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The Addition of Triamcinolone to Testosterone Pellets to Address Extrusions: Is There Any Evidence?

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Abstract: The addition of triamcinolone to compounded testosterone pellets has recently been promoted to decrease the potential for extrusions and pain. However, the data supporting long-term systemic application of a corticosteroid is lacking. In addition, as triamcinolone is a synthetically derived corticosteroid, this pellet combination cannot be considered bioidentical. Until significant safety and efficacy data are made available, this combination pellet should only be used in select cases and with caution.

The addition of triamcinolone to compounded testosterone pellets has been recommended in an unpublished, company-sponsored white paper (DeNeui et al., 2018). This paper sets out to establish a need for and safety of the triamcinolone containing testosterone pellets compounded by Farmakeio Pharmacy and distributed by Evexias.

What is the purpose of triamcinolone in a compounded testosterone pellet?
The initial question that should be asked is: what is the problem that the addition of triamcinolone is solving? The white paper points out that insertion site pain and extrusion of pellets are common side effects seen, and surmise that the triamcinolone anti-inflammatory effects may reduce these complaints. However, in the same paragraph they admit extrusions are often due to provider technique, placement location and body composition, not the product being inserted. As such, one could question why triamcinolone is offered as a solution to a complication that appears to be technique related. In addition, because triamcinolone is a synthetically derived drug, this pellet combination cannot be considered bioidentical—an important disclosure for patients seeking more natural, bioidentical treatment.

What does triamcinolone do in the body?
The second question should be what is triamcinolone and what does it do? Triamcinolone is a synthetic corticosteroid that has anti-inflammatory and immunosuppressive properties. It was first synthesized in 1952 and used to treat a variety of inflammatory conditions such as allergies, asthma, eczema, psoriasis, and arthritis. It works by binding to and activating specific receptors, which inhibit production and release of pro-inflammatory molecules such as cytokines, prostaglandins, and leukotrienes. This leads to a reduction in inflammation, swelling, and redness associated with these various disorders. However, the physiological impact of this addition to traditional testosterone pellet therapy is unknown. There could be differences in hormone uptake, for example. The anti-inflammatory and immunosuppressive response could inhibit the uptake of the delivered hormone leading to a diminished physiologic response which may require increases in testosterone dosing to achieve appropriate serum levels and patient symptom relief. In fact, this has been a complaint of patients who have been treated with testosterone containing triamcinolone pellets after being treated with testosterone pellets alone.

What are the risks of triamcinolone?
Corticosteroids, like triamcinolone, have their place in medical therapy for treatment of certain conditions, such as asthma, eczema, psoriasis and arthritis. They also have well-documented potential side-effects when used long-term including but not limited to: adrenal suppression, osteoporosis, glaucoma, hyperglycemia, cataracts, weight gain, increased infection risk, skin changes, mood changes, and increased blood pressure. As such, medical guidelines have promoted treatment with the lowest dose for the shortest amount of time when using these drugs for years (Bleeker, et al., 2020). The white paper notes that “a side effect of local triamcinolone is the possibility of fat necrosis, fat atrophy and skin hypopigmentation, continuing “this observation has been made from a number of studies dating back to the 1950’s…” This fact has limited it’s use over the years, especially in long-term settings.

However, the white paper attempt to extinguish this concern by referring to 3 publications from the 1960's and the FDA Adverse Events Report System (AERS), stating that the occurrence of fat necrosis is extremely rare, in fact "only occurs at a rate of 0.06%". It appears this number (4 out of 6400 patients) was calculated from the FDA-AERS database. The FDA specifically guides that the data presented in the system should not be used to compare products or to demonstrate safety and efficacy of a particular product because the numbers are neither comprehensive nor representative of actual incidence. (www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard) In addition, of the three papers from the 60s referenced as support, only one provides an occurrence of subcutaneous atrophy at 22%, not 0.06% (Fisherman et al., 1962). Of the other two papers, Beardwell, 1967 is a single case report of subcutaneous atrophy occurring after a local triamcinolone injection. And Pariser, 1963 is a report of psoriasis lesions injected with various concentrations of triamcinolone with coexisting atrophy at higher doses, but no rate was given. As such, none of the sourced references provide support for their claim.

What does the literature say about triamcinolone use?
The white paper quotes one small, non-randomized, non-blinded study of 8 patients using a single triamcinolone acetonide injection into lipomas (Hayward et al., 2018) to claim that it is safe and effective. The problem is this study is extremely limited by its size, the patient population, as well as the method of administration; none of which are relevant to using triamcinolone in testosterone pellets implanted subcutaneously in hypogonadal patients.

Keeping with the lack of supporting evidence, the white paper claims that compared to systemic corticosteroid injections, local injection complications are extremely rare, "less than 1%." However, the sources included do not support this claim:

> Brinks, 2010—the largest study referenced in this white paper is a systematic review (87 relevant studies) of extra-articular corticosteroid injections and reported adverse events. Major adverse events included one death associated with necrotizing fasciitis, osteomyelitis, and tendon ruptures ranging from 0-5.8%. The minor adverse events included atrophy of the plantar fat, cellulitis, ecchymosis and local skin effects such as atrophy and hypopigmentation ranging from 0-81%. These rates are a far cry from the claimed "less than 1%".
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> Hanasano, 2002 reported correction of a common rhinoplasty complication using a local triamcinolone injection. The study reported 2 intralesional injections after surgery in 92 patients, the first at 1 week and 2nd at 4 weeks. No complications were reported. Again, the patient population, mode of administration and length of use is not relevant to the discussion.
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> Kanbe, 2016—intra-articular injection of triamcinolone along with Golimumab treatment (biologic for Rheumatoid Arthritis) of 20 patients. Only the largest and most symptomatic joint was injected to reduce the triamcinolone dose. Complications were not measured or reported; thus this report cannot be used to make a claim of safety.
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> Martins, 2017—single case report reporting that fat grafting can be used to treat local corticosteroid injections caused subcutaneous fat atrophy and hypopigmentation.
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> Neal, 2017—letter to journal, single case report of hypopigmented patch over the left knee with serpiginous hypopigmentation and subtle atrophy, apparently coursing over superficial veins involving an area of approximately 10 x 20cm in a 49-year-old woman after corticosteroid injections for 2 months.
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> Pace, 2018—soft tissue atrophy related to corticosteroid injections review for hand surgeons. 'The incidence of soft tissue complications is reported to be as high as 31% for de Quervain tenosynovitis and up to 40% for lateral epicondylitis.' For patients who continue to have bothersome soft tissue atrophy, fat grafting has been shown to be a safe and effective treatment modality.
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> Parveen, 2015—small RCT (24 patients) comparing conservative treatment for chalazion (chronic lipogranuloma of the eyelid) to 1 injection of triamcinolone acetonide. One patient (8.3%) ended up with hypo-pigmentary skin changes at the treatment site.

Park, 2013—single case report of 46yo woman who had one injection of triamcinolone acetonide into her wrist and developed hypopigmentation, muscle atrophy and nerve injury. She eventually required surgery.

Does the literature support long-term safety claims?
On page 3, the white paper attempts to close the chapter on safety concerns by stating 'the conclusion based on available literature all complications "may be greatly reduced" and using "less than 1mg/1ml can negate these adverse outcomes". However, once again the referenced sources do not support the claims:

Neal, 2017—letter to journal, single case report of irregular, linear hypopigmentation and atrophy of the knee in a 49-year-old woman after corticosteroid injections for 2 months.

Park, 2013—single case report of 46yo woman who had one injection of triamcinolone acetonide into her wrist and developed hypopigmentation, muscle atrophy and nerve injury. She eventually required surgery.

Wu & Goldman, 2018—single, double-blinded RCT (20 patients) received triamcinolone along with calcium hydroxylapatite (CaHA) as a specific soft-tissue filler for the correction of volume loss to the dorsal hands in elderly women. Patients received a one-time injection of triamcinolone and were followed up to 360 days but the study had a high rate of patient drop-out. To decrease the risk of atrophy in this study, they used a low concentration of triamcinolone acetate (2 mg/mL) and a large concomitant volume of normal saline (5 mL).

Not one of these references states that using less than 1mg/ml can negate the adverse outcomes of local corticosteroid use. In addition, none of these references use long-term subcutaneous applications of corticosteroids. Discussion of complications related to individual or single injections are not relevant to a constant long-term exposure to triamcinolone – even at low doses.

Where are the references for 50-75% reduction in extrusion rates?
On page 3, the authors claim subcutaneous testosterone/triamcinolone pellets yield better outcomes, but do not provide any referenced or published data to support the claim. In fact, they state that the triamcinolone/testosterone pellet extrusion rates were reduced by 50% in males and females and 75% in males alone. To demonstrate such a dramatic decrease they would have had to randomize patients to Triamcinolone vs T alone inserted by the same providers in a double-blinded fashion, to date that study has not been reported.

Finally, in what appears to be a concluding statement: "Triamcinolone used subcutaneously in doses of 10mg/ml or less have shown zero side effects of fat atrophy or necrosis and have been deemed safe and efficacious" is made with no reference or supporting data. Such a definitive claim should certainly be backed up with high quality evidence.

Conclusion
In summary, to date there is no published data on the safety and efficacy of triamcinolone containing testosterone pellets used to optimize hormone levels. The data that does exist on the use of triamcinolone in the body has not been used long-term, has not been administered subcutaneously in pellet form, and has not been used in a population of patients who are hypogonadal. Until there is data to support these claims, caution should be used when deciding to add a synthetic corticosteroid (triamcinolone) to a testosterone pellet. Studies assessing circulating steroid levels and long-term immunosuppression with this therapy will be essential before concluding that it is safe. Blinded studies comparing T alone vs T+ triamcinolone pellets inserted by experienced providers are needed before concluding that there is an improvement in pain, scarring or extrusion rates with the addition of triamcinolone.

Bibliography

Beardwell A. Subcutaneous atrophy after local corticosteroid injection. Br Med J. 1967 Sep 2;3(5565):600

Bleeker ER, et al. Systematic literature review of systemic corticosteroid use for asthma management. Am J Respirat Crit Care Med; 201 (3) 276-293

Brinks A, et al. Adverse effects of extra-articular corticosteroid injections: a systematic review. BMC Musculoskelet Disord. 2010 Sep 13;11:206

DeNeui T. Graves J. Subcutaneous testosterone pellet implants understand the role of triamcinolone. *Evexias Health Solutions.* Winter 2018. (unpublished)

Fisherman EW, Feinberg AR, Feinberg SM. Local subcutaneous atrophy. JAMA. 1962 Mar 24;179:971-2.

Hanasono MM, et al. Correction of the soft tissue pollybeak using triamcinolone injection. Arch Facial Plast Surg. 2002 Jan-Mar;4(1):26-30

Hayward WA, et al. Intralesional Injection of Triamcinolone Acetonide for Subcutaneous Lipoma causing Musculoskeletal and Neurologic Symptoms. J Clin Aesthet Dermatol. 2018 May;11(5):38-42.

Kanbe K, et al. Simultaneous Treatment with Subcutaneous Injection of Golimumab and Intra-articular Injection of Triamcinolone Acetonide (K-Method) in Patients with Rheumatoid Arthritis Undergoing Switching of Biologics: Retrospective Case-Control Study. Clin Med Insights Arthritis Musculoskelet Disord. 2016 Apr 4;9:45-9

Martins N, et al. Treatment of Persistent Cutaneous Atrophy After Corticosteroid Injection With Fat Graft. Reumatol Clin (Engl Ed). 2019 Nov-Dec;15(6):e122-e124

Neal D, et al. Serpiginous hypopigmentation secondary to intra-articular corticosteroid injection. Dermatol Online J. 2017 Apr 15;23(4):13030

Ni J, et al. Subcutaneous Injection of Triamcinolone and Lidocaine to Prevent Postherpetic Neuralgia. Pain Physician. 2017 20.5:397-403

Pace CS, Blanchet NP, Isaacs JE. Soft Tissue Atrophy Related to Corticosteroid Injection: Review of the Literature and Implications for Hand Surgeons. J Hand Surg Am. 2018 Jun;43(6):558-563

Pariser H, Murray PF. Intralesional injections of triamcinolone. Effects of different concentrations on psoriatic lesions. Arch Dermatol. 1963 Feb;87:183-7

Park S, et al. Hypopigmentation and subcutaneous fat, muscle atrophy after local corticosteroid injection. Korean J Anesth. 2018 65.6 Suppl S59-E61

Parveen S, et al. Comparison of subcutaneous extralesional and intralesional triamcinolone injection for the treatment of chalazion. Pakistan Armed Forces Med J. 2015; 4:502

Wu D, Golman MP. Randomized, Double-Blind, Sham-Controlled, Split-Hand Trial Evaluating the Safety and Efficacy of Triamcinolone Acetate Injection After Calcium Hydroxylapatite Volume Restoration of the Dorsal Hand. Dermatol Surg. 2018; 44.4:534-541