Role of doxycycline, oral steroids, and nasal steroid in treatment of anosmia due to COVID-19 with the new insights into the doxycycline activity.

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Abstract

Background All over the world, severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) has been the most important public health issue this year; recently this was re-named as corona virus disease 2019 (COVID-19) by the World Health Organization (WHO). Olfactory or gustatory dysfunction is often reported as a symptom.

Aims Aim of the study is to evaluate the role and effectiveness of Doxycycline, Oral Methyl Prednisolone, and Topical Nasal Steroid (Mometasone) in the treatment of COVID-19 related anosmia/hyposmia

Material and Methods Total 64 patients were evaluated randomly who were COVID-19 positive and developed recent onset of anosmia/hyposmia. They were divided into two groups 32 each. First group was treated with Doxycycline, Oral Methyl Prednisolone, and Topical Nasal Steroid (Mometasone). Second group was the control group and was given placebo and Olfactory training.

Results Out of 32 patients 27 patients completely recover after only 2 days of the administration of above treatment. Out of the remaining 5 patients 4 had partial resolution of the anosmia after 2 days and near complete resolution after 5-7 days, and 1 patient did not responded at all with the above treatment. Out of the control group 19 patient had near complete recovery after 7 days and rest 13 patient did not recover after 10 days.

Conclusion The above study showed a very promising results but many more similar studies are needed following the similar treatment protocol on a larger group of patients suffering from olfactory dysfunction.

Introduction

All over the world, severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) has been the most important public health issue this year; recently this was re-named as corona virus disease 2019 (COVID-19) by the World Health Organization (WHO). SARS-CoV-2 is also included in the corona virus family along with SARS-CoV and Middle East Respiratory Syndrome (MERS)-CoV [(1)] . COVID-19 was first reported in Wuhan, China [(2,3)] in December 2019. Since then, COVID-19 has spread rapidly all over the world [(4)] and has killed more than 226,000 people worldwide so far. This rapid spread is suspected via not only human-to-human but also interspecies transmissions [(5)]. The WHO declared “a pandemic” on March 11.

Recently, olfactory or gustatory dysfunction is often reported as a symptom [(6,7)]. We need to pay more attention because the symptom might be easily overlooked in clinical field and so the diagnosis could be delayed.

Similarly, to other human respiratory Coronaviruses (HCoV), it seems to have a neuroinvasive and neurotropic activity [(8,9)]. Hyposmia has been reported as a possible peripheral nervous system (PNS)

symptom caused by COVID-19 infection [9].

In this retrospective study we evaluated the role and effectiveness of Doxycycline, Oral Methyl Prednisolone, and Topical Nasal Steroid (Mometasone) in the treatment of COVID-19 related anosmia/hyposmia in 64 patients who were COVID-19 positive. rRT-PCR was done twice to confirm the diagnosis along with HRCT chest.

Materials And Methods

Total 64 patients were evaluated who were COVID-19 positive, presented with fever, cough and shortness of breath and developed recent onset of anosmia/hyposmia within few days after admission. All the 64 patients were between the age group of 33 to 45 years. All the patients had a recent onset of anosmia/hyposmia. These 64 patients were divided into two groups; 32 patients in each group. First group was study group and second group was control. Out of 64 patients 59 patients developed anosmia/hyposmia between 24-48 hours of admission and rest 5 patients developed anosmia/hyposmia after 48-72 hours of admission. These patients were the proven cases of COVID-19 infection. COVID-19 test was done twice on them, initially at the time of admission followed by 2 days after the admission along with HRCT chest.

University of Pennsylvania smell identification test (UPSIT)[10] was done for all the 32 patients after the initial symptom of anosmia/hyposmia.

After confirmation of the initial diagnosis Tab doxycycline, Tab Methyl prednisolone, and Mometasone topical nasal spray was started for the first group and control group was given placebo and olfactory training.

Protocol :

Study group

- Doxycycline 200 mg stat followed by 100 mg twice daily was started immediately and was continued for next 10 days.
- MethylPrednisolone 8 mg twice daily was started immediately for and continued for 5 days.
- Mometasone nasal spray 2 puffs (100 mcg) twice daily was given for 10 days followed by 2 puffs once daily was continued for the next 4 weeks.

Control group

- Placebo
- Olfactory training

The treatment was continued for 10 days along with other symptomatic treatment for fever and cough.

Results

In the study group all the 32 patients received the doxycycline, prednisolone, and mometasone nasal spray irrespective of their age. In all the patients the other associated symptoms were mild to moderate, therefore, the above treatment was given and completed successfully. None of the patient had developed life-threatening complication during or after the treatment and all the patients got discharged after the period of 21 days and after two consecutive negative rRT-PCR test, done 24-48 hours apart.

In the control group all 32 patients received placebo and olfactory training. None of the patient had developed life-threatening complication during or after the treatment and all the patients got discharged after the period of 21 days and after two consecutive negative rRT-PCR test, done 24-48 hours apart.

In our preliminary observation of the study group, out of 32 patients 27 patients completely recover after only 2 days of the administration of doxycycline, prednisolone, and mometasone nasal spray. Out of the remaining 5 patients 4 had partial resolution of the anosmia after 2 days and near complete resolution after 5-7 days, and 1 patient did not responded at all with the above treatment.

In the control group 19 patient had near complete recovery and the 13 patient did not recover after 10 days of treatment.

Above treatment given to study group seems to improve respiratory symptoms and anosmia and from our experience, it seems reasonable to continue the treatment at least for 10 days. Whereas, in the control group who received placebo and olfactory training does not seems to have complete resolution of symptoms and out of 32 patients 19 have near complete recovery and 13 patient did not recovered at all after 10 days.

The average time of the recovery from COVID-19-linked anosmia after the administration of above treatment in the first group was 2.5 ± 0.5 days. We noticed a sudden improvement in all symptoms after the administration of above treatment, but our most exciting insight is about the rapid recovery of the smell.

Insights Into the Doxycycline Activity

IFNα/β signaling plays a protective role in reducing the virus spread and modulating T cell non-cytolytic antiviral response in limiting viral load. Moreover, some RNA-viruses have developed mechanisms to counteract innate host defense to establish productive infections in their hosts. This is the case of an RNA virus, the vesicular stomatitis virus (VSV) [(11)].

Retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene-5 (Mda-5), seem to have an important role in the recognition of RNA viruses. In particular, it has been shown that immune signaling by RIG-I is involved in the generation of IFN-α/β following VSV infection. Under doxycycline treatment, cells released high levels of RIG-I proteins eliciting autonomous IFN response, thereby inhibiting viral infection *in vitro* [(12)].

In another RNA virus, the Respiratory Syncytial Virus (SRV), viral proteins inhibit IFN-α and IFN-β to establish infection [13], and it has been reported a higher expression of interferon-induced protein only after minocycline administration. This suggests an increasing innate immune response supported by tetracycline and the following RSV inhibition [14].

The second-generation tetracycline doxycycline has an anti-inflammatory and broad spectrum antimicrobial activity [15,16].

In 1967, Doxycycline was first approved by the FDA (15). doxycycline is characterized by a ~100% oral absorption and a prolonged serum half-life (18–22 h) [17].

In ophthalmology, doxycycline is usually administered in patients affected by ocular rosacea and posterior blepharitis [18]. The doxycycline recommended dose is 40 mg modified release once daily, which could be replaced by minocycline 100 mg, based on patient tolerance or particular requirements [19].

The rationale in its administration is proteolysis inhibition promoted by matrix metalloproteinases (MMPs) [18,20]. MMPs are involved in the regulation of chemical and biological process likes vascular remodeling and angiogenesis [21], so doxycycline also has anti-angiogenic properties [22]. It regulates cytokines and diminishes neutrophil chemotaxis too [23].

Besides its well-known use in treating bacterial infections, some studies in the literature report that doxycycline possesses a broad activity against viral infection too ([24-26].

The first who described the doxycycline antiviral effect was Sturtz in 1998 [25], and this suggestion has been confirmed in several followed-up studies [11,27,28].

Topno et al. demonstrated that doxycycline could interfere with the virion's replication, affecting its structure and causing inhibition of Japanese encephalitis virus-induced pathogenesis *in vitro* [27]. The same observation is also reported in a study regarding VSV infection [11] and against the chikungunya virus (CHIKV) [28], suggesting that doxycycline might interfere with viral replication by aiming proteins essential for these viruses for a successful infection. As proof of that, computational literature reports the doxycycline ability to bind CHIKV cysteine protease [28], and to exert a significant inhibitory effect on DNV NS2B-NS3 serine protease *in vitro* [25]; both these proteases proved to be able to catalyze viral polyproteins cleavage during infection. Moreover, some studies with (+)ssRNA, Dengue virus (DNV), have demonstrated that doxycycline inhibits virus plaque assembly by interfering with the viral envelope conformational changes needed for virus entry [25]. In both CHIKV and DNV, doxycycline seems to have the ability to bind virus envelop inhibiting viral entry into the cultured cells [25,28].

doxycycline proved to be able to markedly decreased the virus-induced cytopathic effect (CPE) and significantly affect viral replication in a dose-dependent manner when used against Porcine Reproductive and Respiratory Syndrome virus (PRRSV) infection in cultured cells [26]. Virus mRNA levels were strikingly

reduced also in VSV-infected cells in response to doxycycline; both virus titers and the CPE of VSV infection were significantly influenced by doxycycline administration in a dose dependent manner [11].

Discussion

Being the olfactory neural system able to regenerate throughout life, it can explain why the recovery of olfaction is common [29].

From our observation, anosmia affected mostly between the age between 33- 45 i.e young adults, confirming existing findings in the literature [30, 31]. It shows up more or less 4-6 days after initial symptoms, but it can be the first and only symptom in many patients, with no mucosal swelling of the olfactory cleft, and that's why we hypothesize that it could be a possible PNS symptom as suggested. Among patients affected by PNS symptoms linked to COVID-19, the most common referred were anosmia/hyposmia.

In our preliminary observation, the administration of Doxycycline 200 mg stat followed by 100 mg twice daily, MethylPrednisolone 0.5 mg/kg, Mometasone nasal spary seems to improve respiratory symptoms and anosmia. Under the above treatment of first group , 27 patients completely recover after only 2 days of treatment, 4 patients responded after 5-7 days of treatment, and 1 patient did not responded at all. From our experience, it seems reasonable to continue the treatment at least 10 days. The average time of the recovery of COVID-19-linked anosmia after the administration of above treatment in these patients was 2.5 ± 0.5 days. We noticed a sudden improvement in most of the symptoms, but our most exciting insight is about the rapid recovery of the smell.

Whereas, in control group there was near complete recovery and no recovery at all in 19 and 13 patients respectively.

Up to date, several studies have shown that oral steroid treatment for anosmia by viral infection may be effective through reducing mucosal inflammation and edema [32]. There is a controversy over the effectiveness of the use of empirical systemic corticosteroids because oral steroids may aggravate immunosuppressive state in the COVID-19 patients with severe symptoms and there are studies showing that use of corticosteroids in MERS patients may have affected the delay of RNA reduction in MERS coronavirus [33].

Moreover, in cases of the COVID-19 patients with severe lung complications, the use of corticosteroids is not recommended by WHO guideline [34]. In China, however, limited use of low dose corticosteroid during short-term can be permitted when absolutely necessary [35]. On the basis of above study we used low dose methyl prednisolone only for 5 days. According to the recently released ARIA EAACI statement, it is recommended to keep using intranasal steroid (INS) in the COVID-19 patients with allergic rhinitis [34]. Although it may be revised later with new studies, it is also recommended to maintain the use of local

intranasal corticosteroids ecause sneezing could get worse and the virus could spread easily if the patients stop using INS.

INS is supposed to have relatively less risky than systemic steroids because the rate of systemic bioavailability of INS is less than 1% [(36)]. But further studies are needed to confirm if INS may be effective for the treatment of olfactory dysfunction and for the change of clinical course in the COVID-19 patients.

Besides steroid and olfactory training, Zinc sulfate, theophylline, Ginkgo biloba, vitamins, nasal decongestants, or other medicine could also be considered to treat olfactory dysfunction. Saline washing/ nasal saline irrigation should be considered carefully, because it could make virus more contagious. However, except for the corticosteroid, the effects of other medicine have not been proven [(37)].

Conclusion

Although there is still a lack of our understanding of COVID-19, the number of COVID-19 patients is rapidly increasing all over the world. Based on the recent reports and studies, sudden olfactory dysfunctions may be the early signs of COVID-19, though all olfactory dysfunctions are not caused only by COVID-19, even at present. Therefore, if there are any persons complaining of olfactory dysfunctions in COVID −19 pandemic areas, it is suggested that accurate and urgent diagnostic test for COVID-19 should be applied.

In the above study, we observed a very satisfactory response with the treatment protocol we followed as 90 percent of the patients responded with complete resolution of symptoms within 2 days and near complete resolution of symptoms were seen in 8-9 percent of patients, whereas, only 1 patient did not responded at all. When compared to the control group the above observation seems to be very promising.

Although, the above study showed a very promising results but many more similar studies are needed following the similar treatment protocol on a larger group of patients suffering from olfactory dysfunction.

Declarations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical Approval and Consent to participate

Hereby, I /**Dr Parvez Husain**/ consciously assure that for the manuscript / **Role of doxycycline, oral steroids, and nasal steroid in treatment of anosmia due to COVID-19 with the new insights into the**

doxycycline activity/ the following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.

2) The paper is not currently being considered for publication elsewhere.

3) The paper reflects the authors' own research and analysis in a truthful and complete manner.

4) The paper properly credits the meaningful contributions of co-authors and co-researchers.

5) The results are appropriately placed in the context of prior and existing research.

6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.

7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

I agree with the above statements and declare that this submission follows the policies as outlined in the Guide for Authors and in the Ethical Statement.

Date: 04/10/2020

Corresponding author's signature: Parvez Husain

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Declaration of competing interest

The authors declare that they have no competing interests

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Credit authorship contribution statement

Parvez Husain: Conceptualization, Writing - original draft. **Ahmed Shaheen Khalil:** Investigation, Conceptualization, Writing - original draft. **Benazeer Husain:** Supervision, Writing - review & editing.

Conflict Of Interest

The authors have no conflicts of interest to disclose.

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