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(54) **Title:** PHARMACEUTICAL COMPOSITION FOR TREATMENT OF PHIMOSIS USING TOPICAL CORTICOSTEROID

(57) **Abstract:** This invention addresses the pharmaceutical composition for topical corticosteroid use in association with diffusing enzyme for treatment of phimosis. A pharmaceutical composition for treatment of phimosis using topical corticosteroid characterized by including around 0.025 to 5 percent in weight in relation to the total weight of the mixture composition of one or more corticosteroids and/or hormone steroids, whether or not associated with non-hormonal anti-inflammatory agents and around 25 UTR to 4000 UTR/g of one or more proteolytic diffusing enzymes in proper medium, in different pharmaceutical forms, accompanied with additives known to the technical man. Topical corticosteroid application in association with diffusing enzyme for treatment of phimosis in which 90 percent of the patients had improvements over their clinical complaints, with the prepuce being easily retracted.

PHARMACEUTICAL COMPOSITION FOR TREATMENT OF PHIMOSIS USING TOPICAL CORTICOSTEROID.

This invention addresses the use of pharmaceutical composition for topical corticosteroid and/or hormonal steroids in association with proteolytic diffusing enzyme, whether or not in the presence of non-hormonal anti-inflammatory agents, for treatment of phimosis. The invention scope includes the pharmaceutical industry, prescription compounding services, and physicians.

Phimosis is more often suspected than actually found. What most frequently happens is an adhesion of the prepuce and the glans, which will detach normally from each other over time. Typically, the prepuce will not retract at birth, but this condition is often resolved within the initial four years of age. As the penis gets larger, epithelial debris will build up under the prepuce and eventually separate the prepuce from the glans. In countries where circumcision is not performed commonly, treatment is seldom found to be necessary. Spontaneous improvement comes with maturity.

The incidence of phimosis decreases from 8 percent to 1 percent in adolescents (Oster J, *Further Fate of the Foreskin,* Arch Dis Child, 1968, 43: 200-3). The number of cases is as low as 0.4/1000 boys per year.

In the last few years there has been a heated debate over routine circumcision. Effective as it may be, this procedure may result in bleeding, meatal stenosis and tissue injuries which in turn may lead to an amputated glans or urethral coetaneous fistulas. In 1981 the circumcision rate was 80 percent in the USA. This rate has been diminishing over the last decades.

Phimosis is a vague term used commonly, and it generally means a condition in which the penis skin cannot be retracted. Rickwood described as true phimosis the

presence of a whitish sclerotic ring keeping the prepuce from retracting. Studies conducted in the United Kingdom show that physicians are not trained to distinguish the normal development of preputial adhesions from pathologic phimosis. This indicates that normal development is improperly classified as phimosis. As a result, a large number of unnecessary circumcisions is performed.

The state of the art quotes the article *Phimosis: Is Circumcision Necessary* by Dewan PA, Tiv HC, Chieng BS, Journal of Paediatrics & Child Health, vol 32(4) August 1996 pp 284-289, which comments on the effectiveness of certain treatments that avoided circumcision surgery.

An article published on the British Journal of Urology: *The Conservative Treatment of Phimosis in Boys* by Golubovic Z, Milanovic D et al, vol 78(5), November 1996 , pp 786-788, quotes a successful treatment in boys over three years of age who used 0.05 percent betamethasone cream topically as compared to patients that underwent a topical treatment using neutral cream (petroleum jelly) only. The article *The treatment of Childhood Phimosis with Topical Steroid* by Pless T K, Spjeldness N, Jorgensen T M, Ugeskrift for Laeger (DK), vol 161 (47), pp 6493-6495, 1999, describes the same type of treatment, i.e., topical application of 0.05 percent betamethasone cream.

Another article also describes infant treatment using topical application of 0.05 percent betamethasone cream: *Conservative Treatment of Phimosis in Children Using a Topic Steroid* by Orsola A, Caffaratti J, Garat JM, Urology (Online), 56 (2): 307-10, 2000 Aug 1.

Yet another article, *Topical Steroid Treatment of Phimosis in Boys*, by Chu C C, Chen K C, Diau G Y, The Journal of Urology, vol 162 (3-I) September 1999, pp 861-863, also comments on the results from topical application following

hygienizing using 0.06 percent betamethasone cream. The article *Medical Management of Phimosis in Children: Our Experience with Topical Steroids* by Monsour MA, Rabinovitch HH, Dean GE, The Journal of Urology, vol 162 (3-II) September 1999, pp 1162-1164, comments on the successful topical treatment of boys with phimosis symptoms using 0.05 percent betamethasone cream.

For topical phimosis treatment there is a number of types of steroids, in the form of 0.5 percent betamethasone creams, 1 and 2 percent hydrocortisone, and 0.05 percent betamethasone, 0.05 percent clobetasol, corticoid together with HCG injection, 0.05 percent betamethasone, 0.1 percent strogen; 1 percent hydrocortisone, etc.

Wright reported a significant improvement in 80 percent of 111 patients treated with betamethasone cream (Wright JE, *The treatment of Childhood Phimosis with Topical Steroid.* Aust New Zeal J Surg, 1994, 64: 327-330). Lindhagen reported a 70 percent success using clobetasol propionate, a powerful corticosteroid, but this should be used with caution in these cases (Lindhagen T, *Topical Clobetasol Propionate Compared with Placebo in the Treatment of Unrectractable Foreskin*, Eur J Surg, 1996, 162:969-972). Kirikos et al (Kirikos CS; Beasley SW and Wood AA, *The Response of Phimosis to Local Steroid Application*, Pediatric Surgery, 1993, 8:329-332), showed improvement in around 80 percent using 2 percent hydrocortisone. There are no reports of local or systemic adverse effects (the corticoid absorption surface is as small as 0.1 percent of the body). These studies involved groups of patients with median of age around 6 years (2-15 years).

A conservative treatment is less costly than a surgical one. The betamethasone cream for 4 weeks was found effective, with a success rate of 70-75 percent less costly than circumcision (Van-Howe RS, *Cost-Effective Treatment of*

Phimosis. Pediatrics, 1998, 102 (4):E43).

A controlled study (Atilla KK, Dündaroz R; Odabas Ö; Öztürk H; Akin R and Gökçay, *A Nonsurgical Approach to the Treatment of Phimosis: Local Nonsteroidal Anti-Inflammatory Ointment Application*, J. Urology, 1997, 158:196-197) used a non-steroidal anti-inflammatory agent instead of a corticoid as an alternative for cases in which corticosteroids are contraindicated. Around 75 percent of results – complete or partial improvement – were achieved.

Recent studies have described a more conservative approach to phimosis using both topical steroids and non-steroidal anti-inflammatory agents applied to the fibrotic ring. These reports have shown satisfactory results of 67-95 percent, with no adverse effects (Marzaro M, Carmignola G, Zoppellaro F, Schiavon G, Ferro M, Fusaro F, Bastasin F, Perrino G; Fimosi: *quando and patologia di interesse chirurgico*? Minerva Pediatr, 1997, 49(6):245-248).

None of these articles comments on the association of steroids with diffusing agents to render a treatment more effective.

In order to help fight the morbidity from circumcision, hemorrhage (4-6 percent), ulcer, and meatal stenosis (11 percent), infection (4-6 percent), urethral fistula, removal of improper amounts of skin resulting in a new phimosis, the Applicant developed a new treatment using topical corticosteroid application in association with diffusing enzyme, which proved a new effective treatment. A synergism was found to exist between the properties of proteolytic enzymes and corticosteroids in the treatment of phimosis, with more promising results than those obtained from the use of steroids, or corticosteroids where such enzymes are not present, such as symptoms disappearing within shorter periods of time.

The invention is intended to develop a new composition for topical treatment

of phimosis to help the prepuce detach from the glans by impacting the depolymerization of the hyaluronic acid of the conjunctive tissue between both structures, so that a reduction can be achieved in the resolution time, side effects, effectiveness, and total treatment costs by using corticosteroids either or not associated with hormonal steroids, or non-steroidal anti-inflammatory agents and proteolytic diffusing enzymes.

This invention resulted in resolved phimosis in 90 percent of the patients between 1 and 30 years of age. Therefore, a patient – who in most cases is a child – is not exposed to the surgical trauma/risk. The prepuce skin remains integral, and the sensory and psychological functions are preserved.

This new topical application using composition for topical application using corticosteroids and/or hormone steroids in association with proteolytic diffusing enzyme, whether or not in the presence of non-hormonal anti-inflammatory agents, for treatment of phimosis, helps the prepuce detach from the glans by impacting the depolymerization of the hyaluronic acid of the conjunctive tissue between both structures, thus yielding unusual results.

This invention resulted in phimosis resolution in 90 percent of the patients aged 1 to 30 years. Therefore, patients – mostly children – are not exposed to the surgical trauma/risk. The prepuce skin remains integral, and the sensory and psychological functions are preserved.

This new invention is aimed at the treatment of phimosis in both children and adults using topical corticosteroid application in association with diffusing enzyme to prevent circumcision (surgical treatment), with better (90 percent) results in relation to the topical use of either steroidal or non-steroidal anti-inflammatory agents.

The association with the enzyme helps the prepuce detach from the glans by

impacting the depolymerization of the hyaluronic acid of the conjunctive tissue between both structures, thus accentuating the local anesthetic and leading to the lysis of the adhesions between the prepuce and the glans, with better results than those obtained with the existing treatment of phimosis.

In conclusion, the association of corticosteroid with diffusing enzyme has proved more effective than all existing treatments and is an innovative therapy for both adult patients and pediatric ones.

The Applicant developed a pharmaceutical composition for treatment of phimosis using topical corticosteroid characterized by including around 0.025 to 5 percent in weight in relation to the total weight of the mixture composition of one or more corticosteroids and/or hormone steroids, whether or not associated with non-hormonal anti-inflammatory agents, and around 25 UTR to 4000 UTR/g of one or more proteolytic diffusing enzymes in proper medium, under different pharmaceutical forms, accompanied with additives known to the technical man.

Usable corticoids may be chosen from, for example, the group: Betamethasone, hydrocortisone, cortisone, hydrocortisone acetate or buteprate or butyrate or valerate, clobetasol or clobetasol propionate, propionate or dipropionate or valerate or phosphate or acetate and other esters of betamethasone, alclometasone dipropionate, deoxymetasone, clocortolone pivalate, diflorasone diacetate, fluocinolone acetonide, flurandrenolide, metilprednisolone acetate, mometazone furoate, diflorasone diacetate, amcinonide, fluocinonide, halobetazole propionate, desonide, triamcinolone acetonide and mixtures thereof, etc.

Ideally, around 0.5 to 3 percent in weight should be used in relation to the total weight of the mixture of one or more corticosteroids such as those of the betamethasone family, or 2-phenyl-1,2-benzisoselenasol-3(2H)-one and its by-

products.

Betamethasone is a synthetic fluorinated corticosteroid in the form of a white or almost white crystalline powder, water-insoluble, and partially alcohol-soluble. It is used for this type of application, ideally in the form of ester such as valerate, propionate, dipropionate, phosphate, or acetate.

Hormonal steroids may be used in association with the composition's components such as testosterone.

Figure 1 shows the structural formula of betamethasone in its particularly usable form: Betamethasone valerate.

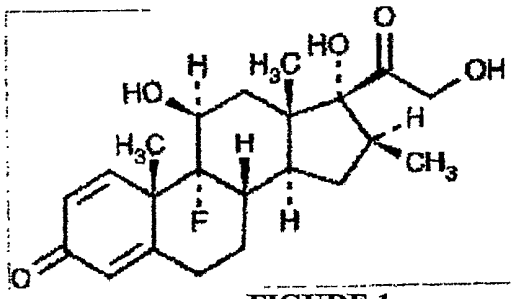

FIGURE 1

The steroidal agent may be alternatively used associated with one or more non-hormonal anti-inflammatory agents such as those chosen from the group: Diclofenac, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, ketoprofen, piroxicam, flurbiprofen, oxaprozin, etc. Ideally, diclofenac is used.

Associated with those, one or more proteolytic diffusing enzymes of about 25 to 4000 UTR/g are used, ideally within around 75 to 2000 UTR/g, such as hyaluronidase.

Hyaluronidase is prepared commercially using bovine or ovine testicles, or biotechnological processes, and is marketed in the form of sterile or nonsterile yophil.

Hyaluronidase depolymerizes the hyaluronic acid present in the interstitial substances of tissues, particularly the skin and synovial fluid. The hyaluronic acid consists of a chain of glycuronic-N-acetylglycosamine units polymerized by stable glycoside links, which are split by hyaluronidase. The resulting decreased viscosity contributes to diffusing the substances through the tissues.

Hyaluronidase may be added to parenteral fluids such as saliva, glucose, lactate, and plasma to accelerate absorption and reduce local tissue distension. The absorption in traumatic edema or post-surgical regions, or hematoma may be accelerated by infiltration of hyaluronidase and use of a garrote. Likewise, the inflammation caused by accidental spilling of irritative solutions may be diminished.

The composition may be applied using gel, ointment, cream, aerosol, or any other form of topical application.

A few examples to illustrate the invention follow.

EXAMPLE 1

A prospective study was conducted with 100 male patients with phimosis diagnosis. Thirty-nine patients were between 1 and 5 years (3.25 years average) – group 1, and 61 between 6 and 30 years (12.49 years average) – group 2. No case referred topical or surgical treatment background, nor local inflammatory process. All patients were treated with topical compound made of 0.2 percent betamethasone added with 150 UTR hyaluronidase prepared in the form of ointment. The patients were directed to use the ointment once or twice a day until process resolution, but not longer than 12 weeks.

The product was applied by the patient, or the parents if infants, to the fibrotic ring, then the prepuce was retracted slightly. Caution was taken to prevent the retraction from causing the patient pain or bleeding.

The treatment was found effective in the cases of complete phimosis resolution following the aforementioned period.

The patients were asked about the presence of local irritative symptoms, terminal dysuria, or bleeding during the treatment.

For analysis of the results both groups were compared for a possible relation between the patient's age and the result from the medication and the time taken to obtain clinical improvement. For this the Student's T-Test was used to compare mean values, using a 5 percent level of significance.

RESULTS

Ninety (90 percent) patients who reacted to the clinical treatment had phimosis resolution, and 32 percent had major prepuce retraction with no pain or bleeding, and 58 percent had complete symptomatology resolution.

Local irritative symptoms such as hyperemia and feeling of local burning were found in 5 percent of the patients, but those regressed completely after the treatment was suspended. After a few days with no application of the ointment the patients began to use it again with satisfactory results.

Five (5 percent) of the patients needed to be retreated, with satisfactory results.

The mean time of medication usage was 38 days for the group between 1 and 5 years and 42 days for the group between 6 and 30 years.

The statistical analysis did not show any differences between the clinical response and the time of usage of the compound between both groups, yielding statistically similar results between the age ranges evaluated ($p > 0.05$).

EXAMPLE 2

A topical cream was prepared including:

Betamethasone	0.2 percent (in weight in relation to mass...)
Hyaluronidase	150 UTR
Ointment	1 g

The procedure here was similar to that of the previous example for three patients with phimosis symptoms, as follows:

PATIENT 1

Patient 18 months of age with phimosis diagnosis, treated earlier with 0.05 percent hydrocortisone ointment with no results. The treatment began with the aforementioned association applied twice a day for four weeks with complete symptomatology resolution.

PATIENT 2

Patient 16 years of age, pubescent, and presenting phimosis.

The same treatment was administered for 8 weeks, with appropriate resolution at the sixth week. This is an evidence of its utility at higher age ranges.

PATIENT 3

Patient 7 years of age with phimosis recurrence following glans exposure with massages as instructed by a pediatrician.

The treatment began with the instruction that for secondary phimosis it could take as long as 12 weeks.

The treatment was effective after 10 weeks using the ointment.

Patient	Age	Cream Composition	Application	Resolution
1	18 months	0.2 percent betamethasone and 150 UTR of hyaluronidase	twice a day for 4 weeks	Complete
2	16 years	0.2 percent betamethasone and 150 UTR of hyaluronidase	twice a day for 8 weeks	Appropriate
3	7 years	0.2 percent betamethasone and 150 UTR of hyaluronidase	secondary phimosis, twice a day for 10 weeks	Effective

These are clinical examples in different situations of good clinical results that may be achieved using the mentioned ointment to prevent both the surgical trauma and additional costs.

CLAIMS

1. A pharmaceutical composition for treatment of phimosis using topical corticosteroid characterized by including between around 0.025 to 5 percent in weight in relation to the total weight of the mixture composition of one or more corticosteroids and/or hormone steroids, whether or not associated with non-hormonal anti-inflammatory agents and around 25 UTR to 4000 UTR/g of one or more proteolytic diffusing enzymes in proper medium, under different pharmaceutical forms, accompanied with additives known to the technical man.

2. A pharmaceutical composition for treatment of phimosis using topical corticosteroid according to claim 1 characterized by ideally using about 0.5 to 3 percent in weight in relation to the total weight of the mixture of one or more corticosteroids.

3. A pharmaceutical composition for treatment of phimosis using topical corticosteroid according to claim 1 characterized by corticosteroids being capable of being chosen from the group: Betamethasone, hydrocortisone, hydrocortisone cortisone, acetate or buteprate or butyrate or valerate, clobetasol or clobetasol propionate, propionate or dipropionate or valerate or phosphate or acetate or other esters of betamethasone, alclometasone dipropionate, deoxymetasone, clocortolone pivalate, diflorasone diacetate, fluocinolone acetonide, flurandrenolide, metilprednisolone acetate, mometazone furoate, diflorasone diacetate, amcinonide, fluocinonide, halobetazole propionate, desonide, triamcinolone acetonide and mixtures thereof, etc.

4. A pharmaceutical composition for treatment of phimosis using topical corticosteroid according to claim 1 characterized by ideally using about 75 to 2000 UTR/ g of one or more proteolytic diffusing enzymes.

5. A pharmaceutical composition for treatment of phimosis using topical corticosteroid according to claim 1 and 2 characterized by the use of corticosteroid of the betamethasone family and its by-products.

6. A pharmaceutical composition for treatment of phimosis using topical corticosteroid according to claim 4 characterized by the use of 2-phenyl-1,2-benzisoselenasol-3(2H)-one, ideally in the form of esters, such as propionate, dipropionate, valerate, phosphate or betamethasone acetate.

7. A pharmaceutical composition for treatment of phimosis using topical corticosteroid according to claim 1 characterized by being capable of including anti-inflammatory agents such as those chosen the group: Diclofenac, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, ketoprofen, piroxicam, flurbiprofen, oxaprozin, etc..., diclofenac being chosen ideally.

8. A pharmaceutical composition for treatment of phimosis using topical corticosteroid according to claim 1 and 7 characterized by ideally using diclofenac as an anti-inflammatory agent.

9. A pharmaceutical composition for treatment of phimosis using topical corticosteroid according to claim 1 characterized by the ability to be used in association with corticosteroids, hormonal steroids such as testosterone.

10. A pharmaceutical composition for treatment of phimosis using topical corticosteroid according to claim 1 characterized by ideally using proteolytic enzyme of the hyaluronidase family.

11. A pharmaceutical composition for treatment of phimosis using topical corticosteroid according to claim 1 characterized by the use of hyaluronidase.

12. A pharmaceutical composition for treatment of phimosis using topical corticosteroid according to claim 1 characterized by its ability to be presented in the form of gel, ointment, cream, aerosol, or any form of topical application.