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Review

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Review

The application of corticosteroids for pathological scar prevention and treatment: current review and update

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Abstract

The prevention and treatment of pathological scars remain challenging. Corticosteroids are the mainstay drugs in clinical scar prevention and treatment as they effectively induce scar regression and improve scar pruritus and pain. Currently, intralesional injections of corticosteroids are widely used in clinical practice. These require professional medical manipulation; however, the significant accompanying injection pain, repetition of injections and adverse effects, such as skin atrophy, skin pigmentation and telangiectasia, make this treatment modality an unpleasant experience for patients. Transdermal administration is, therefore, a promising non-invasive and easy-to-use method for corticosteroid administration for scar treatment. In this review, we first summarize the mechanisms of action of corticosteroids in scar prevention and treatment; then, we discuss current developments in intralesional injections and the progress of transdermal delivery systems of corticosteroids, as well as their corresponding advantages and disadvantages.

Key words: Corticosteroids, Pathological scar, Prevention and treatment, Transdermal drug delivery, Administration method

Highlights

- The mechanisms of action and administration routes of corticosteroids in pathological scar treatment are summarized.
- The advantages and disadvantages of different administration routes of corticosteroids are presented.
- Current progress in transdermal drug delivery systems of corticosteroids are described.

Background

Pathological scars (mainly hypertrophic scars and keloids) are fibroproliferative skin disorders resulting from abnormal skin repair following skin injury or infection. Prominent histological characteristics include excessive fibroblast proliferation and extracellular matrix (ECM) deposition [1,2]. Although not life-threatening, pathological scars may cause cosmetic disfigurement and functional impairments, in

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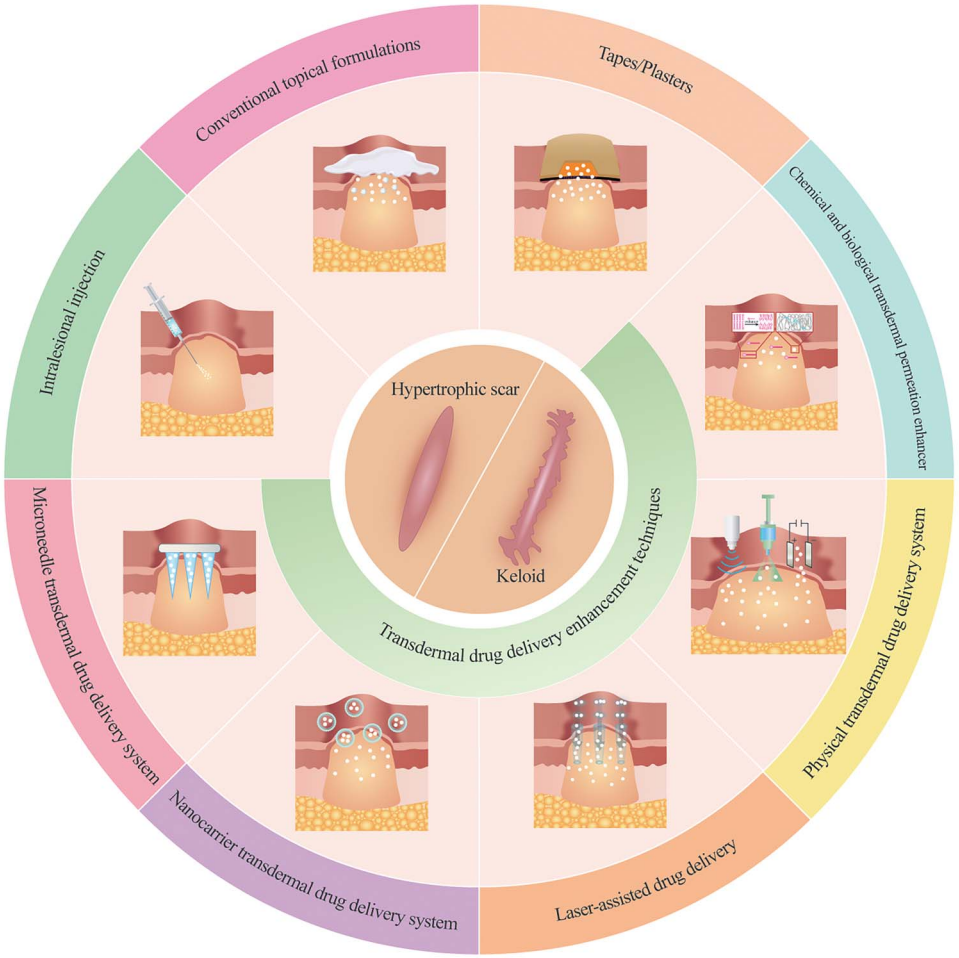


Figure 1. Schematic representation of clinical routes of corticosteroid administration summarized in this review

combination with subjective symptoms including pain and pruritus that significantly affect patients' quality of life. Current algorithms for the prevention and treatment of pathological scars include pharmacologic, pressure, photoelectric and radiation therapies and surgery. Corticosteroids are the mainstay of pharmacological therapy, and intralesional injection with a corticosteroid can induce pathological scar regression faster than an oral medicine used in scar treatment, such as tranilast (an antiallergic drug) [1,3–5]. The intralesional injection of corticosteroid is the most common method used in clinical practice that can achieve effective results for reduction of scar formation and volume, and relieve patients' subjective symptoms including pruritus and pain [6–8]. However, it requires physicians or nurses to perform repeat injections, accompanied by obvious injection pain, in addition to side effects such as skin atrophy, skin pigmentation or telangiectasia, making this treatment modality unpleasant for patients. Consequently, transdermal drug delivery, a non-invasive and simple procedure, is a promising administration method for scar treatment. Therefore, this review describes the mechanism of action of corticosteroids in the prevention and treatment of pathological scars and summarizes the characteristics of the different clinical routes of corticosteroid administration (Figure 1 and Table 1).

Review

Mechanism of action of corticosteroids in pathological scar prevention and treatment

The pathogenesis of pathological scars remains largely unclear, but involves abnormal proliferation and activity of fibroblasts, aberrant angiogenesis, and excessive ECM deposition caused by prolonged inflammation of the dermis [9,10]. The multiplicity of mechanisms of action of corticosteroids in scar prevention and treatment has been reported by studies as follows. (1) Anti-inflammatory effect: lipophilic corticosteroids bind to cytoplasmic glucocorticoid receptors to directly regulate gene expression at the transcriptional level by inducing and activating the anti-inflammatory protein lipocortin-1, which suppresses the activity of phospholipase A_2. Moreover, they inhibit the production of arachidonic acid and arachidonic acid-derived eicosanoids such as prostaglandins and leukotrienes. They also suppress

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Table 1. Summary of the characteristics of different corticosteroid administration routes

Administration route		Treatment interval and course	Administration mechanism	Invasiveness and pain	Drug release mode	Effectiveness	Adverse reactions	Limitations	Reference
Intralesional injection	Triamcinolone acetonide (10–40 mg/ml) Compound betamethasone (5 mg betamethasone dipropionate and 2 mg betamethasone sodium phosphate/ml)	Every 1–4 weeks (2–6 sessions, but can be extended)	Chitosan injected into scar tissue	Invasive Obvious injection pain	Periodic administration and the peak-to-trough phenomenon of corticosteroid	Varies from 50–100%	Relatively high rate of adverse reactions, such as skin atrophy, skin pigmentation and telangiectasia	Pregnancy, glaucoma and Cushing's syndrome, *etc.*	[5,7,28]
Conventional topical formulations	0.1% Betamethasone valerate ointment 0.25% Fluocinolone acetate cream	2–4 times every day for 6 months	Transdermal absorption	Non-invasive Painless	Periodic administration and the peak-to-trough phenomenon of corticosteroid	Lack of large-scale RCTs	Skin immersion, itching, skin atrophy, depigmentation and telangiectasia	Fast-growing and large-sized pathological scars	[5,51]
Tapes/plasters	Fludroxycortide (4 $\mu g/cm^2$) Deprodone propionate (20 $\mu g/cm^2$) Betamethasone valerate (30 $\mu g/cm^2$)	24 h/day for 3–12 months	Transdermal absorption	Non-invasive Painless	Controlled release	Lack of large-scale RCTs	Relatively low rate of adverse reactions, such as contact dermatitis, skin atrophy and telangiectasia	Fast-growing and large-sized pathological scars	[5,53–55]
Microneedle	Loaded with 0.025–0.1 mg TAC every patch	N.A.	Forms reversible microchannels by piercing the skin surface using micrometer-sized needles	Minimal-invasive Painless	Sustained-release	N.A.	N.A.	N.A.	[57–59,61]
Nanocarrier	Triamcinolone acetonide 2.5 $\mu g\ cm^{-2}$ mometasone furoate 20 mg	N.A.	Encapsulates drugs in nano-sized particles and then penetrates the stratum corneum barrier	Non-invasive Painless	Sustained-release	N.A.	N.A.	N.A.	[63,68–70]
Laser-assisted drug delivery	Triamcinolone acetonide (10–40 mg/ml) 0.25% Betamethasone valerate ointment	Every 1–3 months (3–5 sessions, but can be extended)	Controlled disruption of the stratum corneum barrier through laser ablation, thereby increasing the penetration depth and bioavailability of drugs	Minimal-invasive Moderate pain	Periodic administration and the peak-to-trough phenomenon of corticosteroid	Lack of large-scale RCTs	Skin atrophy, skin pigmentation and telangiectasia Different settings of laser parameters may stimulate hypertrophic scars	Pregnancy, glaucoma and Cushing's syndrome, *etc.*	[72,75,76]
Physical transdermal drug delivery system	Corticosteroid injection preparations, ointments or creams	N.A.	Cavitation and thermal and acoustic flow effects (sonophoresis) Forms a high-speed stream of fluid using instantaneous jet high pressure (needle-free jet injection) Drugs on the skin surface can be ionized by low-density electric currents (iontophoresis)	Non-invasive Painless Minimal-invasive No obvious pain Non-invasive Painless	Periodic administration and the peak-to-trough phenomenon of corticosteroid	Lack of large-scale RCTs	Skin atrophy, skin pigmentation and telangiectasia	Pregnancy, glaucoma and Cushing's syndrome, *etc.*	[77,80,83]
Chemical and biological transdermal permeation enhancer	Halobetasol propionate Fluocinolone acetonide	N.A.	Reversibly disrupt the stratum corneum barrier (chemical enhancer) Interact with cells through chemical molecules and biological peptides (biological enhancer)	Non-invasive Painless	Periodic administration and the peak-to-trough phenomenon of corticosteroid	Lack of large-scale RCTs	N.A.	N.A.	[57,85,87]

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the pro-inflammatory mitogen-activated protein kinase signaling pathway through mitogen-activated protein kinase phosphorylase-1 induction [11–13]. Corticosteroids retain the ability to repress the activity of transcription factor nuclear factor-kappa B, activator protein-1 and signal transducer and activator of transcription 3 to indirectly regulate pro-inflammatory gene transcription, ultimately reducing the production of pro-inflammatory cytokines and cytokine-induced proteins [14–17]. Lastly, corticosteroids regulate intracellular calcium mobilization and cell electrophysiology with non-genomic effects to reduce inflammatory responses in scar tissues [17]. (2) Immunomodulatory effect on T cells: overall, corticosteroids suppress T cell activation by interfering with the T-cell receptor signaling pathway, but this effect has been proven to be selective. Specifically, corticosteroids inhibit T helper 1 (Th1) and Th17 cell immune responses but facilitate the differentiation and activation of Th2 cells and regulatory T cells [18,19]. (3) Anti-fibroblast proliferation effect: corticosteroids inhibit the transition of the cell cycle from the G0/G1 phase to the S phase and reduce fibroblast proliferation by suppressing platelet-derived growth factor gene expression. In addition, corticosteroids stimulate the apoptosis of fibroblasts [20,21]. (4) Inhibitory effect on angiogenesis: corticosteroids decrease the mRNA of vascular endothelial growth factor through the glucocorticoid receptor pathway to suppress angiogenesis in scar tissues, thereby inducing scar regression [20,22]. (5) Promotion of ECM remodeling: corticosteroids exert a regulatory effect on the expression of transforming growth factor-β1 and basic fibroblast growth factor to down-regulate the mRNA of type I and III pro-collagens, thus suppressing collagen synthesis [23–26]. Corticosteroids accelerate collagenase degradation via reduced collagenase inhibitors, α1-antitrypsin and α2-macroglobulin [27]. Thus, corticosteroids can not only be used to treat existing scar tissues, but may also be employed to effectively prevent and treat pathological scars by interfering with scar tissue formation.

Corticosteroids in pathological scar prevention and treatment

Corticosteroids can be administered intralesionally and transdermally to treat pathological scars. Triamcinolone acetonide (TAC) and compound betamethasone are the most commonly used corticosteroids in clinical practice [7,28]. Both are long-acting drugs with excellent anti-inflammatory properties and low equivalent dosage. Intralesional injections of these drugs can achieve optimal therapeutic effects.

TAC ointments, fluocinolone acetate cream and fludroxycortide tapes are commonly used for transdermal drug delivery. Clinically, the choice of topical corticosteroids is primarily based on their potency. The potency of topical corticosteroids is mainly classified via vasoconstriction assays [29]. Corticosteroids induce skin blanching by inhibiting the production of vasodilators; this correlates with their clinical effectiveness [30]. The dose–response curve for skin blanching can then be plotted according to clinical visual scores or using a colorimeter [31–33]. On this basis, classification schemes have been proposed by different countries. Notably, this included a seven-group classification system in the USA and a four-category classification system in Europe (Tables 2 and 3, respectively) [34–37]. When applying topical corticosteroids, the appropriate potency and dosage should be selected depending on anatomical site, size of pathological scars and the age of the patient.

Intralesional injection

Intralesional injection of corticosteroids is the most widely used clinical treatment for pathological scars. They are usually injected in combination with 5-fluorouracil (5-Fu) and lidocaine, which improves therapeutic effects and reduces pain [38,39]. Intralesional injections deliver corticosteroids directly into scar tissues, resulting in a high local drug concentration. Numerous randomized controlled trials (RCTs) and meta-analyses have demonstrated their effectiveness in improving the congestion, texture and height of pathological scars, as well as local symptoms such as pain and itching; therefore, their efficacy is ideal in the absence of serious adverse reactions [40–43]. In 2014, an international advisory panel of experts recommended monthly intralesional corticosteroid administration as the first-line treatment for keloids [44]. The efficiency of intralesional injection of TAC varies from 50–100% and the recurrence rate is 9–50% [45]. Moreover, intralesional injections of corticosteroids can also modify scar formation. As revealed in a patient-matched control study, intralesional injection of TAC markedly reduced the volume and increased the elasticity of hypertrophic scars after burns [41]. In another study in which surgical excision of facial keloids with intra- and post-operative local injections of TAC was performed, the recurrence rate was 23.5% after 18 months of follow-up [46]. Additionally, intralesional injection of corticosteroids can be combined with various methods to improve the therapeutic effect. In one study, auricular keloids were treated with core excision surgery, intralesional injection of compound betamethasone or their combination. The effective rates in the surgery and intralesional injection groups were 54.55 and 55.88%, respectively, while the effective rate in the combined group was 96.92%, with only four recurrent cases at 1-year follow-up [28]. Another study adopted a novel multimodal treatment of core excision surgery, intraoperative TAC injection and postoperative radiotherapy for auricular keloids, and the recurrence rate at an average 24.1 months follow-up was only 6.7% [47].

The obvious disadvantages of intralesional corticosteroid injection include injury caused by multiple punctures on the lesion and repeated injections, severe injection pain and a variety of side effects (such as atrophy of the skin, subcutaneous tissues, skin pigment or telangiectasia). Repeated injection of corticosteroids, which have poor aqueous solubility, may lead to drug deposition and

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Table 2. USA seven potency ratings of topical corticosteroids

Potency	Medication	Strength (%)	Formulations
Superpotent (I)	Betamethasone dipropionate, augmented	0.05	G/O/L
	Clobetasol propionate	0.05	C/G/O/L
	Fluocinonide	0.1	C
	Halobetasol propionate	0.05	C/O/L
Potent (II)	Amcinonide	0.1	O
	Betamethasone dipropionate	0.05	C/O
	Clobetasol propionate	0.025	C
	Fluocinonide	0.05	C/G/O/S
Upper mid-strength (III)	Amcinonide	0.1	C/L
	Betamethasone valerate	0.1	O
	Fluticasone propionate	0.005	O
	Triamcinolone acetonide	0.5	C/O
Mid-strength (IV)	Fluocinolone acetonide	0.025	O
	Flurandrenolide	0.05	O
	Hydrocortisone valerate	0.2	O
	Triamcinolone acetonide	0.1	C/O
Lower mid-strength (V)	Betamethasone dipropionate	0.05	L
	Betamethasone valerate	0.1	C
	Fluocinolone acetonide	0.025	C
	Flurandrenolide	0.05	C/L
	Hydrocortisone valerate	0.2	C
	Triamcinolone acetonide	0.1	L
		0.025	O
Mild (VI)	Alclometasone dipropionate	0.05	C/O
	Betamethasone valerate	0.1	L
	Fluocinolone acetonide	0.01	C/S
	Triamcinolone acetonide	0.025	C/L
Least potent (VII)	Hydrocortisone	2.5	C/O/S
		1	C/G/L/O
	Hydrocortisone acetate	2.5/1	C

C cream, *G* gel, *L* lotion, *O* ointment, *S* solution

calcification at the injection site, menstrual disorders and, rarely, Cushing's syndrome. Therefore, non-invasive and simple transdermal delivery of corticosteroids into scar tissues can relieve injection-site pain and reduce side effects, offering an optimal choice for pathological scar prevention and treatment.

Transdermal drug delivery

Transdermal drug delivery enables drugs to be transported across the skin's outermost stratum corneum barrier and into the dermis layer through the intercellular route, transcellular route or skin appendages, thus achieving drug delivery to the target area in a non-invasive and convenient manner [48,49]. In current clinical practice, the main forms of topical corticosteroids include conventional smearable semisolid vehicle formulations and self-adhesive tape/plaster.

Conventional topical formulations

The most common topical formulations of corticosteroids in clinical practice are generally classified into creams, ointments and lotions. Creams are primarily composed of oil-in-water mixtures and feature high-drug loading, whereas ointments comprise easy-to-spread water-in-oil mixtures. Lotions are liquid dosage forms with active dispersed or suspended drug ingredients. Ointments, which are more potent than creams and lotions, can enhance the ability of drugs to cross the stratum corneum barrier through skin hydration. Although widely applied, creams, ointments and lotions have rarely been studied in clinics for their role in pathological scar prevention and treatment. In a prospective study of 32 patients with hypertrophic scars and 9 patients with keloids, the improvement rates in treating pathological scars with TAC lotion that adheres to the scar were 84.4% with hypertrophic scars and 44.4% with keloids. Additionally, the itching and pain symptoms were notably relieved [50]. In another study, TAC injection (once every 2 weeks, five times in total) combined with the application of corticosteroid ointments (twice a day, 6 months in total) were adopted after 1 week of pathological scar excision(removal of sutures), and the recurrence rates of hypertrophic scars and keloids were 16.7 and 14.3%, respectively at an average follow-up of 32 months [51]. Although the Japan Scar Workshop

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Table 3. Europe's classification of topical corticosteroids by potency

Potency	Medication	Strength (%)	Formulations
Very potent	Clobetasol propionate	0.05	C/G/O
	Diflorasone diacetate	0.05	O
	Fluocinonide	0.1	C
Potent	Halcinonide	0.1	C/O/S
	Amcinonide	0.1	O
	Beclomethasone dipropionate	0.025	O
	Betamethasone dipropionate	0.05	C/G/O
	Betamethasone Valerate	0.1	C/O/L
	Fluocinonide	0.05	C/O
	Mometasone furoate	0.1	O
	Triamcinolone acetonide	0.1	O
		0.5	C
Moderate	Mometasone furoate	0.1	C/L
	Hydrocortisone butyrate	0.1	C/O/L
	Triamcinolone acetonide	0.1	C/O/L
	Fluocinonide	0.025	C/O
	Betamethasone valerate	0.025	C/O
	Fludroxycortide	0.0125	C/O
Mild	Desonide	0.05	C/G/L/O
	Hydrocortisone	1.0	C/O
	Prednisone acetate	0.5	O

C cream, *G* gel, *L* lotion, *O* ointment, *S* solution

Consensus Document 2018 recommends corticosteroid ointments for the prevention of hypertrophic scars, they are rarely used in this regard because of the lack of randomized controlled studies with large sample sizes [5].

Semisolid vehicle formulations are easy to apply and rub off, but their transdermal efficiency is low owing to their short action time, making it difficult to achieve sufficient drug concentration in the scar. It is necessary to increase the frequency and dosage of use and occlude the application area to achieve optimal therapeutic effects. Nonetheless, the continuous use of topical corticosteroids also increases the incidence of adverse reactions, such as skin immersion, itching, skin atrophy, depigmentation and telangiectasia. Hence, research on pathological scar prevention and treatment currently prioritizes the development of ointments with higher transdermal efficiency.

Tapes/plasters

Tapes/plasters are formulations loaded with active ingredients of drugs that adhere firmly and consistently to the skin [48]. They mainly consist of a backing layer, an adhesive layer containing drugs and a protective layer. Corticosteroid tapes were first reported to be effective for the treatment of keloids in 1967 [52]. Currently, the available corticosteroid tapes/-plasters contain three different topical corticosteroids, including fludroxycortide, betamethasone valerate and deprodone propionate, and exhibit an optimal therapeutic effect with a low incidence rate of adverse reactions [53,54]. In a prospective and self-controlled study including 16 patients, 6-month follow-up results demonstrated that the betamethasone valerate plaster was effective in preventing pathological scar formation after anterior trunk plastic surgery [55]. When 30 pediatric patients and 30 adult patients with pathological scars treated with fludroxycortide tape daily for 1 year, adults required a more potent deprodone propionate plaster to achieve similar effects to children, possibly due to the relatively thin skin of children, which facilitates the absorption of drugs [53]. Recently, corticosteroid tapes/plasters have been recommended as the first-line treatment for pathological scars in Japan, and they may be an alternative to intralesional injection as a method for long-term scar prevention and treatment [5].

Tapes/plasters are significantly more optimal in clinical applications. First, the occlusive effect of tapes/plasters can enhance corticosteroid absorption, provide mechanical support and limit local tension across scars. Second, the controlled release and continuous accumulation of corticosteroids in scar tissues can avoid the peak-to-trough phenomenon of drugs and contribute to the control of the inflammatory state in scars. Finally, for pathological scars, tapes/plasters combined with other treatments (such as intralesional injection of drugs and postoperative radiotherapy) can shorten the treatment course and improve the therapeutic effect. However, there is also a risk of local adverse reactions, such as contact dermatitis, skin atrophy and telangiectasia, with contact dermatitis being the most common adverse reaction with an incidence rate of 16.7 and 0.55% in fludroxycortide tapes and deprodone propionate plasters, respectively [56]. Nevertheless, corticosteroid

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tapes/plasters are unsuitable for the treatment of large scars.

Transdermal drug delivery enhancement techniques

Penetration of drugs into the dermis is limited by the tight stratum corneum barrier, which is a primary challenge encountered in transdermal drug delivery [57]. Moreover, it is crucial to improve the penetration of drugs into the dense and thickened scar dermis during transdermal drug delivery. Currently, the development and application of advanced nano, laser, and physical, chemical and biological penetration-enhancement techniques provide new opportunities to improve the efficiency and therapeutic efficacy of transdermal drug delivery of corticosteroids.

Microneedle transdermal drug delivery system

The microneedle system forms reversible microchannels by piercing the skin surface using micrometer-sized needles to promote the transdermal permeability of drugs and reduce the incidence of local adverse reactions [57,58]. Common microneedle systems used in scar prophylaxis and treatment are dissolving microneedles prepared using hyaluronic acid (HA) loaded with TAC, which can be self-administered. According to the results of a clinical study on dissolving microneedles, there was a significant reduction in scar volume after 30 days of continuous use [59]. Additionally, researchers have developed a variety of composite dissolving microneedles and applied them to basic research on scar treatment. In one study, hypertrophic scars in rabbit ears were treated with TAC delivered using dissolving microneedles made from sodium hydroxypropyl-β-cyclodextrin (HP-β-CD) and HA. The microneedle group had the most significant reduction in the value of scar elevation index, type I collagen and transforming growth factor-β1 mRNA and protein expression compared to the same dose of injection and cream [60]. Furthermore, researchers prepared bilayer dissolving microneedles with chitosan and dextran loaded with 5-Fu at the needle tip and HA/HP-β-CD loaded with TAC at the needle tail, enabling a biphasic release, namely a rapid release of TAC and a sustained release of 5-Fu. The bilayer dissolving microneedles could remarkably reduce fibroblast proliferation and ECM deposition in the hypertrophic scars of rabbit ears [61]. Li *et al*. [62] manufactured a novel trilayer microneedle consisting of a baseplate and tips loaded with hydrophobic dexamethasone (DE) and its hydrophilic pro-drug dexamethasone sodium phosphate (DSP) to assist the transdermal and intradermal delivery of DE in a biphasic release mode involving a burst release of DSP and slower release of DE. The results of *ex vivo* studies showed that the method could achieve intradermal and transdermal delivery efficiencies of >40 and >50%, respectively. The microneedle system requires high biocompatibility, mechanical strength and drug release performance. Therefore, its clinical transformation has not been completely achieved; however, it will be of high clinical value for pathological scar prevention and treatment in the future.

Nanocarrier transdermal drug delivery system

The nanocarrier transdermal drug delivery system encapsulates drugs in nano-sized particles. The system then penetrates the stratum corneum barrier along with the drug and accumulates in the target area. This approach is non-invasive and has a high delivery efficiency [63]. At present, various lipid- or polymer-based nanocarrier systems are being used for transdermal drug delivery, increasing the topical drug permeation capacity and prolonging the retention time in the skin, thereby reducing the drug dosage, frequency of administration and adverse effects of topical drugs [64]. Among the nanocarrier systems, nanoliposomes with phospholipid membrane structures and transformers have been studied extensively and have been certified to penetrate the stratum corneum barrier into the dermis layer through deformation, proving to be excellent carriers for transdermal drug delivery [65]. At present, nanocarrier systems loaded with corticosteroids are predominately used for the treatment of psoriasis, atopic dermatitis and other skin diseases [66,67]. In comparison with commercially available creams, liposomal gel loaded with mometasone furoate displays a 15.21-fold increase in skin permeability [68]. In a double-blind, placebo-controlled clinical trial, under the equivalent condition of an erythema inhibition test, the dosage of TAC in transfersomes was 10 times lower than that of commercially available creams and ointments, and TAC in transfersomes reduced the incidence rate of skin atrophy [69]. Therefore, the use of TAC in transfersomes reduces overall dosing frequency and side effects without reducing efficacy. Furthermore, nanocarrier systems combined with hydrogel-based drug delivery systems can achieve biocompatibility, biodegradability and extended drug release [70]. Koh *et al*. developed a physical stimulation-responsive method with controlled release of TAC using alginate-polyacrylamide tough hydrogel drug delivery systems and combined them with drug-loaded nanoparticles [71]. The clinical application of nanocarriers is of high value despite concerns about their stability and safety. The safety of nanocarrier transdermal drug delivery systems has been controversial and little relevant research to clarify these concerns is available. Meanwhile, effectiveness is another challenge, as whether the drug delivery efficiency of nanocarriers in humans is as effective as that in animal models (such as rabbit scar models) is still unknown. More clinical studies are needed to investigate the clinical translation of nanocarriers for transdermal delivery of corticosteroids.

Laser-assisted drug delivery

Laser-assisted drug delivery aids drug penetration by controlled disruption of the stratum corneum barrier through laser ablation, creating microscopic treatment zones, thereby increasing the penetration depth and bioavailability of drugs.

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With less damage and a short re-epithelization time, lasers can achieve precise disruption and ablation of the stratum corneum of the skin and controllable drug penetration [72,73]. At present, the most commonly used lasers are fractional Er:YAG lasers (wavelength: 2940 nm) and CO_2 fractional lasers (wavelength: 10600 nm) [73]. Following the re-epithelization process, drug deposits are formed in the epidermis, further prolonging the drug release time [74]. Results from a randomized clinical trial, with a treatment interval of 4 weeks until the keloid resolved or the 1-year treatment was completed, confirmed that both the combination of fractional CO_2 lasers with topical TAC and intralesional injection of TAC alone decreased the Vancouver Scar Scale score and scar volume, showing no statistically significant difference. However, the 1-year follow-up results revealed recurrence rates of 9.1 and 18.2%, respectively. These results indicate that the combination of fractional CO_2 lasers and topical TAC may be an alternative treatment for keloids [75]. In addition, intralesional injections of TAC and desoxymethasone ointments were administered after uniform ablation using fractional Er:YAG lasers. Both methods markedly decreased the Vancouver Scar Scale score with no statistically significant difference; however, the pain score was significantly higher with intralesional injections [76]. Numerous studies have shown that fractional lasers combined with topical corticosteroids can be used as an alternative option for pathological scar prevention and treatment, not only to achieve the therapeutic effects of intralesional injection but also to avoid injection pain. In addition, fractional lasers promote both transdermal penetration of drugs and remodeling of scar collagens. However, there are no clear and feasible criteria for laser-assisted drug delivery in pathological scar prevention and treatment, and its indications and clinical parameters require further investigation.

Physical transdermal drug delivery system

A physical transdermal drug delivery system uses physical factors such as ultrasounds, pressure and ion flow, to promote the formation of pathways in the skin and enhance the transdermal penetration of drug molecules. It has a high safety profile and causes rapid recovery of skin barrier function [57]. Ultrasound sonophoresis disturbs the stratum corneum and contributes to the formation of penetration pathways through cavitation and thermal and acoustic flow effects, thus increasing the efficiency of transdermal drug delivery [77]. According to the results of a randomized controlled clinical trial, low-frequency ultrasound can notably improve the transdermal permeation efficiency of betamethasone 17-valerate cream [78]. Ultrasound sonophoresis is often combined with laser technology to prevent and treat pathological scars. After using fractional lasers or ion beams to create uniform micropores on scars, corticosteroids are imported into scar tissues by ultrasound sonophoresis, thus improving the therapeutic effect and exhibiting promising clinical application prospects [79]. Needle-free jet injection forms a high-speed stream of fluid using instantaneous jet high pressure, which pushes drugs from micrometer-sized pores to penetrate the skin and further penetrate downwards. Such a method can effectively address injection difficulties, uneven distribution of drugs and obvious pain associated with conventional injections. It has been proven that a needle-free injector can reduce the dosage of drugs, distribute them evenly, improve scar scores and relieve pain in scar prevention and treatment [80–82]. Moreover, through the iontophoresis technique, drugs on the skin surface can be ionized by low-density electric currents, and electromigration and electro-osmosis occur under the action of an electric field to impel the directional movement of drugs, thus effectively increasing their transdermal efficiency [83,84]. However, iontophoresis technology is only applicable to charged small molecules or some macromolecules because it does not cause any significant changes in the stratum corneum barrier.

Chemical and biological transdermal permeation enhancers

Chemical and biological permeation enhancers improve drug solubility, reversibly disrupt the stratum corneum barrier and interact with cells through chemical molecules and biological peptides, thus improving the efficiency of transdermal delivery of corticosteroids [85]. Commonly used chemical permeation enhancers include alcohols, fatty acids/esters, surfactants and biological permeation enhancers, such as penetration-enhancement peptides and lipid metabolism regulators [57]. As revealed by an *ex vivo* experiment, menthone significantly increased the cumulative permeation and retention of halobetasol propionate in the skin compared with other chemical enhancers [86]. An animal study on psoriasis confirmed that the application of polypeptides in polymer carriers combined with fluocinolone facilitates the penetration of the drug into the stratum corneum and its continuous release, thus prolonging drug retention [87]. Nonetheless, at present, the complex interactions between chemical and biological penetration enhancers and skin and drugs, safety and mechanisms of penetration enhancement remain elusive and require further study.

Conclusions

Corticosteroids, the most commonly used drugs in pathological scar prevention and treatment, can interfere with scar formation, reduce scar volume and relieve patients' pruritus and pain symptoms with different mechanisms. Intralesional injections are the most common and effective route; however, their widespread use is limited by injection pain and a relatively high rate of local side effects. Transdermal drug delivery, an alternative route for corticosteroid administration, is increasingly favored by physicians and patients because it is a non-invasive and convenient method. For pediatric patients and patients with large-sized scars, transdermal

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drug delivery, with its important advantages and application prospects, has great potential to become the first-line therapy. Meanwhile, focusing on the disadvantages of low efficiency of transdermal delivery, researchers have developed various advanced transdermal drug delivery systems that effectively improve the penetration efficiency and therapeutic effect of corticosteroids in scars. However, although transdermal delivery systems have good application potential, they are still at the animal experiment stage and lack high-quality clinical evidence such as large-scale RCTs to prove their safety and effectiveness. It is obvious that the material science-based transdermal drug delivery system will become a cross-disciplinary research direction for corticosteroids in the prevention and treatment of scars.

Abbreviations

ECM: Extracellular matrix; 5-Fu: 5-Fluorouracil: HA: Hyaluronic acid; HP-β-CD: Hydroxypropyl-β-cyclodextrin; RCT: Randomized controlled trials; TAC: Triamcinolone acetonide; TH1 cell: T helper 1 cell.

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Conflicts of interests

None declared.

Authors' contributions

Writing—original draft preparation: MS; conceptualization, HL; writing—review and editing, ZZ and YC; supervision, ZZ and YZ. All authors have read and agreed to the published version of the manuscript.

Data availability

Data is openly available in a public repository.

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