Residents' Page

Intralesional drug therapy in dermatology

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INTRODUCTION

Intralesional therapy is the injection of a higher concentration of a drug directly into skin lesions without significant systemic absorption. The rationale for this technique is the establishment of a subepidermal depot which bypasses the superficial barrier zone.[1]

The different drugs used for intralesional therapy, along with the indications for their use are given below.

CORTICOSTEROIDS [TABLE 1][1]

Cortisone and hydrocortisone acetate suspensions were used from the early 1950s before introduction of preparations with lower solubility such as triamcinolone acetonide, which is now the most common agent used.[2] Triamcinolone acetonide (2.5–10 mg/ml [1 mg/cm^2]), betamethasone sodium phosphate/acetate (1–2 mg/cm^2/site), dexamethasone acetate (0.8–1.6 mg/site), dexamethasone sodium phosphate (170 μg–5 mg/session), hydrocortisone acetate (5–7.5 mg/session) and methylprednisolone acetate (20–60 mg/session) are used for keloids, alopecia areata, nodulocystic acne, granuloma annulare, granuloma faciale, hidradenitis suppurativa, localized and nail psoriasis, prurigo nodularis, cutaneous lupus erythematosus, vitiligo, lichen simplex chronicus, hypertrophic nail lichen planus, resistant oral pemphigus, hemangiomas, etc.[1] The dose per session is generally 0.1–0.2 ml/cm^2 of involved skin (<1–2 ml/dose) with an interval of 3–6 weeks between two consecutive injections. The number of injections depends on the disease, site of lesions, age of the patient and response to previous injections. The maximum dosage of triamcinolone acetonide should not exceed 40 mg/ml/session. Corticosteroids can be injected in full strength or diluted with normal saline or local anesthetic.[2]

Side effects

Atrophy, pain, hyper- or hypopigmentation, telangiectasias, striae, hirsutism, secondary infection, stellate pseudoscars, hypertrichosis, amaurosis fugax and tachyphylaxis could be possible side-effects of intralesional corticosteroid injections.

5-FLUOROURACIL

Table 2.[3-6] enlists the conditions for which intralesional 5-fluorouracil (available as 50 mg/ml ampoule) is used.

Side effects

Pain, necrosis, hyperpigmentation and atrophic scarring.

FILLERS, BOTULINUM TOXIN A AND PLATELET RICH PLASMA

Platelet-rich plasma has been used, with promising results, at weekly intervals, for alopecia areata, acne scar revision, non-healing ulcers, lipodermatosclerosis, striae distensae, androgenetic alopecia, lichen sclerosus and vitiligo.[7]

Botulinum toxin A and hyaluronic acid fillers have been used successfully for the treatment of traumatic

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Table 1: Recommended strength of intralesional triamcinolone acetonide injections[1]

Indication	Dosage/session (mg/ml)
Keloids	
Thick	40
Moderate/hypertrophic scar	10
Discoid lupus erythematosus/sarcoidosis/ localized psoriasis/hypertrophic lichen planus/nail lichen planus	5-10
Granuloma annulare	3-10
Alopecia areata	3-5
Cystic acne (not on face)	2-3
Cystic acne (face)	1-2
Hidradenitis suppurativa	2-5

Table 2: Recommended doses of intralesional 5-fluorouracil in various diseases

Indications	Dose	Interval and duration
Chronic plaque psoriasis[3]	0.1 ml/cm^2	Per week for 6-8 weeks
Keloids[4]	0.2-0.4 ml/cm^2	Initially once or thrice weekly then 4-6 weekly until resolution
	0.1 ml triamcinolone acetonide (10 mg/ml) + 0.9 ml of 5-FU	Average 5-10 injections
Warts[5]	4 ml 5-FU+1 ml lignocaine 2% + 0.0125 mg/ml epinephrine	Weekly for 4-5 weeks
Squamous cell carcinoma and basal cell carcinoma[6]	0.8-2.4 ml	Weekly for 8-12 weeks

5-FU: 5-fluorouracil

scars, facial rejuvenation [Table 3] correction of contour defects and photoaging.[8]

Botulinum toxin A is also used in the treatment of hyperhidrosis in a dose of 50–200U injected intradermally (the full dose being divided into 10–15 aliquots at spatial intervals of 2 cm). It reduces sweat production for 3–17 months in palmoplantar and axillary hyperhidrosis. Injections may be repeated after 6 months, if required.[9]

Side effects

Autologous platelet rich plasma is safe with no risk of hypersensitivity. Botulinum toxin and fillers can cause edema, pain, erythema, temporary hypoesthesia and over- or under- correction.

INTERFERONS

Use of intralesional interferons in various dermatological indications is shown in Table 4.[10]

Side effects

Flu-like symptoms, pancytopenia, hypocalcemia, hyperlipidemia, depression, cardiac arrhythmias, gastrointestinal upset, renal toxicity, alopecia, xerosis, injection site reactions and menstrual irregularities can all be seen.

MESOTHERAPY

Mesotherapy is a semi-invasive method of drug delivery that consists of multiple dermal or subcutaneous injections of mixture of compounds in minute doses. It is actually a "intra-dermotherapy" instead of an "intralesional therapy". In intralesional therapy, the injection is targeted inside the skin condition to be treated irrespective of whether the skin lesion is in dermis or subcutis. But in mesotherpy, the depth of penetration of needle should not exceed more than 4 mm into the skin and injections are regularly spaced.[14]

Mesotherapy with various drugs is useful for androgenic alopecia and telogen effluvium (biotin, minoxidil and dutasteride), cellulite lipolysis and localized fat dissolution (phosphatidylcholine, vitamin complex, trace elements, collagenases, hyaluronidases, etc.). Meglumine antimoniate (by mesogun) is used for cutaneous leishmaniasis.[14]

Side effects

Side effects observed include pain, edema, erythema, local infection or abscess, lichenoid eruptions, hyperpigmentation and hypersensitivity reactions.

CRYOTHERAPY

Intralesional cryotherapy with liquid nitrogen has been used, together with steroids, for the treatment of keloids and hypertrophic scars.[15]

Side effects

Pain, erythema, hypo- or hyperpigmentation at the site of injections are seen.

SCLEROSANTS

Sodium tetradecyl sulfate (1% and 3%), hypertonic saline, polidocanol, sodium morrhuate, polyiodinated iodine and chromated glycerin are used in pyogenic granuloma, superficial telangiectasias, venulectasias of lower extremities, hemangioma, lymphangioma circumscriptum and venous malformations in a dose of 0.1 to 0.5 ml/site at weekly intervals.[1]

Table 3: Recommended doses of botulinum toxin A in upper facial rejuvenation[8]

Muscle	Dose (U)	Duration (months)	Specific complication
Glabella (procerus and corrugators)	10-40	4-6	Lid ptosis
Periorbital area (orbicularis oculi)	10-30	3-4	Ectropion, diplopia
Forehead (frontalis)	6-15	3-6	Brow ptosis

Table 4: Recommended doses of intralesional interferons in skin disorders[10]

Indication	Interferon	Dose/duration
BCC (superficial and nodular types)[10]	IFN γ IFN α2b	1-3 MIU 3 times/week×3 weeks Higher doses if tumor size >2 cm^2
SCC[10]		2 MIU 3 times/week×7 weeks
Cutaneous B-cell lymphoma[10]	IFN α2a	1-6 MIU
Genital warts[10]	IFN α	1 MIU 3 times/week×4 weeks
Keloids[10]	IFN α2b	1.5 MIU twice daily×4 days
Hemangioma[11]	IFN α	1-3 MIU/m^2 BSA OD×1 week followed by once/week for mean 8 weeks
Keratoacanthoma[12]	IFN α 2b	3 MIU/week×4-6 weeks
Cutaneous leishmaniasis[10]	IFN γ	1-30 μg/m^2 3 times/week
Peyronie's disease[13]	IFN α 2b	1-2 MIU weekly×3-5 weeks

BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, BSA: Body surface area, MIU: Million international units, IFN: Interferon

Side effects

Nicolau syndrome, which manifests with tissue necrosis, was reported with sclerotherapy by Nirmal *et al.*, in a single case of pyogenic granuloma.[16] Other complications include pain, ecchymosis, hyperpigmentation, necrosis, ulceration and thrombophlebitis.

BLEOMYCIN

Although not Food and Drug Administration approved for intralesional therapy, bleomycin has been used in keloids (1.5 IU/ml or 0.1–1 ml/monthly), periungual warts (0.1–2 ml/session, monthly, up to 4 injections/wart), large hemangiomas and venous malformations (0.3–1 mg/kg, up to a maximum of 15 mg/month), keratoacanthomas, cutaneous malignancies and cutaneous leishmaniasis.[17-21] It is available as bleomycin sulfate powder lyophilized 15U/vial (reconstituted with 1–5 ml sterile water for injection or 0.9% normal saline) or 30U/vial (2–10 ml water/normal saline). It requires storage at 2–8°C. Shelf life is 24 h at room temperature and 4 weeks if refrigerated.[18] Bleomycin penetrates poorly through cell membranes. Reconstitution in local anesthetic (lignocaine) improves penetration by disrupting cell membranes.

Side effects

Since intralesional injection is extremely painful, it is given under infiltrative local anesthesia. Jet injectors, modified tattoo machines, monolet needles and pricking through bifurcated needles reduce procedural pain. Redness, swelling, pain and burning subside after 72 h. Rare side effects are Raynaud's phenomenon, narrowing of fingertips, restricted nail growth, scarring, lymphangitis, paresthesias and hematoma formation.

SODIUM STIBOGLUCONATE ANTIMONY

It is a first line therapy in localized cutaneous leishmaniasis in a dose of 50 mg/cm^2/week for 5–7 weeks.[22]

Side effects

Pain and hyperpigmentation may sometimes be seen.

AMPHOTERICIN B

It has been successfully tried in lesions of cutaneous leishmaniasis in a dose of 2 mg/ml/week, intralesionally for up to 12 weeks with an average of 10.31 ± 5.41 injections.[23]

Side effects

Pain, fibrosis, local allergic reaction and systemic absorption are possible side effects.

METHOTREXATE

In a recent study, Yoo and Kim reported complete resolution of keratoacanthomas with 2–7 injections (mean 4.3) of methotrexate, 25 mg/ml with an average total dose of 53.7 mg/treatment course[24] and an average injection interval of 10 days (range 4–28 days). Other indications where intralesional methotrexate has been tried with variable success are cutaneous malignancies such as malignant melanoma, basal cell carcinoma and squamous cell carcinoma, as well as in nail psoriasis.[20,25]

Side effects

Side effects observed have been ulceration and necrosis, and pancytopenia (after systemic absorption).

VINCRISTINE AND VINBLASTINE

These cytotoxic agents are used in Kaposi's sarcoma.[26,27] They act by blocking microtubule

polymerization after binding with tubulin, arresting cell division thus leading to cell death.

Vinblastine is available in 10 ml vials and is used in a dose of 1 mg/ml. About 0.03–0.1 ml of the drug is injected after diluting with 0.9% normal saline. Vincristine is injected in volumes of 0.03–0.08 ml of a 1 μg/ml solution.[26,27]

Side effects

Pain, erythema and pruritus have been noted.

IMMUNOTHERAPY

This mode of therapy utilizes the ability of the immune system to mount delayed type hypersensitivity to various injected antigens and wart or tumor tissue. Older individuals (>40 years) are less likely to respond, due to age-related blunting of immune responses. Different vaccines and antigens have been used with variable results as summarized in Table 5.[28-30]

Other antigens such as trichophyton skin test antigen have also been used with varied success in the treatment of warts.[28]

Side effects

Pain, pruritus, chills, myalgia and arthralgia may be noted.

VERAPAMIL

Margaret Shanthi *et al*. reported a reduction in vascularity, pliability and dimensions of keloids and hypertrophic scars after intralesional verapamil, 2.5 mg/ml every 3 weeks for 6 months.[31] It has also been tried in the prevention and treatment of Peyronie's disease.[32] No side effects have been noted except for rare injection site reactions.

Table 5: Doses of intralesional immunomodulator agents

Intralesional immunomodulator	Dose/duration
MMR[28]	0.1 ml/lesion, 1-3 weekly, up to 3-6 weeks/till complete resolution
Mycobacterium indicus pranii vaccine[29]	0.1 ml/lesion, weekly till 10 weeks or complete resolution
BCG[28,30]	0.1 ml/lesion every 2 weeks, till 5 doses or complete resolution of warts (this dose is also used for palliation in melanoma)[30]
Candida antigen[28]	0.1-0.3 ml (1:1000), repeated after 3 weeks until complete resolution/4 weeks
PPD or tuberculin test antigen[28]	0.1 ml/lesion injected 1-3 weekly till complete resolution/12 weeks

MMR: Measles-mumps-rubella vaccine, BCG: Bacillus Calmette–Guerin, PPD: Purified protein derivative

PHOTODYNAMIC THERAPY

Photosensitizers like aminolevulinic acid have been injected intralesionally and followed by irradiation with a good response in cutaneous malignancies (nodular basal cell carcinoma, squamous cell carcinoma), acne and hidradenitis suppurativa.[6,33-35]

Side effects

Injection site reactions may occur.

RITUXIMAB

This anti-CD20 monoclonal antibody was tried successfully in primary cutaneous B-cell lymphoma (10 mg/ml [3 ml]) 3 times/week followed by a 3-week treatment-free period with acceptable results after nine injections.[36]

Side effects

Injection site reactions may be noted.

INTRALESIONAL CYCLOSPORINE

Ho *et al*., documented statistically significant improvement in chronic plaque psoriasis with 17 mg/ml injected 3 times/week for 4 weeks.[37]

Side effects

Injection site reactions may be seen.

MISTLETOE EXTRACT

It is a whole plant remedy derived from *Viscum album* L., a hemiparasite shrub; and is used in a dose of 20 ml/month [20 mg/ml/ampoule]. Two case reports mention its intralesional use in primary cutaneous B-cell lymphoma with complete remission in 8–12 months.[38]

Side effects

Injection site reactions may be noted.

ADVANTAGES OF INTRALESIONAL THERAPY

1. Faster action
2. Prolonged duration of action due to depot/reservoir effect

3. Eliminates need for long-term topical therapy and avoids side effects of systemic treatment
4. Improves patient compliance
5. Penetrates deeper than topical therapy
6. Can be combined with other modalities for synergistic action. For example, intralesional drugs with cryotherapy for keloids.

CONTRAINDICATIONS FOR INTRALESIONAL THERAPY

a. Active impetigo or herpetic infection at injection site
b. Previous history of hypersensitivity.

CONCLUSION

When used cautiously and judiciously, intralesional therapy is a simple, fairly safe office procedure constituting an integral part of the dermatological therapeutic armamentarium.

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Conflicts of interest
There are no conflicts of interest.

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