

G. CIPRANDI¹, M. CRISTOFOLINI², E. MIRA³

Comano thermal water inhalations in the treatment of allergic rhinitis: preliminary results

¹IRCCS-A.O.U. San Martino di Genova, Genoa, Italy

²Istituto G.B. Mattei, Terme di Comano, Trento, Italy

³Clinica Otorinolaringoiatrica, Università di Pavia, Pavia, Italy

KEY WORDS

Comano water; crenotherapy; allergic rhinitis; symptoms

Corresponding author

Giorgio Ciprandi

Largo R. Benzi 10, 16132 Genoa, Italy

Phone: +39 010 3533 1820

Fax: +39 010 3538 664

E-mail: gio.cip@libero.it

Summary

Background. Comano thermal water, well known for its activity in the treatment of dermatological diseases, has been successfully employed in the treatment of upper airways disorders.

Objective. The present preliminary study aimed to evaluate whether Comano thermal water may be able to improve nasal symptoms severity in patients with allergic rhinitis (AR).

Methods. 30 AR patients were enrolled (mean age 40.9 years; 13 males) and treated with inhalation of Comano thermal water for 15 days. Total symptom score (TSS) and visual analogue scale (VAS) for patient's perception of nasal patency were assessed at baseline, after treatment, and after a 2-week follow-up.

Results. TSS significantly decreased after treatment as well as VAS significantly increased. The effects were partially long-lasting. **Conclusion.** Comano thermal water inhalation as monotherapy for AR was able to relieve nasal symptoms and patient's perception of nasal patency.

Introduction

The term crenotherapy derives from old Greek (κρήνη = spring and θεραπεία = therapy). Crenotherapy, such as the use of thermal water, is popularly recognized as effective and safe, even though there is still a lack of a clear evidence about effectiveness and mechanism of action. Many ENT disorders are widely treated by crenotherapy, including respiratory infections (1). Crenotherapy may be internal or external. Internal crenotherapy includes: hydropinotherapy (such as administration of thermal water as beverage), irrigation, inhalation, and insufflation. External crenotherapy consists of balneotherapy, halotherapy, and pelohydrotherapy (such as mud bath). The fascination for thermal baths began at the time of Romans who spent many time at *Thermae*, that were a community wellness centre attended by all social classes. So, thermal establishments were very popular, insomuch as the term *SPA* derives from the Latin acronym: *salus*

per aquam (health by water). On the other hand, crenotherapy, which is the oldest therapy for upper airways disorders in medical history, has not a unanimous acknowledgement (2). Thermal waters may be classified on the basis of their chemical-physical characteristics as: sulphurous, salso-bromo-iodic, bicarbonate, and bicarbonate-sulphate. Many clinical and empiric studies provided their efficacy in chronic and relapsing inflammatory disorders of upper airways (3).

Comano Terme is a municipality in the province of Trento (Northern Italy) placed at 400 m/a.s.l. and 46°01'00"N 10°52'00"E; in its territory the Terme di Comano is placed. Comano water is bicarbonate-calcium-magnesium. The thermal water of Comano is recommended since long time for cutaneous disorders (4,5) and upper airways diseases (i.e. allergic and vasomotor rhinitis and chronic and recurrent upper airways inflammatory disorders, such as rhinosinusitis, pharyngitis, laryngitis, in both adults and children). Its mechanisms of action

are: mucosal tissue optimisation, immune response stimulation, pro-inflammatory agents clearance, and increased muco-ciliary cleaning. As the sulphurous and salso-bromo-iodic thermal waters are particularly active, they can induce unpleasant side effects in the patients with hyperergic disorders (6). Comano water is mild, so it may be better tolerated. In this regard, there are four studies that investigated the efficacy and tolerability of Comano thermal water in patients with upper airways disorders. The first study showed that it was effective and safe in 40 patients with sub-acute and/or chronic inflammation of upper airways caused by mucosal hyperreactivity (7). The second study (randomized, placebo-controlled, and double-blinded) conducted on 30 patients suffering from vasomotor rhinitis demonstrated that Comano thermal water significantly affected nasal symptoms, improved nasal blood supply, and strengthened local nasal immune response (8). The third study (randomized, placebo-controlled, double blind) was carried out in 30 patients with chronic pharyngitis and showed that pharyngeal blood flow and pharyngeal secretory IgA significantly increased only in Comano group (9). The last open study was confirmatory and reported significant reduction of mucociliary clearance, increase of blood and air flow as well as of secretory IgA (10).

However, there were only anecdotic data about effectiveness in patients with allergic rhinitis (AR). Therefore, the present preliminary study aimed to evaluate whether Comano thermal water may be able to improve nasal symptoms severity in patients with allergic rhinitis.

Materials and Methods

Globally, 30 consecutive patients were enrolled (mean age 40.9 years; 13 males); the inclusion criteria were: i) age range between 18-65 years, ii) AR diagnosis based upon the concordance between typical history of allergic symptoms and documented sensitization, iii) presence of nasal symptoms (with moderate-severe obstruction and/or rhinorrhoea), iv) written informed consent. Exclusion criteria were: i) chronic illness, ii) immune deficiency, iii) continuous use of medications (e.g. antihistamines, corticosteroids) in past 4 weeks, and iv) concomitant use of immune-stimulants.

Patients were treated by Comano thermal water administered by inhalation. Daily, patients were treated with inhalation of 1 L of solution, supplied by Asema inhaler, for 10 minutes. The subjects had to normally breath; the inhaled drops had an 8-12 micron diameter at 37-38 °C temperature. Interfering drugs were prohibited. The thermal course lasted 15 days. Cetirizine syrup (1 drop / 3Kg bw) was permitted as rescue medication along the treatment period.

Nasal symptoms (itching, sneezing, rhinorrhoea, and obstruction) were scored using a four-point scale (0 = no symptom; 1 = mild symptom; 2 = moderate; 3 = severe) assessed by a doctor.

The sum of these symptoms was calculated and expressed as Total Symptom Score (TSS). In addition, a visual analogue scale (VAS) was used for assessing the patient's perception of nasal patency. The VAS is a segment of 10 cm where the patients indicated the actual perception of nasal patency by marking a point. In this study, 0 implied the worst perception (such as complete nasal obstruction), while 10 corresponded to an optimal one (such as nose completely open).

The Patients were visited at baseline (T1), after treatment (T2), and after a 2-week follow-up (T3); all above-mentioned parameters were evaluated during each visit. Symptomatic use of cetirizine was recorded as days. Adverse events were as usually registered.

Statistical analysis was performed by ANOVA Friedman and by post hoc assessment by Wilcoxon test. Data are expressed as median and percentiles (25th and 75th, IQR). A p-value ≤ 0.05 was considered statistically significant. All data were analyzed using the Stata statistical package, Release 13.1 Statistical Software (StataCorp, College Station, TX, USA).

Results

All subjects completed the study, and the treatment was well tolerated without significant adverse event. **Figure 1** reports the findings.

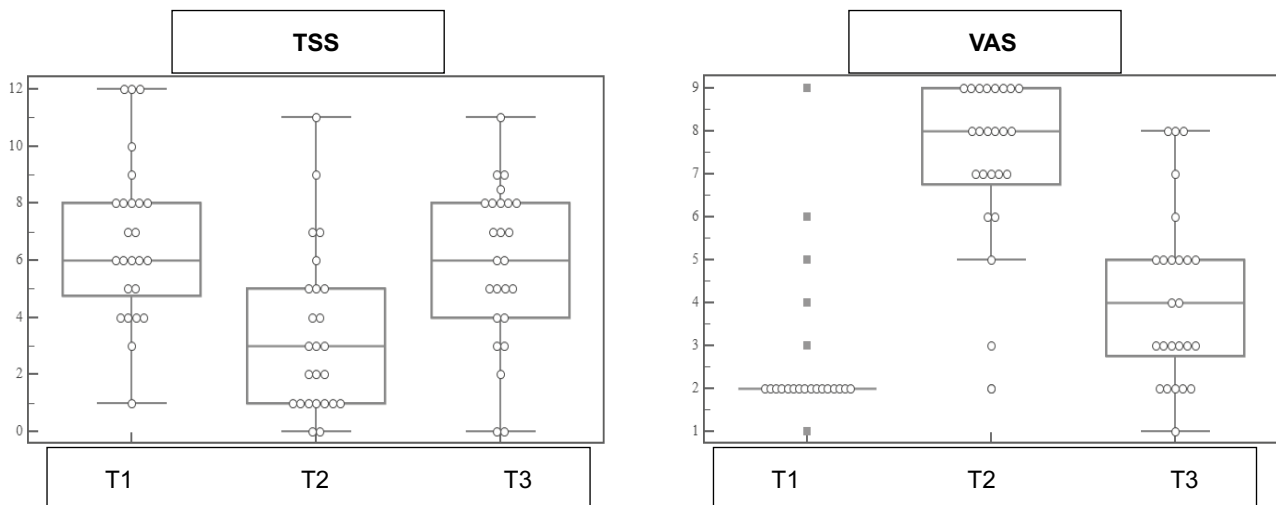
TSS significantly changed during the study ($p < 0.001$): the basal values (M 6, IQR 4.5-8) significantly diminished ($p < 0.0001$) after treatment (M 3, IQR 1-5), but significantly increased ($p < 0.0001$) at follow-up (M 6, IQR 4-8), however a significant difference ($p < 0.04$) remained between T1 and T3. VAS significantly changed during the study ($p < 0.001$): the basal values (M 2, IQR 2-2) significantly increased ($p < 0.0001$) after treatment (M 8, IQR 6.8-9), but significantly decreased ($p < 0.001$) at follow-up (M 4, IQR 2.8-5), however a significant difference ($p = 0.03$) remained between T1 and T3.

The mean number of days with antihistaminic use was 3.5 during the treatment period, and 4.4 during the follow-up.

Discussion

The present study demonstrates that intranasal administration of Comano thermal water was able to significantly reduce nasal symptoms in patients with allergic rhinitis. In addition, this treatment was also able to significantly affect the patient's perception of nasal patency. These findings support the concept that nasal inhalation of Comano thermal water may control allergic symptoms. It is to underline that the current treatment was administered as monotherapy: this aspect reinforces the effectiveness of nasal lavage in AR. The present study is also consistent with previous studies performed using Comano thermal water in patients with upper airways disorders (7-10).

Figure 1 - Left quadrant: Total Symptoms Score (TSS) assessed before (T1) and after treatment (T2) and follow-up (T3). Right quadrant: VAS of nasal patency assessed before (T1) and after treatment (T2) and follow-up (T3).



Comano thermal water has peculiar chemical-physical characteristics that depend on its composition: bicarbonate calcium-magnesium. This thermal water has a mild activity, even though sufficient for adequately treating many upper airways disorders, as evidenced by all these studies, and is well tolerated. So its use is safe and effective. The mechanism of action is based on ion composition and consists of: i) improving local mucosal blood supply, ii) restoring the mucosal integrity, iii) normalizing the epithelial clearance, and iv) stimulating local immune response, including recent evidence on the modulation of expression and secretion of some mediators, such as vascular endothelial growth factor (11), interleukin-6 (12), tumor necrosis factor- α (13). These last mechanisms may be involved in the cascade of events involved in skin regeneration process (14). All these effects may significantly improve clinical symptoms and objective signs. Therefore, Comano crenotherapy could be indicated in the treatment of AR.

The main shortcoming of this study is the lack of a control group. However, it has to be considered that nasal lavage is *per se* able of significantly improve nasal symptoms as clearly evidenced in previous studies. So, this study has been designed including a follow-up period able to evaluate the time without treatment as a control of the active period. Anyway, further controlled studies should be performed to confirm this preliminary experience. In this regard, preliminary studies investigated the microbiota characteristics of Comano water as well as of the skin of patients with cutaneous disorders (15,16). Thus, promising outcomes could derive from this issue.

In conclusion, the present study provided the preliminary evidence that Comano thermal water inhalation as monotherapy

for AR was able of relieving nasal symptoms and patient's perception of nasal patency. Thus, this outcome could suggest that one course of this thermal water could be effective, so reducing the use of pharmacological therapy.

References

1. Passariello A, Di Costanzo M, Terrin G, Iannotti A, Buono P, Balestrieri U, et al. Crenotherapy modulates the expression of proinflammatory cytokines and immunoregulatory peptides in nasal secretions of children with chronic rhinosinusitis. *Am J Rhinol Allergy*. 2012;26:e15-9.
2. Passali D, Bellussi L, Di Benedetto M, Giordano C, Mira E, Paludetti G, et al. Il termalismo e le patologie delle vie aeree superiori. *Acta Otorhinolaryngol Ital*. 2006;26(Suppl 83):5.
3. Keller S, König V, Mösges R. Thermal water applications in the treatment of upper respiratory tract diseases: a systematic review and meta-analysis. *J Allergy*. 2014;2014:943824.
4. Zumiani G, Zanoni M, Agostini G. Valutazione dell'efficacia della fonte termale di Comano vs acqua di acquedotto nella cura della dermatite atopica e delle dermatiti eczematose. *Gior Ital Dermatol Venereol*. 2000;136:34-8.
5. Farina S, Gisondi P, Zanoni M, Pace M, Rizzoli L, Baldo E, Girolomoni G. Balneotherapy for atopic dermatitis in children at Comano spa in Trentino, Italy. *J Dermatol Treat*. 2011;22:366-71.
6. Vidi R. Azione dell'acqua di Comano nel trattamento dei processi infiammatori delle vie aeree superiori. Risultati preliminari. *Riv Orl Aud Fon*. 1987;7:212-5.
7. Mira E, De Bernardi M, Vidi I, Bonfioli F, Zanoni M. Efficacia e tollerabilità dell'acqua di Comano nel trattamento delle infiammazioni delle vie aeree su base allergico-iperergica. *Riv Orl Aud Fon*. 1991;11:78-81.
8. Zanoletti E, De Paoli F, Vidi I, Zanoni M, Giacomini G, Mira E. Effetti del trattamento inalatorio con acqua di Comano nella rinosinopia vasomotoria. *Riv Orl Aud Fon*. 1999;19:49-59.

9. De Paoli F, Zanoletti E, Vidi I, Zanoni M, Giacomini G, Mira E. Effetti del trattamento inalatorio con acqua di Comano nelle faringiti croniche. *Riv Orl Aud Fon.* 1998;18:125-34.
10. Zanoni M, Pagella F, Colombo A, Mira E. Effetti di un ciclo di crenoterapia inalatoria con acqua oligominerale calcico-magnesiaca delle Terme di Comano in pazienti con faringite cronica. *Argomenti Acta Otorhinolaryngol Ital.* 2008;3:67-73.
11. Chiarani A, Dal Pra I, Pacchiana R, Menapace L, Zumiani G, Zanoni M, Armato U. Comano's (Trentino) thermal water interferes with the expression and secretion of vascular endothelial growth factor. A protein isoforms by cultured human psoriatic keratinocytes. A potential mechanism of its anti-psoriatic action. *Int J Mol Med.* 2006;18:17-25.
12. Chiarani A, Dal Pra I, Pacchiana R, Zumiani G, Zanoni M, Armato U. Comano's (Trentino) thermal water interferes with interleukin-6 production and secretion and with cytokeratin-16 expression by cultured human psoriatic keratinocytes: further potential mechanism of its anti-psoriatic action. *Int J Mol Med.* 2006;18:1073-9.
13. Dal Pra I, Chiarani A, Pacchiana R, Zumiani G, Zanoni M, Armato U. Comano's (Trentino) thermal water interferes with tumor necrosis factor-alpha expression and secretion by cultured human psoriatic keratinocytes: yet other mechanisms of its anti-psoriatic action. *Int J Mol Med.* 2007;19:373-9.
14. Faga A, Nicoletti G, Gregotti C, Finotti V, Nitto A, Goglio L. Effects of thermal water on skin regeneration. *Int J Mol Med.* 2012;29:732-40.
15. Nicoletti G, Corbella M, Jaber O, Marone P, Scevola D, Faga A. Non-Pathogenic microflora of a spring water with regenerative properties. *Biomedical Reports.* 2015;7:24.
16. Tett A, Pasolli E, Farina F, Truong DT, Asnicar F, Zolfo M, Jousson O, De Sanctis V, Bertorelli R, Girolomoni G, Cristofolini M, Segata N. Unexplored diversity and strain-level structure of the skin microbiome associated with psoriasis. *Genome Res.* In press 2016.