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Pharmacotherapy for reducing saliva and droplet production in airborne procedures may help to decrease the COVID-19 transmission: A hypothesis

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ABSTRACT

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected health care service practices worldwide. Therefore, a global reaction to prepare health care systems is mandatory. Preventing the transmission of this virus during medical and dental procedures producing airborne particles and droplets, could be considered as one of the main venues in prevention of Coronavirus disease 2019 (COVID-19) transmission in health care facilities. To the best of our knowledge, no intervention has been approved for this purpose, so the major suggestion in this regard is using personal preventive equipment (PPE) and similar measures as well as other sanitizing practices. Since we do not know how long we should face this universal issue, using antecedent pharmacotherapies for reducing oral-respiratory secretions to combat this virus might play a role in this regard. Given that currently there is no definitive cure for COVID-19, so we hypothesize that, considering drug solutions to reduce saliva and droplet production may be helpful in controlling Coronavirus spread during aerosol and respiratory droplet producing procedures.

Introduction

In the last month of 2019 the first reports of the infection were made as a series of pneumonia with an unknown cause in Wuhan, China, which was associated with the new form of coronavirus on the last days of 2019 [1,2]. Coronavirus disease 2019 (COVID-19) is rapidly spreading in all over the world, and the WHO proclaimed the outbreak of the worldwide pandemic on March 11, 2020 [3]. According to the WHO report up to 16 April 2020, there are 1,991,562 and 130,885 confirmed cases and deaths due to COVID-19, respectively [4].

The current pandemic of severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) causing COVID-19 has changed the health care practice worldwide. Health care facilities have been considered as an epicenter for the transmission of disease, and many centers have terminated their elective procedures, especially those that were considered to be aerosol or droplet producing to avoid transmission of disease from the patients both to their relatives and to health staff [5,6].

Due to the fact that, there is no definite treatment for COVID-19 so far, prevention is the cornerstone of COVID-19 control. Up to now, no effective passive or active immunization is approved to prevent this infection. The major recommendation are on the prevention of the infection by adherence to routine infection control protocols such as social distancing, frequent and proper hand hygiene, and using face masks (medical or respirators) in certain conditions [7]. In this study, we offered and described a hypothesis, in which reducing saliva production by medications might be useful in preventing COVID-19 transmission in aerosol and droplet producing medical and dental procedures.

Can airborne and droplet production procedures transmit the Coronavirus 2019?

Although the infection rate of COVID-19 is not clearly determined yet, it is presumed to be highly contagious. As the WHO claims, *during an unprotected close contact between an infector and an infectee, COVID-19 can be primarily transmitted via respiratory droplets* or *fomites* [8]. Respiratory droplets are particles with > 5–10 μm diameter, and droplet transmission usually occurs in the case of either close contact (within 1 m) or indirect contact with the infected individuals. Droplet nuclei, which are < 5 μm in diameter and remain in the air for long periods of time, are responsible for airborne transmission [9].

Airborne spread for COVID-19 has not yet been confirmed, and in

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terms of available evidence, it is not considered as the major cause of transmission. However, some scientists noted that, airborne transmission may be possible in specific circumstances and settings such as endotracheal intubation, bronchoscopy, upper endoscopy, and cardiopulmonary resuscitation [10]. Experts in the field of airborne respiratory diseases and particles declared that, it can take years to collect undeniable evidence for airborne transmission and incur lots of life losses [11].

As human-to-human transmission has been confirmed at the beginning of this pandemic, substantial efforts would be needed to reduce transmission for managing outbreaks. The distinction between airborne particles and droplets in real practice might not be always possible, since the particles that come out with the virus could have a wide range of sizes depending on the stimulant and other conditions. While SARS-CoV-2 is mainly transmitted via droplets, virus particles can build up over time in the enclosed spaces without ventilation or can be transported over longer distances [12].

Hypothesis and discussion

Can the use of effective drugs in the treatment of Sialorrhea (drooling or excessive salivation) be effective on preventing the spread of the COVID- 19?

There are several medical and surgical procedures that can generate aerosolized particles. In most cases, these airborne particles can be generated during manipulation or stimulation of the large airways as follows: manual ventilation with a bag and mask, upper gastrointestinal tract endoscopy, intubation, open endotracheal suctioning, bronchoscopy, cardiopulmonary resuscitation, sputum induction, surgery on the lungs, nebulizer therapy, non-invasive positive pressure ventilation (BIPAP, CPAP), and an autopsy on the lungs [13].

Since the most significant way of transfer of COVID-19 is via droplets, one of the seemingly simple but promising ways could be applying drugs to reduce the patients' oral-respiratory secretions, especially in health care facilities where the medical staff spend more time and have closer distance with the patients. In this area, many studies were conducted on those drugs that can reduce and treat sialorrhea.

Healthy people typically secrete 1–1.5 L of saliva every day [14], with the greatest volume being secreted from the parotid and submandibular salivary glands (about 45% for each). The salivation is controlled by chemoreceptors, mechanoreceptors, sympathetic, and parasympathetic nervous system [15]. Drooling is the uncontrolled and continuous release of saliva from the mouth, which is different from sialorrhea or hypersalivation. In patients with the age greater than 4 years old, it is not normal to have excessive drooling during the waking hours. The etiology of drooling/sialorrhea can be divided into neurological deficits and orofacial problems. Examples for the former etiology is cerebral palsy, mental retardation, Parkinson's disease, amyotrophic lateral sclerosis, and adverse drug reaction (e.g., clozapine). On the other hand, tongue deformities and lip incompetency are orofacial problems that may cause drooling/sialorrhea [16,17].

Management of drooling/sialorrhea is performed based on the correction of neuromuscular imbalances and reducing the salivary flow rate. Achieving these outcomes usually needs a multidisciplinary approach. Also, pharmacotherapy is a reasonable option for treating drooling/sialorrhea, but it is not the only one. Although drug therapy aims to decrease the amount of saliva, it does not tackle other contributing factors that can play important roles in this disease. At the present time, anticholinergic medications are the backbone of drooling drug therapy. The agents used include propantheline, glycopyrrolate, benztropine, and scopolamine, but they are not limited to these [18].

M3, as the main subtype of the muscarinic receptor, is expressed in the salivary glands, but M1 is likewise present. Accordingly, the combined use of selective M1 and M3 antagonists could provide a decent treatment option for sialorrhea [19]. Other medication classes with anticholinergic properties include antihistamines (e.g., diphenhydramine), tricyclic antidepressants (e.g., amitriptyline), other antidepressants (e.g., duloxetine), antipsychotics (e.g., trifluoperazine), and opioids (e.g., morphine). Nevertheless, undesirable adverse effects such as restlessness, constipation, drowsiness, urinary retention, the increased ocular pressure, and irritability and sometimes flushing occur with most of the anticholinergic medications, due to the lack of selectivity of such agents for M3 [18].

In a case report, a 51-year-old man with sialorrhea was successfully treated by the consolidated use of pirenzepine and solifenacin (M1 and M3 muscarinic receptor antagonists). A measurably critical decrement in salivary flow rate was observed by the combined administration of solifenacin (10 mg/day) and pirenzepine (daily dose was not defined) [19]. Based on the findings of another pilot test, sublingual atropine was a helpful adjunctive treatment for sialorrhea secondary to Parkinsonism. Accordingly, the patients received 1 drop of atropine solution (containing 0.5 mg atropine from a 1% w/v solution) sublingually twice a day, with subjective improvement indicators that showed more prominent impacts from the treatment rather than objective measures (direct measurement of saliva). Despite the fact that sublingual atropine is well tolerated and can subjectively and objectively decrease saliva production, there is a concern about side effects occurrence.

An investigation on local anticholinergics in clozapine-induced sialorrhea and sialorrhea caused by other etiologies revealed that, almost all the patients experienced a beneficial effect of this agents. The intervention was either 1% sublingually atropine eye drops or with 0.03% nasal spray of ipratropium bromide. Troublesome aftertaste, xerostomia, and short duration of action of the eye drops have been reported as limitations of this approach. In this study, 67 patients treated by topical atropine for sialorrhea of other origins were included, with overall fruitful effect and few experiencing side effects. The sublingual application of atropine in the treatment of sialorrhea seems to be both useful and safe. Also, the dose is usually 1–2 eye drops 1–3 times per day [20].

In a number of studies performed on children with tracheostomy and mechanical ventilation, with clinical diagnosis of drooling, there was clinical improvement with the use of 20 drops of scopolamine (10 mg/ml) administered via gastrostomy every 12 h, with no interruption during its usage. Pharmacological treatment with scopolamine, which is low cost, available, and has little side effects, has been useful in decreasing the intensity of drooling as well as the risk of aspiration pneumonia in children with neurological sequelae on mechanical ventilation. However, it is noticeable that, scopolamine is contraindicated in the patients with heart problems, glaucoma, prostatic hypertrophy, and pyloric obstruction [21].

Apart from anticholinergics, other classes of medications can induce hyposalivation or xerostomia via different mechanisms (Table 1) [22]. Accordingly, a prominent example is Botulinum neurotoxin (BoNT). Local injection of BoNT has been effectively applied to treat excessive saliva conditions over the last two decades. Injecting BoNT into the salivary glands reduces salivary secretion by inhibiting sympathetic cholinergic and postganglionic activity, which was reported to be successful for symptomatic controlling of drooling [19]. This intervention has been approved by European authorities for the management of chronic sialorrhea. Injecting a dose of 100 units of incobotulinumtoxinA, which also is called botulinum toxin type A, in two parts into parotid and submandibular glands, is suggested. RimabotulinumtoxinB is approved only in the USA. Side effects of BoNT with this dose and in this setting are uncommon and usually mild, transient, and manageable. They include dry mouth, diarrhea, neck pain, and dysphagia. BoNT is currently considered as the most effective agent for treating chronic sialorrhea [23,24].

Conclusion

Since some medical procedures, especially emergencies, are unavoidable; drugs that can reduce salivary and respiratory secretions

Table 1
Medications Which Can Induce Hyposalivation or Xerostomia [22,25].

Medication class	Examples
Antidepressants	Venlafaxine, Duloxetine, Reboxetine, Bupropion
Antihypertensive agents	Metoprolol, Moxonidine, Rilmenidine
Appetite suppressants	Fenfluramine, Sibutramine, Phentermine
Decongestants	Pseudoephedrine
Bronchodilators	Tiotropium
Skeletal muscle relaxants	Tizanidine
Antimigraine agents	Rizatriptan
Tricyclic antidepressants	Amitriptyline, Clomipramine, Amoxapine, Protriptyline, Doxepin, Imipramine, Trimipramine, Nortriptyline, Desipramine
Muscarinic receptor antagonist	Oxybutynin
Alpha-receptor antagonists	Tamsulosin, Terazosin
Antipsychotics	Promethazine, Trifluoperazine, Mesoridazine, Thioridazine, Clozapine, Olanzapine
Antihistamines	Aziridine, Brompheniramine, Chlorpheniramine, Cyproheptadine, Dexchlorpheniramine, Hydroxyzine, Phenindamine, Cetirizine, Loratadine
Diuretics	Furosemide, Bumetanide, Torsemide,
Opioids, hypnotics	Opium, Cannabis, Tramadol, Diazepam
H2 antagonists, proton pump inhibitors	Cimetidine, Ranitidine, Famotidine, Nizatidine, Omeprazole
Cytotoxic drugs	Fluorouracil
Anti-HIV drugs, protease inhibitors	Didanosine

could be considered along with PPE and other preventive measures to reduce the production of respiratory droplets and aerosols during these procedures for maximizing the effectiveness of the prevention of virus transmission in health care centers. Anticholinergic drugs of choice include the followings: pirenzepine, solifenacin, atropine, and scopolamine butylbromide. They are effective on reducing the secretions and the risk of further production of respiratory particles. Therefore, they could be effective on decreasing the virus transmission from the infected person to non-infected subjects in the society. However, due to many side effects of anticholinergics, the best option, especially in processes requiring more long-term exposure, could be a BoNT injection, which is both effective and safe. Cost as well as availability aspects of BoNT should also be considered. Besides, the potential drug-drug interactions between suggested and experimental anti-COVID-19 medications (e.g., chloroquine, hydroxychloroquine, lopinavir/ritonavir, atazanavir, favipiravir, remdesivir, and ribavirin) and anti-sialorrhea/drooling agents in the infected patients should also be noted and checked.

Determination of those who benefit the most from this approach, the procedures in which this approach needs to be considered, and the drug, the right dose, and its route of administration should be accomplished in further real time studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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