Journal of Pharmaceutical Research International

33(63B): 145-152, 2021; Article no.JPRI.80839
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Estimating the Correlation between Autoimmune Thyroid Disorders and Chronic Spontaneous Urticaria: A Study Protocol

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i63B35264

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/80839

Study Protocol

Received 22 October 2021
Accepted 27 December 2021
Published 29 December 2021

ABSTRACT

Background: Chronic spontaneous urticaria is thought to occur due to the patient's predilection to produce self-reactions. Urticaria contributes to loss of sleep, anxiety, depression, lack of motivation and social isolation, which may contribute to a substantial decrease in the patient's quality of life. Chronic spontaneous urticaria is unpredictable and can impair the patient's usual everyday activities. Autoimmune thyroid disorders are as a consequence of immune system dysregulation, that results in a thyroid invasion. A relationship between Chronic Spontaneous Urticaria and Autoimmune Thyroid Disorders is related to the duration and severity of the disease. Chronic Spontaneous Urticaria is associated with the presence of antithyroid antibodies. This study aims to analyze the changes in Patients detected with T3, T4, TSH and anti-TPO of chronic spontaneous urticaria, in contrast to normal healthy individuals and patients with other skin diseases which do not have abnormal thyroid etiopathogenesis.

Materials and Methods: This will be a Case Control study conducted at Department of Dermatology, AVBRH, Sawangi, Wardha. Patients with chronic spontaneous urticaria will be subjected to a thorough clinical review and will be scored based on urticaria severity scoring. To test for autoimmune thyroid disease, the levels of T3, T4, TSH and anti-TPO antibodies will be traced. Data will be collected and analysed with appropriate statistical tests.

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Expected Results: Statistical correlation between chronic spontaneous urticaria and autoimmune thyroid disorders which can aid in the early detection and arrest of progression of autoimmune thyroid disorders in chronic spontaneous urticaria.
Conclusion: Preventive steps toward patient management can be taken with this analysis in chronic spontaneous urticaria, in patients with deranged parameters for the T3, T4, TSH and ANTI – TPO.

Keywords: Autoimmune disorders; thyroid disorders; urticaria; antibodies.

1. INTRODUCTION

Chronic spontaneous urticaria is thought to occur due to the patient's predilection to produce self-reactions [1]. Urticaria is a disorder induced by mast cells. Mast cells that are stimulated release histamine along with other mediators, such as platelet-activating factor and cytokines, resulting in activation of the sensory nerve, vasodilation, plasma extravasation. Different molecules eventually activate mast cells in urticaria, but these are generally not well known [2].

Causes: Autoimmune diseases, urticarial vasculitis, thyroid autoimmunity, connective tissue disorders, infections etc. Chronic urticaria shows various clinical presentations. Urticaria is characterized by wheals. A wheal consists of common characteristics: 1) Variable size 2) itching ,central swelling. Lesions occur anywhere on the body, such as scalp, hands, soles. Wheals are itchy and patients rub rather than scratch on the lesions, due to which there are no excoriation signs. The related systemic symptoms of extreme urticaria can include headache, dizziness, hoarseness of speech, shortness of breath, nausea, vomiting and abdominal pain [3].

Urticaria contributes to loss of sleep, anxiety, depression, lack of motivation and social isolation, which may contribute to a substantial decrease in the patient's quality of life. Chronic spontaneous urticaria is unpredictable and can impair the patient's usual everyday activities [4].

Autoimmune thyroid disorders are a consequence of immune system dysregulation, that results in a thyroid invasion. They are T cell-mediated autoimmune disorders. Lymphocytic invasion of the thyroid parenchyma characterizes these diseases [5].

The clinical hallmarks of autoimmune thyroid diseases include thyrotoxicosis or hypothyroidism. Epidemiological data suggested that interaction with the main factor that contributes to the breakdown of tolerance and the progression of the disease is genetic vulnerability and environmental causes [5].

The significance of cytokines and chemokines in autoimmune thyroid disease pathogenesis has been shown in recent studies [5].

T-helper 1 lymphocytes are responsible for increased development of IFN-γ and TNF-alpha, hence the secretion from thyroid cells of CXCL10 (IFN-γ-inducible Th1 chemokine prototype). This induces a feedback loop that initiates the autoimmune process [6].

1.1 Association of Chronic Spontaneous Urticaria and Thyroid Autoimmune Disorder

There are several immunological pathways in common with autoimmune thyroid disorders and Chronic Spontaneous Urticaria. Such as immune system dysregulation, and decreased lymphocyte number [6]. A relationship between Chronic Spontaneous Urticaria and Autoimmune Thyroid Disorders is related to the duration and severity of the disease. Chronic Spontaneous Urticaria is associated with the presence of antithyroid antibodies. As the occurrence of autoimmune thyroid disorders in patients with recurrent spontaneous urticaria is increased, tests for T3, T4, TSH and ANTI-TPO ANTIBODIES should be conducted as part of the approach.

2. RATIONALE

The most common causes of dysfunction of the thyroid glands are Thyroid Autoimmune Conditions. Owing Interactions of environmental and genetic parameters, these conditions arise. Due to autoreactive lymphocytes that escape tolerance, they have reactivity to self-thyroid antigens. The process includes both cell-mediated and humoral responses that result in injury to the tissue [7].

Chronic spontaneous urticaria involves activation and degranulation of mast cells and basophils. These are the basic mechanisms. As primary effectors of chronic urticaria, mast cells are the most prominent. Other forms of cells include lymphocytes, and the inflammatory infiltrates. Histamine and other mast cell products have been shown to be the primary causes of the development of this disease. Elevated vascular permeability is its unique manifestations of urticaria. This results from the release of mediators of mast cells (e.g. histamine, tryptase, leukotriene) and the synthesis of cytokines. The pathogenesis of chronic urticaria includes two main mechanisms. The first involves dysregulation in mast cells and basophils of intracellular signaling pathways that causes defects in the functioning of these cells. The second requires the manufacturing of antibodies [8]

Chronic urticaria hence includes autoantibodies. It is distinguished by erythematous wheals and a minimum redness of at least 6 weeks present twice a week there is a highly studied correlation between chronic urticaria and autoimmune conditions such as autoimmune thyroid diseases [8].

Hence, increased incidence of autoimmune thyroid diseases in chronic spontaneous urticaria patients can be expected.

With this study we aim to analyze the changes in Patients detected with T3, T4, TSH and anti-TPO of chronic spontaneous urticaria, in contrast to normal healthy individuals and patients with other skin diseases which do not have abnormal thyroid etiopathogenesis. Identification of such association between chronic spontaneous urticaria and thyroid autoimmune disorders at an earlier stage would enable us to take necessary preventive measures minimizing the burden of the disease.

3. AIM AND OBJECTIVES

3.1 Aim

To study the auto immune thyroid disorders in chronic spontaneous urticaria.

3.2 Objectives

The primary goals of this research are:

1. To research the clinical characteristics of chronic spontaneous urticaria.
2. T3, T4, TSH and ANTI-TPO ANTIBODIES analysis in chronic spontaneous urticaria patients and controls
3. To study the correlation between the above parameters and chronic spontaneous urticaria
4. To study the correlation between severity of chronic spontaneous urticaria and autoimmune thyroid disorders.

4. MATERIALS AND METHODS

4.1 Study Design

Case Control.

4.2 Duration of Study

October 2020 to September 2022.

4.3 Place of Study

Department of Dermatology, Leprosy, and Venerology DMIMS (Deemed to be University), Wardha.

Requisite time for collecting data: 2 years

4.4 Study Setting

All patients over 18 years of age, regardless of sex, suffering from chronic spontaneous urticaria, admitting to the Department of Dermatology, Venereology and Leprosy of the Rural Hospital of Acharya Vinoba Bhave, Sawangi, Wardha, Maharashtra

4.5 Sample Size

$$n = \frac{Z_{\alpha/2} \cdot P \cdot (1-P)}{d^2}$$

n = (1.96)2 * 0.01x(1-0.01) / (0.05)2
n = 15.21
n = 20 patients needed in each group in the study.(20 cases + 20 controls)

where,

n = sample size
Zα/2 is the level of significance at 5%, that is, 95% .Confidence interval is 1.96
P = Prevalence of chronic spontaneous urticaria= 1 % = 0.01
D = desired error of margin = 5% = 0.05

For the present analysis, the sample size will be 20 cases and 20 controls:

- Cases any patient over the age of 18 years, regardless of gender, coming to the Department of Dermatology, Venereology and Leprosy and having chronic spontaneous urticaria.
- Controls will be normal healthy adult individuals of comparable age and gender ,and patients having skin diseases which do not have any abnormal thyroid etiopathogenesis

4.6 Inclusion Criteria

- Patients of both sexes over the age of 18 years.
- Patients who are with informed consent to take part in the study
- Patients having chronic spontaneous urticaria will be included
- Patients with other skin diseases who do not have any abnormal thyroid etiopathogenesis.

4.7 Exclusion Criteria

- Patients having any major systemic disease/uncontrolled medical or surgical illness
- Patients having any renal or hepatic disorder.
- Patients with pregnancy or on lactation.

5. METHODOLOGY

Study will be conducted in Dermatology, Venereology and Leprosy Department, AVBRH, Sawangi, Wardha,

Patients having chronic spontaneous urticaria after considering the different inclusion and exclusion requirements, those who will come to the Department of Dermatology, Venereology and Leprosy, AVBRH, Sawangi, Wardha, will be enrolled. Clearance will be sought from the Institutional Ethical Committee (IEC). A comprehensive history will be taken with regard to name, age, gender, family history, past history. Patients with chronic spontaneous urticaria will be subjected to a thorough clinical review. Patients will be scored based on urticaria severity scoring.

Autoimmune thyroid disorders will be screened by taking blood sample (both cases and controls) with all the standard protocols from the peripheral intravenous route {cubital vein} and pouring the blood sample into the respective blood tube . The blood sample is processed by V5600 DRY CHEMISTRY for T3 ,T4,TSH . ANTI-TPO ANTIBODY is processed by ELISA

To test for autoimmune thyroid disease, the levels of T3, T4, TSH and anti-TPO antibodies will be traced.

5.1 Outcome Measure

With this report, preventive steps may be taken in patient care with chronic spontaneous urticaria and in patients with deranged parameters, an assay for T3, T4, TSH and ANTI-TPO. Further, this can facilitate the early detection and arrest of progression of autoimmune thyroid disorders in chronic spontaneous urticaria. If there are any derangements in the T3, T4, TSH and anti-TPO, further referrals may be provided for the care of the patient.

Table 1. Urticaria severity scoring

Score	Wheals	Pruritus
0	None	None
1.	Mild (<20 Wheals /24hours)	Mild (Present but not annoying or troublesome)
2	Moderate (20 -50 Wheals/ 24hours)	Troublesome but does not interfere with sleep
3	Intense (>5O Wheals/ 24hours or large confluent areas of wheals)	Severe pruritus, which is sufficiently Troublesome to interfere with normal Daily activities or sleep

Parameter	Normal range
Serum T3 (Triiodothyronine)	0.970-1.69 ng/ml
Serum T4 (Thyroxine)	5.53-11.0 g/dl
Serum TSH (Thyroid Stimulating Hormone)	0.465-4.68 uTU/ml

ANTI- TPO ANTIBODY: <34 IU/ml (negative)
<34 IU/ml (positive)

5.2 Statistics

Statistical methods can analyze both standard parametric and non-parametric information.

A ‘p’ value of <0.05 will be considered significant

5.3 Scope

This research would help to screen patients with chronic spontaneous urticaria for autoimmune thyroid disorders. It can later be considered as a mandatory protocol to be assessed in patients of chronic spontaneous urticaria.

6. EXPECTED RESULTS

This research will take preventive steps to treat patients with chronic spontaneous urticaria and in patients with deranged parameters, an assay for T3, T4, TSH and ANTI-TPO can be done. Further, this can facilitate the early detection and arrest of progression of autoimmune thyroid disorders in chronic spontaneous urticaria.

7. DISCUSSION AND CONCLUSION

O'farrill-Romanillos et all ,in the year 2019 , investigated that in up to 54 percent of the individuals taken in the study, there is association of Chronic Spontaneous Urticaria (CSU) with thyroid disease in Men and women over the age of 18 with CSU were included in this study; TSH and T3 T4 were quantified. They were graded as euthyroid, hyperthyroid, and hypothyroid according to the results; Antithyroid antibodies have been observed. Demographic and biochemical features of the findings were relevant. More than a third of the patients analysed with chronic spontaneous urticaria had thyroid dysfunction [9].

Magdalena Czarnecka-Operacz et all ,in the year 2017, Chronic urticaria (CU) has been studied to be a skin disease induced by autoantibodies. It is distinguished by a minimum of of 6 weeks, twice a week, of hives, erythematous wheals and redness. A significant correlation is found between chronic urticaria and autoimmune disorders. The research included one hundred and forty-eight Chronic Spontaneous Urticaria patients. It measured presence of the concentrations of anti-TPO, TSH, T3 and T4. The findings showed that anti TPO levels in patients with Chronic Urticaria were much higher.

7.1 Conclusions

There is a statistically important disparity between patients of chronic urticaria and the entire population in the presence of autoimmune thyroid disorder [10].

Collet E et all, in the year 1995 , Study of the relationship Chronic urticaria was carried out for autoimmune thyroid disorders. METHODS AND PATIENTS: There were 45 patients with chronic urticaria in this study (29 men and 16 women, mean age 45.6 years). Both were clinically tested for thyroid disease with TSH, T3 and T4, and assays of anti-TPO antibodies. RESULTS: Most of the patients had autoimmune thyroid disorders.

7.2 Discussion

These findings indicate that in patients with chronic urticaria, a full thyroid analysis with thyroid hormone assay should be performed. The most sensitive and specific tests in patients with autoimmune thyroid disorder tend to be the anti-TPO antibody [11].

Diego S Fernandez Romero et all, in the year 2005, studied that Chronic urticaria, Distinguished by the appearance of hives or angioedema lasting more than 6 weeks, is a common pathology. It functions as an autoimmune disease in a large number of patients, often due to changes in functioning of thyroid and thyroid antibodies. A sequential series of 70 patients diagnosed with chronic urticaria was identified in the study. In the 63 patients, thyroid function and thyroid antibodies were analyzed by measuring thyroid hormone level and anti -TPO levels. Out of 61 patients screened for anti-TPO antibodies, 22 (36 percent) reported positive. Studying thyroid function and the presence of anti-TPO antibodies in patients with chronic urticaria seems clinically important, given the high percentage of thyroid changes in some patients [12].

A G Palma-Carlos et all in 2005, the aim of the research was to evaluate thyroid autoimmunity and thyroid function in chronic urticaria (CU). Evaluation of ANTI-TPO antibodies and TSH, T3, T4 with chronic spontaneous urticaria and without chronic spontaneous urticaria in 56 subjects in a matched control group was done. In 13, Anti-TPO was positive (22.2 percent). In 52 patients, thyroid function was normal, TSH increased in 2 patients, and T3 decreased in 1.

In most circumstances, Chronic Spontaneous Urticaria is associated with thyroid autoimmunity. In all cases of chronic urticaria, thyroid anti-TPO and T3, T4, TSH must be tested [13]. Few of the related studies were reported [14-16]. Studies on thyroid dysfunction were reported by Jose et. al. [17], Raniwala et al. [18], Taksande et. al. [19] and Agrawal et al. [20], Shivkumar et al. reported on prevalence of oral mucosal lesions in patients with dermatological diseases [21]. Gupta et. al. reported a study on Efficacy of some Ayurvedic formulations with special reference to urticaria [22-26].

8. LIMITATIONS

- This is a study focused on hospital, not a study based on the population.
- The other autoimmune thyroid disorders markers are not taken example anti TSH receptor antibody and thyroglobulin antibody

IMPLICATIONS

Preventive steps toward patient management can be taken with this analysis in chronic spontaneous urticaria, in patients with deranged parameters for the T3 , T4 , TSH and ANTI – TPO . Further, this can facilitate the early detection and arrest of progression of auto immune thyroid disorders in chronic spontaneous urticaria patients**.**

CONSENT AND ETHICAL APPROVAL

From The institutional ethics committee (ICE), ethical approval will be received and Informed written consent from the enrolled individuals involved in the research. All participants will obtain written informed consent in their vernacular language for voluntary participation

NOTE

The study highlights the efficacy of " Ayurvedic formulations " which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Fraser K, Robertson L. Chronic urticaria and autoimmunity. Skin Therapy Lett. 2013;18(7):5-9. PMID: 24305753.
2. Puxeddu I, Pratesi F, Ribatti D, Migliorini P. Mediators of inflammation and angiogenesis in chronic spontaneous urticaria: Are they potential biomarkers of the disease?. Mediators Inflamm. 2017; 2017:4123694.
   DOI: 10.1155/2017/4123694
   Epub 2017 Sep 5
   PMID: 29038618
   PMCID: PMC5605794
3. Sachdeva S, Gupta V, Amin SS, Tahseen M. Chronic urticaria. Indian J Dermatol. 2011;56(6):622-8.
   DOI: 10.4103/0019-5154.91817
   PMID: 22345759
   PMCID: PMC3276885
4. Tat TS. Higher levels of depression and anxiety in patients with chronic urticaria. Med Sci Monit. 2019;25:115-120.
   DOI: 10.12659/MSM.912362
   PMID: 30609422
   PMCID: PMC6329254
5. Lee HJ, Li CW, Hammerstad SS, Stefan M, Tomer Y. Immunogenetics of autoimmune thyroid diseases: A comprehensive review. J Autoimmun. 2015;64:82-90.
   DOI: 10.1016/j.jaut.2015.07.009
   Epub 2015 Jul 30
   PMID: 26235382
   PMCID: PMC4628844
6. Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune thyroid disorders. Autoimmun Rev. 2015;14(2):174-80.
   DOI: 10.1016/j.autrev.2014.10.016
   Epub 2014 Oct 25
   PMID: 25461470.
7. Rydzewska M, Jaromin M, Pasierowska IE, Stożek K, Bossowski A. Role of the T and B lymphocytes in pathogenesis of autoimmune thyroid diseases. Thyroid Res. 2018;11:2.
   DOI: 10.1186/s13044-018-0046-9
   PMID: 29449887
   PMCID: PMC5812228
8. Bracken SJ, Abraham S, MacLeod AS. Autoimmune Theories of Chronic Spontaneous Urticaria. Front Immunol. 2019;10:627.
   DOI: 10.3389/fimmu.2019.00627
   PMID: 30984191

PMCID: PMC6450064

9. O Farrill-Romanillos PM, Álvarez-Chávez FE, Xochihua-García JJ. Alteraciones tiroideas en urticaria crónica espontánea [Thyroid disorders in spontaneous chronic urticaria]. Rev Alerg Mex. 2019;66(4):403-408. Spanish.
DOI: 10.29262/ram.v66i4.629
PMID: 32105424
10. Czarnecka-Operacz M, Sadowska-Przytocka A, Jenerowicz D, Szeliga A, Adamski Z, Łącka K. Thyroid function and thyroid autoantibodies in patients with chronic spontaneous urticaria. Postepy Dermatol Alergol. 2017;34(6):566-572.
DOI: 10.5114/ada.2017.72464
Epub 2017 Dec 31
PMID: 29422822
PMCID: PMC5799761
11. Collet E, Petit JM, Lacroix M, Bensa AF, Morvan C, Lambert D. Urticaire chronique et pathologie thyroïdienne auto-immune [Chronic urticaria and autoimmune thyroid diseases]. Ann Dermatol Venereol. 1995;122(6-7):413-6. French.
PMID: 8526423
12. Fernandez Romero DS, Malbran A. Urticaria cronica con alteraciones de la funcion tiroidea y anticuerpos antiperoxidasa tiroidea [Chronic urticaria with alterations of the thyroid function and thyroid peroxidase antibodies]. Medicina (B Aires). 2005;65(3):231-4. Spanish.
PMID: 16042134
13. Palma-Carlos AG, Palma-Carlos ML. Chronic urticaria and thyroid auto-immunity. Eur Ann Allergy Clin Immunol. 2005;37(4):143-6.
PMID: 15916015
14. Vos, Theo, Stephen S Lim, Cristiana Abbafati, Kaja M Abbas, Mohammad Abbasi, Mitra Abbasifard, Mohsen Abbasi-Kangevari, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the global burden of disease study 2019. The Lancet. 2020;396(10258): 1204–22.
Available:https://doi.org/10.1016/S0140-6736(20)30925-9
15. Wang, Haidong, Kaja M Abbas, Mitra Abbasifard, Mohsen Abbasi-Kangevari, Hedayat Abbastabar, Foad Abd-Allah, Ahmed Abdelalim, et al. Global age-sex-specific fertility, mortality, healthy life expectancy (hale), and population estimates in 204 countries and territories, 1950–2019: A comprehensive demographic analysis for the global burden of disease study 2019. The Lancet. 2020;396(10258):1160–1203.
Available:https://doi.org/10.1016/S0140-6736(20)30977-6.
16. Lozano R, Fullman N, Mumford JE, Knight M, Barthelemy CM, Abbafati C, et al. Measuring universal health coverage based on an index of effective coverage of health services in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet;2020.
17. Jose AM, Muntode PA, Sharma S, Mathew SS, Nair RR, Solanki S. Profile of thyroid dysfunctions among the female population in a rural community of Wardha District: A hospital-based study. Journal of Datta Meghe Institute of Medical Sciences University. 2019;14(6):S87–91.
Available:https://doi.org/10.4103/jdmimsu.jdmimsu_231_19.
18. Raniwala A, Wagh DD, Dixit-Shukla A, Shrikhande N, Padmawar M. Study and correlation of clinical, radiological, cytological, and histopathological findings in the diagnosis of thyroid swellings. Journal of Datta Meghe Institute of Medical Sciences University. 2017;12(2):138–42.
Available:https://doi.org/10.4103/jdmimsu.jdmimsu_61_17.
19. Taksande, A.B., A.T. Jagzape, and V.K. Deshpande. Study of Motor Nerve Conduction Velocity in Patients of Thyroid Dysfunction in Central India. Journal of Datta Meghe Institute of Medical Sciences University. 2017;12(4):229–33.
Available:https://doi.org/10.4103/jdmimsu.jdmimsu_100_17.
20. Agrawal D, Bhake AS, Rastogi N, Laishram S, Wankhade A, Agarwal A. Role of bethesda system for reporting thyroid lesion and its correlation with histopathological diagnosis. Journal of Datta Meghe Institute of Medical Sciences University. 2019;14(2):74–81.
Available:https://doi.org/10.4103/jdmimsu.jdmimsu_76_18.
21. Shivakumar KM, Kadashetti V, Chaudhary M, Patil S, Gawande M, Hande A. Prevalence of oral mucosal lesions in patients with dermatological diseases attending tertiary care hospital in central India. Journal of Krishna Institute of Medical Sciences University. 2017;6(3): 55–61.

22. Gupta J, Kuchewar V, Gaidhane S, Chitriv YU. Comparative Study of Efficacy of amrutadi kwath and tablet loratidine in sheetpitta with special reference to urticaria. International Journal of Pharmaceutical Research. 2019;11(3): 1441–44. Available:https://doi.org/10.31838/ijpr/2019.11.03.158.
23. Rai A, Datarkar A, Borle RM. Are maxillomandibular fixation screws a better option than Erich arch bars in achieving maxillomandibular fixation? A randomized clinical study. Journal of oral and maxillofacial surgery. 2011;69(12):3015-8.
24. Bourne R, Steinmetz JD, Flaxman S, Briant PS, Taylor HR, Resnikoff S, Casson RJ, Abdoli A, Abu-Gharbieh E, Afshin A, Ahmadieh H. Trends in prevalence of blindness and distance and near vision impairment over 30 years: An analysis for the Global Burden of Disease Study. The Lancet Global Health. 2021;9(2):e130-43.
25. Borle RM, Nimonkar PV, Rajan R. Extended nasolabial flaps in the management of oral submucous fibrosis. British Journal of Oral and Maxillofacial Surgery. 2009 Jul 1;47(5):382-5.
26. Franklin RC, Peden AE, Hamilton EB, Bisignano C, Castle CD, Dingels ZV, Hay SI, Liu Z, Mokdad AH, Roberts NL, Sylte DO. The burden of unintentional drowning: global, regional and national estimates of mortality from the Global Burden of Disease 2017 Study. Injury prevention. 2020;26(Supp 1):i83-95.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/80839