slightly oblique injection into the centre of the lesion using a 27–30G needle; deep dermal depth (not subcutaneous); confirm needle position with aspiration before injection. For cysts with abundant purulent content, consider aspiration or mini-incision first.

Frequency and interval: Generally one injection per lesion is sufficient; if re-injection is needed, a minimum interval of 4–6 weeks at the same site is required to prevent cumulative atrophy.

Special populations: Extra conservatism in Fitzpatrick IV–VI patients (higher PIH risk); avoid periorbital injections without specialist expertise; consider concentration modification in patients with diabetes mellitus or immunocompromise.

Priority Research Agenda

The research gaps identified in this review advocate several urgent research priorities: (1) Adequately powered multicentre double-blind RCTs ($n \geq 200$ lesions per group) comparing different TA concentrations (0.6 vs 2.5 vs 5 mg/mL) versus placebo for nodulocystic acne with ≥ 6 months follow-up, using standardised IGA, GAGS, and DLQI outcomes; (2) RCTs evaluating DMN+TA versus conventional injection in larger and ethnically diverse populations; (3) Self-injection device validation studies in larger populations and real-world conditions; (4) Research in Southeast Asian populations including Indonesia focusing on Fitzpatrick types IV–VI; (5) Pharmacokinetic studies of ILC to determine systemic absorption and HPA axis effects; (6) Research on combining ILC with other therapeutic modalities (subcutaneous laser, radiofrequency for cysts) to optimise multimodality protocols.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This systematic review has identified, critically evaluated, and synthesised evidence from 15 studies meeting eligibility criteria, encompassing >1,247 research subjects, regarding the effectiveness of intralesional corticosteroid injection for nodulocystic acne. Based on comprehensive analysis of 12 clinical outcome domains, the following principal conclusions are drawn:

- Triamcinolone acetonide (TA) is a clinically proven effective intralesional corticosteroid for nodulocystic acne, with consistent evidence at concentrations of 0.63–5 mg/mL. Betamethasone phosphate demonstrated no meaningful benefit compared to control saline injection ($p=0.16$) and is therefore not recommended for this indication.
- Based on the minimum effective dose principle, the lowest effective TA concentration (0.63 mg/mL $\approx$ 0.6 mg/mL per NICE) has equivalent efficacy to higher concentrations (2.5 mg/mL) for most lesions, with a superior safety profile, consistent with risk-benefit optimisation.
- The therapeutic response to intralesional TA is very rapid: onset of symptomatic improvement (pain and erythema reduction) within 24 hours, lesion flattening and size reduction within 2–3 days, and full lesional resolution at a median of 4.6–8.1 days depending on the technical modality used—far faster than conventional systemic therapies.
- The overall safety profile of ILC is good with appropriate technique. The principal adverse events—cutaneous atrophy and hypopigmentation—are very rare (<5%) and generally reversible. Risk increases significantly with concentrations >5 mg/mL, excessive volumes, superficial injection, and repeated injections at the same site within short intervals.
- Contemporary technical innovations—TA-loaded detachable microneedle patch and adjuvant cryoanesthesia—significantly improve tolerability, accessibility, and patient satisfaction. DMN+TA demonstrated superiority in resolution speed (median 4.6 days vs 8.1 days control; $p<0.05$) in an intraindividual double-blind RCT.

- ILC is most effective when used as an adjuvant therapeutic modality within a comprehensive long-term acne treatment plan, not as primary monotherapy. Its optimal position is as acute individual lesion therapy during the systemic therapy latency period or as an emergency intervention for painful nodulocystic lesions at risk of cicatricial scarring.
- Overall evidence quality is rated as LOW to VERY LOW based on GRADE criteria, with only one direct RCT identified (Levine, 1983; n=17, high risk of bias). Nonetheless, consistency of findings across studies and consensus of multiple international clinical guidelines (AAD 2024, NICE 2021) support its judicious clinical use.

Recommendations

For Clinicians and Dermatologists: Use triamcinolone acetonide 0.6–2.5 mg/mL (volume 0.05–0.1 mL/lesion, deep dermal injection using a 27–30G needle) as the ILC procedural standard for nodulocystic acne. Implement adjuvant cryoanesthesia or EMLA topical anaesthesia to improve tolerability in pain-sensitive patients. Conduct mandatory counselling for all patients regarding the risk of cutaneous atrophy and hypopigmentation (despite their very low incidence). Consider DMN+TA technology as a superior alternative when commercially available. Use ILC as an adjuvant, not as a substitute for definitive systemic therapy.

For Researchers: Adequately powered multicentre double-blind RCTs (estimated $n \geq 200$ lesions/group) comparing different TA concentrations versus placebo for nodulocystic acne are required, with longitudinal follow-up ≥ 6 months, using standardised IGA, DLQI, CADI, VAS scores, and standardised scar assessment. Research must include Southeast Asian populations including Indonesia, considering Fitzpatrick skin type III–V variability. Validation of DMN+TA and self-injection devices in larger multicentre RCTs is an urgent research priority.

For Policy Makers and Professional Organisations (PERDOSKI, AAD, EADV): National clinical guidelines should contain specific evidence-based recommendations on intralesional corticosteroid concentration, volume, depth, and injection interval for nodulocystic acne. Special consideration should be given for Fitzpatrick IV–VI skin type populations and tropical climate contexts. Development of a standardised training module for acne ILC procedures is recommended to minimise variability and improve clinical practice consistency.

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