

Evaluation of Adverse Reactions and Effects of Triamcinolone Acetonide Combined with Compound Betamethasone in Keloid

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Zhang *et al.*: Effects of Triamcinolone Acetonide Combined with Compound Betamethasone in Keloid

To explore the drug effect and adverse reaction of triamcinolone acetonide combined with compound betamethasone in keloid is the objective of the study. 100 patients were randomly divided into study group and control group (50 patients in each group). The research group received sequential treatment with triamcinolone acetonide injection combined with compound betamethasone injection and the control group received compound betamethasone injection. Both groups had 3 courses of treatment and each course of treatment lasted for 3 w. The Vancouver scar scale score, treatment effect and adverse reactions were compared between the two groups and the recurrence rate was followed up for 1 y after the end of medication. Before treatment, there was no significant difference in Vancouver scar scale scores between the two groups but after medication, the study group was better than that of the control group ($p < 0.05$). The total effective rate of the study group (82 %) was higher than that of the control group (54 %, $p < 0.05$). The total incidence of adverse drug reactions in the study group was 8 % while in the control group it was 6 % and the comparison between the two groups was not statistically significant. The recurrence rates of the study group and the control group were 28 % and 34 % 6 mo after the end of medication and 32 % and 42 % after 12 mo. There was a significant difference between the two groups. The sequential injection of triamcinolone acetonide combined with compound betamethasone is effective in the treatment of keloids, with high safety and low recurrence rate, which is worthy of clinical recommendation.

Key words: Triamcinolone acetonide, compound betamethasone, keloid, adverse reactions, recurrence rate

Keloid is a common skin disease caused by skin injury, often secondary to burns, scalds, surgery or other trauma. Keloids are mostly abnormal scar tissue produced by excessive wound healing after the body has been injured^[1]. Its main feature is excessive collagen deposition and its clinical manifestations are abnormal itching, hard skin, reddish color, hypertrophy of extracutaneous tissue and irregular shape. Individuals with scar tissue are often difficult to treat and prone to recurrence because of their strong scar physique. At present, the clinical treatment methods for keloids mainly include compression therapy, surgery, cryotherapy, drug therapy and laser therapy. Surgical treatment, cryotherapy, laser treatment and other methods have quick results, but the recurrence rate is high. At present, drug

treatment of keloid is widely used in dermatology or plastic surgery because of its advantages of low cost, good curative effect, good compliance, high safety and low recurrence rate. Common drugs for keloids include prednisone injection, imiquimod cream, triamcinolone acetonide injection, botulinum toxin type A, compound betamethasone injection, etc. Triamcinolone acetonide belongs to the class of drugs, corticosteroids especially glucocorticoids and it is the earliest clinical drug used in keloids. Triamcinolone acetonide can effectively inhibit the proliferation of fibroblasts and inflammation, inhibit the growth process of scar and the appearance of granulation tissue in the process of normal tissue healing, it can also relieve the exudation of inflammatory fluid and promote the blood circulation

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of wound tissue. Compound betamethasone is a long-acting corticosteroid preparation, the main components of which are betamethasone dipropionate and betamethasone sodium phosphate, which have the effects of anti-inflammation, anti-allergy and inhibition of tissue proliferation. This paper mainly discusses the efficacy, recurrence rate and side effects of triamcinolone acetonide combined with compound betamethasone and compound betamethasone alone in the treatment of keloids.

MATERIALS AND METHODS

Sources of information:

According to the data inclusion and exclusion criteria, 100 keloid patients admitted to our hospital from January 2021 to December 2021 were selected. The researchers divided them into two groups according to the odd and even number of visits, including 50 patients in the study group and 50 patients in the control group. There was no significant difference between the two groups in terms of gender, age, course of disease and disease location ($p>0.05$) as shown in Table 1.

Inclusion criteria: Inclusion criteria include patients with keloids confirmed by clinical diagnosis in our hospital; no other treatment methods were received 3 mo before inclusion and all the patients knew about the purpose of the study and signed the informed consent.

Exclusion criteria: Exclusion criteria include patients with diabetes, hypertension or other steroid hormone contraindications; combined with bacterial, fungal or uncontrolled systemic virus infection; pregnant or lactating patients; Lupus erythematosus or Acquired Immuno Deficiency Syndrome (AIDS) infection and patients with serious adverse reactions of compound beta drugs.

Research methods:

Research group: Triamcinolone acetonide injection combined with compound betamethasone injection was administered sequentially. Triamcinolone acetonide injection is produced by Zhejiang Xianju Pharmaceutical Co., Ltd. (Approval document H20033525, specification 1 ml, 40 mg \times 10 sticks/box). After disinfection of the local skin of the keloid, triamcinolone acetonide injection and lidocaine injection (manufactured by Chengdu First Pharmaceutical Co., Ltd., H51021662, specification 5 ml:0.1 g) were mixed according to the principle of 1:1 and then injected. The injection method was to puncture along the edge of the keloid slowly and evenly injects the drug into the patient's tissue. In the 2nd w, compound betamethasone injection was mixed with lidocaine and then injected. Compound betamethasone injection is produced by Chongqing Huabang Pharmaceutical Co., Ltd., approval document H20093412, specification: 1 ml, 5 mg betamethasone dipropionate (calculated as betamethasone) and 2 mg betamethasone sodium phosphate (calculated as betamethasone). Compound betamethasone injection and lidocaine were dispensed according to the principle of 5:1. The injection method is the same as triamcinolone acetonide injection. Observation was carried out for 1 w after treatment, 1 course of treatment was ended and a total of 3 courses of treatment were performed.

Control group: Compound betamethasone injection as a single drug was used. Compound betamethasone injection and lidocaine were dispensed according to the principle of 5:1. The injection method was the same as that of the research group. One injection every 3 w was given as a course of treatment and a total of 3 courses of treatment were performed.

TABLE 1: COMPARISON OF GENERAL INFORMATION OF TWO GROUPS OF PATIENTS

General information	Research group	Control group
Patients	50	50
Gender: Male/Female	24/26	23/27
Age	35.16 \pm 3.86	36.24 \pm 3.64
Disease duration (y)	8.12 \pm 1.08	8.14 \pm 1.11
Diseased site		
Chest	16	17
Abdomen	9	10
Back	6	6
Neck	3	2
Shoulders	8	7
Buttocks	3	5
Limbs	5	3

Observation indicators and evaluation criteria: Vancouver Scar Scale (VSS) standard is adopted for keloid scoring. The patients were followed up for 3 mo after the end of the medication and the VSS was used for integral evaluation. The lower the total score, the better the effect as shown in Table 2.

Comparison of drug effect between the two groups:

The drug effect is divided into four parameters- Cured, markedly effective, effective and ineffective. Cured-The keloids disappeared completely, the skin color returned to normal and there was no itching; markedly effective-Most of the scars were not obvious, the skin lesions were smoother, the skin color became lighter and intermittent itching was not obvious; effective-Some scars were not obvious, the area of the scars was reduced, the damaged skin became softer, the skin color was redder and there was intermittent itching and ineffective-The symptoms had no sensory improvement compared with before the medication.

Effective rate=Recovery rate+Significant rate+Improvement rate

Observation of adverse drug reactions in the two groups: Adverse drug reactions mainly include local ulceration, early menstruation, pigmentation, subcutaneous tissue atrophy and telangiectasia. The incidence of adverse reactions was counted.

Follow-up time and follow-up drug relapse rate:

6 mo and 12 mo after the end of the medication, the patients were followed up by telephone for their recurrence and the recurrence rate was counted.

Statistical analysis:

Statistical software, Statistical Package for Social

Sciences (SPSS) 16.0 was used to process relevant data and the comparison between the study group and the control group was performed by t-test or Chi square (χ^2) test and $p < 0.05$ was considered as a difference with statistical significance.

RESULTS AND DISCUSSION

Comparison of VVS scores between the two groups of patients before and after treatment was shown in Table 3. Before treatment, there was no significant difference in VSS scores between the two groups. 3 mo after the end of the medication, the VSS scores of the study group and the control group were all reduced, but the score of the study group was much lower ($p < 0.05$).

Comparison of drug effects between the two groups of patients was shown in Table 4. The effective rate of medication in the study group was 82 %, which was significantly higher than that of control group 54 % ($p < 0.05$).

Comparison of adverse drug reactions between the two groups of patients was shown in Table 5. After medication, 4 adverse drug reactions occurred in the study group and 3 adverse drug reactions occurred in the control group. There was no significant difference between the two groups.

Comparison of drug relapse rate between the two groups of patients was shown in Table 6. The drug relapse rate was compared between the two groups of patients. 6 mo after the end of medication, 14 patients in the study group and 17 patients in the control group showed relapse ($p < 0.05$). 12 mo after the end of medication, 16 patients in the study group and 21 patients in the control group showed relapse ($p < 0.05$).

TABLE 2: OBSERVATION INDICATORS AND VSS STANDARD SCALE

Score	Color	Thickness (H) mm	Vascular distribution	Softness
0	Normal skin color	Normal	Normal skin tone similar to the rest of the body	Normal
1	Lighter color	$0 < H \leq 1$	Pinkish skin tone	Supple (skin deformable with minimal resistance)
2	Mixed color	$1 < H \leq 2$	Reddish skin tone	Pliable (deformable under pressure)
3	Darker color	$2 < H \leq 4$	Purple in color	Hard (cannot be deformed, moves in blocks, resists pressure)
4		$H > 4$		Bending (tissue is rope-like and recoils when stretched)
5				Contractures (permanent shortening of the scar causing disability and distortion)

TABLE 3: COMPARISON OF VSS SCORES BEFORE AND AFTER TREATMENT ($\bar{x} \pm s$)

Group	n	Before medication	3 mo after the end of medication
Research group	50	9.42 \pm 1.17	4.29 \pm 0.96
Control group	50	9.41 \pm 1.15	6.88 \pm 1.06
t		0.086	4.72
p		>0.05	<0.05

TABLE 4: COMPARISON OF DRUG EFFECTS BETWEEN THE TWO GROUPS OF PATIENTS (CASES, %)

Group	n	Cured	Markedly effective	Effective	Ineffective	Total effective rate
Research group	50	15 (30)	21 (42)	5 (10)	9 (18)	41 (82)
Control group	20	6 (12)	18 (36)	3 (6)	23 (46)	27 (54)
χ^2						17.53
p						<0.05

TABLE 5: COMPARISON OF ADVERSE DRUG REACTIONS BETWEEN THE TWO GROUPS OF PATIENTS (CASES, %)

Group	n	Partial ulceration	Early menstruation	Pigmentation	Subcutaneous tissue atrophy	Telangiectasia	Total incidence
Research group	50	0	1 (2)	2 (4)	0	1 (2)	4 (8)
Control group	50	0	1 (2)	1 (2)	0	1 (2)	3 (6)
χ^2							0.686
p							0.826

TABLE 6: COMPARISON OF DRUG RECURRENCE RATES BETWEEN THE TWO GROUPS OF PATIENTS (CASES, %)

Group	n	6 mo after the end of medication	12 mo after the end of medication
Research group	50	14 (28)	16 (32)
Control group	50	17 (34)	21 (42)
χ^2		1.656	2.124
p		<0.05	<0.05

The pathogenesis of keloids is unclear. Studies have shown that keloids may be due to the excessive production of collagen fibers in the dermis of the body due to the immune response caused by Immunoglobulin E (IgE) and hyperplastic growth occurred^[2]. Studies have also shown that the rapid increase in the content of alpha (α)-globulin collagenase inhibitors in human scars has caused a rapid decrease in collagenase synthesis, resulting in a significantly high content of collagen fibers^[3]. Some scholars have pointed out that the formation

and regression of scars depend on the proliferation and apoptosis of fibroblasts^[4]. From this point of view, in the guidance of medication, we should pay close attention to the effect of drugs on fibroblasts. Studies have found that corticosteroids can inhibit the proliferation of fibroblasts and can degrade the synthetic matrigel and fibroblast responses^[5]. A variety of cytokines, growth factors and proteolytic enzymes are involved in the formation of keloids, including Transforming Growth Factor-beta (TGF- β), Epidermal Growth Factor (EGF), Vascular

Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF) and so on. In this study, the research on the expression levels of cytokines and extracellular matrix was ignored, which should be concentrated in the subsequent research centers. A hypoxic environment is also considered to be an important factor in wound healing. Some scholars have shown that in a hypoxic environment, it is more difficult to form keloids^[6]. Drug treatment methods, such as triamcinolone acetonide and compound betamethasone, can not only lead to the reduction of collagen and the formation of glycosaminoglycans, but also inhibit the occurrence of inflammation by inhibiting the pathway of fibroblast proliferation and forming a hypoxic environment. According to the previous analysis, the corticosteroid hormone triamcinolone acetonide and compound betamethasone can solve the problem of fibroblasts and hypoxic environment.

The molecular formula of triamcinolone acetonide injection is $C_{24}H_{31}FO_6$ and its main components include benzyl alcohol, sodium carboxymethylcellulose, polysorbate 80, sodium chloride and water for injection. Triamcinolone acetonide injection is essentially a long-acting glucocorticoid with long-acting anti-inflammatory effects. Its pharmacological mechanism is to inhibit the phagocytosis of antigens by macrophages, inhibit the transformation of beta (β) cells into plasma cells and achieve the purpose of immunity by interfering with body fluids; it also inhibits the growth of white blood cells and macrophages in the periphery of blood vessels and reduces the incidence of inflammation. The content of α -globulin collagenase inhibitor decreases rapidly and a large number of collagenase synthesis occurs, thereby promoting the decomposition between fibers, achieving flattening of the skin surface, thinning of the epidermis and reducing the gaps between collagen fibers^[7]. The use of triamcinolone acetonide injection is strictly regulated because when the concentration is too low, the curative effect is poor and when the concentration is too high, it is easy to accumulate in the skin and cause adverse reactions such as pigmentation decline and ulceration. The mechanism of triamcinolone acetonide in the treatment of keloids is mainly to reduce the occurrence of inflammation in the body and promote the shrinkage of scars, so as to indirectly achieve the effect of inhibiting the formation of keloids^[8]. Some scholars have demonstrated that the anti-inflammatory effect of triamcinolone acetonide

is 6.25 times that of cortisone^[9]. The molecular structure of triamcinolone acetonide contains a ketal group, which can enhance the activity of the skin surface and be more conducive to topical application. Triamcinolone acetonide inhibits the synthesis of proteins from amino acids, thereby inhibiting the synthesis of Deoxyribonucleic Acid (DNA) in fibroblasts, reducing the synthesis of collagen fibers and intercellular matrix and interfering with fibrous proliferation. Studies have shown that triamcinolone acetonide cause adverse drug reactions or complications such as telangiectasia and pigmentation and has disadvantages such as easy recurrence of previous condition^[10]. This also explains the occurrence of 4 adverse reactions in the study group, 14 patients in the 6 mo follow-up and 16 patients in the 12 mo follow-up showed recurrence respectively. Therefore, when using triamcinolone acetonide, proper care should be taken to avoid monotherapy.

Compound betamethasone is a long-acting corticosteroid preparation, in which the main components are betamethasone dipropionate and betamethasone sodium phosphate. Compound betamethasone can quickly disperse and shows effect because of the high solubility of betamethasone sodium phosphate in water. Among its components, betamethasone dipropionate is insoluble in water and difficult to be absorbed by human tissues. Its reaction is slow, but its sustainability is long and its curative effect is long. Compound betamethasone can bind to specific receptors and enter the nucleus of fibroblasts smoothly and regulate the expression of some genes, thereby reducing the synthesis of some functional proteins to control the levels of fibroblasts which leads to reduction in collagen production and the growth of granulation tissue is reduced in order to achieve the purpose of scar recovery^[11]. Studies have shown that compound betamethasone has the effects of anti-inflammation, anti-allergy and inhibition of tissue proliferation, but it should be avoided in patients with diabetes, fractures and chronic infection lesions^[12]. Studies have shown that compound betamethasone has the characteristics of relapse after drug withdrawal and it should be used in combination with other long-acting corticosteroids^[13]. In this study, compound betamethasone was used as a single drug and there were 3 adverse reactions. There were 17 patients who showed relapse in the 6 mo follow-up and 21 patients showed relapse in the 12 mo follow-up after the drug

treatment. This shows that compound betamethasone has a higher relapse rate after drug withdrawal.

The results of this study showed that the VSS scores of the two groups of patients were reduced after treatment and the VSS scores of the study group were much lower. According to the analysis, the possible reason is that the addition of triamcinolone acetonide injection can directly act on the fibroblasts of the scar and produce an inhibitory effect causing the keloid to soften and shrink. There were four adverse reactions in the study group and three adverse reactions in the control group, and only one adverse reaction was caused by triamcinolone acetonide. However, compared with the 3 adverse reactions of compound betamethasone, triamcinolone acetonide may be safer.

To sum up, triamcinolone acetonide combined with compound betamethasone in keloid has obvious effect and high safety, but the recurrence rate is not low. In the follow-up research, attention should be paid to the level of expression levels of cytokines and extracellular matrix in patients after treatment, and the issue of recurrence rate should be paid close attention and properly resolved.

Conflict of interests:

The authors declared no conflict of interest.

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