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REVIEW ARTICLE

Impact of Space Environment on Human Body From an Otorhinolaryngologist Perspective: A Brief Review and Future Initiatives for Development of Healthcare, Education and Research Facility in India

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Abstract

Background: Microgravity in space causes changes in the physiology of human body and as a result makes them susceptible to various pathology. As a result astronauts suffer from health disorders which includes otorhinolaryngological disorders

Aim: To gather information about the various otorhinolaryngological manifestations occuring in microgravity by compiling the available scattered data existing in literature

Methods: This is a narrative review article. Using keywords a search was made on the internet, various databases such as googlescholar, pubmed to find out the description of various otorhinolaryngological manifestation in microgravity environment of space. A few proposals or initiatives are given at the end of the discussion so that more research can be conducted on this aspect of otorhinolaryngology

Results: Studies have revealed that the microgravity environment leads to mastoid effusion, predisposes tosinusitis, causes cytoskeletal changes and altered gene expression in thyroid cancer cells, decreases salivary secretion, causes difficulty in airway management, affects temporomandibular joint function, causes impairment of balance. Regarding sleep some studies revealed that microgravity improves sleep whileother studies revealed that microgravity causes increase in sleep disturbances. Important future initiatives include establishment of world class health and research facility, National Health Programme forastronauts, Fellowship courses by NBEMS etc.

Conclusion: Microgravity has a significant impact on mastoid, sinuses, sleep, thyroid cancer cells, salivation, airway, temporomandibular joint and balance. More research needs to be conducted on this topic.

Keywords: Microgravity, Space Medicine, Mastoid, Sinuses, Sleep, Thyroid, Salivation, Airway, Temporomandibular Joint, Vestibular

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Graphical Abstract



Introduction

Astronauts working in various space missions are faced with various challenges. They are exposed to a microgravity environment which makes them susceptible to various changes in body. After sometime the body gets acclimatized to the space environment. Once the scientists return back to earth body must again learn to adapt to the change from microgravity to normal gravity. Similarly when the astronauts land in moon from space they are exposed to a completely different environment. Till now only a limited number of astronauts have been trained to venture into space and most of the space missions in the past have been unmanned space missions, so the lacunaeis that the existing knowledge available till now is still very less. The main objectives of

this review article are to find answers about the various bodily changes from the perspective of an otorhinolaryngologist by compiling the available scattered data in literature. Effect of microgravity on middle ear and mastoid, sinus, sleep, thyroid cancer cells, swallowing and salivation, airway, temporomandibular joint and balance is going to be covered in this review article. Keeping in mind the future plans of Government of India and ISRO to send civilian population in human space flight missions and establishment of Bharatiya Antariksha Station (Indian Space Station), a list of recommendations/proposals are given through which the existing knowledge from the literature review can be implemented on the astronauts. It is hoped that such initiative will encourage academic research and

collaboration on this aspect of otorhinolaryngology and will be a boon in the context of providing health care to the astronauts involved in Human spaceflight program of India (GAGANYAAN) and boosting medical and space tourism in India. The initiatives will also help in establishing India as a pioneer in the field of space medicine in the world.

Methods

This review article is a narrative review. A search was made on various databases such as PUBMED, GOOGLE SCHOLAR and on internet on the effect of microgravity environment on the various bodily systems from an otorhinolaryngologist point of view. Using keywords/research titles such as microgravity and mastoid, microgravity and microgravity sinuses, and sleep, microgravity and thyroid, microgravity and salivation. microgravity and airway. microgravity and temporomandibular joint, microgravity and vestibular, etc an online search was conducted. The articles included those which were free open access articles.

Discussion

Now a brief discussion will be done on the effect of microgravity on ear, nose, sleep, thyroid cancer cells, swallowing and salivation, airway management, Temporomandibular Joint, balance.

Mastoid Effusion

Astronauts in space are at significant risk of developing mastoid effusion [1]. The three important causes of mastoid effusion on earth are eustachian tube dysfunction, eustachian tube obstruction and venous congestion. We will briefly discuss about each of these three causes in earth as well as in space.

Eustachian tube dysfunction is a very common cause of mastoid effusion [2]. In earth function of eustachian tube dependent on gravity. When the body is in a horizontal position there is increase in venous tissue pressure around the eustachian tube. This in turn decrease the airflow from the middle ear as compared to upright position [3].

In space flight because of head ward shift of fluids leads to venous congestion which in turn leads to eustachian tube dysfunction [4].

In both these cases the drainage of fluid from the mastoid mucosa is hampered.

Middle Ear Barotauma occurs in divers and pilots due to failure of a dysfunctional eustachian tube to equalize the ambient pressure with the pressure in mastoid air cells [5,6]. On doing MRI on such subjects we get the findings of mastoid effusion.

In space a recent study was conducted by using two groups ISS (International Space Station) and the space shuttle group. Astronauts in ISS group engaged in extravehicular activities experience changes in barometric pressure [1], in presence of eustachian tube dysfunction they may show features of middle ear barotrauma [1]. In space shuttle group crew members not participating in extra vehicular activities also experienced changes in cabin pressure [1,7]. Now coming to eustachian tube obstruction, sinusitis and middle and upper respiratory inflammation, hypertrophic adenoids are the

common causes [2,8]. There are many risk factors in the space environment which predispose to inflammation of upper respiratory tract hence leading to eustachian tube obstruction [1].

Lastly let us discuss venous congestion. In the earth stagnancy of the venous flow lead to increased upstream hydrostatic pressure and in turn lead tomastoid effusion [9]. Pathological conditions such as lateral venous sinus thrombosis where there is stagnancy of venous flow cause increase in upstream hydrostatic pressure and leads to transudative mastoid effusion [10]. In microgravity there is loss of gravity dependant hydrostatic pressure gradient which leads to head ward fluid shift and venous congestion in head and neck [11]. A lack of gravity leading to impaired venous drainage in head and neck could possibly lead to increased backward pressure and transudative mastoid effusion with a similar venous mechanism as lateral sinus thrombosis. Internal jugular vein thrombosis has been found in 2 ISS astronauts in ultrasonography by Marshall-Gobel et al and the mechanism is similar to lateral venous sinus thrombosis [12].

Sinusitis

Various studies from literature give us an idea about the risk factors, clinical presentation, investigation and the diagnostic workup of sinusitis in space environment.

There are many risk factors present in a microgravity environment which predispose to sinusitis. Gravity dependent drainage of the sinuses is absent leading to impaired clearance of the mucus from the sinuses. Also closed environment in space leads to impaired mucociliary clearance. These factors lead to blockage of the sinus passages and increased chances of upper respiratory infection [13].

In the earth in upright posture a normal head to toe hydrostatic pressure gradient is exerted. This gradient is lost in microgravity which leads to headward shift of fluids [14, 15]. This manifests clinically as facial puffiness and subjective symptoms of nasal stuffiness.

Studies conducted by researchers have also concluded that there is altered presentation of rhinosinusitis in microgravity conditions [16].

It is important to make a prompt early diagnosis and start early treatment to prevent complications [17].

The problems encountered in space is remote location and minimal diagnostic equipment.

Various investigations have been proposed for sinusitis patient which are briefly discussed. The current diagnostic reference standard for Acute Bacterial Rhinosinusitis is needle puncture and bacterial culture of the sinus contents through the canine fossa or the inferior turbinate [18]. The limitations of this investigation is that it is a complicated, traumatic and painful procedure which must performed by be а expert sinus specialist/rhinologist because of requirement of technical expertise [19].

Another important investigation is middle meatal cultures which requires a lot of technical expertise and must be performed in controlled environment [20]. Ultrasonography (US) is a very good technique for detection of maxillary sinusitis in space environment [21-24]. Minimally trained, non physician operators can perform diagnostic US for medical diagnosis of sinusitis [25,26]. The advantages of US it is a painless and noninvasive technique for diagnosis of sinusitis.

Important findings of US done on a animal swine model (anesthetized swine) is disassociation of air fluid interface and uniform dissolution of the fluid to the walls of the sinus with the introduction of microgravity [16].

A very recent study was conducted by Ingles et al using two groups [Space shuttle group And ISS group] in space environment to know whether MRI PNS opacification Lund Mackway scores increased post flight compared to preflight. They have concluded that there was no association between exposure to space flight conditions and changes in PNS opacification [1].

Sleep Disturbances

In the study done by researchers to know the effect of space environment on the sleep pattern various parameters such as number of sleep-related breathing disturbances, number of arousals, the amount of time spent in snoring etc have been studied. All these parameters were reduced in the microgravity environment and it has been concluded that sleep quality improves in such a environment, especially for those human beings with positional sleep disorders, obstructive sleep apnea, upper airway resistance syndrome [27].

However certain physiological changes occur in microgravity which leads to increased sleep disturbances. Microgravity causes a cephalad shift of blood and body fluids [28], which leads to altered respiratory mechanics and chemoreceptor function.

The increased volume of fluids in the head and neck passively reduces the caliber of upper airway and increased chances of obstructive sleep breathing disorder. Altered chemoreceptor function leads to both obstructive and central periodic breathing [29]. Blood gas derangement during apneas also occurs due to altered chemoreceptor function leading to arousal from sleep. [30,31].

Head and Neck Cancer

The effects of the space environment on the cancer cells have been studied by the researchers. Of notable interest from an otorhinolaryngologist perspective are the various studies and review articles demonstrating cytoskeletal changes and gene expression changes in the thyroid cancer cells exposed to both real and simulated microgravity situations [32].

The examples of real microgravity short time exposure study are 31 parabolas of a parabolic flight and TX53 sounding rocket mission [32].

There was observation of upregulation in the ACTB and KRT80 mRNAsin ML-1 cells after 31 parabolas of a parabolic flight [33].

InTX53 sounding rocket mission molecular biological analyses of the FTC-133 cell material were done after the flight. [34,35]. The analyses showed elevation in them RNAs of the ECM genes FN1, SPP1, TGFB1, TIMP1, MMP1, MMP3, and MMP14 [35]. It was also observed that there was upregulation in the cell adhesion genes ICAM1 and VCAM1, the focal adhesion factors CFL1 and CDH1, as well as cytokines IL6 and CXCL8in r-µg samples. All these alterations observed in the molecular biological analysis have demonstrated their sensitivity to gravity [35] and involvement in MCS (multicellular spheroids) formation.

The Shenzhou-8/SimBox experiment is an important study done by researchers in which thyroid cancer cells are exposed for a long time in space [32]. The significant findings are the formation of large 3D aggregates by the thyroid cancer Cells, together with an altered expression of the EGF and CTGF genes [36]. These changes in the gene expression pattern have been observed in parallel to spheroid formation [37].

In case of exposure to a simulated microgravity environment such as Random Positioning Machines (RPMs), thyroid cancer cells showed early cytoskeleton changes and changes in ECM, focal adhesion molecules, proliferation, the rate of apoptosis, migration, and growth [32,38-46]. A very important finding was the formation of MCS.

All these studies give the scientific community knowledge about process of cancer progression and potential development of therapeutic drugs.

Swallowing and Salivation

Various experiments have been carried out under laboratory conditions

which resemble environment of space to understand the effects of microgravity on swallowing and salivation. The examples of various devices used in laboratory conditions include random positioning machines (RPMs), clinostats, and levitating magnets at the cellular level whereas at the subject level examples include a -6° headdown bed rest in humans and tail suspension (TS) or hind limb unloading (HU) in rodents [47].

The oral phase of swallowing involves chewing of food which is accomplished by the activity of muscles of mastication causing movement of mandible, shearing action of teeth. During chewing food is lubricated by the saliva and the digestive juices present in saliva play a role in digestion.

However many things change in microgravity. It has been observed that there is reduction of bone density of the mandible, alveolar bone and also bone mineral content in microgravity [47,48].

It has also been observed in rats exposed to simulated microgravity conditions that the masseter muscle fibres were partially dissolved after 1 week. There was further reduction in second week and complete alleviation in fourth week [47,49].

Changes have also been noted in the salivary proteins and salivary flow in microgravity.

The levels of salivary amylase and proline rich protein reduced which may be related to CAMP signaling pathways [47,50].

Immunoglobulin A in saliva showed increased concentration and secretion rates

which might be related to immune stress experienced under microgravity [47,51].

The level of matrix metalloproteinases MMP-8 and MMP-9 are elevated which might be related to immune response to bacterial virulence due to microgravity [47,48].

There is reduction in salivary flow which occurs as a result of changes in fluid distribution and fluid imbalance in microgravity. This further leads to xerostomia [52].

Difficult Airway Management

In earth due to presence of gravity patient can be properly positioned by the doctor so as to achieve proper alignment of laryngeal, pharyngeal and oral axis and hence visualize the glottis and supraglottic structure for introduction of endotracheal tube [53].

In direct laryngoscopy the elevation of the epiglottis occurs because of the pressure exerted by the laryngoscope blade tip against the vallecula. This elevation of epiglottis is gravity dependent.

However in microgravity the scenario is little different. Lejune has proposed a hypothesis in 1978 which explains difficult endotracheal intubation in microgravity. In microgravity head and neck moves out of the field of vision as a result of force exerted by the laryngoscope because of the lever effect exerted on the head which is generated through the laryngoscope blade. This in turn leads to difficult endotracheal intubation [54].

In such circumstances video laryngoscopy is a good alternative which is associated with higher intubation success rate and can be used for airway management in long duration flight.

Supraglottic airway devices can also be used as an alternative to endotracheal intubation using direct laryngoscopy in microgravity. In a study by Hinkelbein et al in a microgravity simulated environment they have achieved90 % success rate with these devices and also time required to ventilate is also reduced [55].

Temporomandibular Joint Disorder

In a microgravity environment the temporomandibular joint is significantly affected. The possible etiologies are the disfigurement of circadian rhythm, physiological and psychological stress. Stress causes a decrease of bone mineral density of the temporomandibular region. [56, 57] Additionally there is decrease in overall muscle mass, thereby causing an insufficient increase in muscle tonicity during stressful period. On exposure to longer duration space visits, circulating parathormone concentration also decreases leading to reduced Vitamin D metabolism and ultimately Vitamin D deficiency. The effect on disorientation of complete body affects combined homeostasis toward disarrangement of TMJ function [58].

Balance Disorder

Astronauts experience balance disturbances on entering a microgravity environment which is similar to vestibular pathology.

There are 2 situations in which astronauts experience impairment of balance and poor gaze control, one during the initial few days after entering into space environment and secondly while returning back to earth [59,60,61].

In normal situation an internal model is built by the brain of the expected sensory input from active movement [59,62,63]. This model is important for maintaining postural stability, spatial orientation and precise voluntary movement [59,64].

The brain compares the expected sensory input of its model with the actual sensory input it receives from the visual, vestibular, propioceptive and somatosensory system and thus validates the consequences of forces of gravity [59,65,66]. On earth expectation from gravity is an important component of this model of the brain. In space the force of gravity becomes negligible which causes a mismatch between expected and actual sensory input from the unloading of otolith [59]. Microgravity causing an alteration in the sensory input from the vestibular system, which in turn generates а persistent conflict (i.e., mismatch) between expected and actual sensory vestibular inputs during active movements [59,67].

Let us first discuss about posture in microgravity. In microgravity the body acquires a neutral posture characterized by a semicrouched torso, flexed arms and legs and forward bent neck and head [59,68,69]. It is postulated that neural mechanism stabilizing posture in normal gravity persist on entry to microgravity [59,70-74] plays a role in posture maintenance. Hoffman reflex (otolith spinal reflex) [59,75] also play a role in posture. However still it is debatable among many researchers about the role of neural mechanisms in long space missions. Once the astronauts return back to earth, there is disruption of the neural mechanism leading to transient postural instability [59,76,77]. Gradually there is improvement in postural stability [59,78,79].

Oscillopsia is also experienced by the astronauts suggestive of head trunk in coordination [80]. To be more precise, oscillopsia occurs because the coherence between pitch head and vertical trunk movement is decreased after spaceflight. [59,80,81]. In earth patients with peripheral vestibular loss [81] and on galvanic vestibular stimulation [82] also have a reduction in coherence between pitch head and vertical trunk movement.

In the micro gravity environment astronauts experience spatial disorientation and destabilizing sensation and perception is affected [59]. This impaired perception compromises the astronauts ability to control the spacecraft [59,83]. On earth the brain computes the head and body orientation relative to gravity using inputs from the vestibular and sensory system. This is violated in space environment [59,84]. For instance, loss of otolith input that normally orients relative to gravity, there is loss of spatial anchoring to the surroundings in space when the eyes are closed [59,85]. If the eyes are open astronauts may intellectually know their position but normal sense of orientation with respect to surroundings is not experienced. They experience sensations of inversion and tilt which tend to abate as astronauts adapt to the new environment. This perceptual adaptation to altered gravity has been studied using centrifugation on the ground as well as in space [59,86].

Lastly accurate control of voluntary movements such as reaching is affected in a space environment [59,87–90]. In earth on instruction to reach up or down, there is demonstration of asymmetric arm kinematic in humans. This suggests that the brain has an internal model to predict and take advantage of its mechanical properties to optimize efforts [59, 89].

In microgravity this asymmetry disappears [59,87,89,91]. Possible causes are reduction of arm weight in microgravity [59, 92] or increased vestibular activity as suggested by EEG findings in a comparable visuo motor task [59,93]. Similar effects were observed in a ground model when vestibular input was abated via labyrinthectomy [59, 94].

There are changes in the peripheral vestibular system in a microgravity environment which is briefly discussed.

In the earth the otoliths are stimulated by changes in the spatial orientation of the head. However in space environment they are not stimulated because of unloading of otoliths.

Experiments carried out on rats and dogs suggest that the mass of the otoconia increase following short exposure to microgravity due to unloading of otoliths [59,95-98]. Similar experiments carried out in model systems have concluded that opposite changes in mass of otoconia occurs in hyper gravity [59,99-102].

Recent studies using electron microscopy have found out that mass of otoconia outer shell increase in long duration space flight as compared to short duration spaceflight or hindlimb unloading [59,103]. Additional finding are thinning of the inner shell and cavitation of otoconia following centrifugation. Structural changes following hindlimb unloading have been reported following long but not short duration hindlimb unloading [103,104].

Recent studies point out about various structural changes in type II hair cells following long exposure to microgravity [59,105-107]. Such changes include increase in number of type II utricular hair cells synapses [106]. In addition to that there is increase in the mean number of presynaptic processes of type I cells [108]. However another study has found out a reduction of synapse densities in hair cells in the utricle of mouse following exposure to microgravity [109].

Studies also point out that on entry to a microgravity environment there is increase in the baseline activity and sensitivity of the otolith afferents [110]. This finding was common in all the nonmammalian animal models used for testing [59,111-115]. These baseline activities and sensitivities return back to control levels after 5 days exposure to microgravity [114] and 24 hour after return to ground [111]. It has been proposed that the presynaptic adjustment of synaptic strength in the hair cells contributes to the initial hypersensitivity of otolith afferents on entry into microgravity conditions [107].

The above discussion has been summarized in Table 1.

Limitations

This review article has scarcity of data in otorhinolaryngological manifestations inhuman beings who have actually ventured into space. Many of the studies mentioned in this article involve simulation experiments or animals. Also the information available from the review article are only preliminary findings and cannot be generalized or confirmed unless and until original studies of civilian missions involving the common man are conducted by the space agencies. The various academic societies of otorhinolaryngology also need to be involved to reach at a consensus and frame guidelines on various aspects of otorhinolaryngology in relation to space.

A lot of initiatives need to be undertaken to make our understanding of the concepts more clear in this topic.

MASTOID	MASTOIDEFFUSION
	EUSTACHIAN TUBE DYSFUNCTION
	EUSTACHIAN TUBEOBSTRUCTION
	VENOUS CONGESTION
SINUS	SINUSITIS
	GRAVITY DEPENDANT
	SINUSDRAINAGE ABSENT
	CLOSED ENVIRONMENTLEADING
	TOIMPAIRED MUCOCILIARY
SI FEP	IMPROVED SLEEP
SELLI	DECREASE IN NUMBER OF AROUSAL
	DECREASE IN TIME SPENT IN
	SNORING
	DISTURBED SLEEP
	CEPHALAD SHIFT OFBLOOD AND DODY FLUDGLE ADDIG TO ALTERED
	BODY FLUIDSLEADING TO ALTERED RESPIRATORY MECHANICS AND
	CHEMORECEPTORFUNCTION
HEAD AND NECK [THYROID]CANCER	CYTOSKELETALCHANGES
	GENE EXPRESSION CHANGES
	MULTICELLULAR SPHEROIDS
	FORMATION
SALIVATION AND SWALLOWING	DECREASED SALIVARY FLOW
	LEVELS OF SALIVARY
	AMYLASEAND PROLINERICH
	PROTEIN REDUCED
	MASSETER MUSCLE FIBRESWERE PARTIALLY DISSOLVED
AIRWAY	DIFFICULTAIRWAY MANAGEMENT
	• ALIGNMENT OF LARYNGEAL,
	PHARYNGEAL AND ORAL
	AXISAFFECTED
TEMPOROMANDIBULAR JOINT	TEMPOROMANDIBULARJOINTISAFFECTED

Table 1. Different Aspects of Otorhinolaryngology in Microgravity

	 DISFIGUREMENT OF CIRCADIAN RHYTHM PHYSIOLOGICAL AND PSYCHOLOGICAL STRESS
BALANCE	 OSCILLOPSIA SPATIAL DISORIENTATION DESTABILIZING SENSATION PERCEPTION IS AFFECTED ACCURATE CONTROL OF VOLUNTARY MOVEMENTS AFFECTED UNLOADING OF OTOLITHS STRUCTURALCHANGES IN TYPEII HAIR CELLS



Figure 1. Future Initiatives for Development of Space Medicine and its Otorhinolaryngological Aspects in India

Future Initiatives/Proposals

1. There is a need to have a tertiary referral center for the astronauts of India and other countries having space missions and facing ENT and other health disorders. This center will have world class health and research facilities.

2. National Health Programme On Space Medicine Disease. Such a programme will be definitely be needed as more manned space missions are being planned and the health of the astronauts be prioritized. The should main objectives are to determine the burden of diseases among the astronauts, to prevent and treat diseases among the astronauts, rehabilitate the astronauts suffering from diseases. In addition the programme will aim to promote education and research. This can be achieved through training of doctors and paramedical staff, building simulation laboratory, starting orientation program in various medical colleges.

- To start various fellowship courses accredited by the National Board Of Examinations In Medical Sciences (NBEMS) on the topic of space medicine.
- 4. To add various aspects of space medicine Otorhinolaryngology in the undergraduate [MBBS] and postgraduate Otorhinolaryngology [M.S ENT, DNB ENT] curriculum in consultation with National Medical Commission (NMC) and National Board of Examinations in Medical Sciences (NBEMS).
- 5. To include these topics as a panel discussion in national conference of Association Of Otolaryngologists Of India [AOICON], other prominent ENT conferences in India, Indian Medical Association Conference.
- 6. To collaborate with International Federation Of Otorhinolaryngological Societies for more research on this aspect of otorhinolaryngology.
- 7. To collaborate with prominent vestibular societies such as Barany Society and

undertake research studies on balance disorders

- 8. To appoint visiting faculty/doctors from prominent medical institutes from all over the world who have done research in space medicine and have treated astronauts suffering from various health disorders.
- Expert opinion and advise can be taken from scientists and researchers working in ISRO, ICMR, Indian Institute Of Science, IIT, National Academy Of Medical Sciences, A.I.I.M.S, Institute Of Aerospace Medicine, Medical Colleges, NBEMS, members of Indian Medical Association and policy makers in NITI AAYOG.
- 10. To host International Space Medicine Conference where doctors and researchers can share their ideas on this topic.
- 11. To start short term internships for doctors working in medical colleges and NBEMS accredited DNB training institutes.
- 12. To develop International exchange scholar programmes for Indian doctors .

The important future initiatives proposed have been diagrammatically represented in Figure 1.

Conclusion

Microgravity has a significant impact on mastoid, sinuses, sleep, thyroid cancer cells, salivation, airway, temporomandibular joint and balance. More research needs to be conducted on this topic.

The list of recommendations which are proposed will help in applying the

existing knowledge in this subject practically in the future and lead to development of world class health and research facility In India.

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Conflict of interest

The author declares that they do not have conflict of interest

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