

# Efficacy of intravenous glutathione vs. placebo for skin tone lightening

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## Abstract

**Objective** To evaluate the efficacy and possible side effects of intravenous glutathione used for lightening the skin tone.

**Methods** This placebo-controlled study was conducted in department of dermatology, City Hospital, Multan from January 2014 to August 2015. Out of 50 enrolled patients 32 patients completed the study. All patients were females with age ranging from 25 to 47 years. In group A, 8 patients had deranged liver function tests and one patient who developed anaphylactic shock were excluded from study along with their controls from group B. Final results were concluded in only those patients who completed the study. 32 patients were treated in two groups (A & B). In group A 16 patients were given intravenous glutathione and vitamin C. Patients in group B were given intravenous normal saline as placebo. Taylor hyperpigmentation scale was used to measure the skin tone. Two body sites, which were non-exposed to sun, were measured with Taylor hyperpigmentation cards. Injection GSH Detox forte 1200 mg (aqua, glutathione 1200 mg, ascorbic acid, hydrolyzed collagen 35 mg and sodium chloride) was given. Two injections per week for 6 weeks (total of 12 injections) were given. The effectiveness and side effects were assessed at the end of therapy and 2 months, 4 months and 6 months after cessation of treatment.

**Results** After 12 injections of glutathione, 6 of 16 (37.5%) subjects showed significant improvement, whereas 3 (18.7%) subjects improved with placebo ( $p = 0.054$ ). After stopping the treatment, this improvement was gradually lost and at six-month posttreatment follow-up only one patient maintained this improvement. Adverse effects were noted in all subjects. Severe adverse effects warranting discontinuation of treatment were deranged liver function tests ( $n=8$ ) and patient anaphylaxis ( $n=1$ ).

**Conclusion** Glutathione is not very effective for skin tone lightening; moreover treatment loses its efficacy with time. The side effects of the treatment are common.

## Key words

Taylor hyperpigmentation scale, glutathione, anaphylaxis, skin tone.

## Introduction

Desire for skin whitening among males and females is increasing day by day. People are using different drugs in topical, oral and intravenous formulations to get the desired

complexion.<sup>1</sup> Glutathione is a new tool in the cosmetic industry. It is an antioxidant that is naturally synthesized in the body.<sup>2</sup> Glutathione is also found in many foods like fresh uncooked meat, dairy products and eggs.<sup>3</sup> Oral absorption is not reliable because of degradation by enzymes in digestive tract.<sup>4</sup> The proposed mechanism of action of glutathione for skin lightening is by direct inactivation of enzyme tyrosinase, mediating the switch from eumelanin to pheomelanin, quenching of free radicals and

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peroxidase and modulation of depigmenting abilities of melanocytotoxic agents.<sup>5-8</sup> Glutathione is available in market as oral, inhaled or topical formulations besides soaps and intravenous injectables.<sup>9</sup>

Measuring the exact skin tone is a challenging task. Different scientific devices are available which can assess the index of melanin and erythema.<sup>10,11</sup> Most of them are very expensive and require expertise to use. Taylor hyperpigmentation score is an easy and inexpensive way of measuring skin complexion. It can measure from skin type I to skin type VI.<sup>12</sup> More than 100 different skin hues can be measured.

This study was undertaken to evaluate the efficacy and safety of intravenous glutathione for skin tone enhancement in Pakistani population.

## **Methods**

This placebo-controlled study was conducted in department of dermatology, City Hospital, Multan from January 2014 to August 2015. As glutathione is not FDA approved, prior approval of study was taken from the hospital ethical committee. All patients were explained about the possible side effects and written informed consent was taken. Twenty-five healthy females, aged 25 to 47 year willing to participate in the study and pay for injection's cost were enrolled (group A). For every patient in group A, control of same skin tone and age was kept in group B, treated with placebo (normal saline). A thorough physical examination of all patients was carried out by a medical specialist. Complete blood count and liver function tests were conducted fortnightly. Exclusion criteria were age below 25 years, pregnancy and breast-feeding, personal or family history of vitiligo, deranged liver

function tests and history of any skin or systemic illness.

Skin tone was measured with Taylor hyperpigmentation scale. Taylor hyperpigmentation cards were used to measure skin lightening from dark to light shades. Even change of one shade is considered significant. Two body sites, unexposed to sun, were chosen; upper inner arm below the axilla and upper outer thigh of all patients were noted with Taylor hyperpigmentation cards. Measurements were done by two independent observers.

Injection GSH Detox forte® 1200 mg (aqua, glutathione 1200 mg, ascorbic acid, hydrolyzed collagen 35 mg and sodium chloride) was given. Two injections per week for 6 weeks with a total of 12 injections were given. One 5ml injection was diluted in 10ml distilled water. Butterfly needle was used to give slow intravenous injections over 30 minutes. Side effects were noted during each injection session. Skin tone assessment was done before starting treatment after completing 12 injections and then 2 months, 4 months and 6 months after completing injections.

## **Results**

The initial study was conducted in 50 patients (25 in group A treated with glutathione and 25 in group B i.e. controls) but only 32 patients completed the study. In group A, 8 patients had deranged liver function tests and 1 patient developed anaphylactic shock which were excluded along with their controls from study. Final results were evaluated in only those patients who completed the study i.e. 16.

**Table 1** shows the improvement in skin tone in two groups. After 12 injections of glutathione, 6 of 16 subjects i.e. (37.5%) showed significant improvement whereas 3 (18.7%) subjects

noticed improvement in skin tone ( $p = 0.054$ ). When two groups were analyzed individually,

treatment, as well as, placebo had insignificant

**Table 1** Improvement of skin tone after completion of 12 injections of glutathione.

Follow-up duration after completion of treatment	Group A (Glutathione) N=16	Group B (Placebo) N=16
0 (after completing 12 injections)	6 (37.5%)	3 (18.7%)
2 months	3 (18.7%)	2 (12.5%)
4 months	3 (18.7%)	0
6 months	1 (6.2%)	0

**Table 2** Side effects seen during glutathione treatment (n=25).

Side effect	N (%)
Feeling of warmth during injection	11 (44)
Abdominal cramps	10 (40)
Deranged liver functions	8 (32)
Feeling of heart sinking	7 (28)
Diarrhea	4 (16)
Paresthesia	4 (16)
Dizziness	3 (12)
Anaphylactic shock	1 (4)
Vomiting	1 (4)

effect on skin tone ( $p = 0.895$  and  $=0.998$ , respectively). After stopping the treatment, this improvement was gradually lost and at six-month posttreatment follow-up only one patient maintained this improvement.

Regarding side effects, all subjects in group A (n=25) encountered side effects (**Table 2**). No adverse effect was noted in any patient of group B.

## Discussion

In spite of much popularity, role of glutathione in skin whitening has not been properly evaluated. Search on *Pubmed* did not reveal any study assessing the role of intravenous glutathione in skin whitening, hence our results could not be compared. Nonetheless, results of our study challenge the skin lightening ability of glutathione. After 12 injections of glutathione administered in 6 weeks, only 6 (37.5%) subjects noticed at least one level improvement in their skin tone but similar to the placebo group. This improvement was not sustainable and six months after discontinuation of

treatment only one (6.2%) subject maintained this result. Besides poor efficacy, the treatment is also not cost-effective.

Theoretically, higher serum levels of glutathione are achieved after intravenous administration; nonetheless, it is also associated with higher risks and side effects. Hence, glutathione has been tried through other routes. Most of such studies have emanated from South Asia. Arjinpathana and Asawanonda<sup>1</sup> in their double-blind study compared oral glutathione 500mg daily in two divided doses with placebo in 60 healthy medical students. The primary end point of the study was reduction in melanin indices. At 4 weeks, they noticed a statistically significant reduction in melanin indices in the study population. Handog *et al.*<sup>4</sup> used glutathione lozenges in 30 Filipino females (skin type IV or V) daily for 8 weeks. They noticed a significant decrease in the melanin indices. No serious clinical or laboratory adverse effects were seen. In the double-blind study by Watanabe *et al.*<sup>13</sup>, 30 healthy adult women aged 30 to 50 years, applied glutathione 2% (weight/weight) lotion to

one side of the face and a placebo lotion to the other side twice daily for 10 weeks. At week 10, melanin indices were significantly lower on the glutathione-treated side. No significant side effects were observed with treatment. Why our results were lower than those using the oral, buccal and topical routes remains unanswered. Different genetic background of study population, the degree of sun exposure or different tool of assessment may contribute to lower results.

Safety of a new treatment modality is also a very important factor. All patients in our study experienced mild to severe adverse effects ranging from minor palpitation to anaphylactic shock and treatment had to be discontinued in 9 patients. This emphasizes that intravenous glutathione treatment needs special settings where anaphylaxis can be promptly managed. Compared to intravenous route, drug used through oral, buccal or cutaneous route is relatively safe. As glutathione shifts melanin synthesis pathway from eumelanin to pheomelanin, this may increase the risk of sun-induced malignancies, at least theoretically.<sup>14</sup> As glutathione is relatively newer treatment, its long-term safety remains a problem. Moreover, intravenous administration of very high doses of a powerful antioxidant like glutathione might subject the cells to potential risks of reductive stress.<sup>14</sup>

In addition to its many recognized biological functions, glutathione has skin lightening ability.<sup>2</sup> The role of glutathione as a skin whitening was discovered as a side effect of high doses of glutathione.<sup>15</sup> Glutathione utilizes different mechanisms to exert its action as skin whitening agent at various levels of melanogenesis.<sup>16</sup> It inhibits melanin synthesis by inhibiting L-DOPA to interact with tyrosinase in the process of melanin production.<sup>2,3,5</sup> Glutathione inhibits the production, as well as,

agglutination of melanin by interrupting the function of L-DOPA.<sup>2,3</sup> Glutathione also inhibits melanin formation by direct inactivation of the enzyme tyrosinase by binding and chelating copper within the active site of enzyme.<sup>2</sup> Antioxidant property of glutathione allows it to inhibit melanin synthesis by quenching of free radicals and peroxides that contribute to activation of tyrosinase and formation of melanin.<sup>3</sup> Increases in glutathione level induce the pigment cell to produce pheomelanin instead of eumelanin.<sup>2</sup> As a result, it is assumed that depletion of glutathione would result in eumelanin formation.<sup>2</sup>

Glutathione is an active ingredient in many cosmetic preparations. Glutathione for skin whitening is available in cream, soap, lotion, nasal spray and injectable form.<sup>7,8</sup> Topical application of glutathione in the form of lotion is not efficiently absorbed by the skin cells as the thiol group undergoes rapid formation of disulfide.<sup>9</sup> Oral absorption of glutathione is hydrolyzed by enzymes in the gastrointestinal tract leading to its reduced bioavailability.<sup>9</sup> The level of glutathione increased in small amounts temporarily when large oral doses were administered.<sup>2,7</sup> On the contrary, intravenous glutathione delivers very high doses directly into the systemic circulation and is the preferred mode of administration.

Glutathione can be combined with vitamin C to increase its absorption or N-acetyl cysteine to boost its level.<sup>17</sup>

This study has important limitations. Blood levels of glutathione could not be measured due to unavailability of facility. Additionally, assessment method of skin colour and tone in this study was not an ideal one. Though the Taylor hyperpigmentation score is used but it is not a gold standard. Maxameter and other more

effective tools couldn't be used due to financial limitations.

## Conclusion

Our study does not recommend glutathione for skin lightening. Its safety as an intravenous drug is also questioned. Further well-controlled trials are required to evaluate glutathione efficiency as skin lightening agent. Intravenous glutathione administration should be carried out with more sophistication and blood levels monitoring.

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