Observational study on the use of Neem and Hypericum oils in non-hospitalized COVID-19 patients

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Précis: An observational study on the effect of Neem and Hypericum perforatum nasal and oral spray on the severity and duration of COVID-19 symptoms

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Abstract

This report describes the efforts of a healthcare worker in the Campania region badly affected by COVID-19 to repurpose a pre-existing medical device with the intent to benefit patients and ease pressure on local hospitals. **Materials and Methods:** The study consist of self-reported symptoms, collected over a two month period on an unscreened cohort of patients in a wide age range presenting mild to moderate symptoms consistent with COVID-19, treated with a spray containing Neem and Hypericum (1 Primary Wound Dressing, Kerecis, Iceland) with directions for oral and nasal self-administration for two weeks. The severity and nature of the symptoms were captured on a scale of 0 (not present) to 3 (serious). After beginning treatment, the patients were followed up by phone call or visits and their self-reported symptoms were documented in the form of a score. **Results:** Out of the 64 treated patients, 63 had recovered eventually as of May 2020 and none of them had received hospital care or died, only 29 patients gave consent for their data to be presented here. Due to limited resources, only 4 out of these 29 patients were screened for SARS-CoV-2 and all tested positive. All have recovered fully, except for one 25-year-old female who still has a low-grade fever after 2 months of illness. No side effects or discomfort were reported from using the spray. Patients who started treatment early after the onset of symptoms had a much shorter course of the disease than those who started treatment later: the average time to recovery was 17.9 ± 9.8 days (range 5-38 days). **Discussion:** The spray described here contains 50% neem oil and 50% Hypericum (St. John´s Wort). The antiviral properties of these two spray constituents have been previously reported, including against another related Corona virus, the Infectious bronchitis virus (IBV). Direct comparison to the recovery trajectory of other Neapolitan COVID-19 patients is impossible as most mildly symptomatic patients were never screened. However, due to the nature of the outbreak in the city, it can be assumed that the majority of the patients were indeed SARS-Cov-2 positive. In light of the statistics published for the Italian outbreak, it is encouraging that all except one of the larger 64 patient cohort have at the time of this report recovered without hospitalization.

Introduction

The circumstances of this informal case series are unusual due to the unprecedented nature of the SARS-CoV-2 outbreak overwhelming the healthcare resources in Italy. This report describes the efforts of a healthcare worker in the Campania region badly affected by COVID-19 to repurpose a pre-existing medical device with the intent to benefit patients and ease pressure on local hospitals. According to surveys undertaken by the healthcare facilities of the Campania and the Regional Department of Civil Protection,

almost 5000 Sars-CoV-2 cases have been confirmed in the region.1 Due to this unique situation there is no control group and the data shown in the present study consist of self-reported symptoms, collected over a two month period on an unscreened cohort of patients in a wide age range as they progress through their infection.

The primary author is the medical manager at the 'Ospedale Del Mare' in Naples. Thanks to his professional experience, he was familiar with a commercially available medical device, registered as a topical medical device intended for treating wounds and inhibiting infections. The spray contains a high concentration of Neem (Azadirachta indica) and St. John's wort (Hypericum perforatum) oils which both have well known anti-viral and anti-inflammatory properties.2–12 The author began, after obtaining informed consent, to advice suspected COVID-19 patients who presented with upper respiratory symptoms to use the spray and then monitored their progress as efficiently as the circumstances allowed.

Materials and Methods

The data were collected in Naples between February 11 and April 14, 2020. 64 patients, presumed to be infected with SARS-CoV-2, and presenting mild to moderate symptoms consistent with COVID-19, were prescribed a spray containing Neem and Hypericum with directions for oral and nasal self-administration for two weeks (1 Primary Wound Dressing, Kerecis). The severity and nature of the following symptoms were captured on a scale of 0 (not present) to 3 (serious): general symptoms (body temperature, general condition), upper airway symptoms (runny nose, nasal congestion, loss of sense of smell, loss of sense of taste, inflammation of the throat, cough), deep airway symptoms (bronchi-level symptoms) and other symptoms (nausea, vomiting, fatigue, other). The grades were then summed up for each patient for their total symptom score. After beginning treatment, the patients were followed up by phone call or visits and their self-reported symptoms were documented.

Results

Out of the 64 treated patients, 63 had recovered eventually as of May 2020 and none of them had received hospital care or died. Eventually, 29 patients gave consent for their data to be presented here (**Table 1**). Due to limited resources, only 4 out of these 29 patients were screened for SARS-CoV-2 and all tested positive. Due to the unique circumstances, follow up was somewhat irregular. The patient cohort included 14 females and 15 males, with an average age of 40.9 ± 20.1 years (range 1-73). All had some upper respiratory symptoms, and around 80% had fever and loss of sense of taste. The patients had checkups roughly every twelve days (range 4-43 days) and each patient had on average 2.6 time points on which data were collected. At data cutoff on April 14th, 21 out of the 29 patients (72.4%) had fully recovered, while 8 (27.6%) remained symptomatic on April 14th with an average symptom point sum of 2.8. These 8 patients had then been followed between 10 and 37 days (average 24.8 days). All have since recovered fully, except for one 25-year-old female who still has a low-grade fever after 2 months of illness. It was noted that for some patients, their last follow up showing 0-symptom point sum happened more than a month after the previous follow up. Thus, as regards the analyses focusing on time to recovery, these data points have been omitted, which excludes two patients from the cohort and the last data point for a third patient, bringing the total population to 27 patients, of which 19 fully recovered before 14th of April. For those who recovered before the cutoff date, the average time to recovery was 17.9 ± 9.8 days (range 5-38 days). No side effects or discomfort were reported from using the spray. The healing trajectories for the 27 included patients are depicted in **Figure 1**, and an overview of symptoms presented at D0 is shown in Table 1. The eight patients who had not recovered at the end of the study had been followed between 10 and 37 days (average 24.8 days). Out of these eight, three had been screened for the virus. The symptoms in the patients screened tended to be more serious at D0 (9.5 on average compared to 6.6 for non-screened)

which might explain why they were tested, but the difference was not significant. However, due to the nature of the outbreak in the city, it can be assumed that the majority of the patients were indeed SARS-Cov-2 positive.

Discussion

The spray described here contains 50% neem oil and 50% Hypericum (St. John´s Wort) oil along with a propane/butane propellant. For more details on the biological activities of Hypericum and Neem extracts, there are several reviews available.13–15 While there have been no studies published so far on their effectiveness against SARS-CoV-2, based on the available evidence it is not unreasonable to hypothesize that could be the case. The antiviral properties of these two spray constituents have previously been reported, including against another related Corona virus, the Infectious bronchitis virus (IBV).3–8,16,17 A recent preliminary report (not yet peer reviewed) suggests that Hypericin, one of the active principle constituents of Hypericum perforatum, binds to the SARS-CoV-2 S protein-human ACE2 interface and could potentially limit recognition of host cells and/or disrupt host-virus interactions.18 Meanwhile, nimbolide, a natural chemical constituent isolated from the Neem plant, has been shown to have anti-nitrosative, antioxidant, and anti-inflammatory properties in an Acute respiratory distress syndrome (ARDS), which is a common cause of death in COVID-19 patients.11 It is worthy to note that although the spray consists of Neem and Hypericum oils, it is unknown whether those constituents, or any clinically active degradation products thereof, are present in the product in any meaningful quantities. In any case, a randomized, placebo-controlled clinical trial for the spray has been announced at the University hospital in Iceland on COVID-19 patients which should provide some clinical data needed to address this issue (ClinicalTrials.gov Identifier: NCT04357990). SARS-CoV-2 is generally associated with upper respiratory symptoms and high viral loads in upper respiratory tract secretions.19 As the active ingredients in the spray could display anti-viral activity, and the oils can form a lipid barrier in the oropharyngeal and nasal mucosa, this could potentially inhibit the spreading of the infection down into the lower airway and reduce the local viral load in order to give the immune system more time to launch an adaptive response. The immunomodulatory effects of Neem could furthermore reduce local symptoms by limiting inflammation and heightening anti-viral specific immune responses.11 In that context, it is worth noting that the patients recruited during the first weeks of the study (before March 10th) had a longer duration of symptoms prior to treatment while the patients recruited later were mostly in the early stages of their infection. Incidentally, those early patients took longer to recover, even accounting for severity of symptoms ($p=0.0035$ in a simple linear regression). This might indicate that early intervention with the spray was more helpful than later in the disease progression when the viral spread was more systematic. These cases were collected during the climax of the COVID-19 outbreak in Naples. The death rate of those diagnosed with COVID-19 in the region of Campania has been reported at 8.7%, with ICU admission rates at a much lower 0.5%, reflecting the difficulties of getting intensive care for critical patients. 1 Since both COVID-19 infections and deaths are almost certainly underrepresented, the true death rate is unknown but substantial. Earlier numbers reported for Italy indicated that the hospitalization rate for actively infected patients was around 40%, with around a quarter of those (9-11%) in intensive care20,21 Direct comparison to the recovery trajectory of other Neapolitan COVID-19 patients is impossible as most mildly symptomatic patients were never screened, and their data therefore never captured and made public. However, in light of the statistics published for the Italian outbreak, it is encouraging that all except one of the larger 64 patient cohort have at the time of this report recovered without hospitalization.

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Table 1. Distribution and average severity of symptoms displayed by 29 presumed COVID-19 patients at the beginning of treatment with Neem and Hypericum oral and nasal spray. Values are shown as numbers of patients positive (out of 29 patients) and positive patients as % of the cohort.

Symptoms at D0	Positive out of 29 patients	% positive	Average grade (severity 0-3)
Fever	23	79	1.7
General Condition	21	72	1.6
Runny Nose	22	76	1.3
Nasal Congestion	3	10	1.0
No smell	5	17	2.0
No taste	24	83	1.8
Throat Inflammation	17	59	1.4
Cough	25	86	1.3
Bronchi-level symptoms	5	17	1.8
Chest auscultation	4	14	1.8
Nausea	0	0	0.0
Vomit	1	3	1.0
Other (fatigue etc.)	0	0	0.0
COVID-19 Swab	4	14	1

Figure 1. Healing trajectories of 27 presumed COVID-19 patients, self-treating with Neem and Hypericum spray.