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Original Research Article

Analysis of usage pattern of glutathione by dermatologists: Results of a cross-sectional study

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ABSTRACT

Background: Glutathione is one of the non-enzymatic antioxidants that is also involved in regulation of cellular proliferation and apoptosis. The application of Glutathione for skin lightening and depigmentation in dermatology started after discovery of its anti-melanogenic properties. There is still a lack of evidence regarding its patient population, dosage schedule, and safety on long-term use. The objective of this study is to analyze the usage pattern of Glutathione from dermatologists in India based on their clinical experience.
Materials and Methods: Questionnaire-based cross-sectional study conducted amongst dermatologists to understand indications, administration, safety, and adverse events associated with Glutathione therapy. Data entry was done in Microsoft Excel and descriptive statistics was applied.
Results: Seventy-one responses were collected with the average experience of dermatologists being 5.24 + 7.32 years. 52.11% of these dermatologists routinely prescribe Glutathione therapy. The most common use is skin lightening given through the oral route. The preferred dose for oral route is 250mg given twice daily empty stomach for 4 weeks, topical route is 2% (w/w) applied once daily for 10 weeks, and intravenous route is 1200mg injection given weekly over 30 minutes. Only 3 out of 37 prescribing doctors have seen side effects. 54% of dermatologists feel that there is insufficient safety data available for this therapy.
Conclusion: This study shows the current practices of Glutathione therapy by dermatologists while also pointing to the need for more studies to be done with a larger sample size for a longer duration so that the use is standardized with improved safety.

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1. Introduction

Out of the range of antioxidants present in mammalian cells, Glutathione is one of the non-enzymatic ones that plays a key role in protecting cells from free radicals and pro-oxidants and acts as a cofactor for antioxidant and detoxifying enzymes.[1] It also plays a part in nutrient metabolism and regulation of cellular events like gene expression, DNA and protein synthesis, cell proliferation and apoptosis.[2]

The concentration of Glutathione, a tripeptide (glutamic acid, glycine, and cysteine) is around 5 millimolar in most cells.[3] Glutathione exists in 2 forms in human body-reduced and oxidized. The ratio of oxidized and reduced Glutathione determines the redox status of the cell. The ratio is >100 in a healthy cell and it drops to 1 to 10 in cells exposed to oxidant stress.[4] The availability of Glutathione in body depends on three energy dependent processes which involves de novo synthesis, reduction of the oxidized form and then recycling of cysteine from

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conjugated Glutathione.[3]

Low levels of Glutathione are implicated in several conditions like neurodegenerative disorders (Alzheimer's, Parkinson's', Huntington's), pulmonary disease (Chronic obstructive pulmonary disease, asthma), immune disorders (HIV, autoimmune disorders), cardiovascular conditions (myocardial infarction, hypertension), and liver disorders (fatty liver).[5–7] Chronic exposure to chemical toxins and alcohol is also associated with low levels of Glutathione.[8]

In India, Central Drug Standard Control Organization (CDSCO) has approved Glutathione for intravenous use in cases of alcoholic fatty liver, alcoholic liver fibrosis, alcoholic cirrhosis, and alcoholic hepatitis while Food and Drug Administration (FDA) in Philippines approved the same to reduce neurotoxicity associated with cisplatin chemotherapy.[9] The number of clinical trials showing positive results with use of Glutathione in cases of non-alcoholic steatohepatitis and non-alcoholic fatty liver disease are limited but there is a future potential in this therapy area. Clinical trials are also being done to evaluate its role in patients with mild cognitive impairment or other neurodegenerative disorders.[10]

After the discovery of its anti-melanogenic properties, Glutathione has gained popularity amongst dermatologists and cosmetologists who are using it as a skin lightening agent. It is postulated to inhibit melanogenesis by inhibiting the enzyme tyrosinase during melanogenesis, either directly or indirectly.[11] Studies have been done to evaluate the effect of Glutathione as a skin lightening agent, using all three routes-oral, topical, and intravenous. All the studies have shown positive results for skin lightening using the topical and intravenous route but for oral Glutathione out of three studies, two have shown positive effects but one of them opposed these findings as compared to placebo.[9]

The dose and duration of treatment by oral Glutathione varied in all the three studies.[12–14] Because of its antioxidant properties, it is also being used by some dermatologists for allergic disorders of the skin like eczema. There has been an increase in the safety concern about the long-term use of Glutathione with FDA releasing a warning bulletin in 2011.[15] The bulletin talks about the lack of guidelines regarding the dosage regimen and duration of therapy. Theoretical risk of skin cancer on long term use has also been raised due to lowering of the melanin index. Another concern by FDA was that Glutathione therapy is sometimes paired with Vitamin C which can lead to kidney stones if the urine is acidic.

Currently, there is a lack of evidence about how Glutathione should be used for skin depigmentation or in other allergic disorders with huge variations in the dose, duration, and route of administration. This study was done to understand the perspective and concerns about Glutathione therapy by the dermatologists. The main objective of the study was to analyze the usage pattern of Glutathione by dermatologists in India from their clinical experience.

2. Materials and Methods

A questionnaire-based study was conducted from October 2023- December 2023. The study protocol was approved by the Institutional Ethics Committee for Biomedical and Healthcare Research. The study was started after the approval. The questionnaire was validated by circulating it amongst practicing dermatologists in India. Face validity and content validity was done by five experts. Face validity was done to ensure that the questions are not confusing or misleading to the responders and content validity helped us get rid of the non-essential questions to ensure optimum response in less duration. After incorporation of their suggestions and approval, validated questionnaire using Google form was circulated through WhatsApp to practicing dermatologists and post-graduate dermatology residents in India.

Apart from the relevant demographic details, the responders were requested to answer a total of 16 questions. These questions were related to indications, administration, safety, and adverse events associated with Glutathione therapy. Out of these 16 questions, four were dichotomous. Eight of the questions were open ended and 3 were close ended. Answer to one of the questions was requested in the form of a Likert scale.

Data entry was done in Microsoft Excel and descriptive statistics was applied. Categorical data were analyzed by frequency and percentages while continuous data were represented as mean with standard deviation. Subset analysis was done based on formulation of Glutathione for understanding practice pattern for different formulations.

3. Results

A total of 71 responses were collected. The experience of the responders in the field of dermatology was 5.24 + 7.32 years. Out of the 71 responders, 37 (52.11%) reported using Glutathione for therapeutic purposes while the remaining 34 (47.88%) did not use it in their practice. Out of the 50 doctors who had an experience of less than five years, 29 (58%) did not use Glutathione whereas 76% of doctors with more than five years of experience reported using Glutathione.

Figure 1 gives the reasons dermatologists gave for not using Glutathione therapy.

Out of the dermatologists prescribing Glutathione, 24 (64.8%) preferred giving it by the oral route, followed by 8 (21.6%) using via topical route and remaining 5 (13.5%) using the intravenous route. A total of 4 (80%) of doctors using the intravenous route have less than five years of experience. A total of 17 (70%) doctors prescribing oral Glutathione use it for its antioxidant and skin lightening

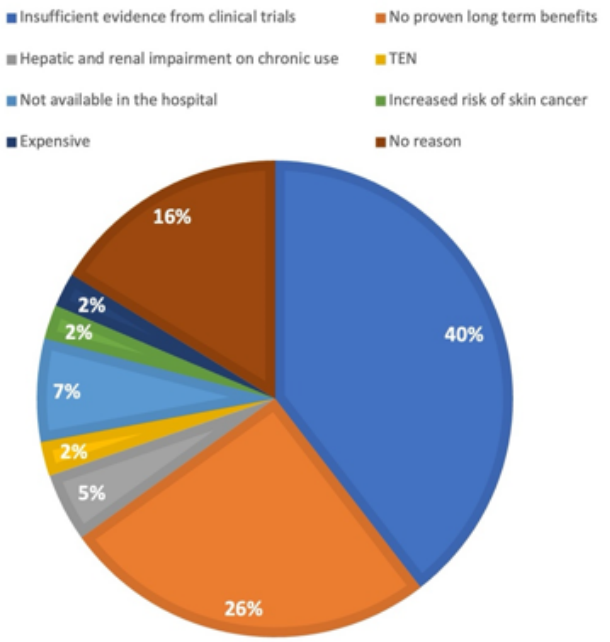

Figure 1: Reason for not using Glutathione by dermatologists in India. (TEN- Toxic Epidermal Necrolysis)

action while only 9 (37%) use it for skin depigmentation. All the doctors prescribing topical route use it for skin lightening, while only 6 (40%) use it as an antioxidant and 1 (12.5%) as a skin depigmentation agent. For intravenous Glutathione, all the prescribers use it for skin lightening with only 2 (25%) using it as an antioxidant and 1 (12.5%) as a skin depigmentation agent.

The dose recommended by 59.3 % doctors using oral Glutathione was 250 mg tablet taken on empty stomach twice daily for four weeks. The other common oral dose by 34.3% doctors was the 500mg Glutathione lozenge taken once daily for eight weeks. A total of 60% of the doctors prescribing topical Glutathione recommend the oxidized lotion (2% w/w) to be taken once daily for 10 weeks while the other 40% recommend a twice daily application. A total of 85% of doctors prescribing intravenous Glutathione reported giving a dose of 1200mg over 30 minutes weekly. The dose of intravenous Glutathione is repeated based on the patient's response to therapy or requirement, most commonly after a duration of 3-6 months.

Figure 2 shows the preference of dermatologists about other prescribing aspects of Glutathione.

Only three (8.1%) doctors out of 37 reported seeing adverse effects with Glutathione therapy. These adverse events included anaphylactic reaction, skin rashes and abdominal pain. None of these doctors reported them to the nearest adverse drug reaction (ADR) monitoring centre. A total of 19 (51.3%) out of 37 doctors reported being aware of the potential risk of developing skin cancer in case of long term use of Glutathione therapy.

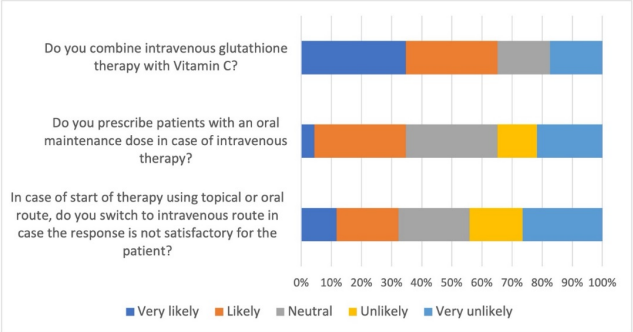

Figure 2: Prescribing details of Glutathione by dermatologists

Figure 3 shows the percentage of dermatologists getting satisfactory response in various proportion of patients using this therapy.

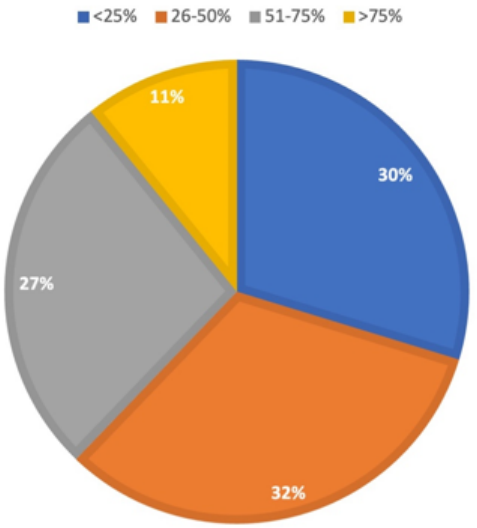

Figure 3: Percentage of dermatologists getting satisfactory response to Glutathione therapy in various proportion of patients.

A total of 56.7% doctors reported to have received information about Glutathione therapy from scientific conferences, followed by publication in peer-reviewed journals (48.3%), continuing medical education lectures (29.7%), clinical trials (24%) and information shared by pharmaceutical companies (27%). A total of 54% of the dermatologists felt that there is insufficient safety data available for this therapy. About 32.4% dermatologists recommended need of more clinical trials for these indications while 37.8% also felt the need for more regulated recommendations about the dose and duration of this therapy.

4. Discussion

The use of Glutathione therapy is expected to grow globally as well as in India at a Cumulative Average Growth Rate (CAGR) of 8.8% every year till 2030.[16] A majority of this can be attributed to the growing demand of the present population for a fairer skin color. There is also an increasing demand of nutricosmetics in the busy urban lifestyle that is spreading.[16] Glutathione therapy proclaimed as the "magical skin whitening" molecule in countries like the Republic of Philippines for years has now spread across globally for skin lightening, skin depigmentation and as an antioxidant.[9]

The mechanism of these effects of Glutathione has been researched and documented. It mediates the antioxidant effect by scavenging on the free radicals during hydrogen peroxide and lipid peroxide detoxification process.[17,18] It inhibits tyrosinase enzyme by both directly chelating copper ions on the active site of the enzyme and indirectly through its antioxidant property.[9,14] There is also a production shift of the eumelanin (darker pigment) to pheomelanin (lighter pigment) due to spontaneous conjugation of Glutathione and cysteine with L-dopaquinone to glutathionyldopa and cysteinydopa.[19] The suppression of Reactive Oxygen Species (ROS) production also prevents melanogenesis.[20] All these pathways combine to explain the anti-melanogenic properties of Glutathione which has led to the start of its usage in the field of dermatology.

In our study, we found that most of the dermatologists prefer using oral Glutathione, followed by topical and intravenous use. Glutathione has shown positive results with reduction in melanin index in clinical trials conducted for all these three routes of administration.[12,14,21] Zubair et. al (2016) conducted a study in which after intravenous injection of Glutathione, 37.5% of patients vs 18.7% in the placebo group noticed an improvement in the score on the Visual Taylor hyperpigmentation scale. After two months, it changed to 18.7% in the treatment group vs 12.5% in the placebo group, at four months it was 18.7% vs 0% in the placebo group. At six months, the response dropped to 6.2% patients in the treatment group[21]. This shows a reduction in the effect of Glutathione therapy which could lead to repeat administration. This has also been shown in our study as most dermatologists recommend repeating it after six months. Another clinical trial conducted by Wahan S. et al (2021) showed that a combination of topical (2% Glutathione with Vitamin C) and oral Glutathione 600mg is superior to monotherapy with either of the routes as it showed a more consistent result.[22] Similar to this even in our study, majority of the doctors were likely to combine Vitamin C with intravenous Glutathione.

The dose of Glutathione use in all three routes recommended by dermatologists in our study is similar to the clinical trials that have been previously conducted.[9,23] In a study conducted by Weschawalit et. al (2017), patients were given a dose of 250mg/day. In this study, there was no difference in the response as compared to the placebo group which could be attributed to the lower dose.[13] This validates the usage of 250mg twice daily or the 500mg once daily oral dosage recommended by dermatologists in our study.

Glutathione therapy is well tolerated by patients, as has been reported in clinical trials and from the experience of dermatologists recommending this therapy. Anaphylactic reaction and abdominal pain have also been reported in the trial conducted by Zubair et al. in which intravenous Glutathione therapy was given to the patients.[21]

Despite its widespread use by dermatologists and continuous growth year on year, there is also reluctance by some doctors due to insufficient evidence about this therapy, smaller number of participants and shorter duration in the trials that have been conducted, side effects due to chronic use, risk of Toxic Epidermal Necrolysis (TEN) and skin cancer. Despite issuance of a warning by FDA and around 50% doctors in our study being aware of the long-term potential risk of developing skin cancer with this therapy, the use continues. There is a need for further long-term research to be done in this therapy area to get more clarity about the safe use.

Our study has limitation of the smaller number of responses from dermatologists which could be due to the lack of a central database to have access to a greater number of eligible doctors. A uniform system where we could reach to more number of doctors can help us in better conduct of such studies in the future.

5. Conclusion

Glutathione therapy shows potential as an antioxidant and a skin lightening and depigmentation agent. The study gives insights about the dose and duration of Glutathione being given to the patients in clinical practice and sheds light on the safety and other concerns about this therapy which stops few doctors from prescribing it. There is a need for more long-term research on a larger sample size to be done so that the treatment is offered in a standardized manner and risk of serious adverse event can be reduced.

6. Source of Funding

None.

7. Conflict of Interest

None.

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