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Efficacy of a Topical Aromatic Rub (Vicks VapoRub®)-Speed of Action of Subjective Nasal Cooling and Relief from Nasal Congestion

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Abstract

Vicks VapoRub® (VVR) is a pharmaceutical preparation containing a combination of levomenthol, eucalyptus oil, turpentine oil and camphor as active ingredients, and thymol, cedarwood oil, and white soft paraffin as excipients. VVR is a petrolatum-based ointment to be either applied topically to the chest, throat, and back or added to hot water and the aromatic vapours inhaled. When used topically, the actives are evaporated by body temperature and inspired. The main therapeutic effects are the feeling of relief from nasal congestion and relief from cough. These were primarily experienced by patients as the trigeminal and olfactory impact of the aromatics and were hypothesized to be experienced within minutes. This was a randomized, single- (Investigator) blind, controlled, 2-arm (VVR vs. petrolatum), parallel design pilot study in 50 otherwise healthy adult patients suffering from common cold and experiencing nasal congestion. Speed to detection of a sensation of nasal cooling and nasal decongestion was assessed following application of the recommended amount of product. The time to first experience of a sensation of nasal cooling was significantly ($p < 0.001$) faster for patients who received VVR compared to control (median times of 23 and 99 seconds respectively). VVR delivered a statistically significant sensation of nasal cooling at all times from 12 seconds to 15 minutes after product application. The time to first experience of a sensation of nasal decongestion was significantly ($p = 0.0102$) faster for patients who received VVR compared to control (median times of 62 and 126 seconds respectively). VVR delivered a statistically significant sensation of nasal decongestion at all times from 62 seconds to 15 minutes after product application. No adverse events were reported during the study. Conclusion: Patients using Vicks VapoRub® as directed experienced significant differences from control for sensation of nasal cooling in 12 seconds and the sensation of nasal decongestion in 62 seconds.

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Keywords

VapoRub, Common Cold, Flu, Topical Decongestion, Nasal Decongestion

1. Introduction

The common cold (Upper Respiratory Tract Infection) is the most common reason for illness among adults. The literature indicates that adults can experience two to four episodes a year and children five to seven [1] [2].

The common cold is generally a mild illness of the upper respiratory tract, primarily affecting the nose, nasopharynx and paranasal sinuses. Rhinoviruses are the most common causative agent [1]. The main symptoms of common cold include nasal congestion, nasal discharge, sneeze, headache, sore throat, and cough [3].

Nasal congestion is a combination of the subjective feeling of stuffiness and the objective narrowing of the nasal passages due to vasodilatation, increased nasal blood flow, and vascular permeability. The resulting engorgement of nasal venous sinusoids and swelling of the turbinates result in a reduction in the size of the nasal passages which restricts airflow and is experienced by the patient as nasal congestion (blocked nose) [4]. Nasal congestion is distressing to patients since it is bothersome during the day and night, affecting the ability to carry out normal daily activities and to sleep well. Therefore, many patients seek a remedy to relieve this symptom.

Vicks VapoRub® (VVR) is a pharmaceutical preparation containing a combination of levomenthol (2.75% w/w), eucalyptus oil (1.5% w/w), turpentine oil (5% w/w) and camphor (5% w/w) as active ingredients, and thymol, cedarwood oil, and white soft paraffin as excipients. It is presented as a petroleum-based ointment (petrolatum) to be either applied topically to the chest, throat, and back or added to hot water and the aromatic vapours inhaled. When rubbed on the skin, the actives are evaporated by body temperature and are inspired into the airways. The therapeutic effects are exerted by interaction of the vaporised essential oils with airway receptors, including members of the transient receptor potential (TRP) channel family and in particular TRPM8 which mediates the sensation of cold [5] [6].

The licensed indications for VVR in the UK where the study was conducted (and many other countries) include symptomatic relief from nasal congestion and cough due to colds. These effects are primarily experienced by patients as the trigeminal and olfactory impact of the aromatics. It was hypothesized that this impact is experienced within minutes and is a valid indicator of onset of efficacy and this study was designed to test this. The study protocol was reviewed and approved by the UK Medicines and Healthcare Products Regulatory Agency and South East Wales Research Ethics Committee.

2. Material and Methods

2.1. Study Design

This was a randomized, single- (Investigator) blind, controlled, 2-arm (Vicks VapoRub® [VVR] vs. petrolatum), parallel design pilot study in 50 otherwise healthy adults suffering from a common cold and experiencing nasal congestion.

The study was conducted in accordance with International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP), 1997; the US Code of Federal Regulations (CFR) Title 21 parts 50, 56 and 312; applicable national laws and regulations; the ethical requirements of Directive 2001/20/EC; and the ethical principles that have their origin in the Declaration of Helsinki. All patients gave written informed consent. The basic elements of informed consent are specified in the ICH Harmonized Tripartite Guideline for GCP E6 Section 4.8.10. The study was registered on EudraCT (European Union Drug Regulating Authorities Clinical Trials)—number 2013-005006-66. The investigators had full access to all collected data and statistical analyses.

Volunteers were excluded if they had: a clinically significant nasal abnormality (e.g., deviated septum, ulcer, septal perforation, or polyp) discovered during the nasal examination at Screening; a history of clinically relevant anosmia; a history of allergy or hypersensitivity to the following ingredients: menthol, eucalyptus, turpentine, camphor, thymol, cedarwood; a history of airway disease or pronounced hypersensitivity of the airways/asthma; an oral body temperature > 100.5˚F (38.1˚C); had used nasal decongestants (including but not limited to phenylephrine, oxymetazoline, or pseudoephedrine) in the past 24 hours; had used inhaled, topical, or oral ne-

docromil or cromolyn sodium, tricyclic antidepressant medications, or MAO inhibitors for 14 days prior to screening; had a history of alcohol or drug abuse within the past 2 years; were currently enrolled in another clinical trial, or had received any other investigational drug within the past 30 days; if female and of child-bearing potential, had a positive urine pregnancy test at screening or reported they were pregnant, trying to become pregnant, or were lactating; had a history of malignancy within the past 2 years, other than treated basal cell carcinoma; had a condition (e.g., history of clinically significant pulmonary, autoimmune, psychiatric, neurologic, hematologic/oncologic, metabolic, endocrine, gastrointestinal, hepatic or renal disease) or were taking a medication, wearing devices, utilizing medicated skin ointments or creams and aromatic body creams or solutions that the Investigator believed would interfere with the evaluation of the study, pose a safety risk, or confound the interpretation of the study results.

The study was conducted at a single study site (Cardiff University, Cardiff) in the UK. In the UK and many other countries, VVR is indicated to help relieve nasal congestion and other symptoms including cough. Participants were recruited through local advertising and on visiting the centre, after reading the patient information leaflet and providing written informed consent, were interviewed to establish whether they were suffering from a cold with nasal congestion that started less than 5 days previously. The patients were asked to score their cold symptoms (nasal congestion, runny nose, sore throat, sneezing) on a 4-point ordinal scale: 0 = not present, 1 = mild, 2 = moderate, 3 = severe. To qualify for the study patients had to score at least 'mild' nasal congestion.

Participants made a single visit to the study site. After eligibility was confirmed, each patient was stratified by baseline nasal congestion (mild versus moderate/severe) then randomly assigned to 1 of 2 test products (VVR or petrolatum) and instructed regarding procedures to assess the test products. A nose clip (Speedo®, Competition) was placed on the patients before entering a well-ventilated treatment room. The study staff also wore nose clips before entering the treatment room and throughout the test period, in order to maintain the treatment blind.

2.2. Statistical Methods

The Intent-To-Treat (ITT) population comprised all randomized patients who had one dose of post-baseline test product applied by the study staff. The ITT population was intended for use in all safety analyses.

The Per Protocol population comprised all patients in the ITT population who, in addition, met the following criteria: 1) were generally compliant with test product usage instructions, and 2) met key inclusion and exclusion criteria. The Per Protocol population was used for efficacy analyses.

Patients who had evaluable data for the given endpoint were included in the efficacy analysis provided they met the other defined Per Protocol criteria. The primary efficacy endpoint was comparing the time to first experiencing sensation of nasal cooling for VVR versus petrolatum. The secondary efficacy endpoint was comparing the time to first experiencing sensation of nasal decongestion for VVR versus petrolatum.

Survival analysis methods were carried out separately on the primary and secondary endpoints. The Kaplan-Meier method was used to estimate the survivor function for time to desired sensation up to 15 minutes for each treatment. As results were significant at overall timeframe (15 minutes) the timeframe was reduced by 1 second intervals to arrive at the earliest timeframe in which treatment separation occurred (censoring would be re-vised to coincide with the reduced time interval). Once that point was obtained no additional testing was done for that endpoint. In addition to the Kaplan-Meier analysis, Cox regression analysis was performed to compute hazard ratios to quantify the ratio of incidence rates with the baseline congestion score modelled as a covariate in the analysis.

2.3. Power and Sample Size Considerations

The sample size (25 patients per arm) was based on advice obtained from the Coordinating Investigator, a recognized expert in the clinical effects of aromatic oils that 25 patients per arm ought to be sufficient.

2.4. Test Products

Approximately 7.5 grams of commercially available UK Vicks VapoRub® and petrolatum base were packaged in identical individual 25 gram jars identifiable only by patient number.

2.5. Procedures

The Investigator applied approximately 7.5 g of the randomly assigned test product on the skin of the patients

sequentially over the regions of the chest, throat, and back. A flannel cloth was placed over the treated area and secured loosely to allow the vapours to permeate the nose. The patient's nose clip was removed simultaneously with starting 2 stop-clocks positioned in front of the patients. One stop-clock was labelled with the instruction: "Stop the clock immediately when you feel any sensation of nasal cooling". The other stop-clock was labelled with the instruction: "Stop the clock immediately when you feel any sensation of nasal decongestion". Patients were instructed to stop the specific clock when that particular sensation (nasal cooling or decongestion) was first experienced. Patients continued the observation period until each clock had been stopped or 15 minutes had elapsed (observational window) indicating the end of the test period.

3. Results

Demographic and other baseline characteristics were similar between the treatment groups (**Table 1** & **Table 2**) with a slight imbalance in baseline sneezing as that tended to be more severe in VVR group.

The amount of test product applied was similar between the treatment groups with mean value applied for VVR of 7.0 grams and 7.1 grams for Petrolatum.

A total of 52 patients were screened, with 2 considered screening failures for failing inclusion criteria. A total of 50 patients were enrolled and randomly assigned to 1 of 2 test products (VVR, 25 patients; petrolatum, 25 patients). All patients completed the study. There were no per-protocol exclusions so the ITT population (safety) and per-protocol population (efficacy) are identical.

Table 3 and **Figure 1** and **Figure 3** show the time to first experience of a sensation of nasal cooling was significantly ($p < 0.001$) faster for patients who received VVR compared to petrolatum, with median times of 23 and 99 seconds, respectively.

VVR delivered a statistically significant sensation of nasal cooling at all times from 12 seconds to 15 minutes after application of product. The hazard ratio indicates that at any time point patients who received VVR were approximately 4.4 times more likely to experience their first sensation of nasal cooling before patients who received petrolatum (95% CI: 2.180, 8.728).

Table 1. Summary of demographic characteristics.

Parameter Statistic/Category	VapoRub (N = 25)	Petrolatum (N = 25)
Age		
n	25	25
Min-Max	18.0 - 24.0	18.0 - 24.0
Mean (SD)	20.4 (1.83)	20.1 (1.69)
Median	20	20
Sex		
Female	18 (72%)	18 (72%)
Male	7 (28%)	7 (28%)
Race		
Asian Oriental	1 (4%)	0 (0%)
Caucasian	22 (88%)	24 (96%)
Asian Indian	1 (4%)	1 (4%)
Multi-Racial	1 (4%)	0 (0%)
Ethnicity		
Hispanic or Latino	1 (4%)	0 (0%)
Not Hispanic or Latino	24 (96%)	25 (100%)

N = number of patients within specified treatment; n(%) = number and percentage of patients within specified parameter, treatment, and category.

Table 2. Summary of baseline assessment of cold symptoms.

Category Parameter	VapoRub (N = 25)	Petrolatum (N = 25)
	n (%)	n (%)
NASAL CONGESTION		
1-Mild	7 (28%)	7 (28%)
2-Moderate	14 (56%)	15 (60%)
3-Severe	4 (16%)	3 (12%)
RUNNY NOSE		
1-Mild	5 (20%)	7 (28%)
2-Moderate	14 (56%)	10 (40%)
3-Severe	6 (24%)	8 (32%)
SORE THROAT		
0-Not Present	6 (24%)	5 (20%)
1-Mild	7 (28%)	13 (52%)
2-Moderate	3 (12%)	5 (20%)
3-Severe	9 (36%)	2 (8%)
SNEEZING		
0-Not Present	1 (4%)	2 (8%)
1-Mild	7 (28%)	12 (48%)
2-Moderate	11 (44%)	11 (44%)
3-Severe	6 (24%)	0 (0%)

N = number of patients within specified treatment; n(%) = number and percentage of patients within specified parameter, treatment, and category.

Table 3. Survival analysis results: nasal cooling and nasal decongestion are censored at 15 minutes.

				Life Test		Cox Regression	
Symptom	Treatment	Events	Censored	Median	Log-Rank p-value	Hazard Ratio	95% CI
Nasal Cooling	VapoRub	25	0	23	<0.0001	4.362	(2.180, 8.728)
	Petrolatum	23	2	99			
Nasal Decongestion	VapoRub	25	0	62	0.0102	2.165	(1.210, 3.877)
	Petrolatum	23	2	126			

Table 3 and **Figure 2** and **Figure 3** show the time to first experience of a sensation of nasal decongestion was significantly (p = 0.0102) faster for patients who received VVR compared to petrolatum, with median times of 62 and 126 seconds, respectively.

VVR delivered a statistically significant sensation of nasal decongestion at all times from 62 seconds to 15 minutes after application of product. The hazard ratio indicates that at any time point patients who received VVR were approximately 2.2 times more likely to experience their first sensation of nasal decongestion before patients who received petrolatum (95% CI: 1.210, 3.877).

No adverse events were reported during the study.

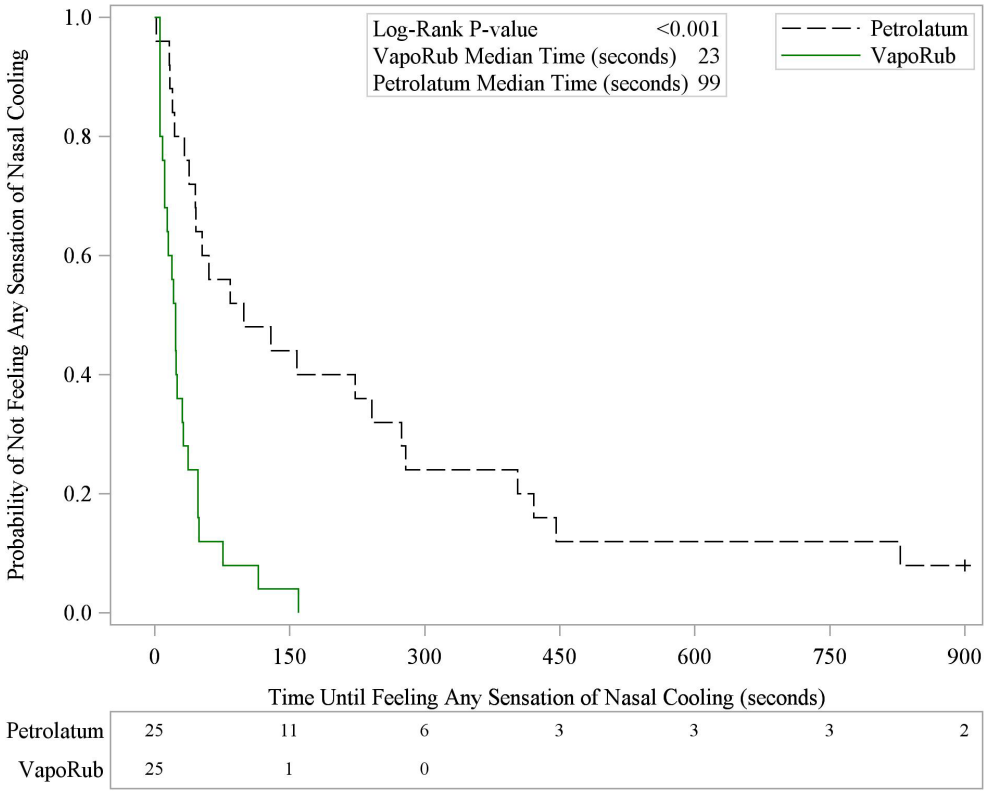

Figure 1. Time to first experiencing a sensation of nasal cooling.

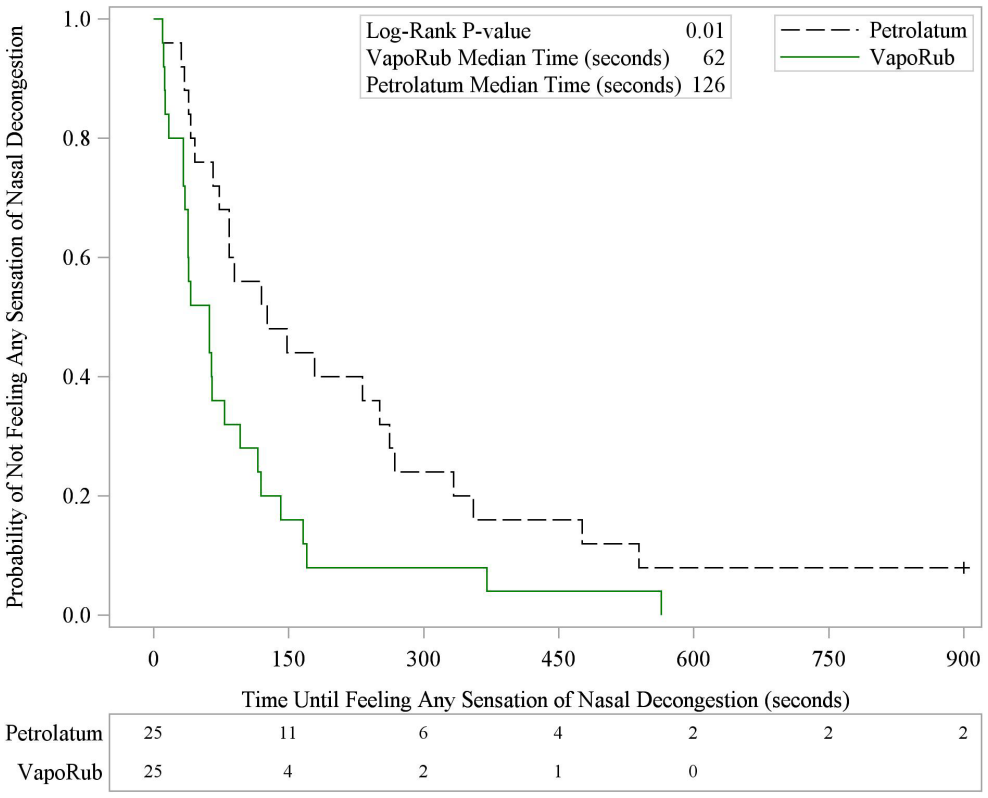

Figure 2. Time to first experiencing a sensation of nasal decongestion.

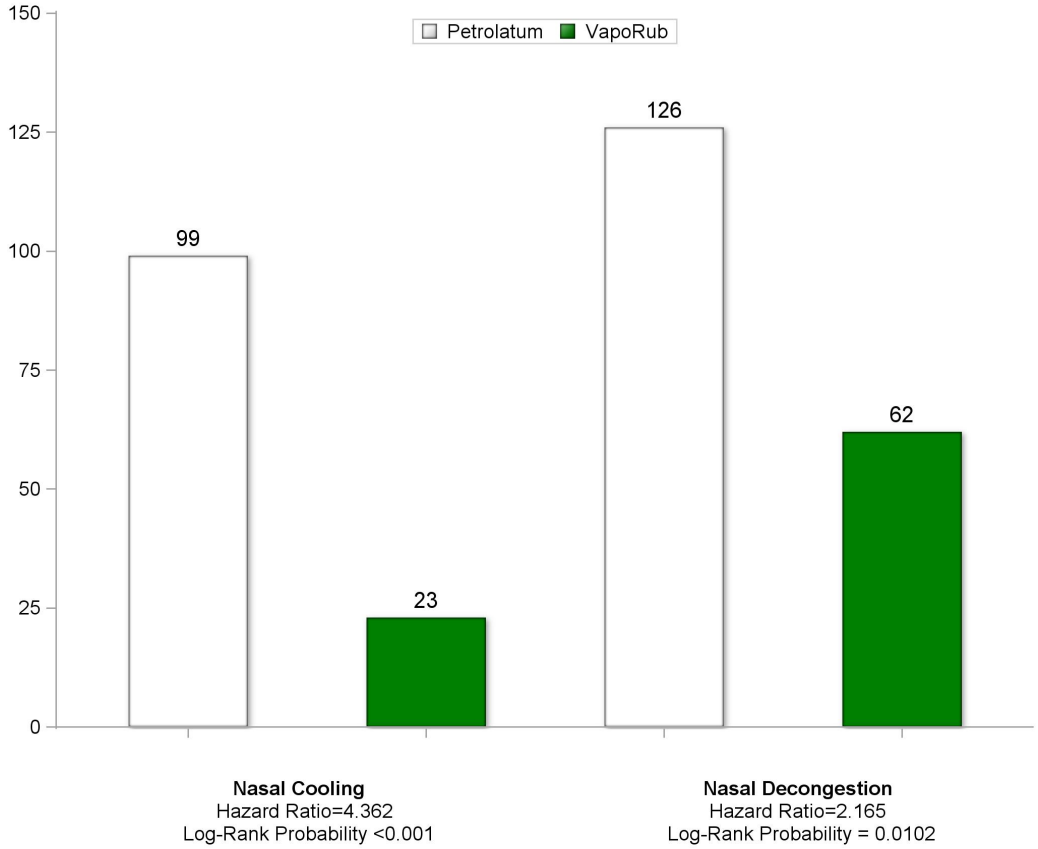

Figure 3. Median time (seconds) to first experiencing sensations of nasal cooling and nasal decongestion.

4. Discussion

The clinical effects of inhaled aromatic oils are intuitively expected to be faster than oral medication. This is particularly true for those such as menthol and eucalyptus oil which have the TRPM8 "cold" receptor (also called CMR1) as a part of their pharmacology [5] [6]. Aside from one early unpublished study measuring speed of action for Vicks VapoRub® from 5 minutes post-application (Procter & Gamble internal study CRD 90-06), the authors believe this study is the first to try to quantify how quickly an effect may be experienced.

Two endpoints were chosen, time to first sensation of nasal cooling was used to measure the very first indication of the aromatics being registered by patients and the second, time to first sensation of nasal decongestion was used to get a preliminary indication when key treatable symptoms may be first experienced by patients. To quantify the actual speed of meaningful nasal congestion relief will require additional work employing endpoints similar to those common in the pain relief field. In these studies it is common to examine both "first perceptible pain relief" and when they experienced "significant pain relief". The former typically suggest when the patient starts to feel the product working and the latter indicates confirmation of that the drug is working. These endpoints used collectively give an indication of clinically meaningful pain relief and ensure durability of the effect [7].

The present study confirms that a cooling sensation is experienced by 50% of VVR patients as early as 23 seconds after application and a sense of decongestion by 62 seconds. As normal application of VVR would require at least 1 minute and probably longer it is reasonable to suggest that the cooling sensation of aromatics will be experienced by patients immediately, that is, during the application/administration process itself.

One finding in this study that warrants discussion is the response by patients receiving the control petrolatum base. As no such experiment has been reported previously it is not possible to say whether the median recorded times of 99 seconds for cooling sensation and 126 seconds for decongestion are typical under the conditions of the study design. Arguably this numerical difference is of lesser importance than the statistically significant differences between the treatment groups.

One explanation for this lies with the design of the study. Firstly, as part of the informed consent process, all patients were told that the objective of the study was to investigate speed of action. This understanding may have pre-disposed them to stopping the clock. Secondly, all patients knew the study was a test of an aromatic product and that the study would end as soon as the clock was stopped so they were potentially mentally sensitised to reacting to any nasal sensation.

Possibly most important was the fact that all patients wore a nose-clip for the time taken to get into the room, be seated and have the product applied (estimated at 3 - 5 minutes maximum) during which time they were forced to mouth-breathe and experienced minimal/no airborne nasal sensations. When the nose clips are in place the nasal cold receptors will be at a temperature of close to 37C as there is no airflow to cool the receptors, but when the nose clip is removed the cold receptors will be immediately cooled by the inspired air at room temperature (around 20C). The control response may be the reaction of the patients to the cooling effect of the inspired air on removing the nose clip. The nose-clip procedure was introduced to the design to enable a standard start to the inhalation process and it fulfilled that role well. It may however have introduced an exaggerated placebo effect to the study. Nevertheless, the reported (clock stopped) experience of cooling was 4.4 times faster after VVR than control and 2.2 times faster after VVR than control for congestion.

A limitation of this study is that it was not double-blind in that once the patient's nose clip was removed they were exposed to the product's aroma or lack of aroma. As informed consent made clear that they would be treated either with an aromatic or non-aromatic product, patients receiving VVR would have been aware that they had received active product as soon as they sensed the aroma, potentially before they would sense nasal cooling. The difficulty in designing double-blind studies with VVR is a recognized design limitation [8]. It is unclear how to blind a study wherein the aroma of the product represents its pharmacology. The main precaution taken here was that the study staff wore nose clips from prior to opening the product jar through the entirety of the test period and the patients wore a nose clip until timing began, which ought to have preserved the single-blind.

5. Conclusion

Patients using Vicks VapoRub® as directed experienced significant differences from control for sensation of nasal cooling in 12 seconds and the sensation of nasal decongestion in 62 seconds. As summarized by the hazard ratio, patients using Vicks VapoRub® were respectively 4.4 and 2.2 times more likely to experience their first sensation of nasal cooling and nasal decongestion compared to control patients.

Financial & Competing Interests

This work was funded in total by The Procter & Gamble Company. At the time of conducting this study and preparing this manuscript, D. Hull and D. Ramsey were full-time employees of The Procter & Gamble Company and may have stock and/or stock options in the company.

RE has worked as a consultant for The Procter and Gamble Company to provide advice on common cold. MJ has no competing interests to declare.

Study Involvement: D. Hull and D. Ramsey were responsible for statistical analysis (DR) interpretation of study results (DH, DR) and publication drafting (DH).

M. Jawad and R. Eccles were responsible for study execution and they did not receive any financial payments or other inducement apart from their usual university salary, for conducting this study. All attributed authors participated in the development and review of this manuscript.

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References

[1] Wat, D. (2004) The Common Cold: A Review of the Literature. *European Journal of Internal Medicine*, **15**, 79-88.

http://dx.doi.org/10.1016/j.ejim.2004.01.006

[2] Heikkinen, T. and Jarvinen, A. (2003) The Common Cold. *Lancet*, **361**, 51-59. http://dx.doi.org/10.1016/S0140-6736(03)12162-9

[3] Eccles, R. (2005) Understanding the Symptoms of the Common Cold and Influenza. *Lancet Infectious Diseases*, **5**, 718-725. http://dx.doi.org/10.1016/S1473-3099(05)70270-X

[4] Naclerio, *et al.* (2010) Pathophysiology of Nasal Congestion. *International Journal of General Medicine*, **3**, 47-57. http://dx.doi.org/10.2147/IJGM.S8088

[5] McKemy, D.D., *et al.* (2002) Identification of a Cold Receptor Reveals a General Role for TRP Channels in Thermosensation. *Nature*, **416**, 52-58. http://dx.doi.org/10.1038/nature719

[6] Bautista, D.M., *et al.* (2007) The Menthol Receptor TRPM8 is the Principal Detector of Environmental Cold. *Nature*, **448**, 204-208. http://dx.doi.org/10.1038/nature05910

[7] Møller, *et al.* (2000) Time to Onset of Analgesia and Analgesic Efficacy of Effervescent Acetaminophen 1000 mg Compared to Tablet Acetaminophen 1000 mg in Postoperative Dental Pain: A Single-Dose, Double-Blind, Randomized, Placebo-Controlled Study. *The Journal of Clinical Pharmacology*, **40**, 370-378. http://dx.doi.org/10.1177/00912700022009071

[8] Paul, I.M., *et al.* (2010) Vapor Rub, Petrolatum, and No Treatment for Children with Nocturnal Cough and Cold Symptoms. *Pediatrics*, **126**, 1092-1099. http://dx.doi.org/10.1542/peds.2010-1601

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