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EFFECT OF FOCUSED ULTRASOUND (HIFU) ON NASAL MUCOCILIARY CLEARANCE

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ABSTRACT

Objective: The aim of the study is to evaluate physiological function and effects of high intensity focused ultrasound on nasal mucosa and mucociliary clearance time with saccharin test before and after HIFU treatment on patient with allergic rhinitis.

Methods: 35 AR patients were selected randomly in this test. Saccharin test was performed for evaluation of nasal mucociliary clearance time (NMCT) prior to patients undergoing HIFU treatment and recorded at 30 minutes before and after the procedure and were compared to see if there is any statistical significance between them using paired T test .

Results: The patients undergoing HIFU treatment and evaluation of NMCT with saccharin test before and after the focused ultrasound was not statistically significant. NMCT, paired data T test P value = 0.869>0.05.

Conclusion: when the therapeutic dose focused ultrasound was focused at the nasal mucosa, The energy could be deposited specifically at the subepithelia layer, ablate the targeted nasal mucous tissues which were rich in blood vessels, nerves and glands. There was no damage on the non-target area such as the epithelial layer and no effect on cleaning function of nasal mucosa.

Key words: nasal mucociliary clearance, Saccharin test, focused ultrasound, allerigic rhinitis

INTRODUCTION

Lynn et al in 1942 developed High-intensity focused ultrasound originally. HIFU is a non-invasive and safe therapy with great potential and application [1]. It has been applied in an increasing number of areas, including oncology, neurology, urology, ophthalmology, neurology and otorhinolaryngology [2-5]. Allergic rhinitis is mediated by IgE and involves a variety of mediators, and is associated with chronic inflammatory reaction of nasal mucosa with various immune cell (mainly histamine) and cytokines, when the sensitive individual is exposed to allergens. Rhinosinuitis, nasal polyps, otitis media and allergic conjunctivitis are closely related to asthma and are one of the risk factors [6-8]. The main clinical manifestations of allergic rhinitis are nasal congestion, nasal itching, runny nose, sneezing, and olfactory dysfunction. AR itself is not a serious disease but symptoms might occur at any time and decrease the quality of life (sleep, learning, and work, social and recreational activities) and gives huge psychological and finical burden to the patients. Over nearly half a century, AR has increased continuously in most parts of the world [9].

The evaluation of allergic rhinitis (AR) includes a detail patient's history, a careful physical examination and then appropriate diagnostic tests, such as skin prick test and serum analysis for allergen specific IgE. World health Organization (WHO) in 2008 published the updated diagnostic and management guidelines "Allergic Rhinitis and its Impact on Asthma" (ARIA) the ARIA expert panel based its recommendations on evidence using an extensive review of the literature available up to December 1999. According to ARIA guidelines, AR is generally classified as intermittent or persistent and more specifically classified as mild, moderate and severe, which is based on the symptoms severity and impact on the quality of life [10]. AR management include avoidance of the allergen, pharmacotherapy, immunotherapy and education. Typically used drugs for pharmacotherapy in AR includes antihistamines, decongestants, anticholinergic agents and corticosteroids, they are used either alone or in combination in the initial treatment of AR. However drug therapy can induce side effects, while immunotherapy has generally poor compliance and is expensive.

Ultrasound Imaging guided HIFU (USgHIFU) system was developed in China (Chinqqing Haifu Tech Co.,Ltd., Chonqqing, China.) In the United States, Food and Drug Administration approved the use of focused ultrasound surgery (MRgFU) for treatment of uterine fibroid in October 2004, it was demonstrated to be safe and effective and feasible in treating solid tumors [11]. There are many direct mechanical and thermal mechanisms of focused ultrasound that can be utilized to treat many diseases, as well as methods to augment and/or optimize other treatment approaches. Thermal ablation is the primary mechanism utilized by the currently approved HIFU devices. As an acoustic wave spreads through the applied area of tissue, some part of it is absorbed and then converted to heat. Very small area of heating can be achieved deep inside tissues, with focused beams (usually on the order of millimeters). Tissue damage occurs as a function of both the temperature to which the tissue is heated and duration for how long the tissue is exposed to this heat. The level of heat which is exposed in a metric referred to as "thermal dose". Focusing at more than one area or by

scanning the area of focus, a area of diseased tissue can be thermally ablated [12, 13]. There are several ways to focus ultrasound—via a lens, a phased array, a curved transducer, or any combination of the three. This concentrates it into a small zone of focus; it is similar in concept to focusing light via a magnifying glass. HIFU beams are focused on a small region of targeted tissue to locally deposit high levels of energy and ablate the area. The temperature of targeted tissue at the focus will rise to between 65° and 85 °C, which destroys the required tissue by coagulative necrosis. Higher temperatures will lead to boiling of liquids inside the tissue and are usually avoided. Each application of sonication treats a precisely defined tissue portion. The therapeutic target is treated by using multiple application of sonication to create required volume of treated tissue [14].

Nasal airway mucus lines the epithelial surface and provides an important innate immune function, moisture and warmth to sensitive lower airway, trap noxious chemicals, particulates, and pathogens which are removed from airway before they can invade the mucosa by mechanism called mucociliary clearance or mucocilary transport. Throughout the respiratory tract, mucous is composed of 1% sodium chloride, 0.5% free protein, 0.5-1% mucins, 1% lipids and phospholipids, and approximately 95% water [15]. It possesses different rheological properties, such as viscosity, elasticity, humidification, and adhesiveness. The viscoelastic property is an important determining factor for mucus transport capacity. An intermediate viscoelasticity is required for optimal mucociliary transport [16, 17] . Transport of mucous is regulated by the cilia. Any mechanism mechanical or chemical from the environment, thermal conditions humidity, aging, thyroid disease any sort of sinonasal surgery, structural variations in nose (Deviated Nasal Septum, turbinate hyperthropy), nasal polyps and allergy can separately or in combination alter normal ciliary beat resulting in impaired nasal mucous transport [18-22]. Nasal Mucociliary clearance , a vital key defense mechanism is especially important in the upper airways and sinuses, as it protects the body against noxious inhaled materials [23] . The nasal mucociliary clearance (NMCC) system functions to transport the mucous layer lining the nasal epithelium towards the naso-pharynx by ciliary bearing in metachronous fashion at a frequency of 7-16 Hz at body temperature [24,25] .

LITREATURE REVIEW

The review of literature regarding the use of HIFU in treatment in allergic rhinitis with first line of drugs and its efficacy, methods of studying mucocilary transport, saccharin test as indicator of mucociliary transport, the role of mucocilary clearance as primary defense mechanism.

Use of HIFU in treatment AR as first line and its efficacy:

The main principles of Allergic Rhinitis management include avoiding allergens, drug therapy, immune therapy, and education. According to the ARIA classification system, the WHO has recommended a step-by-step treatment approach for Allergic Rhinitis [26]. However, drug therapies can induce side effects, while immune

therapy generally has poor compliance and is expensive. Therefore, an important topic of current clinical AR investigations is the identification of an effective and economical treatment for AR, associated with minimal or no side effects.

A studied was conducted in Department of Otolaryngology Head and Neck Surgery, First Affiliated Hospital of Chinese PLA General Hospital, Beijing, China, The aim of this study was to determine whether high intensity focused ultrasound (HIFU) therapy under nasal endoscopy guidance could provide better efficacy and safety in patients with persistent allergic rhinitis (PAR) than the first-line drugs recommended by the World Health Organization. The showed shows the total number of patient 120 were divided into group of 60 each (N=60 each), one group underwent HIFU treatment and the other medical management with corticosteroid nasal spray and oral cetirizine hydrochloride. All patients underwent follow-up treatment for one year, after which th`e efficacy and safety were evaluated. There was no significant difference between the two groups ($P > 0.05$) in the total effective rate. Moreover, no complications such as nasal adhesion, septal perforation, mucosal atrophy, and hyposmia were observed, indicating that HIFU was as effective as the first-line drug treatments recommended by the World Health Organization for symptom relief in Persistent Allergic Rhinitis patients. The treatment efficacy, repeatability, safety, economical aspects, ease of performance, and few complications of HIFU therapy strongly suggest that HIFU should be routinely incorporated into clinical practice [27].

There was a study conducted in Chengdu second peoples hospital of china, in the study 68 cases of perennial allergic rhinitis were treated using HIFU and its clinical efficacy was observed After follow-up for six months, the therapeutic effect was excellent in 28 cases, good in 31 cases, and invalid in 9 cases. The total effective rate was 86.7%.Differences were statistically significant in total scores of symptoms and signs before and after treatment, and in scores of different symptom. Showing HIFU is an effective method for treatment of allergic rhinitis, with obvious near-term effect and fewer side effects [28].

Methods of studying mucociliary transport, saccharin test as its indicator:

The most widely used method for in vivo assessment of NMCC is the saccharin test [29,30].There is a study conducted in India where the measurement of nasal mucociliary clearance is performed via various method in that study the researcher used various methods available to determine nasal mucociliary transport the two basic principle to determine used were measurement of the transport of markers placed on the mucosa (• Mucociliary transit time with saccharin –Saccharin test • Mucus flow rate with - 99m Tc-labelled particles– Rhinoscintigraphy - 99m Tc-labelled resin particle • Mucus flow rate with radiopaque Teflon dicks • Mucociliary transit time with colouring substances • Mucociliary with combination dye and saccharin) and measurement of total nasal clearance of deposited dose (• Gamma scintigraphy[total clearance of 99m Tc-labelled solutions[23]). Techniques are employed for measuring NMC namely saccharin test and tests using

dyes or radio labeled particles. Saccharin test is an inexpensive, simple and non-invasive method while methods using radio labeled particles are time consuming, cumbersome and expensive [31].

There is study used to evaluate the respective role of the nasal mucus quality and ciliary activity in determining nasal mucociliary clearance and to study changes in these variables across time and with environmental conditions. In 20 healthy nonsmoking volunteers, the *in vivo* nasal mucociliary clearance was measured with the saccharin test. Then, nasal mucus and ciliated cells were collected. The *in vitro* ciliary beat frequency of the nasal cells was evaluated by a photometric analysis. The *in vitro* nasal mucus transport rate was evaluated by use of the frog depleted-palate model. The nasal mucociliary transport time (NMTT) of saccharin was greater than 30 min in seven subjects and was 13.6 ± 6.1 min (mean ± SD) in the remaining 13 subjects. NMTT was correlated to the *in vitro* transport rate of the nasal mucus ($r = -0.75$, $p < 0.001$), but not to the ciliary beating frequency or to ambient temperature, relative humidity, or air pollution indices measured. Moreover, large intra-individual variations of NMTT, measured on two occasions 4 to 8 week apart, were found to be significantly correlated with changes in mucus transport rate ($r = -0.60$, $p < 0.05$) [32].

The role of mucociliary clearance as primary defense mechanism of upper airway:

A study was conducted in Department of Pathobiology, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore 5, Maryland on the role of mucociliary clearance as defense mechanism of upper airway, the study shows the activity or function of the mucociliary system in the upper respiratory tract is important in response to the infection [33]. Comparative anatomy, physiology, pathogenesis, and the study of cells in organ culture, it is clear that the process of mucous secretion, the consequent formation of a blanket which covers the ciliated cells and is propelled by them in a particular direction, plays a large role in the eventual outcome of the infection and serves as primary defense mechanism of upper airway [33].

Another Perspective study was performed in Cystic Fibrosis/Pulmonary Research and Treatment Center, The University of North Carolina, Chapel Hill, North Carolina, USA by Michael R. Knowles and Richard C. Boucher on Mucus clearance as a primary innate defense mechanism for mammalian airways, the study shows many aspects of the airway defense system, however, remain to be elucidated. First, it is not yet clear at the physiologic level how this non-innervated epithelial system can regulate mucus transport rates over a more than threefold range. The preliminary observations that nucleotides are released by airway epithelia and interact with luminal purinorceptors provide the most tantalizing clues about the local regulation of mucus transport rates. Second, it is not yet clear how airway epithelia sense and regulate the volume of liquid on their surfaces. Although recent data indicate that regulation of ASL(air way surface liquid) by airway epithelia involves the reciprocal regulation of active Na+ absorption and Cl−secretion[34], it is not known whether the signals to the epithelium emanate from the ASL, or how such signals are transduced by the epithelium. Finally, whereas β-agonists and other agents that increase mucociliary clearance via regulation of ciliary beat frequency have become clinical mainstays, it now appears that other classes of drugs that affect the volume of

Airway Surface Liquid may be equally, or more, effective in many conditions and could be uniquely effective in specific diseases, such as Cystic Fibrosis. Thus, studies of airway function in health and disease have provided unique insights into how "wet-surface" epithelia can achieve a functional form of innate defense by unique adaptation of mechanical clearance mechanisms [25].

The role of saccharin test as indicator for nasal mucociliary clearance in patients with various nasal conditions:

Many chronic nasal conditions may have detrimental effects on mucociliary transport. There was a study conducted in Department of Otolaryngology. Pramongkutklao College of Medicine. Bangkok, Thailand showing the mean mucocillary transit time for the normal control group (n =40) was 12 ninutes, while allergic rhinitis patients (n =40) had a mean of 14.6 minutes. The smoker group (n =40) could be further divided Into the following subcategories: (a) those who had been smoking for less than 5 years (n = 10) had a mean of 15.2 minutes, (but those who had been smoking for more than 5 years at less than one-pack a day (n=11) had a mean of 14 minutes, and (c) those who had been smoking for more than 5 years at more than one-pack a day (n=19) had a mean of 16.5 minutes. For the sinusitis patients (n=20) the mean was 16.6 minutes. The study shows that sinusitis patients, along with those smokers who had been smoking for more than 5 years at more than one-pack a day, had a mucocillary transit time that was considered to be prolonged when compared to the normal control group ($p< 0.05$) [35] .

In a study with aim of this study was to compare the nasal mucociliary clearance in allergic and non-allergic patients with perennial rhinitis and a healthy control group. One hundred and three patients and 14 healthy control subjects were studied. Nasal mucociliary clearance was assayed with the saccharin test modified with a food dye to add a visual parameter. The aspect of the nasal mucosa was not considered for categorizing the patients. Fifty-seven patients (29 males, mean age: 22.2 years) with allergic perennial rhinitis and 46 patients (15 males, mean age: 24.8 years) with non-allergic perennial rhinitis were compared with 14 controls (6 males, mean age: 35 years). A significant difference in nasal mucociliary clearance was observed between the three groups, with a mean of 8.8 minutes for the controls, 10.27 minutes for allergic rhinitis and 11.73 minutes for non-allergic patients [36] .

The saccharin test was used to measure mucociliary clearance in 50 patients with symptoms of chronic sinusitis. Samples of the nasal mucosa were also examined under transmission electron microscopy before and after functional endoscopic sinus surgery (FESS). Before surgery, the mean saccharin clearance (ST) was 37.0 ± 15.7 min, with nasal mucosa exhibiting ciliary loss as well as other ultrastructural changes. Three months after surgery, the mean ST had improved to saccharin20.3 ± 7.5 min and significant regeneration of cilia was observed [37].

There is study conducted where average values for MCT in the patients with hypertrophy of the inferior turbinates and septal deviation were measured with saccharin and charcoal powder. In patients with

hypertrophy of the inferior turbinates, the average times were 11.9 min for charcoal powder and 17.5 min for saccharin. In patients with septal deviations, times were 13.3 min for charcoal and 16.5 min for saccharin. In contrast, patients with chronic sinusitis had an average transit time of 21.3 min for charcoal powder and 28min for saccharin. Hypertrophy of the inferior turbinates and deviation of the nasal septum did not interfere significantly with MCT. In contrast, sinusitis must be considerated an inflammatory pathology that can involve the whole mucosa of nose and paranasal sinuses [22].

Mucociliary function of the nasal mucosa of patients who were undergoing various nasal surgeries was assessed by the Saccharin test by placing 5 mg saccharin granule on the anterior end of the inferior turbinate 1 day prior to the surgery. The time required for the test subject to experience a sweet taste was measured in minutes. Post-operatively the test was repeated 6 weeks after the surgery and the test times were compared. A total of 60 patients were part of this study. Of the 60 cases, 19 cases had undergone only septoplasty, 13 cases had undergone only functional endoscopic sinus surgery (FESS), 25 cases had undergone septoplasty with FESS, 2 cases underwent septoplasty with bilateral partial inferior turbinectomy (PIT) and one case was submucous resection (SMR). Significant improvement in nasal mucociliary clearance was observed in all the patients after the procedures. Out of the 19 cases of septoplasty, 57.9 % showed improvement on the right side and 47.4 % on the left side. Out of the 13 cases of FESS, 61.5 % showed improvement on the right side and 69.2 % on the left side. Out of the 25 cases of FESS with septoplasty, 76.0 % showed improvement on both sides. Sub mucosal resection did not show improvement. The 2 cases of septoplasty with PIT showed improvement. Statistically, highly significant improvement of test time was seen postoperatively as compared to pre-operatively. Among the surgical procedures, FESS with septoplasty showed better improvement as compared to the other procedures. Based on the study, we can conclude that nasal surgeries done for correction of septal deviation and rhino sinusitis significantly improves nasal mucociliary clearance mechanism thereby improving the physiological functions of the upper airway [38] .

Summary of Reviewed Literature:

It can be concluded that there is insufficient study regarding the use of HIFU and its effects on nasal mucociliary clearance, as we know that HIFU is very reliable method for treatment of AR and NMCC is primary defense mechanism of upper air way and saccharin test convenient and easy way of measuring nasal mucociliary function. This study is aimed to study the effect of high intensity focused ultrasound (HIFU) treatment and its effect on normal mucocilliary cleareance function of nose with the help of saccharin test.

MATERIALS AND METHODS

Experimental study was performed over period of one year (March, 2017- March, 2018) to analysis the effect of HIFU treatment in patient with AR and its effect on nasal mucociliary clearance. During study period 200 patients with allergic rhinitis were selected to receive high intensity focused ultrasound treatment, full filing the diagnostic criteria of persistent allergic rhinitis according to allergic rhinitis and its impact on

asthma (ARIA) classification [26]. These patients were selected on the basis that they were not satisfactory managed with medical pharmacotherapy. Out of total 200 patients undergoing HIFU treatment only 35 patients were selected for this study based on selection criteria of the study. It is important to find the current clinical Allergic Rhinitis investigations and the identification of an effective and economical treatment for AR with HIFU and its effects on normal nasal mucociliary function with minimal or no side effects.

Standard technique for measurement of Nasal mucociliary clearance was done with the help of saccharin test with the help of rigid nasal endoscope before patients undergoing focoused ultrasound treatment and the test was again repeated after the procedure and note.

The only disadvantage of this method is that the determination of transit time may be influenced by the taste threshold of the patient [23]. Saccharin test was used to detect nasal mucociliary clearance 30 min before focused ultrasound and 30 min after irradiation and relevant findings noted.

After saccharin test was done , patient underwent standard application of focused ultrasound treatment under local anesthesia, maintaining sterilization , where nasal mucosa of bilateral inferior turbinate was irradiated linearly from the rear to the front and each irradiated line was irradiated for two times.

Statistical Analysis:

The values obtained 30 minutes before and after high intensity focused ultrasound therapy and evaluation of nasal mucociliary clearance time with saccharin test were done and value obtained with saccharin test were plotted in IBM SPSS software version 20 and used to analyze paired T test.

Saccharin test	Before HIFU	After HIFU
NMCT(min)	10.63±1.98	10.60 ± 1.64

Table 2: showing the NMCT between prior- scanning and post- scanning

We can see from the table: before and after focused ultrasound nasal mucociliary delivery time is basically the same with regular follow up of up to six months, there is no difference between the unification Significance of the calculation, T = -0.135, P = 0.869. Showing there is no effect of high intensity focused ultrasound in normal defense mechanism of nasal mucosa.

DISCUSSION AND CONCLUSION

Nasal mucociliary system on the nasal cavity has protective effect, is one of the nasal defense mechanism. Mucosal mucociliary clearance of nasal mucosa detection methods are many, such as saccharin test, radiographic method and radioactivity Isotope method, etc., but the radiographic method requires the patient exposed to radiation, and the success rate is not high; radioactive The isotope method is considered the most accurate method of measuring nasal mucociliary clearance system[103, 104] , But the method needs expensive equipment and poor test reproducibility, not suitable for a wide range of clinical use. Saccharin test

is done by Saccharin granule placed on the inferior turbinate or other parts of the nose reach the pharynx and get the time to perceive the sweet taste in mouth. Mucosal ciliary clearance via saccharin test has the advantage of being simple, the disadvantage is subjective and vulnerable to impact of nasal secretions. Saccharin test used and the granule is placed in the inferior turbinate anterior edge from the inferior turbinate front 1cm is not easily be affected by the secretion of the nose. Therefore, since 1974 Andersen And Grossan first application of saccharin test as indicator of mucociliary transport time (Nasal mucociliary transport time, NMCT), this method has been widely used commonly. The average value of NMCT is 20 to 60 minutes [39].

High intensity focused ultrasound energy can accumulate in the nasal mucosa, so that the corresponding blood vessels, after and gland coagulation necrosis and eventually absorbed, and nasal mucosa epithelium and other non-irradiated tissue does not cause any Injury, the dose of focused ultrasound applied to the treatment of patients with allergic rhinitis, through the patient's NMCT Test and found that 30min before focusing ultrasound irradiation and 30min after focusing ultrasound irradiation patients with NMCT no significant ($P = 0.869 > 0.05$), indicating that focused ultrasound had no effect on normal physiological function mucociliary clearance of nasal mucosa.

High intensity Focused ultrasound is a safe for management of allergic rhinitis, a dose of focused ultrasound can be energy-specific act on the nasal submucosa, and do not cause damage to structures such as cilia and microvilli on non-irradiated areas such as the nasal mucosa epithelium and has no effect on nasal mucociliary clearance system of the nose.

Focused ultrasound is a new thermal ablation technique developed in the field of management of allergic rhinitis therapy, which can be specific use of Ultrasound energy that will accumulate in the nasal mucosa, rich in blood vessels, nerves and glands nasal mucosa and performs thermal ablation, Non-irradiated areas such as the nasal mucosa goblet cells, microvilli and cilia and other structures are not damaged. At fixed safe dose of focused ultrasound, ciliary swinging and cupping of nasal epithelial cells there was no obvious change in the secretory function of the cells, has no effect on the nasal mucociliary clearance time, indicating focused ultrasound does not affect the scavenging function of the mucociliary system of the nasal cavity.

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