Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/11939
DOI URL: http://dx.doi.org/10.21474/IJAR01/11939

RESEARCH ARTICLE

USE OF GLYCOPYRROLATE AS AN ADJUNCT FOR REDUCTION OF AEROSOL TRANSMISSION OF COVID-19 DURING DENTAL PROCEDURES: A HYPOTHESIS

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Manuscript Info

Manuscript History
Received: 27 August 2020
Final Accepted: 30 September 2020
Published: October 2020

Key words:-
Aerosols, Antisialogogues, COVID-19, Glycopyrrolate, Saliva, SARS-COV 2, Transmission

Abstract

COVID-19 global pandemic has become the biggest challenge by causing health crisis across the world due to its contagious nature. Salivary gland acts as a reservoir of virus due to which contaminated saliva plays a pivotal role in COVID-19 transmission among humans. Infection transmission from symptomatic patients as well as asymptomatic carriers is inevitable while performing aerosol generating procedures because contaminated aerosols have potential to float in the air for a considerable amount of time and be inhaled by dentist, dental auxiliary and other patients. Hence, it is a matter of utmost importance to keep upgrading the strategies for prevention of transmission as the outbreak of SARS-COV 2 has clearly placed the health care professionals at highest risk. As excess salivary secretion results in more aerosol contamination in dental procedures, leading to higher risk of transmission; antisialogogues can be used to reduce salivary production. This new strategy will be helpful towards reducing aerosol transmission inorder to prevent and control the spread of this highly infectious disease. The aim of this present review is to propose the possible use of antisialogogues (glycopyrrolates) as an adjunct aid in reducing the risk of transmission from contaminated aerosols.

Introduction:-

The ongoing pandemic, corona virus disease 2019 (COVID-19) caused by novel Corona virus (nCoV), is a severe acute respiratory disease that is currently spread all across the world affecting the health and economy of the people in every walk of life.WHO(World Health Organization), on Jan 31,2020, declared the COVID-19 crisis as a "Public Health Emergency of International Concern" [1].

Infected patients are the main sourcefor transmission of the disease. Though contact transmission plays a minor role [2,3] but spread by touching hands, nose, mouth, etc.is common. Saliva plays a major role in transmission of COVID-19 directly or indirectly.COVID- 19 is present in saliva by 3 different pathways i) Infection present in the lower and upper respiratory tract, which can enter the oral cavity along with the liquid droplets exchanged by these organs. ii) Infection inthe major and minor salivary glands can cause the salivary ducts to release viral particles in saliva.iii), COVID-19 in blood can gain access to the oral cavity via gingival crevicular fluid [4]. Possible transmission of SARS-CoV (severe acute respiratory syndrome coronavirus) from sweat has also been reported

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[5].Potential risk of transmission by blood transfusion from asymptomatic individuals is of no significance asit has been reported that respiratory viruses have never been transmitted through blood or blood components [6].

Since excess salivary secretion results in more aerosol contamination in dental procedures, leading to higher risk of transmission, antisialogogues canbe used to reduce salivary production.

Occupational Safety and Health Administration (OSHA), have placed dental health care personnel (DHCP) in the very high exposure risk category because dental professionals are bound to work in close proximity to patients' mouth [7]. In dentistry, there are a significant number of potential carriers or infected individuals who are either asymptomatic or pre-symptomatic who cannot be identified by routine screening questions or temperature checks. Treating such patients with aerosol generated dental procedures could risk the health of the dental healthcare workers or other patients. The current evidence shows that the primary route of direct transmission is by droplet spread or contact route.

The present review highlights the role of saliva and bioaerosol in the transmission of SARS-COV 2 and the significance of glycopyrrolate (antisiaogogue) as a treatment strategy to reduce the risk of COVID-19 transmission.

Discussion of hypothesis:
Glycopyrrolate (antisialogogue) has successfully been used in the treatment of sialorrhea (drooling or excessive salivation). But, the strategy of its use to prevent salivary transmission of COVID-19 while performing routine dental procedures, can still be considered as a topic of further discussion. Since the most prevalent course of transmission of COVID-19 is through the contaminated aerosols; one of the apparently simple but propitious ways could be the administration of drugs so as to reduce the patient's oral-respiratory secretions, especially in dental practices where the operators work at a closer proximity to patients' mouth.

Aerosols and their significance in the transmission of diseases:
Aerosols are a suspension of fine solid particles or liquid droplets in air or another gas which when combined with bodily fluids in the oral cavity, such as blood and saliva, become bioaerosols [8].

Sources:
Dental proceduresrequirethe use of instruments such as high-speed handpiece or ultrasonic instruments, air polisher, and other instruments like airwater syringe which may aerosolize the virus into the surroundings. About 100,000 microbes per cubic foot can be transmitted by dental ultrasonic instrumentation with aerosolization extending upto 1.82 meters. These microbes can survive until 17 hours [9].

Transmission:
The respirable particle size fraction of bioaersol is 1-10µm which is of prime importance when compared to the overall particle size which ranges from 0.3 -100µm. Only particles which range from 1.0-5µm remain in the air, whereas larger and heavier particles are deposited on the surface [10]. There is a possibility of the aerosolized droplet nuclei to remain present in the air, because of which the health care workers can get infected and the surface can get contaminated even after the patient leaves. [11].Droplets of saliva discharged by people while sneezing or coughing, and their particle size is generally 1-5 µm which spread in a space of about 1-2 meters from the source of infection [10].Larger droplets are responsible for the transmission of virus to nearby subjects where as long distance transmission occurs because of smaller droplets infected with air-suspended viral particles [12].An infected person can give out particles which can travel up to 6.09 meters and can trigger secondary infections [11].

The virus in aerosols can remain viable and infectious from several hours to days on surfaces dependingupon the inoculum shed. Therefore, the SARS COV 2 transmission through aerosoland fomite is quite reasonable [11].

Aerosols may enter the respiratory tract through ill-fitting/uncertified masks [13] and contact mucous membranes by going around protective devices such as safety glasses/eyewears. As aerosols may last in the air of the operatory for upto 30 minutes after a routine dental procedure [14], this increases the potential risk for the operator to get in contact with airborne contaminated residues if the operator removes a protective barrier such as a face mask immediately after completion of the dental procedure.

Role of saliva in transmission of SARS-CoV-2:
Saliva plays a crucial role in person-to-person transmission of COVID-19,as the virus may spread directly or indirectly among patients even without coughing or respiratory symptoms. The reason of asymptomatic infections could be that SARS-CoV RNA can be found in the saliva before the emergence of lung lesions [15]. Epithelial cells of infected salivary glands have elevated ACE-2 (critical COVID-19 receptor) expression [16]. Thus, salivary gland acts as a reservoir of the virus in saliva. This shows that the spread of COVID -19 through asymptomatic infection may be due to contaminated saliva [15].

Inhalation of airborne particles and aerosols produced during most of the dental procedures on COVID-19 infected patients can be a high-risk procedure as dental personnel are directly exposed to the virus. Thus, it is important that the dentist improve their preventive strategies to avoid COVID-19 infection, by focussing more on hand hygiene, donning and doffing of the personal protective equipment (PPE) and utmost caution in performing procedures known to generate aerosols.

Glycopyrrolate – A special measure to be taken in routine dental practice?:
The spread of COVID 19 infection cannot be completely controlled by standard infection control measures alone, especially in the incubation period. In many instances, asymptomatic carriers are unaware, they are infected, or choose to conceal their infection. We know that it is not always possible to identify asymptomatic carriers early or without testing. Therefore, apart from following universal precautions, an additional special precautionary measure to prevent bioaersol transmission should be taken to prevent and control the spread of this highly contagious disease.

Dental aerosols can be reduced by following three layers of defense. The first layer includes the use of personal protective equipment (PPE) such as masks, gloves, face shields, and eyewear. The second layer comprises of routine use of preprocedural mouth wash and the third layer is the routine use of HEPA (High efficiency particulate arrestance) air filters and dental vaccum suctions [40].

An additional layer of defense possibly may be the use of glycopyrrolate (antisialogogue) to reduce aerosol contamination by reducing the salivary flow, respiratory secretions, sputum, sweat, etc.

Although complete elimination of the risk posed by contaminated dental aerosols is not possible, but it is possible to minimize the risk by controlling the salivary secretion thereby reducing the viral load; with a relatively simple and inexpensive method.

Pharmacology:
Glycopyrrolate is an anticholinergic drug which has a highly polar structure and is a white, crystalline, water-soluble solid [17] with a molecular weight of 398.34 g/mol and a melting point between 193.2-194.5°C [18 ,19]. It is a quaternary ammonium compound with the following structural formula [20].

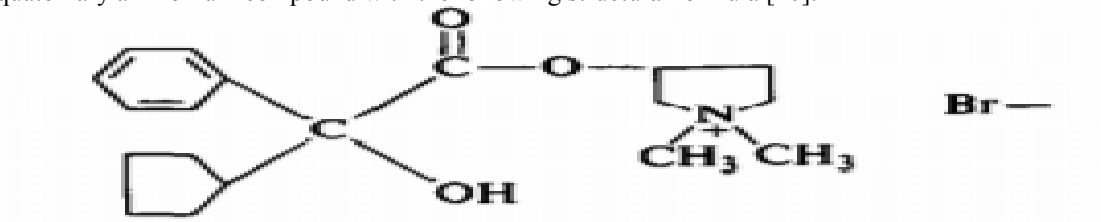

Figure1:- (1-methyl-3-pyrrolidyl -phenyl-cyclopentane glycolate methobromide).

Glycopyrrolate being an anticholinergic drug, blocks secretory reflexes, reduces glandular output and sputum volume, and is frequently used as mucoregulator [21–23]. An active stimulus for mucous secretion in humans is by cholinergic parasympathetic nerve activity, which is mediated through receptors expressed on submucosal airway cells and is known as M3 muscarinic receptors.

Safety aspects:
In July 2010, Cuvposa (a glycopyrrolate oral solution) was the first drug to be approved in the US for the treatment of drooling in children with neurologic conditions[24].Glycopyrrolate tablets (Robinul® and Robinul® Forte

Tablets) have also been approved by the U.S. Food and Drug Administration (FDA) since 1961 for the adjunctive treatment of peptic ulcer disease in adults [25,26] and are widely used in clinical practice to prevent parasympathetic stimulation and to decrease secretions such as saliva, sputum, respiratory secretions, sweat, etc. Since 1975, Robinul® Injection has been used in adults and children (2 years of age and older), to reduce salivary, tracheobronchial, and pharyngeal secretions and it has also been FDA approved.[25,26]. Inhaled glycopyrrolate is FDA and EMA(European Medicines Agency) approved for the maintenance treatment of patients with COPD[27,28]. Glycopyrronium tosylate was approved by FDA in 2018 as a topical applicant to treat primary axillary hyperhidrosis in adults and children of 9 years of age and above [26].

Glycopyrrolate has been used in dentistry for many years for a short and temporary reduction of salivary flow [29]. During orthodontic procedures, it is usually administered one hour before bonding takes place to prevent bond failure [4].

Mode of administration and effects:
Glycopyrrolate has been available in various forms and routesof administration (Intravenous, Intramuscular, and Oral) to reduce airway secretion and oral salivation since 1960 among healthy individuals [30-32].

When compared to injected formulation, oral administration hasgradual onset and more duration of decreased salivation [30]. It should be administrated atleast 60 minutes prior or 120 minutes post meal [33]because bioavailability of oral glycopyrrolate is reduced by high fat meals such as cheese, egg, etc if taken within meal time and its effect can last for 8-12 hours [34].

After glycopyrrolate is administered, the entire saliva resting flow rate decreases sharply initially and slowly thereafter; oral dryness can be noted within 15minutes to 1 hour [35]. The potency of the antisialogogic effect of glycopyrrolate is 5 times more than that of atropine[31]. Also, the extent of the antisialic effect of glycopyrrolate is directly proportional to the dose.

Overview of studies regarding glycopyrrolate administration:
Overview of studies on the effect of glycopyrrolate on salivation [4]. (Table-1)

(Table-1):-

AUTHOR (YEAR OF PUBLICATION)	EXPERIMENTAL PERIOD	EFFECT ON SALIVATION	REPORTED SIDE EFFECTS
Wolff and Kleinberg (1999)	Baseline, 0, 15, 60, 105, 150 minutes	Reduction of salivation, reduction of mucosal wetness	No side effects present.
Mirakhur and Dundee (1980)	Baseline, 6 hours observation	Dose-dependent reduction of saliva secretion. (5.6 times potency of atropine)	Various degree of Bradycardia. Effects being statistically significant.
Wyant and Kao (1974)	5, 10, 20, 30, minutes, then 2, 3, 4, 5, 7 and 10 hours	Dose- dependent reduction of saliva secretion	No side effects present.
Lahteenmaki and Colleagues (2000)	0, 1, 3, 6, 12, 24, and 48 hours	Salivary flow rate reduced for 12 hours	No side effects present.

Drug interactions and adverse effects:
Gastrointenstinal transit time is lessened by glycopyrrolate leading to altered release of certain drugs if coadministered such as potassium chloride, digioxin, levodopa, metformin, and atenolol [36]. On the contrary, coadministration of glycopyrrolate and amantadine may result in increased anticholinergic effects of glycopyrrolate; thus glycopyrrolate dosage may need to be decreased [36]. Because of minimal oral bioavailability of the quaternary amine structure to penetrate through the blood-brain barrier [34]; the adverse effects of glycopyrrolate on the central nervous system (CNS) are less likely to occur [37]. Likewise, no treatment-related side-effects were seen on the CNS (except for slight and transient pupil dilation)in safety pharmacological studies [37].

Glycopyrrolate can be harmful to patients who have a systemic disease or condition related to hyposalivation. Long-term use of glycopyrrolate (prescribed for chronic severe drooling or sialorrhea, hyperhidrosis, peptic ulcers, etc.) can increase the risk for occurrence of oral diseases and make patients susceptible to mucositis, especially candidiasis [38]. It should also be used with caution in patients with conditions that are exacerbated by such drugs, including autonomic neuropathy, ulcerative colitis, intestinal obstruction, renal impairment, and hyperthyroidism [36,33].Also, caution needs to be maintained for patients with preexisting cardiac comorbidities as glycopyrrolate can precipitate tachyarrhythmias [39].

Conclusion:-

Dental professionals have successfully been performing dental clinical procedures by using all possible protective equipment with strict aseptic measures. At this critical juncture, the controversy regarding the dental aerosol and aerosol generating dental procedures has risen to a point of special focus.

Glycopyrrolate administration aims at reducing the oro-pharyngeal secretions that reportedly play a significant role in the viral contamination of bioaerosols being produced during dental procedures. This may reduce therisk of exposure to the lowest possible level even though complete elimination of the risk may not be guaranteed because COVID-19 is a new disease, we might not have all the facts for quite some time, but we believe there is enough current and historical data to arrive at some plausible conclusions.

The above knowledge might be helpful inestablishing the effectiveness of glycopyrrolate as a premedication for reducing the transmission of contaminated bioaerosols during routine dental procedures. Further research in this regard is needed to arrive at some reasonable conclusions.

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