

Original Research Paper

Impact of Proven Viral Load on Common Cold Patients Treated with *Pelargonium sidoides* Preparation EPs 7630

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Abstract: The Common Cold (CC) is an acute respiratory tract disorder with viral etiology in at least 90% of the cases. Nevertheless, molecular diagnostic testing often confirms the presence of viral Nucleic Acids (NA) in only about half of the patients. Based on the results of a non-comparative, interventional multicenter study we compare the course of CC between patients with and without proof of viral NA, who were treated with *Pelargonium sidoides* extract preparation EPs 7630. 120 adults with CC and at least 2 out of 10 common cold symptoms received 3×1 film-coated 20 mg tablet EPs 7630 daily for 10 days. At baseline, tests for viral NA were performed. CC-associated symptoms and treatment satisfaction were evaluated after 5 days and at treatment end. Out of 119 patients with molecular nucleic acid based assessments, 61 (61.3%) were tested positive for viral NA. Patients with and without proof of viral NA showed a similar time course of recovery from CC associated symptoms and had a comparable global outcome. In both subsets, less than 20% of the patients received concomitant paracetamol for antipyresis and only 2 required antibiotic treatment. Independently of whether or not viral NA was confirmed at baseline the course of CC treated with EPs 7630 was comparable. The results do not support the necessity to measure the viral load in order to treat CC patients effectively.

Keywords: Pelargonium Sidoides, Acute Rhinopharyngitis, Adults, Clinical Trial, Viral Analysis

Introduction

The Common Cold (CC) is a very common, acute respiratory tract infection. It has been estimated that at least 90% of all cases of CC are caused by viruses such as rhinovirus, corona virus, and respiratory syncytial virus (Dreschers *et al.*, 2007; Herendeen and Szilagy, 2000; Niroumand and Grossman, 1998; van Kempen *et al.*, 1999). The characteristic symptoms of CC include nasal congestion and discharge, sneezing, sore throat and cough. Complaints usually peak 2-3 days after the onset of infection, although some symptoms, e. g., cough and general discomfort, may persist for several weeks (Simasek and Blandino, 2007). The symptoms of CC are

understood to be mainly attributable to the inflammatory host response to replicating viruses (Hasday *et al.*, 2000). Viral infection of the nasal mucosa results in vasodilatation and increased vascular permeability, which in turn cause nasal obstruction and rhinorrhea. Cholinergic stimulation leads to increased mucous gland secretion and sneezing (Heikkinen and Järvinen, 2003).

Although CC is a predominantly trivial, self-limiting disorder, it may cause profound suffering and it is also associated with an important economic burden due to loss of productivity (Bertino, 2002; Birnbaum *et al.*, 2002). Moreover, the inflammation of the nasal mucosa may cause an obstruction of the ostia of the paranasal sinuses and the Eustachian tubes, abetting the

development of secondary inflammation such as sinusitis or otitis media (Pitrez and Pitrez, 2003). Pharmacological treatment of CC therefore appears to be justified. Since no antivirals have been licensed for the treatment of CC to date, current strategies aim at relieving symptoms, shortening the illness and reducing the risk of complications as well as the infectivity to other individuals (Arroll, 2011).

EPs 7630 (EPs[®] 7630 is the active ingredient of the product Umckaloabo[®] (ISO Arzneimittel, Ettlingen, Germany)) is a herbal drug preparation from the roots of the medicinal plant *Pelargonium sidoides*. Pharmacological activities of EPs 7630 and several of its isolated constituents have been demonstrated in in-vitro studies. They include a moderate direct antibacterial and antiviral action as well as notable immune-modulatory capabilities (Kolodziej, 2011; Moyo and Van Staden, 2014).

EPs 7630 has a prominent cytoprotective effect (Thäle *et al.*, 2011) and has been shown to interfere with the replication of seasonal influenza A virus strains (H1N1, H3N2), respiratory syncytial virus, human coronavirus, parainfluenza virus and coxsackie virus (Michaelis *et al.*, 2011). The non-specific, immune-modulatory effects of EPs 7630 appear to be mediated mainly by the release of tumor necrosis factor α and nitric oxides, the stimulation of interferon- β and an increase in natural killer cell activity (Kayser *et al.*, 2001; Kolodziej *et al.*, 2003; Kolodziej and Kiderlen, 2007). Moreover, a recently completed in-vitro study showed that EPs 7630 strongly and dose-dependently induced the production of the pro-inflammatory cytokines TNF- α and IL-6 in human blood immune cells, suggesting that the extract acts as an immunostimulant (Witte *et al.*, 2015).

Clinically, EPs 7630 has been demonstrated to be efficacious in the symptomatic treatment of acute respiratory tract infections (Agbabiaka *et al.*, 2008; Matthys *et al.*, 2014; Timmer *et al.*, 2013). While the majority of controlled clinical trials were performed in acute bronchitis, studies are also available for acute rhinosinusitis, acute tonsillopharyngitis and CC. Moreover, therapeutic evidence for adults having CC with acute rhinosinusitis as an overlapping symptom has also been included in a European guideline, including a recommendation for viral and post-viral acute rhinosinusitis directly based on category I evidence (Fokkens *et al.*, 2012).

In a recently completed clinical trial the tolerability and course of EPs 7630 treatment in adult patients suffering from CC were observed (Keck *et al.*, 2015). The study procedures involved virus testing at baseline. We investigate the association between the detection of virus NA at the start of treatment and the subsequent course of the disease specific symptoms.

Materials and Methods

Design and Participants

We report on an open-label, non-comparative, interventional multicenter study in patients suffering from CC, who were treated with EPs 7630 for 10 days. Assessments were performed at baseline, after 5 days, as well as at end of treatment. Participants maintained a diary to record the intensity of their disease-related symptoms on a daily basis.

The protocol was reviewed and approved by an independent ethics committee. All patients provided written informed consent. The principles of Good Clinical Practice and the Declaration of Helsinki were adhered to.

Eligible participants had to be female or male out-patients ≥ 18 years of age, with a clinical diagnosis of CC and at least 2 out of the following 10 pre-defined symptoms (Common Cold Symptoms, CCS): nasal discharge, sore throat, nasal congestion, sneezing, scratchy throat, hoarseness, coughing, headache, malaise, fever. Patients with obstructive anatomic nasopharyngeal lesions (e.g., nasal polyps), severe septal deviations, previous or planned surgery of the nose or paranasal sinuses, chronic pulmonary diseases, allergic rhinitis, conditions known to cause sore throat (e.g., tonsillopharyngitis, drugs, aphthous ulcers, candida), or any acute respiratory tract disease other than CC, were excluded from participation.

Treatments

The study medication was EPs 7630, a herbal drug preparation from the roots of *Pelargonium sidoides* (1: 8-10), extraction solvent: ethanol 11% (w/w). Patients had to administer 3 \times 1 film-coated tablets per day (Marketed product used in this trial: Kaloba[®] (Austroplant Arzneimittel, Vienna, Austria).), each containing 20 mg of dried EPs 7630, for 10 consecutive days.

Treatment compliance was assessed by counting the number of remaining film-coated tablets at study exit. Except for paracetamol taken in case of fever $>38.5^{\circ}\text{C}$, up to a maximum dose of 500 mg every 6 hours, concomitant CC medications that might impair the interpretation of trial results was not allowed.

Molecular Diagnostic Assays

Molecular testing for viruses was performed at baseline, by taking a nasopharyngeal swab from both nostrils with a sterile brush. Total nucleic acid (DNA and RNA) was isolated from the samples using the QIAamp nucleic acid isolation kit (Qiagen, Hilden, Germany). The amount of isolated nucleic acid was measured by absorbance. For viral testing, an aliquot was applied to the xTAG[®] Respiratory Viral Panel (RVP) FAST assay

(Abbott, Vienna, Austria). cDNA were generated from RNA by Reverse Transcription (RT) and then amplified by PCR. Subsequent to RT-PCR the amplicons were hybridized onto virus species specific DNA probes immobilized on Luminex beads. Virus species were identified using Luminex technology, with signal measurements of virus specific hybridization signals specified for the xTAG[®] RVP FAST assay. Viruses detectable by the assay include influenza A and B, Respiratory Syncytial Virus (RSV), corona virus, parainfluenza virus, human metapneumovirus, enterorhinovirus, adenovirus and human bocavirus. Testing of bacterial DNA was done using PCR amplification targeting a 738bp 16S rRNA gene sequence and microarray hybridization using the AIT Chip HD PathoID test enabling detection of 73 known human bacterial pathogens (Austrian Institute of Technology).

Measures for Course of Disease

Patient information included demographic, anthropometric and medical history data. The course of CC was assessed at each visit based on investigator ratings of each of a set of 10 CCS on a 4-point verbal rating scale ranging from 0 ('not present') to 3 ('severe'), which are summed up to a total score based on a scale developed by Jackson and colleagues (Jackson *et al.*, 1958). Observer assessments also included 8 additional CC-relevant complaints (CRC; pulmonary rales at auscultation, sputum production, chest pain during coughing, chilliness, exhaustion, loss of appetite, diarrhea and muscle aches) which the investigators rated using the same scale and which were summed up to a separate total score. Moreover, an over-all symptom score was computed from the 10 CCS and the 8 CRC.

Recovery from CC (rated by patients and investigators) as well as the patients' satisfaction with the treatment course were assessed using the Integrative Medicine Outcomes Scale (IMOS) and the Integrative Medicine Patient Satisfaction Scale (IMPSS), respectively (Steinsbekk *et al.*, 1999). Moreover, the patient diary included daily global assessments of how ill a patient felt. Further measures to assess the course of the disease were the number of days off work or education, the need for antibiotic treatment and the use of paracetamol.

Statistical Methods, Sample Size

We performed descriptive post-hoc comparisons between patients with viral NA proof at baseline and those in whom no viral NA could be confirmed. Within each subset, descriptive summary statistics were computed and p-values and 95% Confidence Intervals (CIs) were determined for change over time using. For eligibility of the analyses of course of CC, at least one post-baseline assessment of the analyzed outcome was

required (Full Analysis Set, FAS). Missing data were imputed by carrying forward the last valid observation provided that at least one post-baseline assessment had been performed.

For statistical tests two-sided p-values up to 0.05 were considered to be descriptively significant. A total of 120 patients were planned to be treated based on practical considerations.

Results

Participant Characteristics

A total of 120 participants were included and treated in the out-patient clinics of 8 hospitals in Austria between January 2011 and November 2012. One hundred and seventeen participants completed the trial as scheduled. All patients included were analyzed for parameters to assess the course of the disease in the FAS.

For 119 patients, swab samples were available for analysis. Virus NA was detected in the samples of 61 patients (51.3% of 119; Fig. 1). The most frequently detected viruses were enterovirus/rhinovirus (29% of the samples), followed by corona HKU1 virus (11%) and by Corona OC43 virus (7%). The samples of 50 of the 61 patients (82.0%) showed infection with 1 virus species whereas more than 1 species was found in the samples of the remaining 11 patients (18%).

The following sections present the results of the 119 patients for whom nasopharyngeal swab samples were available for analysis. The results of the pre-planned safety and disease course analyses performed on all treated patients (n = 120) have been reported elsewhere (Keck *et al.*, 2015).

Baseline Characteristics

Table 1 shows the study participants' demographic and anthropometric characteristics. On average, patients with proof of viral NA were about 5 years younger than those without confirmed viral NA, but only minor subgroup differences were observed otherwise. Although ethnic group was not a selection criterion, all subjects except 1 were Caucasians. About 75% of the subjects in both subsets reported to drink alcohol occasionally or regularly. 55.7% of the patients with proof of viral NA and 41.4% of those without confirmed viral NA were current smokers or ex-smokers.

At baseline, patients with viral NA had been suffering from symptoms of Acute Rhinopharyngitis (ARP) for an average of 50.1±16.4 hours (mean ± SD; range 16-72 hours) compared to 42.3±19.6 hours (range: 6-72 hours) in patients without confirmed viral NA. The baseline severity of CCS and CRC showed no monotonic association with symptom duration upon enrolment.

Table 1: Baseline characteristics (number (%) of patients or mean \pm SD, by pathogen detection)

Virus NA	Confirmed (n = 61)	Not confirmed (n = 58)
Female	44 (72.1%)	39 (67.2%)
Male	17 (27.9%)	19 (32.8%)
Age (years)	36.3 \pm 12.4	41.4 \pm 14.5
Height (cm)	171.9 \pm 8.7	170.7 \pm 7.5
Weight (kg)	71.7 \pm 13.4	74.7 \pm 15.4
Duration of ARP symptoms [hours]	50.1 \pm 16.4	42.3 \pm 19.6

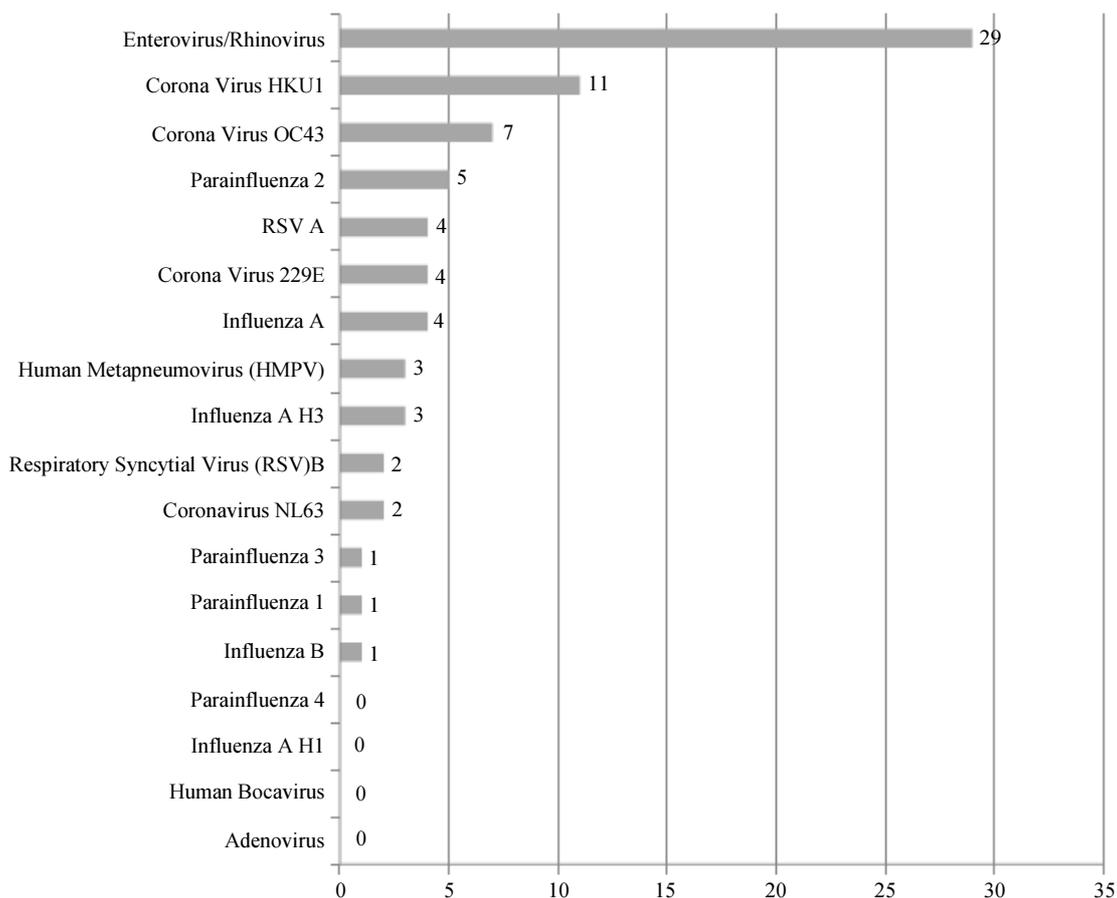


Fig. 1: Detection of virus NA in the nasal swab samples of 119 patients (% of patients, by virus species)

Time Course of Common Cold Associated Symptoms

According to the investigators' rating, patients with proof of viral NA showed a slightly higher CCS total score at baseline than those without confirmed viral NA, but a comparable time course of symptom recovery was observed for both subsets. Differences between the subsets regarding the CRC total score were also marginal throughout the period of observation (Fig. 2). For both CCS and CRC, only a minimum symptom burden remained at treatment end, with individual maximum scores of 2 and 1 points for CCS (theoretical maximum score of scale: 30 points) and of 2 and 2 points for CRC

(theoretical maximum: 24 points), for patients with or without confirmed viral NA, respectively.

Table 2 presents the average intraindividual change of the CCS and CRC total scores. According to the investigators' rating, patients with and without proof of virus NA achieved descriptively significant average score reductions by about 50% of the baseline value already after 5 days of treatment and continued to improve until treatment end. Since the majority of patients in both subsets had only minimal, if any residual symptoms at day 10, the observed differences in average change between patients with and without proof of virus NA, particularly for CCS, likely reflect baseline differences rather than differences in the time course of symptom recovery.

Table 2: Common cold associated symptoms – baseline total score and change between baseline and subsequent visits (investigator ratings; mean ± SD and Wilcoxon test for change versus baseline; FAS)

Virus NA		Confirmed			Not confirmed		
		n	Mean ± SD	p	n	Mean ± SD	p
Common Cold Symptoms (CCS)	Baseline	61	11.5±3.4		58	10.1±3.7	
	Change, day 5	59	-6.2±4.4	<0.01	57	-5.0±2.9	<0.01
	Change, day 10	60	-9.5±3.8	<0.01	55	-7.9±3.9	<0.01
Further common Cold Relevant Complaints (CRC)	Baseline	61	3.3±2.4		58	3.5±3.0	
	Change, day 5	59	-2.0±2.0	<0.01	57	-2.2±2.8	<0.01
	Change, day 10	60	-2.6±2.1	<0.01	55	-3.0±3.1	<0.01
Grand total (CCS + CRC)	Baseline	61	14.8±4.9		58	13.6±5.8	
	Change, day 5	59	-8.2±5.3	<0.01	57	-7.2±5.0	<0.01
	Change, day 10	60	-12.0±5.0	<0.01	55	-10.9±6.1	<0.01

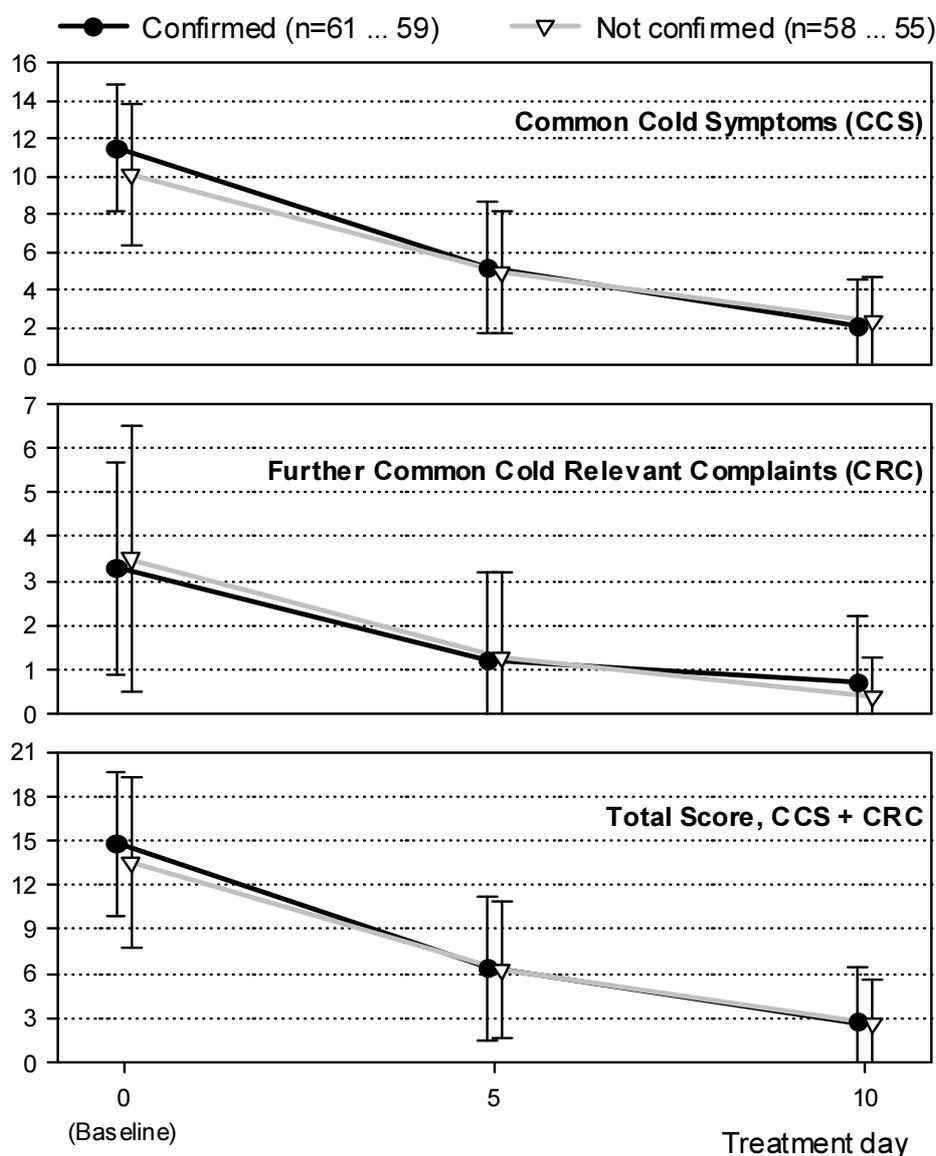


Fig. 2: Time course of common cold symptoms and further common cold relevant complaints, by confirmation of virus NA (investigator ratings; mean ± SD; FAS)

The results for the observer ratings of CCS were supported by the patients' self-ratings obtained in the diary on a daily basis (data not shown).

Global Disease Course Measurements, Patients' Impression of Treatment Satisfaction

According to the investigators' IMOS ratings, about half of the patients with confirmed viral NA and close to 40% of patients without proof of viral NA showed at least major improvements after 5 days of treatment with EPs 7630 (Fig. 3). At treatment end, 28 of 60 patients with valid data and proof of viral NA (46.7%) were completely recovered and 22 (36.7%) showed major improvement, compared to 21 (37.5%) and 26 (46.4%) out of 56 patients in the subset without confirmed viral NA. The data suggest that although the total rates of patients with major improvements or complete recovery were comparable for patients with or without confirmed viral NA, those with confirmed viral infection had a higher complete recovery rate at treatment end. The investigators' assessments were supported by the patients' IMOS self-ratings which also indicated a slightly higher rate of patients with a favorable impression of the disease course after 5 and 10 days. These results were in line with the daily self-assessments if severity of illness obtained in the patient diaries: by

day 5 (viral NA) and day 4 (no confirmed viral NA), more than 50% of the patients with valid data reported that they felt only very mildly ill or not ill at all. The rates increased to at or above 90% by day 8 (viral NA) and 10 (no proof of viral NA), respectively.

The results of the IMOS assessments were also consistent with the treatment satisfaction self-ratings obtained with the IMPSS (Fig. 3): 22 of 60 patients with valid data and proof of viral NA (36.1%) were very much satisfied and 18 (29.5%) were satisfied, compared to 15 (25.9%) and 19 (32.8%) out of 58 patients in the subset without proof of viral NA. In each subset, 1 patient indicated that she/he was dissatisfied or very dissatisfied with the disease outcome at the end of the observational period.

Need for Antibiotics or Paracetamol

Paracetamol, which was allowed in accordance with the study protocol in case of fever $>38.5^{\circ}\text{C}$, was taken at least once by 11 of the 61 patients (18.0%) with proof of viral NA and by 11 of the 58 patients (19.0%) without confirmed viral NA. One patient in each subset (1.6% and 1.7% for patients with and without proof of viral NA, respectively) received antibiotic treatment in accordance with the investigator's medical judgment.

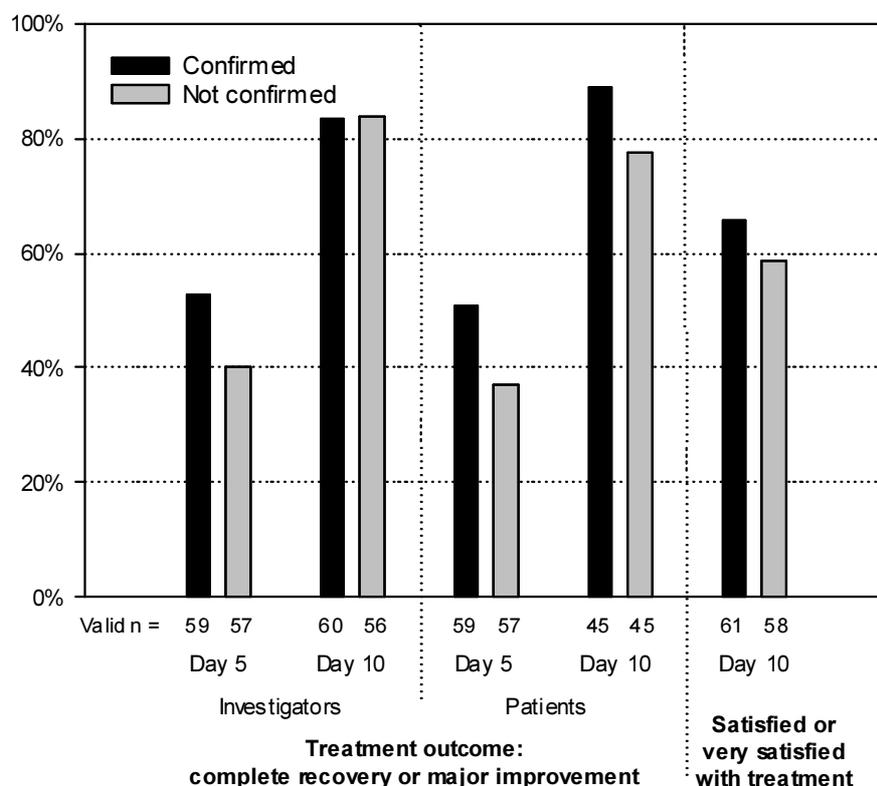


Fig. 3: Treatment outcome (IMOS) and satisfaction with treatment - % of patients with a favorable response, by confirmation of virus NA (FAS)

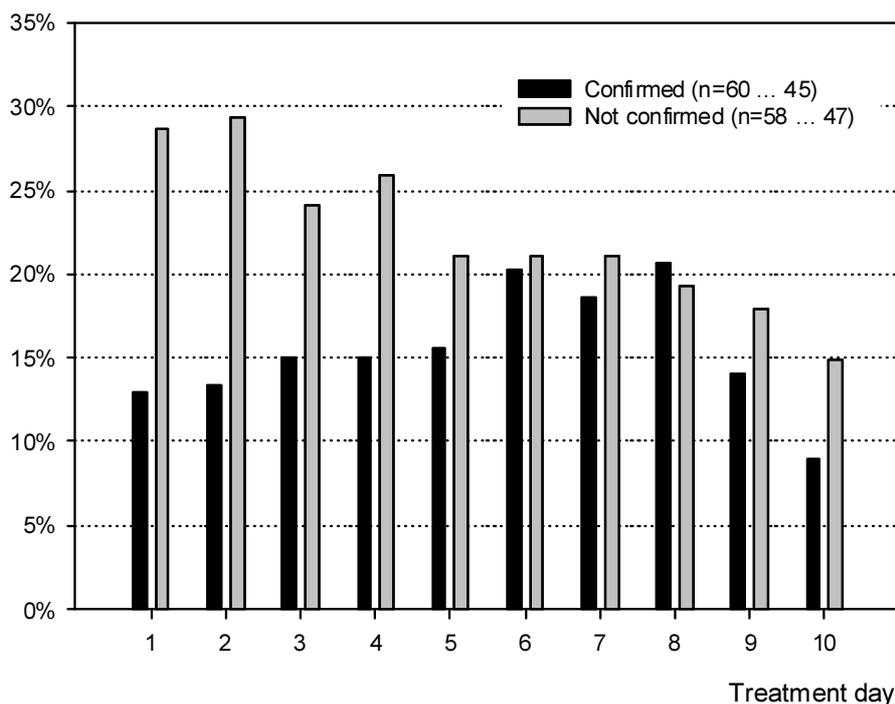


Fig. 4: Percent of patients who did not attend work or school/college, by confirmation of virus NA (FAS)

Inability to Work

In the subset with proof of viral NA between 13% and 21% of the patients did not attend work or school/college throughout the majority of days of observation. The rate decreased to 8.9% by day 10. Patients without confirmed viral NA had initially higher non-attendance rates just below 30% which decreased gradually to 14.9% at the end of the observational period (Fig. 4).

The average intraindividual number of days off work or school/college was 1.2 ± 2.7 days in patients with proof of viral NA and 2.3 ± 3.8 days in patients without confirmed viral NA, with maximum values of 10 and 11 days, respectively.

Discussion

Acute respiratory tract infections such as CC are almost exclusively viral in origin (Dreschers *et al.*, 2007; Herendeen and Szilagy, 2000; Mäkelä *et al.*, 1998; Niroumand and Grossman, 1998; van Kempen *et al.*, 1999). Despite the fact that highly sensitive assays have become available during recent years (Ginocchio and McAdam, 2011), diagnostic tests still vary widely with regard to their sensitivity and specificity. The virus NA detection rate has been shown to decrease significantly with increasing symptom duration (Brittain-Long *et al.*, 2010). In many investigations, only about half of the infected patients show a positive virus test result (e.g., Brittain-Long *et al.*, 2010; Lam *et al.*, 2007), although detection rates exceeding 90% have also been reported

when patients were assessed within 48 hours after the onset of the first symptoms. Moreover, virus detection rates have also been found to vary with the type of specimen (e.g., nasopharyngeal vs. throat/saliva) (Robinson *et al.*, 2008) as well as with the type of transport medium used (Walsh *et al.*, 2008). These observations are consistent with the analysis of the swab obtained at baseline of our trial, which confirmed viral NA in about half of the samples. It is important to note, however, that the results do by no means imply that patients in whom the test for viral NA remained negative were not suffering from viral infection.

As regards the clinical manifestations and course of CC in patients treated with EPs 7630, our analyses found no evidence of major differences between patients in whom viral NA could or could not be confirmed at baseline. Both subsets showed a comparably favorable course, with significant improvement of symptoms already during the first 5 days while the patients had largely recovered after 10 days. The results also indicate that patients with and without proof of viral NA were most probably not suffering from different clinical conditions, but that those in whom no virus could be confirmed may either have been already in a post-viral state, or may have had a false negative test.

Paracetamol is among the most widely used medications in CC (Li *et al.*, 2013). In this trial, co-medication with paracetamol was permitted for antipyresis, but was actually used by less than 20% of patients in both subsets. Since EPs 7630 has no known direct antipyretic effect, we interpret the comparatively

low use of paracetamol as an indicator of a favorable course of the infection during the administration of the herbal medicinal product, so that only a minority of patients developed fever in a range that prompted antipyresis. Remarkably, only 1 patient in each subset was switched to an antibiotic.

Our investigation thus shows that patients with or without proof of virus NA treated with EPs 7630 exhibited a similarly favorable course of CC symptoms and rarely required additional or different drug treatment. In acute respiratory tract disorders such as CC, testing for viral NA therefore appears to be dispensable in clinical routine practice because the results of the test will probably not modify the appropriate treatment to be administered.

A limitation of the study is that the design did not include a placebo control group and thus the treatment effect in a self-limiting condition like CC is difficult to assess. However, as argued previously (Keck *et al.*, 2015), the extent of symptom relief observed in this study was comparable to that in a double-blind, randomized trial performed by Lizogub and colleagues (Lizogub *et al.*, 2007) in CC, in which EPs 7630 was significantly superior to placebo.

Conclusion

Our analysis showed no association between the presence of virus NA confirmed by a microbiological assessment performed at baseline and the course of CC in patients treated with EPs 7630. Although the design of this study was not intended for demonstrating treatment efficacy, the favorable course of clinical symptoms is comparable to the course observed earlier in the active treatment group of a placebo-controlled trial (Keck *et al.*, 2015). The results may also be explained by the antiviral effect of EPs 7630 that has been demonstrated in preclinical investigations (Kolodziej, 2011; Moyo and Van Staden, 2014).

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Author Contributions

Tilman Keck: Was principal investigator of the study and provided input into the study design, the interpretation of the data and the drafting of the manuscript.

Andreas Strobl: Was investigator of the study and provided input into the study design, the interpretation of the data and the drafting of the manuscript.

Andreas Weinhaeusel: Was responsible for the molecular diagnostics and was involved in the interpretation of the data and the drafting of the manuscript.

Berenike Stracke: Was involved in the interpretation of the data and helped to draft the manuscript.

Conflict of Interest

Tilman Keck, Andreas Strobl and Andreas Weinhaeusel have received honoraria from Dr. Willmar Schwabe GmbH and Co. KG, Karlsruhe, Germany. Berenike Stracke is an employee of Dr. Willmar Schwabe GmbH and Co. KG, Karlsruhe, Germany.

References

- Agbabiaka, T.B., R. Guo and E. Ernst, 2008. *Pelargonium sidoides* for acute bronchitis: A systematic review and meta-analysis. *Phytomedicine*, 15: 378-385. DOI: 10.1016/j.phymed.2007.11.023
- Arroll, B., 2011. Common cold. *Clin. Evid.*, 03: 1510-1510. PMID:21406124
- Bertino, J.S., 2002. Cost burden of viral respiratory infections: Issues for formulary decision makers. *Am. J. Med.*, 112 Suppl 6A: 42S-49S. DOI: 10.1016/S0002-9343(01)01063-4
- Birnbaum, H.G., M. Morley, P.E. Greenberg and G.L. Colice, 2002. Economic burden of respiratory infections in an employed population. *Chest*, 122: 603-611. DOI: 10.1378/chest.122.2.603
- Brittain-Long, R., J. Westin, S. Olofsson, M. Lindh and L.M. Andersson, 2010. Prospective evaluation of a novel multiplex real-time PCR assay for detection of fifteen respiratory pathogens-duration of symptoms significantly affects detection rate. *J. Clin. Virol.*, 47: 263-267. DOI: 10.1016/j.jcv.2009.12.010
- Dreschers, S., P. Franz, C.A. Dumitru, B. Wilker and K. Jahnke *et al.*, 2007. Infections with human rhinovirus induce the formation of distinct functional membrane domains. *Cell Physiol. Biochem.*, 20: 241-254. DOI: 10.1159/000104170
- Fokkens, W.J., V.J. Lund, J. Mullol, C. Bachert and I. Alobid *et al.*, 2012. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinology*, 50: 3-3 p preceding table of contents, 1-298.
- Ginocchio, C.C. and A.J. McAdam, 2011. Current best practices for respiratory virus testing. *J. Clin. Microbiol.*, 49: S44-S48. DOI: 10.1128/JCM.00698-11
- Hasday, J.D., K.D. Fairchild and C. Shanholtz, 2000. The role of fever in the infected host. *Microbes Infect.*, 2: 1891-1904. DOI: 10.1016/S1286-4579(00)01337-X

- Heikkinen, T. and A. Järvinen, 2003. The common cold. *Lancet*, 361: 51-59.
DOI: 10.1016/S0140-6736(03)12162-9
- Herendeen, N.E. and P.G. Szilagy, 2000. Infections of the Upper Respiratory Tract. In: Nelson Textbook of Pediatrics, Behrman, R.E., R.M. Kliegman and H.B. Jenson (Eds.), W. B. Saunders, Philadelphia, pp: 1261-1266.
- Jackson, G.G., H.F. Dowling, I.G. Spiesman and A.V. Boand, 1958. Transmission of the common cold to volunteers under controlled conditions. I. The common cold as a clinical entity. *AMA Arch. Intern. Med.*, 101: 267-278.
DOI: 10.1001/archinte.1958.00260140099015
- Kayser, O., H. Kolodziej and A.F. Kiderlen, 2001. Immunomodulatory principles of Pelargonium sidoides. *Phytother. Res.*, 15: 122-126.
PMID: 11268110
- Keck, T., A. Strobl and B. Stracke, 2015. Tolerability and treatment effects of Pelargonium sidoides preparation EPs 7630 in adults suffering from acute rhinopharyngitis – a prospective, open-label trial, *Altern. Integ. Med.*, pp: 204.
- Kolodziej, H., 2011. Antimicrobial, antiviral and immunomodulatory activity studies of Pelargonium sidoides (EPs® 7630) in the context of health promotion. *Pharmaceuticals*, 4: 1295-1314.
DOI: 10.3390/ph4101295
- Kolodziej, H., O. Kayser, O.A. Radtke, A.F. Kiderlen and E. Koch, 2003. Pharmacological profile of extracts of Pelargonium sidoides and their constituents. *Phytomedicine*, 10 Suppl 4: 18-24.
PMID: 12807338
- Kolodziej, H. and A.F. Kiderlen, 2007. In vitro evaluation of antibacterial and immunomodulatory activities of Pelargonium reniforme, Pelargonium sidoides and the related herbal drug preparation EPs® 7630. *Phytomedicine*, 14 Suppl 6: 18-26.
DOI: 10.1016/j.phymed.2006.11.020
- Lam, W.Y., A.C. Yeung, J.W. Tang, M. Ip and E.W. Chan *et al.*, 2007. Rapid multiplex nested PCR for detection of respiratory viruses. *J. Clin. Microbiol.*, 45: 3631-3640.
DOI: 10.1128/JCM.00280-07
- Li, S., J. Yue, B.R. Dong, M. Yang and X. Lin *et al.*, 2013. Acetaminophen (paracetamol) for the common cold in adults. *Cochrane Database Syst. Rev.*, 7: CD008800.
DOI: 10.1002/14651858.CD008800.pub2
- Lizogub, V.G., D.S. Riley and M. Heger, 2007. Efficacy of a Pelargonium sidoides preparation in patients with the common cold: A randomized, double blind, placebo-controlled clinical trial. *Explore*, 3: 573-584.
DOI: 10.1016/j.explore.2007.09.004
- Mäkelä, M.J., T. Puhakka, O. Ruuskanen, M. Leinonen and P. Saikku *et al.*, 1998. Viruses and bacteria in the etiology of the common cold. *J. Clin. Microbiol.*, 36: 539-542. PMID: 9466772
- Matthys, H., F.A. Malek and W. Kamin, 2014. EPs® 7630 in acute respiratory tract infections – a systematic review and meta-analysis of randomised clinical trials. *Forsch. Komplementmed.*, 21: 57-58.
DOI: 10.1159/000362397
- Michaelis, M., H.W. Doerr and J. Cinatl, Jr., 2011. Investigation of the influence of EPs® 7630, a herbal drug preparation from Pelargonium sidoides, on replication of a broad panel of respiratory viruses. *Phytomedicine*, 18: 384-386.
DOI: 10.1016/j.phymed.2010.09.008
- Moyo, M. and J. Van Staden, 2014. Medicinal properties and conservation of Pelargonium sidoides DC. *J. Ethnopharmacol.*, 152: 243-255.
DOI: 10.1016/j.jep.2014.01.009
- Niroumand, M. and R.F. Grossman, 1998. Airway infection. *Infect. Dis. Clin. North Am.*, 12: 671-688.
PMID: 9779384
- Pitrez, P.M. and J.L. Pitrez, 2003. Acute upper respiratory tract infections: Outpatient diagnosis and treatment [in Portuguese]. *J. Pediatr. (Rio. J.)*, 79 Suppl 1: S77-S86. PMID: 14506520
- Robinson, J.L., B.E. Lee, S. Kothapalli, W.R. Craig and J.D. Fox, 2008. Use of throat swab or saliva specimens for detection of respiratory viruses in children. *Clin. Infect. Dis.*, 46: e61-64.
DOI: 10.1086/529386
- Simasek, M. and D.A. Blandino, 2007. Treatment of the common cold. *Am. Fam. Physician*, 75: 515-520.
PMID: 17323712
- Steinsbekk, A., J. Biolchini, M. Heger, C. Rezzani and N. Tsamis *et al.*, 1999. Data collection in homeopathic practice. A proposal for an international standard. *HomInt R&D Newsletter*, 2: 3-23.
- Thäle, C., A.F. Kiderlen and H. Kolodziej, 2011. Anti-infective activities of Pelargonium sidoides (EPs® 7630): Effects of induced NO production on Leishmania major in infected macrophages and antiviral effects as assessed in a fibroblast-virus protection assay. *Planta Med.*, 77: 718-725.
DOI: 10.1055/s-0030-1250567
- Timmer, A., J. Günther, E. Motschall, G. Rücker and G. Antes *et al.*, 2013. Pelargonium sidoides extract for treating acute respiratory tract infections. *Cochrane Database Syst. Rev.*, 10: CD006323.
DOI: 10.1002/14651858.CD006323.pub3
- van Kempen, M., C. Bachert and P. Van Cauwenberge, 1999. An update on the pathophysiology of rhinovirus upper respiratory tract infections. *Rhinology*, 37: 97-103. PMID: 10567986

Walsh, P., C.L. Overmyer, K. Pham, S. Michaelson and L. Gofman *et al.*, 2008. Comparison of respiratory virus detection rates for infants and toddlers by use of flocced swabs, saline aspirates and saline aspirates mixed in universal transport medium for room temperature storage and shipping. *J. Clin. Microbiol.*, 46: 2374-2376.
DOI: 10.1128/JCM.00714-08

Witte, K., E. Koch, H.D. Volk, K. Wolk and R. Sabat, 2015. The Pelargonium sidoides extract EPs 7630 drives the innate immune defense by activating selected MAP kinase pathways in human monocytes. *PloS One*, 10: e0138075.
DOI: 10.1371/journal.pone.0138075