Version 4

Jun 22, 2020

Hypertonic saline nasal irrigation and gargling for suspected or confirmed COVID-19: pragmatic web-based Bayesian adaptive randomised controlled trial (ELVIS COVID-19) V.4

Aziz Sheikh[1], Sandeep Ramalingam[2], John Norrie[3], Emma Ward[4], Catriona Graham[5]

[1]Professor of Primary Care R&D, Director of the Usher Institute, Usher Institute University of Edinburgh Nine Edinburgh BioQuarter 9 Little France Road Edinburgh, EH16 4UX Tel: 0131 650 8102 Email: Aziz.Sheikh@ed.ac.uk;

[2]Consultant Virologist Department of Laboratory Medicine Royal Infirmary of Edinburgh 51 Little France Crescent Edinburgh, EH16 4SA Tel: 0131 242 6014 Email: Sandeep.ramalingam@nhslothian.scot.nhs.uk;

[3]Chair of Medical Statistics & Trial Methodology Director, ECTU Usher Institute University of Edinburgh Nine Edinburgh BioQuarter 9 Little France Road Edinburgh EH16 4UX Tel: 0131 651 7895 Email: j.norrie@ed.ac.uk;

[4]ECTU, Usher Institute University of Edinburgh Level 2, Nine Edinburgh BioQuarter 9 Little France Road Edinburgh, EH16 4UX Tel: 0131 651 9910 Email: ELVIS-COVID19@ed.ac.uk;

[5]Epidemiology & Statistics Core Manager Wellcome Trust Clinical Research Facility Western General Hospital Crewe Road South Edinburgh, EH4 2XU Tel: 0131 537 3350 Email: C.Graham@ed.ac.uk

1 Works for me dx.doi.org/10.17504/protocols.io.bhrnj55e

Coronavirus Method Development Community

Emma Ward
University of Edinburgh

ABSTRACT

Post-hoc secondary analysis of data from our recent Edinburgh and Lothians Viral Intervention Study (ELVIS) pilot randomised controlled trial (RCT) indicates that hypertonic saline nasal irrigation and gargling (HSNIG) reduced the duration of coronavirus upper respiratory tract infection (URTI) by an average of two-and-a-half days. As such, it may offer a potentially safe, effective and scalable intervention in those with Coronavirus Disease-19 (COVID-19) following infection with the betacoronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

ELVIS was undertaken in 66 adults with an URTI. Results have been reported in detail elsewhere. Briefly, volunteers with URTI were, within 48 hours of symptom onset, randomised to intervention (n=32) or control (n=34) groups. The intervention group made hypertonic saline at home and performed HSNIG as many times as needed (maximum of 12 times/day). Control group participants dealt with their URTI as they normally did. Nose swabs collected at recruitment and first thing in the morning on four consecutive days were sent to the laboratory for testing. Both groups kept a diary (which included the Wisconsin Upper Respiratory Symptom Survey-21 questionnaire) for a maximum of 14 days or until they were well for two consecutive days. Follow-up data were available for 92% of individuals (intervention group: n=30; control group: n=31). HSNIG reduced the duration of URTI by 1.9 days (95% CI = 0.4 to 3.3) (p=0.01), over-the-counter medication use by 36% (p=0.004), transmission within household contacts by 35% (p=0.006) and viral shedding by $\geq$0.5 $\log_{10}$/day (p=0.04) in the intervention group when compared to controls.

We also recently reported that epithelial cells mount an antiviral effect by producing hypochlorous acid (HOCl) from chloride ions. HOCl is the active ingredient in bleach. Epithelial cells have this innate antiviral immune mechanism to clear viral infections. Since bleach is effective against all virus types, we tested to see if a range of DNA, RNA, enveloped and non-enveloped viruses were inhibited in the presence of chloride ions supplied via salt (NaCl). All the viruses we tested were inhibited in the presence of NaCl. The human viruses we tested were: DNA/enveloped: herpes simplex virus; RNA/enveloped: human coronavirus 229E (HCoV-229E), respiratory syncytial virus, influenza A virus; and RNA/non-enveloped: coxsackievirus B3.

In COVID-19, high titres of SARS-CoV-2 are detectable in the upper respiratory tract of asymptomatic and symptomatic individuals. The titres are higher in the nose than the throat suggesting measures that control the infection and viral shedding will help reduce transmission. In the context of the COVID-19 pandemic, we have undertaken a post-hoc re-analysis of the ELVIS data with a focus on those infected with coronaviruses. Coronaviruses were the second most common cause of URTI (after rhinoviruses). Fifteen individuals were infected by a coronavirus (intervention group (n=7), control group (n=8)). In the intervention group, four participants were infected by an alphacoronavirus (HCoV 229E=3, HCoV NL63=1) and three by a betacoronavirus (HCoV HKU1=3).

Citation: Aziz Sheikh, Sandeep Ramalingam, John Norrie, Emma Ward, Catriona Graham (06/22/2020). Hypertonic saline nasal irrigation and gargling for suspected or confirmed COVID-19: pragmatic web-based Bayesian adaptive randomised controlled trial (ELVIS COVID-19). https://dx.doi.org/10.17504/protocols.io.bhrnj55e

In the control group, two were infected by an alphacoronavirus (HCoV NL63=2) and six by a betacoronavirus (HCoV OC43=1, HCoV HKU1=5). An individual in the control group with HCoV HKU1 had dual infection with rhinovirus.
The duration of illness was lower in the intervention group compared to the control group in the subset of patients infected with coronavirus (mean days (SD): 5.6 (1.4) vs 8.1 (2.9)). Using a two-sample t-test, this was difference of -2.6 days (95%CI -5.2, 0.05; p=0.054). The difference in the duration of blocked nose was -3.1 days (95%CI -6.0, -0.2; p=0.04), cough -3.3 days (95%CI -5.9, -0.7; p=0.02) and hoarseness of voice -2.9 days (95%CI -5.6, -0.3; p=0.03) in favour of HSNIG.
In the absence of a suitable antiviral agent or a vaccine, we need a safe and effective intervention that can be globally implemented. Our in-vitro data gives the evidence that NaCl has an antiviral effect that works across viral types. The findings from this post-hoc analysis of ELVIS need to be interpreted with caution. These data do however suggest that HSNIG may have a role to play in reducing symptoms and duration of illness in COVID-19.

Primary research objective

To investigate whether the use of Hypertonic Saline Nasal Irrigation and Gargling (HSNIG) performed by adults with symptoms consistent with COVID-19 reduces the duration of symptoms when compared to participants managed using standard care.

Secondary research objective

To determine the effect of HSNIG on:
1. Severity of all symptoms
2. Duration and severity of individual symptoms
3. Over-the-counter medication use
4. Contact with primary care, NHS 24/111 and out-of-hours (OOH) primary care, COVID-19 hubs
5. Hospital attendance (i.e. A&E attendance and/or hospital admission) and diagnosis
6. Number of household contacts infected
7. Side-effect of HSNIG.

Trial design

ELVIS COVID-19 is a pragmatic web-based Bayesian adaptive randomised controlled, parallel group trial of hypertonic saline nasal irrigation and gargling compared to standard care in participants with clinically suspected or confirmed COVID-19 being managed at home. Participants from Scotland will be self-recruiting via web based system which will randomise in a 1:1 ratio to perform HSNIG or not.

Eligibility criteria

Inclusion:
·Adults (≥18 years)
·Those living within Scotland
·Those self-isolating at home within 48 hours of the start of the illness with:
(a)Clinical symptoms suggestive of COVID-19 (i.e. those who have at least one of the following symptoms: recent onset of (i) new continuous cough and/or (ii) high temperature) and/or (iii) loss of, or change in, sense of smell or taste (anosmia) OR
(b)Those with virologically confirmed SARS-CoV-2 infection and clinical symptoms indicative of COVID-19 (as detailed in (a) above).
·Provision of informed consent

Exclusion:
·Onset of illness >48 hours
·People ≤17 years
·Inability to consent
·Pregnancy
·Immunosuppression
·Inability to perform HSNIG
·Those taking part in another interventional medical trial

Citation: Aziz Sheikh, Sandeep Ramalingam, John Norrie, Emma Ward, Catriona Graham (06/22/2020). Hypertonic saline nasal irrigation and gargling for suspected or confirmed COVID-19: pragmatic web-based Bayesian adaptive randomised controlled trial (ELVIS COVID-19). https://dx.doi.org/10.17504/protocols.io.bhrnj55e

·Those without access to a supply of salt
·Those who have had a negative COVID-19 swab result for the present symptoms
·Those with suspected/confirmed COVID-19 in whom hospital admission is recommended
·Those who do not have access to email/internet
·Those living in a household with another person currently participating in this study

Setting

This study will look for participants across Scotland, who are 18 years old or older and who are self-isolating with confirmed or suspected COVID-19, with symptoms that have developed no more than 48 hours before consent to the study. The study is conducted online and everything we ask participants to do will be done at home with items they will already have.

Randomisation

Participants will be allocated in 1:1 ratio to either HSNIG or standard care.The randomisation will be performed using a web-based system utilising a block randomisation with varying block sizes and will be stratified on the variables: age (<50, 50-<70, ≥70) and gender (male, female).

Intervention

Participants will be randomised into either the intervention or the control group. The intervention group will be asked to perform HSNIG up to 12 times daily for a maximum of 14 days or until they report that they feel well. The control group will be given standard NHS guidance for the management of their symptoms and household hygiene. Both groups will be sent a daily diary via email to complete online as soon as possible that day. If a participant reports that they are feeling well before the end of the 14 days, they will receive an End of Illness questionnaire to complete, as well as a short questionnaire on Day 14.

Primary Endpoint

Self-reported time to resolution as assessed by completion of the validated self-reported UK-adapted short form of the Wisconsin Upper Respiratory Symptom Survey (WURSS-24), which will be used to collect daily symptom data

Secondary Endpoints

1. Severity of all symptoms
2. The length of time for individual symptoms to resolve
3. Severity of individual symptoms
4. Contacting healthcare (NHS 24, OOH, GP) (Number of participants and frequency of contacts)
5. Participants needing GP appointments (Number of participants and frequency of contacts)
6. Participants attending hospital (Number of participants)
7. Length of stay in hospital if admitted
8. Number of participants reporting over the counter medication use
9. Reduction in transmission to household contacts
10. Number of participants reporting side effects of nasal irrigation
11. Types and severity of side effects reported
12. Cost of over the counter medication used

Sample size

We aim to recruit a total of 405 participants from within Scotland. 50% of these patients will be randomised to the study intervention and 50% will be randomised to standard care.

EXTERNAL LINK

http://www.ed.ac.uk/usher/elvis-covid-19

ATTACHMENTS

ELVIS COVID-19 Protocol V4.0 10June2020.pdf

Citation: Aziz Sheikh, Sandeep Ramalingam, John Norrie, Emma Ward, Catriona Graham (06/22/2020). Hypertonic saline nasal irrigation and gargling for suspected or confirmed COVID-19: pragmatic web-based Bayesian adaptive randomised controlled trial (ELVIS COVID-19). https://dx.doi.org/10.17504/protocols.io.bhrnj55e

DOI

dx.doi.org/10.17504/protocols.io.bhrnj55e

PROTOCOL CITATION

Aziz Sheikh, Sandeep Ramalingam, John Norrie, Emma Ward, Catriona Graham 2020. Hypertonic saline nasal irrigation and gargling for suspected or confirmed COVID-19: pragmatic web-based Bayesian adaptive randomised controlled trial (ELVIS COVID-19). **protocols.io**
dx.doi.org/10.17504/protocols.io.bhrnj55e

EXTERNAL LINK

http://www.ed.ac.uk/usher/elvis-covid-19

KEYWORDS

COVID-19, Nasal Irrigation, Gargling, Hypertonic Saline, Saline, Upper Respiratory Tract Infection

CREATED

Jun 22, 2020

LAST MODIFIED

Jul 06, 2020

PROTOCOL INTEGER ID

38414