A Randomised Controlled Trial of Sodium Citrate Spray for Non-Conductive Olfactory Disorders

Mr Carl Philpott¹, Miss Sally Erskine², Dr Allan Clark³, Dr Alexander Leeper², Mr Mahmoud Salam⁴, Mr Rishi Sharma², Mr George Murty³, Professor Thomas Hummel⁵

¹University of East Anglia, Norwich Medical School, University of East Anglia, Norfolk NR4 7TJ, United Kingdom, E-mail: C.Philpott@uea.ac.uk,

²The Smell & Taste Clinic, ENT Department, James Paget University Hospital NHS Foundation Trust, Gorleston, Norfolk, NR31 6LA, United Kingdom.

³ENT Department, University Hospitals of Leicester NHS Foundation Trust, Leicester, UK

⁴ENT Department, The Ipswich Hospital NHS Foundation Trust, Ipswich, Suffolk, UK

⁵The Smell & Taste Clinic, Department of ORL, TU Dresden, Dresden, Germany
ABSTRACT

Background: Previous research has suggested that sodium citrate improves hyposmia by decreasing mucus calcium levels in the nose. This study aimed to confirm or refute this effect in a single application and assess potential side effects.

Methodology: Study design was a randomised double-blind controlled trial of sodium citrate nasal spray (intervention) versus sterile water (control) in a tertiary care clinic. Fifty-five patients with non-conductive olfactory loss were randomised to receive the intervention or placebo. The primary outcome measure was improvement in measured olfactory thresholds for phenyl ethyl alcohol (PEA) over 2 hours. Other outcome measures assessed were improvement in olfactory thresholds in 1-butanol, eucalyptol and acetic acid; number of responders with a clinically relevant response in each arm; adverse effects.

Results: A significant effect was seen in the intervention arm for PEA and for 1-butanol and eucalyptol when compared to the control arm (P<0.05); 32% of the intervention arm responded in terms of improved sensitivity towards some of the odours. Minor adverse effects noted included
sore throat, nasal paraesthesia, slight rhinorrhea and itching. The duration of effect of the citrate is transient, peaking at 30-60 minutes after application.

**Conclusions:** Sodium citrate yields some potential as a treatment for non-conductive olfactory loss, however these findings require corroboration in further clinical trials looking at longer-term regular use of the spray as a viable therapeutic option for patients where it would be applied at frequent intervals such as before meal times.

Keywords: olfaction disorders, clinical trial, smell, sodium citrate, viral respiratory tract infections

**INTRODUCTION**

**Background**

Olfactory disturbances represent a frustration for both patients and otorhinolaryngologists; the effects may be profound for some patients especially if their profession or safety depends upon it and clinicians often feel unable to do much more than identify the problem. Disorders of olfaction have a widespread heterogeneous aetiology from nasal to central causes. They lead to a significant impact on nutritional intake, are frequently associated with weight loss, decreased social pleasure, diminished interpersonal relationships and poor psychological well-being \(^1\). Olfactory disorders increase in incidence with age and may be as common as 1 in 5 in the over 65 population\(^2,3\). Underlying the challenge of management has been a lack of understanding of the olfactory system and a lack of therapeutic options available to clinicians.

The current understanding of olfactory transduction suggests that olfactory receptor cells in the olfactory cleft bind odour molecules to a large family of receptors in the ciliary membrane. These subsequently activate a G protein-coupled intracellular cascade ending with synthesis of cAMP by adenyl cyclase. The rise in intracellular cAMP leads to the opening of cyclic nucleotide-gated...
channels and an influx of Na\(^+\) and Ca\(^{2+}\), which eventually may lead to axonal firing. Calcium plays a key, conflicting, role in the responses of the olfactory receptor cells. It acts both as an excitatory second messenger to increase the magnitude of receptor current but also as an inhibitory messenger important in response termination and adaptation. It is well established that cytoplasmic Ca\(^{2+}\) regulates sensitivity to cAMP\(^4,5\). By entering the cilium during the odorant response Ca\(^{2+}\) reduces the sensitivity of cyclic nucleotide gated (CNG) channels to cAMP\(^6\).

A rise in mucosal Ca\(^{2+}\) through the above-described mechanism increases negative feedback on the olfactory pathway ultimately reducing sensitivity to odorant stimulus. In the normosmic patient this provides a mechanism for long-term odour adaptation. It is therefore possible that in the patients with olfactory loss, reducing mucosal Ca\(^{2+}\) levels may reduce the negative feedback, which in these circumstances may contribute to their anosmia/hyposmia. This effect is supported by an animal study that found prolonged olfactory stimulation in frog olfactory receptor cells when creating a similar environment\(^5,7\). Modulation of calcium concentrations in the olfactory environment would therefore certainly be an attractive target for pharmacologic intervention in humans, with an established underlying physiological basis.

Sodium citrate, a solution licenced and used safely in other body cavities (e.g. stomach and bladder) is known to buffer calcium ions, leading to a reduction in mucosal Ca\(^{2+}\) and subsequent reduction in negative feedback. A previous study by Panagiotopoulos et al has suggested that the application of sodium citrate improves hyposmia by decreasing mucus calcium levels in the nose\(^8\). On the basis of the above physiological rationale, reduction in free Ca\(^{2+}\) ions is likely to increase the excitability of olfactory neurons, thus improving the sense of smell. The sodium citrate solution douched in the nose should have the effect of binding free calcium ions in the nasal mucus, thus reducing mucosal calcium. The Panagiotopoulos study did, however, have certain limitations including the small number of participants and the method of application as well as the use of an identification test as the main assessment of olfactory performance.
Objectives
Primary objective: To measure the effect of sodium citrate nasal spray on short-term olfactory performance compared to placebo.

Secondary objectives: To determine the acceptability of sodium citrate nasal spray as a treatment for olfactory disorders.

MATERIALS AND METHODS

Ethical approval and funding
Ethical approval was sought and obtained from the Eastern Multicentre Research Ethics committee (REC reference number 06/MRE05/16) in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. Sodium citrate solution and corresponding sterile water placebo were supplied by the James Paget University Hospital pharmacy. The study was funded by the James Paget University Hospital Research & Development Department and sponsored by the University Hospitals of Leicester NHS Trust.

Trial Design
The study was conducted as a randomised double-blind controlled trial recruiting 55 patients who met criteria below.

Participants
Patients referred to a tertiary Smell & Taste Disorders clinic were assessed for eligibility and approached by the lead author. Basic demographic data including age and sex were collected.
Inclusion criteria:
- All patients with non-conductive olfactory disorders (NCODs) as confirmed by history and examination

Exclusion criteria:
- Patients with any endoscopic findings of conductive loss including chronic rhinosinusitis with/without nasal polyposis and severe nasal septal deviation (preventing passage of 4mm endoscope)
- Patients with congenital anosmia
- Patients with any inhalant allergies
- Patients with asthma
- Children under the age of 16

All patients provided written informed consent after the aims and methods of the study had been described to them and after they had received an information sheet.

Interventions
Participants were randomly allocated to one of two groups. In the treatment arm, participants were sprayed with 1ml of 9% sodium citrate solution; 0.5ml to each side of the nose. Participants in the control arm received the corresponding volume of sterile water. The solution was applied using a nozzle adapted to target the olfactory cleft (figure 1) as can be found on other nasal spray kits such as co-phenylcaine; the nozzle was manipulated to point upwards prior to insertion into the nose. Sodium citrate concentrations used did not exceed those used in other body cavities. Sterile water was chosen as the control agent as the ionic composition of saline may have a local effect on the Na⁺ ion concentrations that we hypothesised might modulate olfaction.
Outcomes

Primary outcome measure:
Best improvement in olfactory thresholds compared to baseline as defined by threshold shift in logarithmic dilutions in the direction of the weaker odour concentration for PEA odour.

Secondary outcome measures:
• Best improvement in olfactory threshold compared to baseline for all odours as defined by a threshold shift of at least more than one in the direction of the weaker odour concentration.
• Number of individuals who responded; (for those individuals who responded we also recorded the time until best improvement)
• Adverse events

Subjects underwent a series of threshold smell tests using the phenyl ethyl alcohol (roses), 1-butanol (pear), acetic acid (vinegar) and eucalyptol (menthol) on the basis of previous work by the senior authors\(^9\) and in conjunction with accepted threshold testing formats previously validated\(^{10,11}\). A 50ml volume of each of 4 odours in 250ml bottles were arranged in seven 10-fold dilutions from \(10^{-1}\) to \(10^{-7}\) for 1-Butanol, Acetic acid and Eucalyptol and \(10^{-2}\) to \(10^{-8}\) for phenyl alcohol. At the beginning of the trial the odour mercaptan was used but was subsequently replaced with 1-Butanol due to the need to replenish the odour solutions more frequently than the others and was deemed an unreliable test odour.

The format of the test had been fully explained to the subject beforehand by the research nurse who tested the patient. This format of olfactory testing was chosen as it would allow for quicker reassessment at repeat intervals compared to a full Sniffin’ Sticks test battery, but would provide a more accurate assessment of olfactory performance than an identification only test\(^{12}\). The subject was then started with the smallest concentration of each odour and with sterile water for comparison, ascended through the odour concentrations in a forced response format until they
correctly detected the odour as distinct from the sterile water. Once the subject had correctly identified two concentrations of a single odour in a row, the weaker concentration of the odour detected was taken as their threshold and recorded. This was then repeated for the remaining 3 odours and the four thresholds obtained were considered the baseline olfactory performance. The format of the test had been fully explained to the subject beforehand by the research nurse who tested the patient.

After application of the intervention, the olfactory threshold tests to the four odours were then repeated every fifteen minutes up to a maximum of 120 minutes. At each 15-minute interval, patients were started two places below their previous threshold to avoid unnecessary extra steps. The maximum change in threshold was recorded for each odour, as was the duration of any effect if seen. If no improvement was noted for all four odours by 60 minutes then further testing was abandoned.

At the end of the trial participants were asked to report any adverse effects from the spray they had received.

Sample size
To detect a moderate to large Cohen's effect size of 0.75 (mean difference /standard deviation of the difference), at 80% power at the 5% level of significance, would need 30 patients in each arm.

Randomisation
Sequence generation, allocation concealment and implementation:
The code randomisation sequence was computer generated and coded bottles of solution were provided to researchers who had no knowledge of the contents of each bottle. The random
sequence was generated by Microsoft Excel number randomiser generator in the hospital pharmacy who assigned enrolled participants to the intervention. Once the participant agreed to be in the study the study nurse phoned the pharmacy who then provided a coded bottle to use in the clinic.

Blinding:
Both the research team and the participants were blinded to the intervention. At the end of the trial the bottle code was obtained from the pharmacy and revealed showing allocation of participants to the two groups.

Statistical methods:
The analysis included all randomised individuals who had valid outcome measurements. The primary analysis compared the best improvement with the PEA odour between control and intervention groups using a Mann-Whitney test as the outcome was not normally distributed. The same analysis was also performed separately for each odour tested for the best improvement and the duration. Response to treatment, defined by a difference of at least two thresholds, was tested using a chi-squared test. We considered p<=0.05 as significant and all statistical analyses were conducted using Stata 14.0/SE.

RESULTS
Participant flow:
A total of 98 patients were assessed for eligibility and after exclusion or declining, 61 participants were randomised, with 31 allocated to the treatment arm and 30 to the control arm, but 4 participants did not attend their appointment on the day and 2 didn’t complete the sequence of testing after application (see figure 2). The trial ran from October 2007 to December 2014 and stopped when the target sample size had been recruited.
Baseline data:
Female participants accounted for 76% of those in the trial with an age range of 20 to 79 (mean of 53) in all subjects. The underlying diagnoses were post-viral olfactory loss (26, 42%), post-traumatic olfactory loss (9, 16%) and idiopathic (20, 36%). On psychophysical olfactory testing (using the Sniffin’ Sticks), 29 (52%) were functionally anosmic and 17 (30%) were hyposmic; the TDI score was irretrievable for 2 subjects and not performed in 7 subjects. The balance of the two treatment arms is shown in table 1, it can be seen that there is some difference between the groups in terms of gender and diagnosis.

Numbers analysed:
As participation in the trial only required one visit and one intervention, all participants completed the trial once randomised except for four in the control arm who failed to attend the study visit and a further two that failed to complete the sequence of tests on the study visit. Due to the small number of participants that had been tested with mercaptan (7), no specific analysis of this data was undertaken.

Outcomes and estimation:
Based on a best improvement in thresholds (logarithmic concentration being lower than baseline), there were significant differences between the intervention and control groups (p<0.05) for all odours except for ACA (Table 2a). Based on a clinically significant shift in thresholds of 2 or more, 10 participants responded to PEA, 10 to 1-BUT, 9 to ACA and 9 to EUC; again these were clinically significant for 1-BUT and EUC and approaching significance for PEA (table 2b). In seven patients who were evaluated with mercaptan instead of 1-butanol, 4 hyposmic patients (out of the 7) showed a positive threshold shift of ≥2 places in response to citrate. Table 3 shows the proportions of anosmic and hyposmic patients demonstrating that baseline olfactory performance does not necessarily appear to be a reliable indicator of potential to respond to the intervention.
Ancillary analyses
Of the 10 intervention subjects (32%) who found an improvement for at least one odour, 5 of the 10 had improved at 15 minutes with 3 reaching peak improvement at 15 minutes. For the other 7, peak improvement was reached at 30 minutes for five subjects, 45 minutes for one and 60 minutes for another one (two examples are provided in figure 3). The average time for subjects to register 2 logarithmic dilution improvements in threshold was 38.7 minutes with the average time to maximum effect 47.4 minutes and the average duration 54 minutes. In most patients the threshold levels for all odours had returned to baseline (+/- 1 threshold step) by the end of the 2-hour test period. Fourteen patients did not continue repeat threshold testing beyond 60 minutes due to a lack of response following the intervention.

Harms:
None of the participants in the trial reported any persistent symptoms but transient localised symptoms were reported in both arms with rhinorrhea and sore throat affecting only the citrate recipients (Table 4). None were reported as excessively unpleasant.

DISCUSSION
Generalisability
These results mark a promising development in the treatment of NCODs disorders. We have shown that sodium citrate nasal spray may temporarily improve the ability to detect certain odours in those quantitative olfactory disorders. Sodium citrate therefore has the potential to be a treatment or adjunct to treatment to improve the olfactory performance of those with NCODs. We have shown that sodium citrate spray appears to be relatively quick acting in those who find improvement, is acceptable to patients, and could feasibly be used in a clinical setting. The current treatment armory for this condition is limited with oral and topical corticosteroid and methylxanthine class
drugs (e.g. Theophylline \textsuperscript{13}) showing the most promise to date. Of these the only level I evidence is for prednisolone \textsuperscript{14,15} in NCODs. The topical intranasal spray allows an easy and well-tolerated mode of application that is vital when considering its development as a therapeutic solution. It may facilitate short-term olfactory enhancement allowing patients greater enjoyment of meals, improving quality of life and nutritional intake, or it may be used as a regular application to allow better baseline olfactory function; the specific nature of the improvement cannot be elucidated from these results, although the quick time to improvement is encouraging since it would make timing of use of the spray practicable. It is notable that amongst those who responded, the effect was not universal across all 4 odours.

**Limitations**

Whilst a positive effect was seen in 10 participants in the intervention arm, there remained 21 participants who perceived no discernible effect on their olfactory performance and therefore this cannot be seen as a panacea for all patients with NCODs. The sample size here is too small to allow for a subgroup analysis by diagnosis, however, there does not appear to have been a specific clustering of responders within one subgroup (PVOL), suggesting that more than one group may stand to benefit from this intervention (table 5). Therefore although the diagnostic group with the greatest number of responders is the PVOL group, it is notable that patients in the idiopathic group also responded. It is however possible that the idiopathic cases are indeed post-viral in nature even if lacking in the temporal relation to an upper respiratory tract infection. It should also be noted that the different subgroups may well reflect different sites of pathology within the olfactory apparatus (i.e. olfactory epithelium/receptors in PVOL, olfactory nerves/secondary cortex in PTOL, etc), so future studies will need to power for individual subgroups. Seven participants were tested with mercaptan rather than 1-butanol but and so this data was not used in the analysis, but we do not believe this detracts from the findings presented here.
The trial as reported here is designed to assess the use of sodium citrate in a single application for NCODs. However, to be effective as a treatment for patients, this positive effect would need to be repeatable on subsequent applications and to be tolerated by patients. In practice, due to the short duration of effect, this would involve patients having to apply the spray to their noses at frequent intervals such as meal times, however, feedback from patient panels at our institution favour this possibility. Other concentrations of sodium citrate could have been considered, however we decided to select the highest concentration currently available to reduce the sample size needed for this trial. As our primary outcome we used was olfactory threshold tests that only assessed 4 odours, it is possible that testing a wider array of odours might have enabled more positive responses, albeit that practically speaking this would have been difficult to achieve with 15-minute intervals for threshold tests, but achievable with an identification test.

**Interpretation**

The data presented here do not thrust sodium citrate spray forwards as a therapeutic option immediately, but do suggest merit in undertaking further multicentre trials to evaluate this intervention further. Seen in conjunction with the previous trial of sodium citrate in olfactory disorders, the results do not appear to be spurious. In fact a recent trial at the Dresden Smell & Taste Clinic performed using one nostril as the test site and the contralateral one as a control has shown benefit in the PVOL diagnostic group too. A subsequent trial would need to address the issue of subgroup analysis by diagnosis as well as age, gender and degree of olfactory impairment with an appropriate sample size. As this trial evaluated a single application of sodium citrate spray, further work needs to consider the benefits or otherwise of repeated use of the treatment over the short to medium term. Comparing efficacy between pH and sodium matched controls using validated olfactory outcome measures would also test our hypothesis that it is the citrate and our postulated mechanism of action that is conferring the improvement, rather than adjustment of any other intracellular signalling pathway or enhancement of the enzymatic mediators of olfaction through optimisation of their acid-base environment.
CONCLUSION
This work offers proof of concept that sodium citrate nasal spray may enhance olfaction in some patients with NCODs. Further investigation through well-designed clinical trials may deliver better evidence to suggest that it has a place in the rhinologist’s armamentarium. If further proven to enhance olfaction, sodium citrate could safely and easily be formulated into a commercial applicator to allow temporary relief of smell loss. This may serve to enhance the quality of life of such patients with few side effects or contraindications, by providing relief for meal times for example.

ACKNOWLEDGEMENTS
The trial has been reported according to the CONSORT guidelines
Miss Jane Woods, Research Nurse for her dedicated recruitment and delivery of the trial.
Sources of funding include: James Paget University Hospital Research & Development Funds and the Bernice Bibby Trust

CONFLICT OF INTEREST
There are no declared conflicts of interest.

AUTHORSHIP CONTRIBUTION
Carl Philpott – Led the study development and delivery and wrote the first draft of the paper
Sally Erskine – Contributed to subsequent drafts and analysis of the results
Allan Clark – Study design, statistics and final draft
Alexander Leeper – Data collection and contribution to manuscript
Mahmoud Salam – Contribution to manuscript
Rishi Sharma – Data collection and contribution to manuscript
George Murty – Chief Investigator and contribution to manuscript
Thomas Hummel – Contribution to manuscript and analysis of results
REFERENCES
6 Kleene S.J. (1999) Both external and internal calcium reduce the sensitivity of the olfactory cyclic-nucleotide-gated channel to CAMP. J Neurophysiol. 81, 2675-2682.
CORRESPONDING AUTHOR

Carl Philpott

University of East Anglia, Norwich Medical School, University of East Anglia, Norfolk NR4 7TJ, United Kingdom, E-mail: C.Philpott@uea.ac.uk

The Smell & Taste Clinic, ENT Department, James Paget University Hospital NHS Foundation Trust, Gorleston, Norfolk, NR31 6LA, United Kingdom.

TABLES

Table 1: Demographic and baseline information

<table>
<thead>
<tr>
<th></th>
<th>Control (n= 24)</th>
<th>Intervention (n= 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>16 (66.7)</td>
<td>26 (83.9)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.5 (10.4)</td>
<td>54.1 (14.3)</td>
</tr>
<tr>
<td>Threshold score</td>
<td>2.0 (1.7)</td>
<td>2.4 (2.5)</td>
</tr>
<tr>
<td>Discrimination score</td>
<td>6.5 (3.4)</td>
<td>6.8 (2.7)</td>
</tr>
<tr>
<td>Identification score</td>
<td>7.7 (3.5)</td>
<td>5.6 (2.5)</td>
</tr>
<tr>
<td>TDI score *</td>
<td>16.2 (7.3)</td>
<td>14.8 (5.9)</td>
</tr>
<tr>
<td>Diagnosis n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDIOPATHIC</td>
<td>7 (29.2)</td>
<td>13 (41.9)</td>
</tr>
<tr>
<td>PTOL</td>
<td>5 (20.8)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>PVOL</td>
<td>12 (50.0)</td>
<td>14 (45.2)</td>
</tr>
<tr>
<td>Classification (Based on TDI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional anosmia</td>
<td>13 (61.9)</td>
<td>16 (64.0)</td>
</tr>
<tr>
<td>Hyposmia</td>
<td>8 (38.1)</td>
<td>9 (36.0)</td>
</tr>
</tbody>
</table>

* Not available in 9 subjects
Table 2a: Best improvement measured in number of threshold levels improved

<table>
<thead>
<tr>
<th>Odour tested</th>
<th>Control (n= 24)</th>
<th>Intervention (n= 31)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td></td>
</tr>
<tr>
<td>PEA</td>
<td>0 (0-0.5)</td>
<td>1 (0-2)</td>
<td>0.0139</td>
</tr>
<tr>
<td>BUT</td>
<td>0 (0-1)</td>
<td>1 (0-2)</td>
<td>0.0111</td>
</tr>
<tr>
<td>ACA</td>
<td>0 (0-1.5)</td>
<td>1 (0-2)</td>
<td>0.2827</td>
</tr>
<tr>
<td>EUC</td>
<td>0 (0-0)</td>
<td>1 (0-2)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 2b: Number of respondents

<table>
<thead>
<tr>
<th>Odour tested</th>
<th>Control (n= 24)</th>
<th>Intervention (n= 31)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td></td>
</tr>
<tr>
<td>PEA</td>
<td>3 (12.5)</td>
<td>10 (32.3)</td>
<td>0.087</td>
</tr>
<tr>
<td>BUT</td>
<td>3 (12.5)</td>
<td>14 (45.2)</td>
<td>0.009</td>
</tr>
<tr>
<td>ACA</td>
<td>6 (25.0)</td>
<td>9 (29.0)</td>
<td>0.739</td>
</tr>
<tr>
<td>EUC</td>
<td>1 (4.2)</td>
<td>9 (29.0)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Table 3: Number of responders to citrate by baseline olfactory performance in the intervention arm

<table>
<thead>
<tr>
<th>Responders by odour</th>
<th>Functionally anosmic</th>
<th>Hyposmic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEA</td>
<td>3</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>BUT</td>
<td>4</td>
<td>6</td>
<td>10*</td>
</tr>
<tr>
<td>ACA</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>EUC</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

* 4 unclassified as did not have a TDI score
Table 4: Side-effects of the intranasal spray

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Citrate</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal irritation</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Rhinorrhoea</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Sneezing</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Sore throat</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 5: Numbers of responders to citrate by diagnostic group in the intervention arm

<table>
<thead>
<tr>
<th>Responders by odour</th>
<th>PVOL</th>
<th>PTOL</th>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEA</td>
<td>6</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>BUT</td>
<td>6</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>ACA</td>
<td>5</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>EUC</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

FIGURE LEGENDS

Figure 1: Spray bottle and nozzle
Figure 2: Citrate RCT participant flow chart
Figure 3 and 4: Time and duration of effect in two example responders by odour
Citrate RCT Flow Diagram

Enrollment

Assessed for eligibility (n=98)
- Excluded (n=37)
  - Not meeting inclusion criteria (n=17)
  - Declined to participate (n=12)
  - Other reasons (n=8)

Randomised (n=61)

Allocated to intervention (n=31)
- Received allocated intervention (n=31)
- Did not receive allocated intervention (n=0)

Allocated to control (n=30)
- Received allocated intervention (n=25)
- Did not receive allocated intervention (n=4)

Follow-Up

Lost to follow-up (n=0)
- Discontinued intervention (n=0)

Analysis

Analysed (n=31)
- Excluded from analysis (n=0)

Analysed (n=30)
- Excluded from analysis (n=0)