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The nutraceuticals: a new therapeutic strategy in the management of digestive and respiratory disorders

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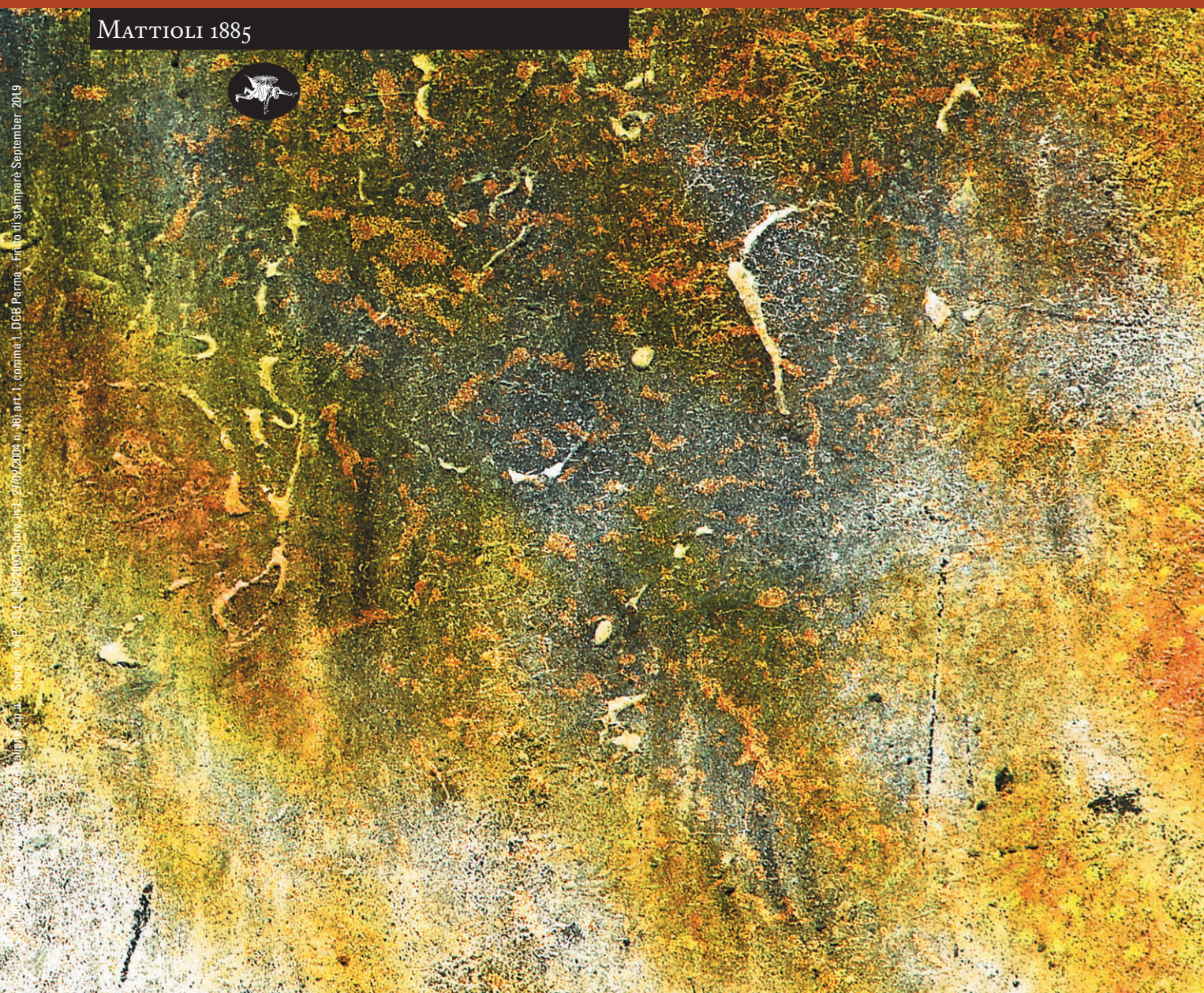

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Index

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Foreword

The nutraceuticals: a new therapeutic strategy in the management of digestive and respiratory disorders

Giorgio Ciprandi[1], Salvo Emanuele Aragona[2], Lorenzo Drago[3], Ignazio La Mantia[4]

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Summary. Nutraceuticals represents an intriguing challenge in clinical practice. They are currently used worldwide in all fields of Medicine. The present Supplement reports two Italian surveys concerning a probiotic mixture employed in patients with chronic intestinal disorders and a Medical Device used in patients with upper respiratory diseases. These surveys were conducted on a group of Italian gastroenterologists and on a group of Italian otolaryngologists respectively. Both surveys demonstrated that these compounds may represent a useful therapeutic option in clinical practice. (www.actabiomedica.it)

Key words: nutraceuticals, probiotics, gastroenterologist, otolaryngologist, survey

The term 'nutraceutical' has been coined by Stephen L. Defelice in 1989 (1). The use of this term, evaluated from frequencies in papers indexed in PubMed, has progressively increased since 2000. However, there is no internationally recognized definition of a nutraceutical, and various confusing and contradictory definitions have appeared. In this regard, the European Nutraceutical Association defines nutraceuticals as "nutritional products which have effects that are relevant to health, which are not synthetic substances or chemical compounds formulated for specific indications, containing nutrients partly in concentrated form" (2). Nutraceuticals are neither nutritious nor pharmaceutical (3). However, nutraceuticals represent an interesting and exciting challenge in clinical practice. Actually, many doctors and patients look at complementary medicine as they scare the pharmacological compounds because of their adverse effects. At present, nutraceuticals are used in every field of Medicine.

On the basis of this background, this Supplement reports two surveys concerning the therapeutic effectiveness and safety of two nutraceuticals, the first tested in patients with chronic intestinal disorders and the second used in patients with upper respiratory diseases), in clinical practice. These surveys have been conducted on a group of Italian gastroenterologists and on a group of Italian otolaryngologists respectively.

The first innovative product is an oral nutraceutical containing a probiotic mixture with *Lactobacillus plantarum* LP01 (1 billion of living cells), *Lactobacillus lactis subspecies cremoris* LLC02 (800 millions of living cells), and *Lactobacillus delbrueckii* LDD01 (200 millions of living cells). The survey about this probiotic mixture included patients with chronic intestinal disorders, patients undergoing bowel preparation, or patients undergoing abdominal surgery.

Probiotics are living microorganisms that confer a health benefit to the host when administered in adequate amounts; when ingested, probiotics produce microbial transformation in the intestinal microbiota and exert several health-promoting properties, including maintenance of the gut barrier function and modulation of the host immune system (4). Moreover, the effects of probiotic mixtures may be complementary (also referred to additive) or synergistic (5). In general, probiotic strains produce growth factors that strengthen

the gut epithelium and antimicrobial-anti-inflammatory mediators (e.g., short chain fatty acids, bacteriocins, hydroperoxides, bile acids, and lactic acids) killing harmful microorganisms (6). As a consequence, their cellular components are released in the gut environment, activating immune responses by modulating the pro-inflammatory cytokines production and immunoglobulin synthesis, besides of improving macrophage and lymphocytes activity (7). In addition, non-immunological benefits associated to probiotics include the digestion and absorption processes, competition with potential pathogens for nutrients and intestinal adhesion sites, pH alterations, agglutination of pathogenic microorganisms, and sequestration of metabolic toxins (8). Animal models and *in vitro* assays describe that probiotics also decrease the apoptosis, increase the mucus synthesis, tissue repair, redistribution and production of tight junctions in gut epithelial cells, thus reducing the intestinal permeability and enhancing the barrier protection and function (9). However. It has to underline that the underlying mechanisms of probiotics are dependent on the specific microbial strain and the effectiveness is also disease-specific. Thus, the probiotic choice should be carefully oriented to a specific strain in a specific disease.

The second product is a Medical Device class II CE formulated as solution for aerosol. This innovative compound contains salso-bromo-iodine thermal water (spring of Medesano, PR, Italy), hyaluronic acid (HA), and grapefruit seed extracts. The salso-bromo-iodine thermal waters are very well known and appreciated for their positive effects in the treatment of upper respiratory tract infections, indeed it has been demonstrated that enhance mucociliary clearance, as well as improve the cough due to post-nasal drip (10). HA is a fundamental component of the connective tissue. HA is able to modulate inflammatory response, cellular proliferation, and remodelling of extracellular matrix (11). Grapefruit seed extract exerts an antimicrobial activity (12). Therefore, the reported survey was conducted on patients suffering from acute, chronic or flare-up upper respiratory tract infections.

This Supplement contains also 3 clinical studies concerning: i) the use of visual analogue scale (VAS) in assessing the perception of antihistamines took by patients with allergic rhinitis, ii) the impact of tobacco smoke in allergic rhinitis, and iii) the relevance of sleep-disordered breathing (SDB) on oral health in children. The first study pertained the use of VAS as a parameter widely measured in the second survey, reinforcing its validity in clinical practice. The second study confirmed the negative impact of tobacco smoke on airways in patients suffering from allergic disorders. The last study demonstrated that SDB significantly affect oral wellbeing in childhood. Notably, as these conditions are chronic and frequently associated with inflammatory/infectious comorbidity, it may be fruitful to combine pharmacological treatments with complementary medicine, including thermal water, hyaluronic acid, and food supplements, such as bromelain and grapefruit seed. Actually, complementary medicine usually is associated with very few side effects and may be consequently assumed safely for long periods.

In conclusions, the current outcomes have a clinical relevance as they were obtained in real-world settings. There are also some implications considering the close link between upper and lower airways, so improvement of upper airways disorders may also ameliorate lower airways comorbidity (13,14). Therefore, nutraceuticals, including probiotics and plant-derived components, may represent a reliable therapeutic option in clinical practice.

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Original article

Abincol® (*Lactobacillus plantarum* LP01, *Lactobacillus lactis subspecies cremoris* LLC02, *Lactobacillus delbrueckii* LDD01), an oral nutraceutical, pragmatic use in patients with chronic intestinal disorders

*Luigi Bonavina[1], Andrea Arini[2], Leonardo Ficano[3], Donato Iannuzziello[4], Luigi Pasquale[5], Salvo Emanuele Aragona[6], Giorgio Ciprandi[7], and Italian Study Group on digestive disorders**

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Summary. Chronic intestinal disorders (CID), including inflammatory bowel disease (IBD), such as ulcerative colitis and Crohn's disease, irritable bowel syndrome (IBS), and diverticular disease (DD), are diseases that relapse episodes. There is evidence that patients with CID have intestinal dysbiosis, so probiotics may counterbalance the impaired microbiota. Therefore, the current survey evaluated the efficacy and safety of Abincol®, an oral nutraceutical containing a probiotic mixture with *Lactobacillus plantarum* LP01 (1 billion of living cells), *Lactobacillus lactis subspecies cremoris* LLC02 (800 millions of living cells), and *Lactobacillus delbrueckii* LDD01 (200 millions of living cells), in 3,460 outpatients (1,660 males and 1,800 females, mean age 55 years) with chronic intestinal disorders. Patients took 1 stick/daily for 8 weeks. Abincol® significantly diminished the presence and the severity of intestinal symptoms and improved stool form. In conclusion, the current survey suggests that Abincol® may be considered an effective and safe therapeutic option in the management of patients with chronic intestinal disorders. (www.actabiomedica.it)

Key words: inflammatory bowel disease, irritable bowel syndrome, diverticular disease, probiotic, survey

Introduction

Chronic intestinal disorders (CID), including inflammatory bowel disease (IBD), such as ulcerative colitis and Crohn's disease, irritable bowel syndrome (IBS), and diverticular disease (DD), are diseases that relapse episodes; CID have still unknown etiology (1). It has been widely accepted that IBD is the conse-

***Italian Study Group of digestive disorders:** Annicchiarico Raffaele, Antongiulio Bucci, Arrigoni Arrigo, Bargiggia Stefano, Beretta Paolo, Berni Canani Marcella, Bertino Antonino, Bova Filippo, Bresci Giampaolo, Buda Carmelo, Camilleri Salvatore, Caronna Stefania, Cavallo Gregorio, Chahin Nabil Jamil, Clara Virgilio, Corrado Selvaggio, Cozzoli Giovanni, Crescenzi Ugo, Dario Raimondo, D'arpa Francesco, Dattola Antonello, Deiana Davide, Dell'Anna Armando, Di Fenza Sergio, Di Lorenzo Fernando, Di Napoli Angelo, D'onofrio Vittorio, Ferrini Giovanni, Ferrulli Domenico, Finizio Roberto, Gaffuri Nicola, Garcea Maria Rita, Genova Salvatore, Giorgio Pietro, Giovannone Maurizio, Giuseppe Giuliana, Guarnieri Giovanni, Gullotta Renzo, Leonardi Giuseppe, Magrì Giovanni, Maisto Tammaro, Mancino Mariagrazia, Manes Gianpiero, Marchi Santino, Marin Renato, Marino Maria, Mazzi Manuele, Menasci Francesca, Morabito Lo Prete Antonio, Murer Francesca, Neri Bortoluzzi Francesco, Pallio Socrate, Palma Antonio, Pardocchi Davide, Pinto Antonio, Pio Palieri Antonio, Pisani Antonio, Privitera Antonello, Pulitanò Raffaela, Pumpo Rossella, Quatraro Francesco, Raguzzi Ivana, Rainisio Cesarina, Razzolini Giulia, Revello Olimpia, Rinaldo Nicita, Rivellini Giuseppe, Sabadini Guidorenato, Salvia Marcello, Sarrantonio Gennaro, Savarino Edoardo, Scarcelli Antonella, Schettino Pietro, Schicchi Angelo, Schiffino Luigi, Sediari Luca, Shaini Endrit, Spada Cristiano, Spinelli Fernando, Tifi Lorenza, Trovato Claudio, Vassallo Roberto, Vinti Maurizio, Zappatore Francesca, Zulli Claudio.

quence of overly activated response of mucosal immune system to the environmental, dietary, or infectious antigens in a genetically susceptible host (2). Studies on the animal models have indicated that aggressive cell-mediated immune reaction caused by commensal enteric bacteria plays a vital role in the development and maintenance of IBD. Evidence from patients also showed innate immune system would be activated and aberrant immune response would be initiated through secreting inflammatory mediators caused by endogenous bacterial flora, which would result in IBD (3).

A chronic, low-grade, subclinical inflammation has been also implicated in the disease process and is thought to perpetuate the symptoms of IBS (4). A recent meta-analysis of 13 studies has reported a high prevalence of IBS symptoms in patients with IBD (up to 40%), even in those with quiescent disease and under remission (5). Thus, an overlap exists between IBS and IBD as both share common pathogenic mechanisms.

Several studies have showed clearly the role of a low-grade inflammation both in the occurrence of symptoms in people having diverticulosis, both in symptom persistence following acute diverticulitis (6).

Therefore, increasing attention has been payed to the potential role of probiotics in the treatment of CID as they could solve inflammation through improving an intestinal microbial balance (7). In particular, there is evidence that patients with CID have intestinal dysbiosis, so probiotics may counterbalance the impaired microbiota (8).

Initially, Mecnikov suggested in 1907 that microbial ingestion improved host health, as the consumption of lactic-acid-producing bacteria (LAB) strains found in yogurt might enhance longevity (9). LAB is a heterogeneous group of microorganisms that are often present in the gut, introduced through the ingestion of fermented foods. Some of these strains have probiotic effects. In particular, strains belonging to *Bifidobacterium*, *Enterococcus*, and *Lactobacillus* are the most widely used probiotic bacteria (10). In current use, the term probiotic refers to living microorganisms that confer a health benefit to the host when administered in adequate amounts; when ingested, probiotics produce microbial transformation in the intestinal microbiota and exert several health-promoting properties, including maintenance of the gut barrier function and modulation of the host immune system (11). Probiotics are therefore commonly used as therapeutic option in the management of CID based on the assumption that dysbiosis is present in CID patients (12-15).

Abincol® is an oral nutraceutical containing a probiotic mixture with *Lactobacillus plantarum* LP01 (1 billion of living cells), *Lactobacillus lactis subspecies cremoris* LLC02 (800 millions of living cells), and *Lactobacillus delbrueckii* LDD01 (200 millions of living cells) and it has been recently placed on the market.

On the basis of this background, an Italian survey explored the pragmatic approach of a group of gastroenterologists in the management of CID in clinical practice. Therefore, the aim of the current survey was to evaluate the efficacy and safety of Abincol® in outpatients with chronic intestinal disorders.

Materials and Methods

The current survey was conducted in 83 Italian Gastroenterology centers, distributed in the whole Italy, so assuring a wide and complete national coverage, during the fall-winter 2018-2019. Gastroenterologists were asked to recruit all consecutive outpatients visited because of chronic inflammatory disorders, including IBD, IBS, and uncomplicated diverticulitis.

Patients were consecutively enrolled during the specialist visit. The inclusion criteria were: to have chronic intestinal symptoms, both genders, and adulthood. Exclusion criteria were to have comorbidities and concomitant medications able to interfere the evaluated outcomes.

All patients signed an informed consent. All the procedures were conducted in a real-world setting.

The treatment course lasted 8 weeks. The oral nutraceutical Abincol® (Aurora Biofarma, Milan, Italy) was taken following the specific indications, such as one stick/daily. Patients were visited at baseline (T0), after 4 weeks (T1), and after 8 weeks (T2).

Clinical examination was performed in all patients at T0, T1, and T2. The following parameters were investigated: abdominal pain, abdominal bloating, flatulence, borborygmi, eructation, malaise, weakness, headache. These symptoms were assessed as present/absent and were scored using a four-point scale

(0=absent, 1=mild, 2=moderate, 3=severe), but for abdominal pain the scale was 5-point (4=very severe).

A physical examination of stool was performed using the Bristol stool form scale (16).

Safety was measured by reporting the occurrence of adverse events.

All clinical data were inserted in an internet-platform that guaranteed the patients' anonymity and the findings' recording accuracy.

The paired T-test was used. Statistical significance was set at $p < 0.05$. Data are expressed as medians and 1th and 3rd quartiles. The analysis was performed using STATA, College Station, Texas, USA.

Results

Globally 3,460 outpatients (1,660 males and 1,800 females, mean age 55 years) were visited and completed the treatment course.

The frequency of symptoms (abdominal pain, abdominal bloating, flatulence, borborygmi, eructation, malaise, weakness, headache) at baseline (T0), and at T1 and T2 is reported in Table 1 and 2. In particular, abdominal pain and abdominal bloating were the most common symptoms at baseline. The frequency of both significantly diminished after the treatment course.

Consistently, the severity of the most relevant symptoms did significantly diminish after the treatment (Figure 1). In particular, abdominal pain and bloating significantly diminished at T1 and T2 ($p<0.001$ respectively for both symptoms).

In addition, stool form significantly improved as a normal form (type 3 and 4) was detectable in 29.1% at baseline, in 47.8% at T1, and in 49.5% at T2 ($p<0.001$ as linear trend).

The treatment was well tolerated by all patients and no clinically relevant adverse event was reported.

Table 1. Frequency of patients for each symptom at baseline (T0). M=males; F=females, Mean age in years

N= 3,460				
	n	%	M/F	Mean age
Abdominal pain	3084	89.2%	1468/1616	55
Abdominal bloating	2808	81.2%	1318/1490	55
Flatulence	2639	76.3%	1249/1390	55
Borborygmi	2265	65.5%	1029/1236	55
Eructation	1945	56.2%	925/1020	55
Malaise	1312	37.9%	601/711	56
Weakness	877	25.4%	407/470	56
Headache	371	10.7%	168/203	56

Table 2. Comparison of proportion of patients with symptoms at baseline (T0), and at T1 and T2

Symptoms	T0	T1				T2			
	n	n	%	Diff %	p	n	%	Diff %	p
Abdominal pain	3084	1748	56.7%	-43.3%	<0.001	961	31.2%	-68.8%	<0.001
Abdominal bloating	2808	1568	55.8%	-44.2%	<0.001	897	31.9%	-68.1%	<0.001
Flatulence	2639	1351	51.2%	-48.8%	<0.001	745	28.2%	-71.8%	<0.001
Borborygmi	2265	1089	48.1%	-51.9%	<0.001	539	23.8%	-76.2%	<0.001
Eructation	1945	868	44.6%	-55.4%	<0.001	488	25.1%	-74.9%	<0.001
Malaise	1312	410	31.2%	-68.8%	<0.001	111	8.5%	-91.5%	<0.001
Weakness	877	228	26.0%	-74.0%	<0.001	66	7.5%	-92.5%	<0.001
Headache	371	84	22.6%	-77.4%	<0.001	45	12.1%	-87.9%	<0.001

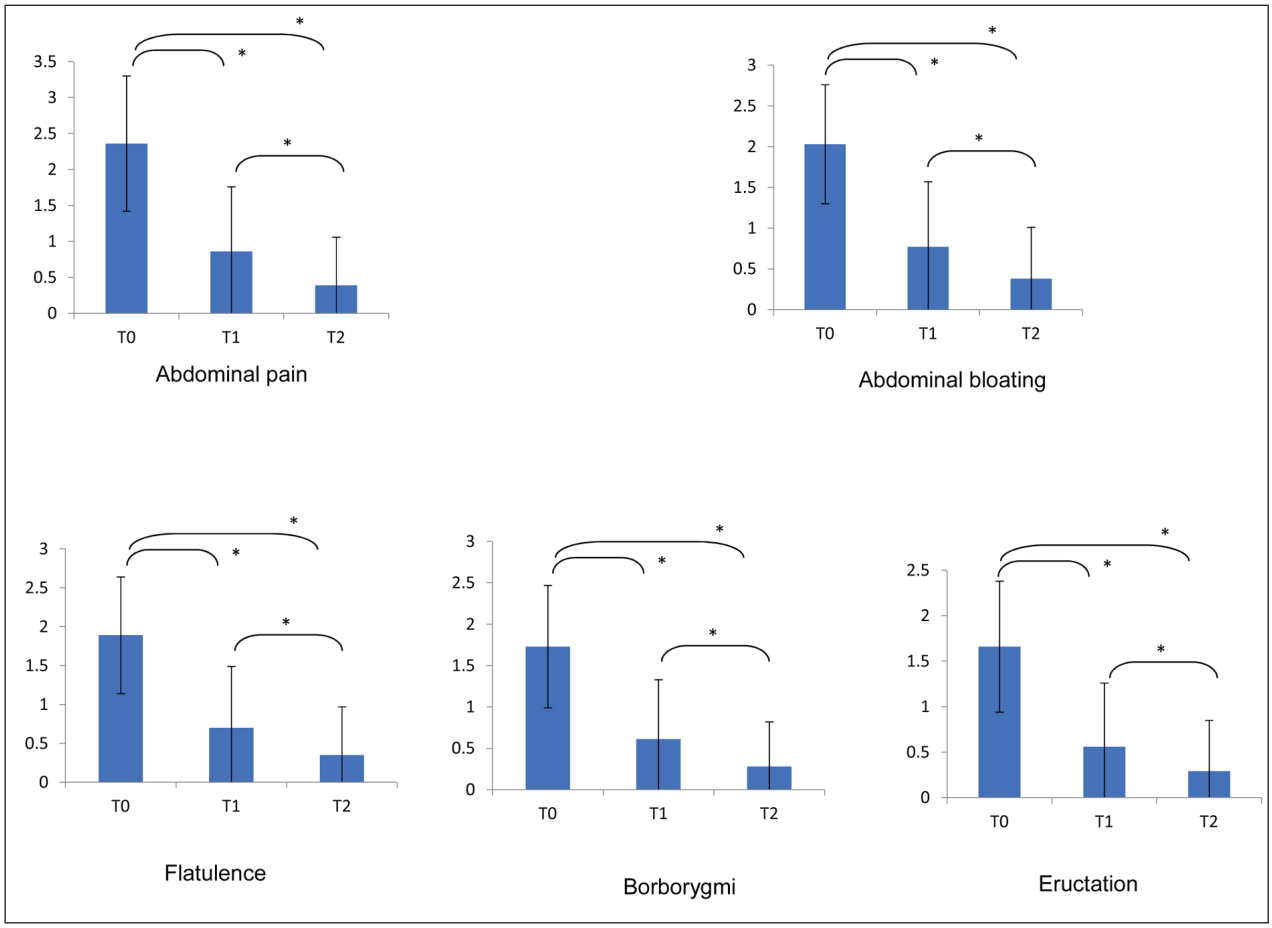

Figure 1. Symptoms severity at baseline (T0), at T1 and T2. Symptoms' score scale was 0-3 for all symptoms but abdominal pain (0-4). Comparisons were made by paired Wilcoxon test. *= p<0.001

Discussion

There is no standard therapy for IBD and the most common treatment option is to establish systemic or topical immunoregulation with different medications, including mesalazine, sulfasalazine, anti-TNFα agents, and thiopurines which could also reduce the associated risk of cancer in bowel (2). Unfortunately, serious adverse effects may occur after long time treatment; thus, an alternative therapy may be required in many patients. It has been reported that almost 40% of adults and children who suffered with IBD have been treated with alternative therapies, including probiotics (17). A recent meta-analysis concluded that, according to its pathogenesis, the use of some types of probiotics could prevent the induction of inflammatory reactions in patients with IBD (1).

Current evidence from systematic reviews and meta-analyses supports the use of probiotics also for symptomatic relief of IBS, however, no recommendation on the specific species/strains or combinations has been defined at present (14).

The goals of treatment in diverticular disease are symptom relief, inflammation control, and prevention of disease progression or recurrence (18). The basis for preventing disease progression remains a high-fiber diet and physical exercise, although the evidence level is poor. Other current strategies include modulation of gut microbiota dysbiosis with rifaximin or probiotics, or using mesalazine for low-grade inflammation in uncomplicated symptomatic diverticulosis. (18).

Therefore, probiotics could be considered a fruitful therapeutic option in the management of CID.

The current survey demonstrated that Abincol®

was able to significantly and progressively reduce the most common digestive complaints occurring in patients suffering from chronic intestinal disorders. In particular, Abincol® did diminish impressively abdominal pain and bloating that are bothersome symptoms and significantly affect the quality of life. The improvement of stool form in many patients could be considered the indirect proof of the mechanism of action of Abincol® as it modified the intestinal microbiota inducing a physiological digestive function.

In addition, Abincol® was safe and well tolerated.

All these issues suggest that this probiotic mixture may be a useful option in the management of patients with chronic intestinal disorders, including IBD, IBS and DD.

Of course, the present survey cannot be considered a formal investigative study. Consequently, further studies should be conducted by a rigorous methodology, such as designed according to randomized-controlled criteria.

On the other hand, the strength of this survey is the huge number of enrolled patients and the real-world setting. The reported outcomes could therefore mirror the facts observable in clinical practice.

In conclusion, the current survey suggests that Abincol® may be considered an effective and safe therapeutic option in the management of patients with chronic intestinal disorders.

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Original article

Lactobacillus plantarum LP01, *Lactobacillus lactis subspecies cremoris* LLC02, and *Lactobacillus delbrueckii* LDD01 in patients undergoing bowel preparation

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Summary. Bowel preparation (BP) for colonoscopy induces significantly changes in gut microbiota and elicit intestinal symptoms. Impaired microbiota causes an intestinal dysbiosis. Consequently, probiotics may counterbalance the disturbed microbiota after BP. The current survey evaluated the efficacy and safety of Abincol®, an oral nutraceutical containing a probiotic mixture with *Lactobacillus plantarum* LP01 (1 billion of living cells), *Lactobacillus lactis subspecies cremoris* LLC02 (800 millions of living cells), and *Lactobacillus delbrueckii* LDD01 (200 millions of living cells), in 2,979 outpatients (1,579 males and 1,400 females, mean age 56 years) undergoing BP. Patients took 1 stick/daily for 4 weeks after colonoscopy. Abincol® significantly diminished the presence and the severity of intestinal symptoms and improved stool form. In conclusion, the current survey suggests that Abincol® may be considered an effective and safe therapeutic option in the management of patients undergoing BP. (www.actabiomedica.it)

Key words: bowel preparation, gut microbiota, colonoscopy, probiotics, survey

Introduction

The human intestinal tract contains a large number of diverse microbes, some of which are associated with the faeces, while others are associated with the gut mucosa. Most of these microbes are bacteria and constitute a unique and dense ecosystem named microbiota (1). Many studies investigated human gut

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microbiota, including the Human Microbiome Project in the United States, to define its physiological and pathological role (2).

It is well known that antibiotics may significantly affect the intestinal microbiota (3). Bowel preparation (BP) may also modify critically microbiota (4). BP consists of large doses of laxatives to evacuate most if not all of the stool from the colon. Typically, such a preparation is taken by the patient overnight before the procedure, resulting in 10–20 bowel movements, most of which are diarrheal stools. Therefore, BP significantly affect the colonic ecosystem. In particular, polyethylene glycol-type BP causes loss of superficial mucus in 96% of patients: it contributes consequently to profound alteration of microbiota (5). In addition, BP effects vary in health and in disease as it has been reported that BP affects various microbiota-related diversity metrics in inflammatory bowel disease (IBD) and non-IBD samples and the mucosal and luminal compartments, differently (4). Overweight also influences microbiota changes after BP (6).

The relevance of these concepts relies on the huge number of colonoscopies performed worldwide, e.g. just 14 millions/year in the United States (7). In addition, colonoscopy induces also symptoms persistence for some days; symptoms can be also so severe as to cause the loss of working days (8). These symptoms mainly depend on BP-induced microbiota disturbance (9). Notably, microbiota changes may persist until one month after colonoscopy (10, 11). Therefore, there is the need to counterbalance microbiota alteration in a short time. In this regard, probiotics may offer a potential therapeutic option to restore the altered gut microbiota. Two recent studies provided evidence that probiotic may significantly improve both symptoms and gut microbiota after BP (12, 13).

Abincol® is an oral nutraceutical containing a probiotic mixture with *Lactobacillus plantarum* LP01 (1 billion of living cells), *Lactobacillus lactis subspecies cremoris* LLC02 (800 millions of living cells), and *Lactobacillus delbrueckii* LDD01 (200 millions of living cells) and it has been recently placed on the market.

On the basis of this background, an Italian survey explored the pragmatic approach of a group of gastroenterologists in the management of intestinal dysbiosis after BP in clinical practice. Therefore, the aim of the current survey was to evaluate the efficacy and safety of Abincol® in outpatients after colonoscopy.

Materials and Methods

The current survey was conducted in 83 Italian Gastroenterology centers, distributed in the whole Italy, so assuring a wide and complete national coverage, during the fall-winter 2018-2019. Gastroenterologists were asked to recruit all consecutive outpatients undergoing BP for colonoscopy.

Patients were consecutively recruited during the specialist visit. The inclusion criteria were: to have the indication for colonoscopy, such as presence of intestinal complaints, both genders, and adulthood. Exclusion criteria were to have comorbidities and concomitant medications able to interfere the evaluation of outcomes.

All patients signed an informed consent. All the procedures were conducted in a real-world setting.

The treatment course lasted 4 weeks. The oral nutraceutical Abincol® (Aurora Biofarma, Milan, Italy) was taken following the specific indications, such as one stick/daily. Patients were visited at baseline (T0), and after 4 weeks (T1).

Clinical examination was performed in all patients at T0, and T1. The following symptoms were investigated: abdominal pain, abdominal bloating, flatulence, and borborygmic. They were evaluated before BP and at T1.

These symptoms were assessed as present/absent and were scored using a four-point scale (0=absent, 1= mild, 2=moderate, 3=severe), but for abdominal pain the scale was 5-point (4=very severe).

A physical examination of stool was performed using the Bristol stool form scale (16).

Safety was measured by reporting the occurrence of adverse events.

All clinical data were inserted in an internet-platform that guaranteed the patients' anonymity and the findings' recording accuracy.

The paired T-test was used. Statistical significance was set at $p < 0.05$. Data are expressed as medians and 1^{th} and 3^{rd} quartiles. The analysis was performed using STATA, College Station, Texas, USA.

Results

Globally, 2,979 outpatients (1,579 males and 1,400 females, mean age 56 years) were visited and completed the treatment course.

The frequency of symptoms (abdominal pain, abdominal bloating, flatulence, and borborygmi) at baseline (T0) and at T1 is reported in Table 1 and 2. In particular, abdominal pain and abdominal bloating were the most common symptoms at baseline. The frequency of both significantly diminished after the treatment course.

Consistently, the severity of the most relevant symptoms did significantly diminish after the treatment (Figure 1). In particular, abdominal pain and bloating significantly diminished at T1 ($p<0.001$ respectively for both symptoms).

Table 1. Frequency of patients for each symptom at baseline (T0). M=males; F=females, Mean age in years

N=2,979	T0			
	n	%	M/F	Mean age
Abdominal pain	2387	80.1%	1256/1131	55
Abdominal bloating	2102	70.6%	1090/1012	56
Flatulence	1936	65.0%	1037/899	56
Borborygmi	1690	56.7%	872/818	56

Table 2. Comparison of proportion of patients with symptoms at baseline (T0) and at T1

	T0	T1			
	n	n	%	Diff %	p
Abdominal pain	2387	1124	47.1%	-52.9%	<0.001
Abdominal bloating	2102	1039	49.4%	-50.6%	<0.001
Flatulence	1936	948	49.0%	-51.0%	<0.001
Borborygmi	1690	677	40.1%	-59.9%	<0.001

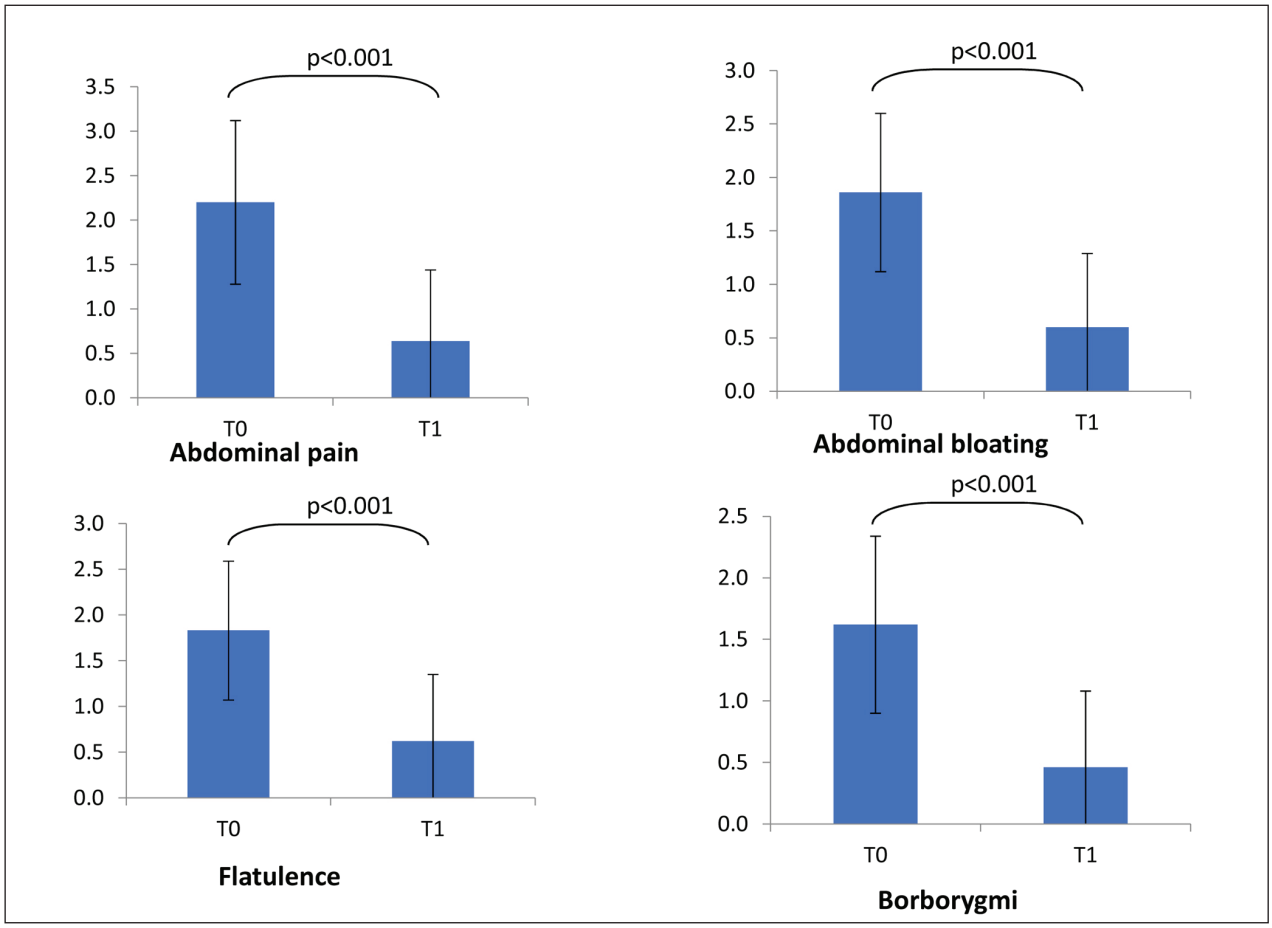

Figure 1. Symptoms severity at baseline (T0) and at T1. Symptoms' score scale was 0-3 for all symptoms but abdominal pain (0-4). Comparisons were made by paired Wilcoxon test. *= p<0.001

In addition, stool form significantly improved as a normal form (type 3 and 4) was detectable in 36.3% at baseline, and in 53.5% at T1 ($p<0.001$ as linear trend).

The treatment was well tolerated by all patients and no clinically relevant adverse event was reported.

Discussion

Drago and colleagues reported relevant and persistent changes in the intestinal bacteria composition after colonic lavage (10). Actually, the relative abundance among the different bacterial phyla had reduced after the BP, in particular, there was a significant increase in *Proteobacteria* abundance and a decrease in *Firmicutes* abundance. This intestinal dysbiosis has been linked to diarrhea, and more interestingly, it has been reported an association between the increase in *Proteobacteria* and the onset of moderate to severe diarrhea in children from low-income countries (14). An increased frequency of *Enterobacteriaceae* has been observed immediately after BP (10). It has to be noted that *Enterobacteriaceae* include a number of nosocomial pathogens with considerable antibiotic resistance, which may proliferate and act as pathogens when not counteracted by the physiological gut microbiota, but also act as a clinically relevant antibiotic-resistance reservoir in the intestinal environment (15). Moreover, *Enterobacteriaceae* were markedly changed even after one month (10). These microbiota changes are associated with BP-dependent clinical feature. Hence, there is the need to improve the impaired gut microbiota after BP: in this regard, probiotics could be an attractive therapeutic strategy.

The current survey demonstrated that a 4-week course of Abincol® was able to significantly improve digestive symptoms and stool form. These outcomes are consistent with a previous randomized and placebo-controlled study showing that a single capsule of a probiotic containing 2.5 x 10^{10} CFUs of *L. acidophilus* NCFM and *B. lactis* Bi-07 taken daily starting on the night after colonoscopy resulted in an earlier resolution of abdominal pain from 2.78 to 1.99 days (12). Nevertheless, a sub-analysis of that study revealed that there was no significant difference between groups in post-procedural discomfort, bloating nor time to return of normal bowel function (13). However, a subgroup analysis of the patients with preexisting symptoms showed a reduction in incidence of bloating with the use of probiotics. This subset of patients is consistent with our population as presented symptoms before BP.

Therefore, the current survey demonstrated that an oral probiotic mixture with *Lactobacillus plantarum* LP01 (1 billion of living cells), *Lactobacillus lactis subspecies cremoris* LLC02 (800 millions of living cells), and *Lactobacillus delbrueckii* LDD01 (200 millions of living cells) administered for 4 weeks after colonoscopy was able to significantly reduce intestinal symptoms. The significantly improvement of stool form in many patients could be considered the indirect proof of the mechanism of action of Abincol® as it modified the intestinal microbiota inducing a physiological digestive function.

In addition, Abincol® was safe and well tolerated.

It is conceivable that the present survey cannot be considered a formal investigative study. Consequently, further studies should be conducted by a rigorous methodology, such as designed according to randomized-controlled criteria.

On the other hand, the strength of this survey is the huge number of enrolled patients and the real-world setting. The outcomes could therefore mirror the facts observable in clinical practice.

In conclusion, the current survey suggests that Abincol® may be considered an effective and safe therapeutic option in the management of patients undergoing BP.

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Original article

Post-surgical intestinal dysbiosis: use of an innovative mixture (*Lactobacillus plantarum* LP01, *Lactobacillus lactis subspecies cremoris* LLC02, *Lactobacillus delbrueckii* LDD01)

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Summary. Abdominal surgery represents a high risk for hospital-acquired infections and complication that may compromise the surgery outcome. Patients with recent abdominal surgery have an intestinal dysbiosis. There is evidence that probiotics may counterbalance the impaired microbiota. Therefore, the current survey evaluated the efficacy and safety of Abincol®, an oral nutraceutical containing a probiotic mixture with *Lactobacillus plantarum* LP01 (1 billion of living cells), *Lactobacillus lactis subspecies cremoris* LLC02 (800 millions of living cells), and *Lactobacillus delbrueckii* LDD01 (200 millions of living cells), in 612 outpatients (344 males and 268 females, mean age 58 years) undergoing digestive surgery. Patients took 1 stick/daily for 8 weeks. Abincol® significantly diminished the presence and the severity of intestinal symptoms and improved stool form. In conclusion, the current survey suggests that Abincol® may be considered an effective and safe therapeutic option in the management of patients undergoing digestivesurgery. (www.actabiomedica.it)

Key words: digestive surgery, dysbiosis, microbiota, probiotic, survey

Introduction

It is well known that complications after abdominal surgery, mainly concerning in cancer patients, are often a result of bacterial infections, leading to a significant increase in morbidity and mortality, as well as the duration of hospitalization and the subsequent economic costs (1). The gut pathophysiology exerts a crucial role in this context. Indeed, impaired gut barrier function may lead to an imbalanced intestinal physi-

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ology. In addition, bacteria and their toxins may enter the blood stream and provoke systemic inflammatory response, which may lead to multiple organ failure or even death. It has been reported that some patients after open-abdomen surgery have experienced translocation of live bacteria to the mesenteric lymph nodes or to the serosa of the bowel wall (2, 3).

In recent years, there has been growing interest in the human gut microbial ecosystem, which ultimately appears to be involved in both disease onset and progression, as well as in the development of complications. The complex gut ecosystem coexists in a fragile balance (symbiosis), that can easily be disturbed (dysbiosis). Actually, dysbiosis has been linked with severe diseases, not only infections, but also autoimmune and autoinflammatory disorders, (4, 5).

In addition, the use of probiotics to prevent and cure the surgery complications has become popular in hospital setting as recently pointed out (6). The rational for probiotics use in abdominal surgery derives from the evidence that probiotics significantly affect gut dysbiosis resulting from both intestinal preparation and abdominal operation. Actually, peri-operatory use of probiotics reduces the mucosal damage consequent to surgery and medications.

Abdominal surgery is also associated with bowel preparation and antibiotic prophylaxis: both have additional detrimental effects on the ecology of commensal bacteria, ranging from self-treated "functional" diarrhoea to life-threatening pseudomembranous colitis (7, 8). Moreover, food restriction, even in the setting of complete intravenous nutrition, leads to a scarcity of macronutrients for the bacteria within the gut, and thus to a relative loss of *Firmicutes* and to an expansion of *Proteobacteria* and *Bacteroidetes*. All these factors contribute to the severity of intestinal dysbiosis associated to abdominal surgery.

Probiotics are live microbial food supplements, such as nutraceuticals, that may beneficially improve the host by acting on the intestinal microbial balance (9).

Probiotics are able to maintain gut barrier function by restoring intestinal permeability and ameliorating the intestinal anti-inflammatory response and the release of cytokines, and can also maintain the homeostasis of the normal gut microbiota. Therefore, probiotics have been extensively studied as an adjuvant perioperative treatment modality to reduce infectious complications in surgical patients (10). There is therefore evidence that modulation of the intestinal microbiota with probiotics seems to be an effective method to reduce infectious complications in surgical patients. In this regard, probiotics may have an additional indication concerning the endurance of surgical anastomosis as they modulate the oxidative metabolism and peptide metabolism (11). Consistently, Van Praagh and colleagues demonstrated an association between *Lachnospiracea* and anastomosis failure (12). In addition, a recent review reported a microbiota change including the increase of pathogens and reduction of protective bacteria after abdominal surgery (13).

Abincol® is an oral nutraceutical containing a probiotic mixture with *Lactobacillus plantarum* LP01 (1 billion of living cells), *Lactobacillus lactis subspecies cremoris* LLC02 (800 millions of living cells), and *Lactobacillus delbrueckii* LDD01 (200 millions of living cells) and it has been recently placed on the market.

On the basis of this background, an Italian survey explored the pragmatic approach of a group of gastroenterologists in the management of patients undergoing abdominal surgery in clinical practice. Therefore, the aim of the current survey was to evaluate the efficacy and safety of Abincol® in outpatients after digestive surgery.

Materials and Methods

The current survey was conducted in 83 Italian Gastroenterology centers, distributed in the whole Italy, so assuring a wide and complete national coverage, during the fall-winter 2018-2019. Gastroenterologists were asked to recruit all consecutive outpatients visited because of recent digestive surgery.

Patients were consecutively recruited during the specialist visit. The inclusion criteria were: to have recent abdominal surgery, both genders, and adulthood. Exclusion criteria were to have comorbidities and concomitant medications able to interfere the evaluation of outcomes.

Digestive surgery included appendicectomy, polypectomy, hemorrhoidectomy, gastrectomy, adherence lysis, ileum resection, sigma resection, hemicolectomy, and rectal resection.

All patients signed an informed consent. All the procedures were conducted in a real-world setting.

The treatment course lasted 8 weeks. The oral nutraceutical Abincol® (Aurora Biofarma, Milan, Italy) was taken following the specific indications, such as one stick/daily. Patients were visited at baseline (T0), after 4 weeks (T1), and after 8 weeks (T2).

Clinical examination was performed in all patients at T0, T1, and T2. The following parameters were investigated: abdominal pain, abdominal bloating, flatulence, borborygmi, eructation, malaise, weakness, headache. These symptoms were assessed as present/absent and were scored using a four-point scale (0=absent, 1=mild, 2=moderate, 3=severe), but for abdominal pain the scale was 5-point (4=very severe). A physical examination of stool was performed using the Bristol stool form scale (16).

Safety was measured by reporting the occurrence of adverse events.

All clinical data were inserted in an internet-platform that guaranteed the patients' anonymity and the findings' recording accuracy.

The paired T-test was used. Statistical significance was set at $p < 0.05$. Data are expressed as medians and 1th and 3rd quartiles. The analysis was performed using STATA, College Station, Texas, USA.

Results

Globally, 612 outpatients (344 males and 268 females, mean age 58 years) were visited and completed the treatment course.

The frequency of symptoms (abdominal pain, abdominal bloating, flatulence, borborygmi, eructation, malaise, weakness, and headache) at baseline (T0), and at T1 and T2 is reported in Table 1 and 2. In particular, abdominal pain and abdominal bloating were the most common symptoms at baseline. The frequency of both significantly diminished after the treatment course.

Consistently, the severity of the most relevant symptoms did significantly diminish after the treatment (Figure 1). In particular, abdominal pain and bloating significantly diminished at T1 and T2 ($p<0.001$ respectively for both symptoms).

In addition, stool form significantly improved as a normal form (type 3 and 4) was detectable in 25.8% at baseline, in 46.4% at T1, and in 47% at T2 ($p<0.001$ as linear trend).

The treatment was well tolerated by all patients and no clinically relevant adverse event was reported.

Table 1. Frequency of patients for each symptom at baseline (T0). M=males; F=females, Mean age in years

N=612	T0			
	n	%	M/F	Mean age
Abdominal pain	503	82.2%	282/221	58
Abdominal bloating	464	75.8%	253/211	58
Flatulence	421	68.8%	241/180	58
Borborygmi	352	57.5%	199/153	57
Eructation	325	53.1%	176/149	57
Malaise	206	33.7%	116/90	60
Weakness	140	22.9%	84/56	61
Headache	43	7.0%	26/17	57

Table 2. Comparison of proportion of patients with symptoms at baseline (T0), and at T1 and T2

Symptoms	T0	T1				T2			
	n	n	%	Diff %	p	n	%	Diff %	p
Abdominal pain	503	319	63.4%	-36.6%	<0.001	191	38.0%	-62.0%	<0.001
Abdominal bloating	464	318	68.5%	-31.5%	<0.001	185	39.9%	-60.1%	<0.001
Flatulence	421	258	61.3%	-38.7%	<0.001	166	39.4%	-60.6%	<0.001
Borborygmi	352	183	52.0%	-48.0%	<0.001	105	29.8%	-70.2%	<0.001
Eructazioni	325	190	58.5%	-41.5%	<0.001	132	40.6%	-59.4%	<0.001
Malaise	206	58	28.2%	-71.8%	<0.001	14	6.8%	-93.2%	<0.001
Weakness	140	39	27.9%	-72.1%	<0.001	10	7.1%	-92.9%	<0.001
Headache	43	7	16.3%	-83.7%	<0.001	2	4.7%	-95.3%	<0.001

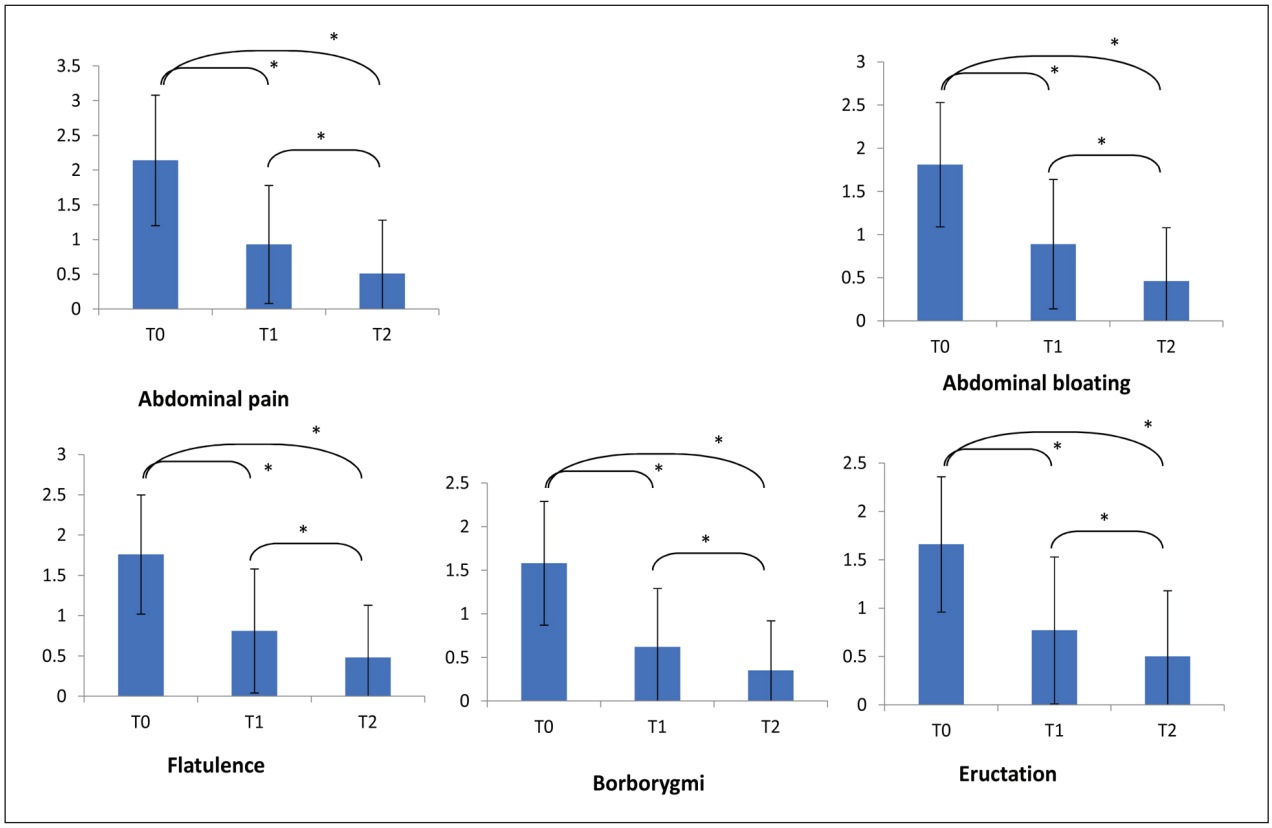

Figure 1. Symptoms severity at baseline (T0), at T1 and T2. Symptoms' score scale was 0-3 for all symptoms but abdominal pain (0-4). Comparisons were made by paired Wilcoxon test. *= p<0.001

Discussion

There is evidence that any surgery represents a high risk for hospital-acquired infections (HAIs): in fact, surgical site infections (SSIs) are the most frequent HAI in the surgical population, in particular, abdominal surgery has the highest ratio (2-20%) as recently reported (14, 15). In this regard, a promising novel infection-prevention strategy may be the administration of probiotics, which are live microbial preparations that may confer a positive benefit to the host when taken in sufficient amounts. A recent systematic review and meta-analysis of RCTs suggests that probiotics/synbiotics in adult patients undergoing elective abdominal surgery reduce the risk of SSIs compared to placebo or standard of care (14). However, the currently available evidence was found to be of low to very low quality, mainly due to risk of bias and imprecision; thus, a large, methodologically sound RCT is needed to corroborate the safety and efficacy of their use in surgical patients.

The rational for probiotic use in preventing infections depends on the characteristics of microbiota (16). However, it has to be underlined that the efficacy of probiotic products is both strain-specific and disease-specific. Important factors involved in choosing the appropriate probiotic include matching the strain(s) with the targeted disease or condition, type of formulation, dose used and the source, including manufacturing quality control and shelf-life (17). Therefore, choosing an appropriate probiotic is multifactored, based on the mode and type of disease indication and the specific efficacy of probiotic strain(s), as well as product quality, formulation, and conservation. For example, it has been very recently demonstrated that two probiotic mixtures obtained by combining

taxonomically similar species produced with different manufacturing methods exert divergent effects in mouse models of colitis (18).

Anyway, we know that gut microbiota is associated with the pathogenesis of many diseases and the emerging new therapeutic targets in gut microbiota represent an intriguing challenge (19, 20).

The current survey demonstrated that Abincol® was able to significantly and progressively reduce the most common digestive complaints occurring in patients after abdominal surgery. In particular, Abincol® did diminish impressively abdominal pain and bloating that are bothersome symptoms and affects the quality of life. The improvement of stool form in many patients could be considered the indirect proof of the mechanism of action of Abincol® as it modified the intestinal microbiota inducing a physiological digestive function.

In addition, Abincol® was safe and well tolerated.

All these issues suggest that this probiotic mixture may be useful in the management of patients undergoing abdominal surgery.

Of course, the present survey cannot be considered a formal investigative study. Consequently, further studies should be conducted by a rigorous methodology, such as designed according to randomized-controlled criteria. Another relevant issue is the need of investigating the microbiota before and after probiotics supplementation.

On the other hand, the strength of this survey is the huge number of enrolled patients and the real-world setting. The outcomes could therefore mirror the facts observable in clinical practice. In particular, the sample consisted of patients undergoing elective surgery.

Finally, it has to be noted that the probiotics effects are strain-dependent and outcomes cannot be generalized for all probiotic species.

In conclusion, the current survey suggests that Abincol® may be considered an effective and safe therapeutic option in the management of patients undergoing digestive surgery.

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Original article

Broncalt®, class II medical device, in patients with acute upper airways disease: a survey in clinical practice

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Summary. Inflammation is a common pathogenic mechanism involved in many otorhinolaryngological (ORL) disorders. Broncalt® is a class II Medical Device containing: thermal water (Medesano, PR, Italy), hyaluronic acid, and grapefruit seed extract. It has been reported that it exerted a safe and effective anti-inflammatory, washing, and antimicrobial activity by virtue of these components. Therefore, the aim of the current survey, conducted in clinical practice of 84 Italian ORL centers, was to evaluate its safety and efficacy in the treatment of patients with acute upper airways disease. The 3,533 (1,797 males, mean age 43.5 years) patients were evaluated at baseline (T0) and after a 2-week treatment (T1) with or without Broncalt®. Signs and symptoms severity were measured by visual analogue scale. Broncalt® significantly and safely diminished the clinical features in all sub-groups ($p<0.001$ for all). Interestingly, Broncalt® significantly induced a faster symptom relief already within 3 days after the start of the treatment. In conclusion, Broncalt® is a class II Medical Device able to exert a safe and effective activity in patients with acute ORL disorders. (www.actabiomedica.it)

Key words: upper airways, acute disease, thermal water, hyaluronic acid, grapefruit seed extract

Introduction

In clinical otorhinolaryngological (ORL) practice, the airways disorders represent the most frequent cause of visit. From a clinical point of view, the respiratory ORL diseases may be subdivided in 3 categories: i) acute illness, including common cold, acute rhinosinusitis, acute rhinopharyngitis, acute pharyngitis, acute otitis, bacterial tonsillitis, acute laryngitis and acute laryngotracheitis; ii) chronic illness, includ-

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ing chronic rhinosinusitis, chronic rhinopharyngitis, chronic pharyngitis, chronic tonsillitis and chronic laryngitis; and iii) acute-chronic illness, i.e. the chronic disease when exacerbates.

Common cold is the most frequent respiratory disease and involves entirely the upper respiratory tract, it is usually self-limiting (1). The best pragmatic approach for rhinosinusitis management has been recently pointed out in clinical practice (2, 3). Alike, pharyngitis, laryngitis, and tracheitis are very common and are usually managed as proposed by *ad hoc* guidelines (4-7).

Acute ORL diseases may be commonly caused by bacterial, viral or fungal aetiology, even though non-infectious acute disease may also exist. However, infectious illness is the most frequent acute ORL disorders, apart allergic and non-allergic rhinitis. The acute infectious diseases share a common pathogenic mechanism: the inflammation. Therefore, the treatment of acute airways diseases is targeted to fight both infection and inflammation, usually using antibiotics and anti-inflammatory medications (8-10). These medications are effective, but antibiotics may be associated with bacterial resistance and anti-inflammatory drugs may induce serious adverse events. Therefore, the option of complementary medicine has having even more interest by doctors and also patients (11).

In this regard, Broncalt® is a new class II medical device containing salso-bromo-iodine thermal water (spring of Medesano, PR, Italy) 8%, hyaluronic acid (HA) 0.1%, and grapefruit seed extract 0.35%.

Salso-bromo-iodine thermal water may exert some relevant therapeutic effects, including enhancing the mucociliary clearance, anti-edema activity, and washing effect (12). HA is a fundamental component of the connective tissue. HA is able to modulate inflammatory response, cellular proliferation, and remodeling of extracellular matrix (13). Grapefruit seed extract exerts an antimicrobial activity (14).

Recently, it has been reported that Broncalt® was effective in the treatment of postnasal drip-related cough in children with upper respiratory tract infections (15).

On the basis of this background, an Italian survey explored the pragmatic approach of a group of otolaryngologists in the management of acute upper-airways disorders in clinical practice. Therefore, the aim of the current survey was to evaluate the efficacy and safety of Broncalt® in outpatients with acute ORL diseases.

Materials and Methods

The current survey was conducted in 84 Italian ORL centers, distributed in the whole Italy, so assuring a wide and complete national coverage. Otolaryngologists were asked to recruit all consecutive patients visited because of acute respiratory ORL disease.

Patients were consecutively recruited during the specialist visit. The inclusion criteria were: to have a diagnosis of acute respiratory ORL disease, both genders, and adulthood. Exclusion criteria were to have comorbidities and concomitant medications able to interfere the evaluation of outcomes.

As this survey was based on a real-world practice, the doctors had the complete liberty of choosing the preferred medications on the basis of the personal best practice. Actually, patients were subdivided in 2 subgroups: i) patients treated with standard therapy plus Broncalt® (active group), and ii) patients treated with standard therapy alone (control group).

Patients were suffering from acute illness, including common cold, acute rhinosinusitis, acute rhinopharyngitis, acute pharyngitis, acute otitis, bacterial tonsillitis, acute laryngitis or acute laryngotracheitis.

All patients signed an informed consent. All the procedures were conducted in a real-world setting.

The treatment course lasted 2 weeks. The medical device Broncalt® (Aurora Biofarma, Milan, Italy) was taken following the specific indications, such as two tablets/daily. Patients were visited at baseline (T0), after 1-week treatment (T1), and after 2-week treatment (T2).

Clinical examination and fiber-endoscopy were evaluated in all patients at all visits.

All clinical data were inserted in an internet-platform that guaranteed the patients' anonymity and the findings' recording accuracy.

The following clinical parameters were evaluated: nasal obstruction, mucosal edema, hyperemia, earache, nose swelling, sore throat, dysphonia, and cough. These issues were considered both as the quote of patients having them and their perceived severity. Symptom

severity was assessed by a visual analogue scale (VAS). VAS is a psychometric test widely used to measure the patient's perception of symptom severity, emotions, pain, etc. Currently, VAS is a reliable and valid tool to assess the perception of symptoms and signs (16). The VAS consisted of one ruler asking for signs and symptoms severity perception. In this study, the VAS was a 10-cm horizontal line on which 0 implied the absence of sing or symptom, while 10 corresponded to maximal severity. VAS is considered a routine and validated parameter to assess disease severity in clinical practice and inflammatory markers are closely related with nasal obstruction perception (17).

In addition, the symptom disappearance duration was also considered, such as 3 period were established for symptom receding: by 3 days, between 4-7 days, and beyond 7 days.

Doctors also evaluated: the effectiveness (scored as very effective, effective, scarcely effective, and ineffective), the tolerability (scored as very good, quite good, poorly good, no good), and the compliance (very good, good, scarcely good, and no good).

Safety was measured by reporting the occurrence of adverse events.

The paired T-test was used. Statistical significance was set at $p < 0.05$. Data are expressed as medians and 1th and 3rd quartiles. The analysis was performed using STATA, College Station, Texas, USA.

Results

Globally, 3,533 (1,797 males, mean age 43.5 years) patients were visited and completed the treatment course. The demographic characteristics and type of acute respiratory disease are reported in Table 1.

In particular, the two subgroups were similar concerning the age and the gender. The distribution

Table 1. Clinical characteristics in patients with acute respiratory disease and treated with or without Broncalt

	Broncalt N=2784		No Broncalt N=749		p-value
Demografic characteristics					
Males, n(%)	1406	50.5%	391	52.2%	0.409
Mean age, years, (SD)	43.6	20.9	43.4	18.4	0.432
Disease					
Otitis, n(%)	**408**	**14.7%**	**137**	**18.3%**	**0.014**
Tubaritis, n(%)	359	12.9%	79	10.6%	0.084
Rinosinusitis, n(%)	**604**	**21.7%**	**129**	**17.2%**	**0.007**
Rinopharyngitis, n(%)	**652**	**23.4%**	**107**	**14.3%**	**<0.001**
Bacterial Tonsillitis, n(%)	**165**	**5.9%**	**108**	**14.4%**	**<0.001**
Pharingytis, n(%)	**365**	**13.1%**	**144**	**19.2%**	**<0.001**
Laryngitis, n(%)	338	12.1%	102	13.6%	0.277
Laryngotracheitis, n(%)	196	7.0%	49	6.5%	0.634
Concomitant Tretaments					
Antibiotics	**280**	**10.0%**	**199**	**26.6%**	
Cefalosporins	197	7.1%	119	15.9%	
Chinolones	26	0.9%	31	4.1%	
Macrolides	26	0.9%	30	4.0%	
Other	31	1.1%	19	2.5%	
Anti-inflammatory drugs	**484**	**17.4%**	**221**	**29.5%**	
Antipyretics	11	0.4%	10	1.3%	
Corticosteroids	368	13.2%	101	13.5%	
FANS	44	1.6%	76	10.1%	
Other	61	2.2%	34	4.5%	
Anti-inflammatory+antibiotic	**212**	**7.6%**	**312**	**43.3%**	
No drug	**1808**	**64.9%**	**17**	**2.2%**	

Table 2. Proportion of patients without symptoms and signs after treatment in the two subgroups: treated with or without Broncalt

Symptom	Broncalt	No Broncalt	P
Nasal Obstruction	**48.4%**	**28.8%**	**<0.001**
Rhinorrea	**44.3%**	**28.3%**	**<0.001**
Post nasal drip	**32.7%**	**19.4%**	**<0.001**
Earache	26.2%	24.6%	0.369
Nose swelling	**33.3%**	**23.1%**	**<0.001**
Sore throat	27.1%	33.1%	0.001
Dysphonia	22.5%	21.8%	0.688
Cough	**39.9%**	**34.5%**	**0.006**
Hyperaemia	**55.2%**	**50.3%**	**0.017**
Edema	25.3%	32.7%	<0.001

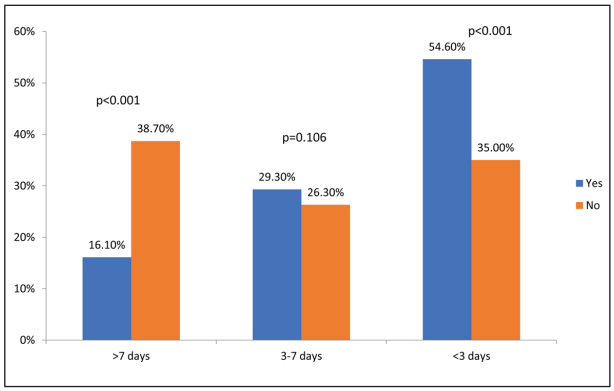

Figure 2. Percentages of patients treated with or without Broncalt with symptom disappearance within 3 days, between 3 and 7 days, and over 7 days

of acute respiratory diseases was different about some types. Subgroup treated with Broncalt took less antibiotics and anti-inflammatory drugs than the other subgroup; interestingly Broncalt-treated subgroups did not take any medication more frequently.

Considering the frequency of patients without symptoms or signs after the treatment, Broncalt treatment induced higher percentages of symptomless patients for nasal obstruction, rhinorrhea, post nasal drip, nose swelling, cough, and hyperemia (Table 2). On the contrary, a larger percentage of patients not treated with Broncalt had no more sore throat and edema.

Considering the severity of symptoms, patients treated with Broncalt showed less severe earache and sore throat than not treated patients (Figure 1).

The percentages of patients treated with or without Broncalt with global symptom disappearance within 3 days, and over 7 days were significantly different between groups (Figure 2). In particular, 54.6% of Broncalt-treated patients and 35% of patients without Broncalt treatment had no more symptoms within 3 days (p<0.001). On the contrary, 38.7% of patients without Broncalt treatment and 16.1% of Broncalt-treated patients still present symptoms over one week (p<0.001).

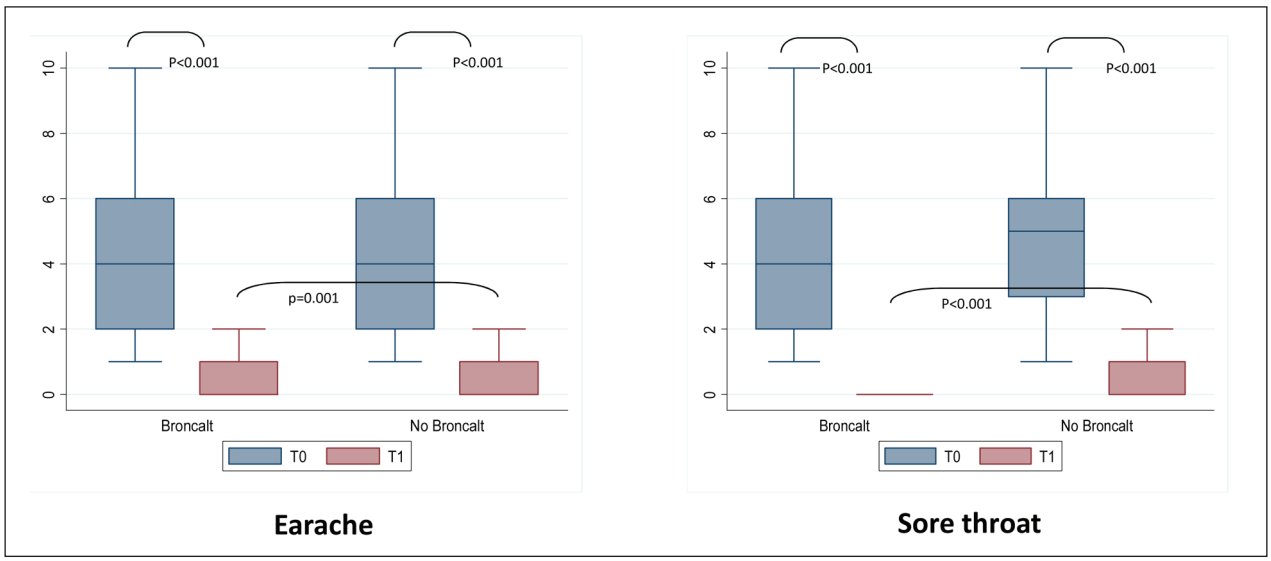

Figure 1. Visual Analogue Scale scores at T0 and T1 in patients treated with or without Broncalt for Earache and Sore throat

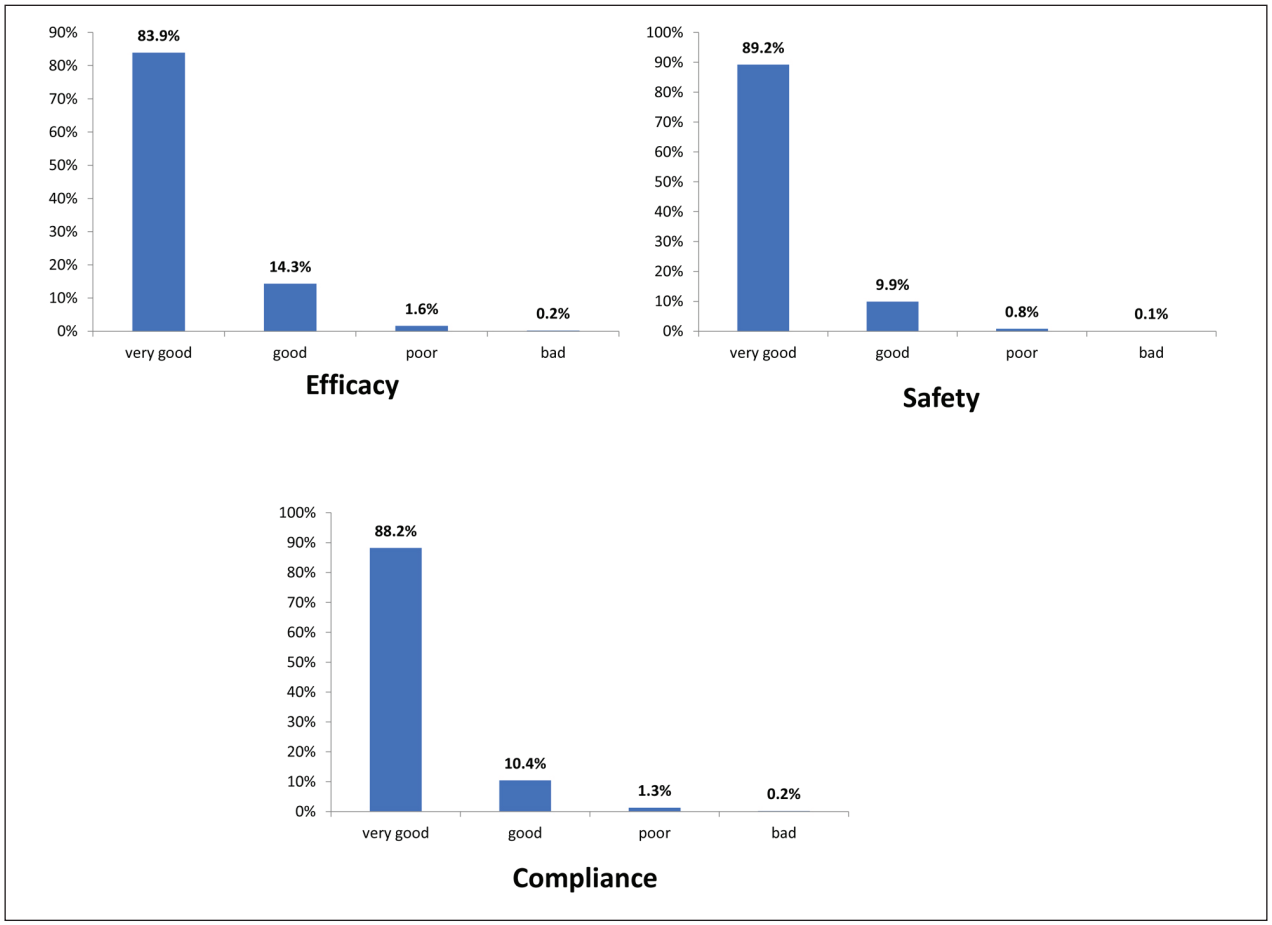

Figure 3. A= Patients' perception of Broncalt efficacy; B= Patients' perception of Broncalt tolerability; C= Patients' perception of Broncalt Compliance.

In patients treated with Broncalt, the perception of efficacy was very good in 88.2% and good in 10.4% (Figure 3A); the tolerability was very good in 89.2% and good in 9.9% (Figure 3B); the compliance was very good in 88.2% and good in 10.4% (Figure 3C).

No clinically relevant adverse event was reported.

Discussion

The role of natural non-pharmacological products as remedies has been respected since ancient times. At present, there is popular and scientific interest in the use of medical device to improve human diseases, so sparing the use of conventional medications. In spite of major scientific and technological progress in combinatorial chemistry, products derived from natural products, including thermal water, still make an enormous contribution to medication discovery today.

Inflammatory reaction is a common pathway in acute infectious ORL disorders. In this regard, the medical device Broncalt® contains 3 main components: salso-bromo-iodine thermal water, HA, and grapefruit seed extract. All of them provide anti-inflammatory, antimicrobial, and washing properties. Consequently, this medical device seems to be indicated in the acute ORL respiratory disorders as recently reported (15).

The current survey demonstrated that Broncalt® treatment significantly improved the clinical feature. In particular, Broncalt significantly reduced the percentage of patients still reporting symptom occurrence after the treatment and the symptom severity. Interest-

ingly, the Broncalt treatment induced a faster disappearance of symptoms as more than 50% of patients had no more symptoms already within 3 days after the start of the treatment.

The present findings are consistent with previous studies that explored the therapeutic effects of similar multi-component nutraceuticals in the treatment of ORL diseases (12-15).

In addition, it has to be mentioned that upper airways are closely linked with lower ones, so, these outcomes could have a clinical relevance if there is a lower respiratory co-morbidity (18, 19).

Therefore, the present survey confirms that Broncalt® may significantly reduce clinical features in acute ORL diseases characterized by an infectious/inflammatory reaction. However, the current experience has some limitations, mainly concerning the open design and the lack of objective functional data. On the other hand, the strength of this survey is the high number of enrolled patients and the real-world setting, so the findings may mirror what occurs in the daily practice.

In conclusion, the present survey evidenced that Broncalt® may induce a safe control of respiratory complaints in acute ORL disorders.

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Original article

Broncalt®, class II medical device, in patients with chronic upper airways disease: a survey in clinical practice

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Summary. Inflammation and infection are common pathogenic mechanisms involved in many otorhinolaryngological (ORL) chronic diseases. Broncalt® is a class II Medical Device containing: thermal water (Medesano, PR, Italy), hyaluronic acid, and grapefruit seed extract. It could exert a safe and effective anti-inflammatory, washing, and antimicrobial activity by virtue of these components. Therefore, the aim of the current survey, conducted in clinical practice of 84 Italian ORL centers, was to evaluate its safety and efficacy in the treatment of patients with chronic upper airways disease. The 1,817 (958 males, mean age 49 years) patients were evaluated at baseline (T0) and after one (T1) and two (T2) weeks of treatment, they were treated or not treated with Broncalt®. Signs and symptoms severity were measured by visual analogue scale. Broncalt® significantly, quickly, and safely diminished the clinical features in all sub-groups ($p<0.001$ for all). In conclusion, Broncalt® is a class II Medical Device able to exert a safe, quick, and effective activity in patients with chronic ORL disorders. (www.actabiomedica.it)

Key words: upper airways, chronic disease, thermal water, hyaluronic acid, grapefruit seed extract

Introduction

Chronic otorhinolaryngological (ORL) airways disorders are frequent in clinical practice. Chronic respiratory ORL illness include chronic rhinosinusitis, chronic rhinopharyngitis, chronic pharyngitis, chronic tonsillitis, and chronic laryngitis.

Chronic progression of an upper acute airways disease usually depends on worsening pathogenic factors, including host immune defect, virulence of

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pathogens, autoinflammatory/autoimmune disorders, climate and environmental effects, concomitant pharmacological treatment, metabolic disease, etc (1-3). Therefore, the management of chronic upper airways disease is more complex than in acute ones and requires a careful work-up.

The treatment of chronic airways diseases is targeted to fight both infection and inflammation usually using antibiotics and anti-inflammatory medications. However, pharmacological medications may have contraindications and may implicate adverse events. Therefore, the option of complementary medicine is up-to-date in clinical practice.

Broncalt® is a new class II medical device containing salso-bromo-iodine thermal water (spring of Medesano, PR, Italy) 8%, hyaluronic acid (HA) 0.1%, and grapefruit seed extract 0.35%.

Recently, it has been reported that Broncalt® was effective in the treatment of postnasal drip-related cough in children with upper respiratory tract infections (4).

On the basis of this background, an Italian survey explored the pragmatic approach of a group of otolaryngologists in the management of chronic upper-airways disorders in clinical practice. Therefore, the aim of the current survey was to evaluate the efficacy and safety of Broncalt® in outpatients with chronic ORL diseases.

Materials and Methods

The current survey was conducted in 84 Italian ORL centers, distributed in the whole Italy, so assuring a wide and complete national coverage. Otolaryngologists were asked to recruit all consecutive patients visited because of chronic ORL disease.

Patients were consecutively recruited during the specialist visit. The inclusion criteria were: to have a diagnosis of chronic respiratory ORL disease, both genders, and adulthood. Exclusion criteria were to have comorbidities and concomitant medications able to interfere the evaluation of outcomes. As this survey was based on a real-world practice, the doctors had the complete liberty of choosing the preferred medications on the basis of the best practice. Actually, patients were subdivided in 2 sub-groups: i) patients treated with standard therapy plus Broncalt® (active group), and ii) patients treated with standard therapy alone (control group).

Patients were suffering from acute illness, including chronic rhinosinusitis, chronic rhinopharyngitis, chronic pharyngitis, chronic tonsillitis and chronic laryngitis.

All patients signed an informed consent. All the procedures were conducted in a real-world setting.

The treatment course lasted 2 weeks. The medical device Broncalt® (Aurora Biofarma, Milan, Italy) was taken following the specific indications, such as two tablets/daily. Patients were visited at baseline (T0), after 1-week treatment (T1), and after 2-week treatment (T2).

Clinical examination and fiber-endoscopy were evaluated in all patients at all visits.

All clinical data were inserted in an internet-platform that guaranteed the patients' anonymity and the findings' recording accuracy.

The following clinical parameters were evaluatated: nasal obstruction, mucosal edema, hyperemia, earache, swelling, sore throat, dysphagia, dysphonia, and cough. These issues were considered both as the quote of patients having them and their perceived severity. Symptom severity was assessed by a visual analogue scale (VAS). VAS is a psychometric test widely used to measure the patient's perception of symptom severity, emotions, pain, etc. Currently, VAS is a reliable and valid tool to assess the perception of symptoms and signs (14). The VAS consisted of one ruler asking for signs and symptoms severity perception. In this study, the VAS was a 10-cm horizontal line on which 0 implied the absence of sing or symptom, while 10 corresponded to maximal severity. VAS is considered a routine and validated parameter to assess disease severity in clinical practice and inflammatory markers are closely related with nasal obstruction perception (5).

In addition, the symptom disappearance duration was also considered, such as 3 period were established for symptom receding: by 3 days, between 4-7 days, and beyond 7 days.

Doctors also evaluated: the effectiveness (scored as very effective, effective, scarcely effective, and ineffective), the tolerability (scored as very good, quite

good, poorly good, no good), and the compliance (very good, good, scarcely good, and no good).

Safety was measured by reporting the occurrence of adverse events.

The paired T-test was used. Statistical significance was set at $p < 0.05$. Data are expressed as medians and 1th and 3rd quartiles. The analysis was performed using STATA, College Station, Texas, USA.

Results

Globally, 1,817 (958 males, mean age 49 years) patients were visited and completed the treatment course.

The demographic characteristics and type of chronic respiratory disease are reported in Table 1.

In particular, the two subgroups were similar concerning the gender, but the age was higher in patients not-treated with Broncalt. The distribution of chronic respiratory diseases was significantly different about some types, i.e. patients not-treated with Broncalt had more frequently recurrent otitis an chronic tonsillitis, whereas Broncalt-treated patients suffered more commonly from chronic pharyngitis. Subgroup treated with Broncalt took significantly less antibiotics and anti-inflammatory drugs than the other subgroup; interestingly Broncalt-treated subgroups did not take any medication more frequently (72.8% versus 3%).

Considering the frequency of patients without symptoms or signs after the treatment, Broncalt treatment induced higher percentages of symptomless patients for nasal obstruction, rhinorrhea, post nasal drip, and hyperemia (Table 2).

Considering the severity of symptoms, patients treated with Broncalt showed less severe facial pain, earache, and sore throat than not treated patients (Figure 1).

The percentages of patients treated with or without Broncalt with global symptom disappearance

Table 1. Demographic and clinical characteristics of patients, treated with or without Borncalt

	Broncalt N=1553		No Broncalt N=264		p-value
Characteristic					
Male gender, n (%)	826	53.2%	132	50.0%	0.338
Mean age, (SD)	**48.2**	**21.5**	**54.1**	**19.8**	**<0.001**
Chronic disease					
Recurrent Otitis, n(%)	**260**	**16.7%**	**64**	**24.2%**	**0.003**
Chronic Tonsillitis, n(%)	**56**	**3.6%**	**25**	**9.5%**	**<0.001**
Chronic Laryngitis, n(%)	244	15.7%	39	14.8%	0.697
Chronic Rhinosinusitis, n(%)	6	0.4%	1	0.4%	0.985
Chronic Rhinopharyngitis, n(%)	**408**	**26.3%**	**32**	**12.1%**	**<0.001**
Chronic Pharyngitis, n(%)	234	15.1%	28	10.6%	0.056
Dysphonia, n(%)	165	10.6%	26	9.9%	0.704
Concomitant treatments					
Antibiotics	**65**	**4.2%**	**44**	**16.7%**	
Cefalosporins	44	2.8%	26	9.8%	
Chinolones	8	0.5%	7	2.7%	
Macrolides	4	0.3%	8	3.0%	
Other	9	0.6%	3	1.1%	
Anti-inflammatory drugs	**308**	**19.8%**	**130**	**49.2%**	
Antipyretics	3	0.2%	3	1.1%	
Corticosteroids	248	16.0%	92	34.8%	
FANS	20	1.3%	20	7.6%	
Other	37	2.4%	19	7.2%	
Anti-inflammatory+antibiotic	**50**	**3.2%**	**82**	**31.1%**	
No drug	**1130**	**72.8%**	**8**	**3.0%**	

Table 2. Proportion of patients without symptoms and signs after treatment in the two subgroups: treated with or without Broncalt, evaluated at T1

Symptom	Broncalt	No Broncalt	P
Facial pain	20.2%	25.4%	0.054
Nasal Obstruction	**39.9%**	**31.4%**	**0.009**
Rhinorrea	**40.9%**	**34.5%**	**0.049**
Post nasal drip	**27.71%**	**18.9%**	**0.003**
Earache	16.6%	18.6%	0.435
Nose swelling	29.6%	26.9%	0.379
Sore throat	21.1%	25.4%	0.121
Dysphonia	24.9%	21.2%	0.202
Cough	33.6%	32.6%	0.741
Hyperaemia	**50.1%**	**40.5%**	**0.004**
Edema	24.3%	23.9%	0.885

within 3 days, and over 7 days were significantly different between groups (Figure 2). In particular, 51.4% of Broncalt-treated patients and 42.4% of patients without Broncalt treatment had no more symptoms within 3 days (p=0.007). On the contrary, 24.5% of patients without Broncalt treatment and 36.4% of Broncalt-treated patients still present symptoms over one week (p<0.001).

In patients treated with Broncalt, the perception of efficacy was very good in 77.8% and good in 19.5% (Figure 3A); the tolerability was very good in 87.8% and good in 11.9% (Figure 3B); the compliance was very good in 85.5% and good in 13% (Figure 3C).

The treatment was well tolerated by all patients and no relevant adverse event was reported.

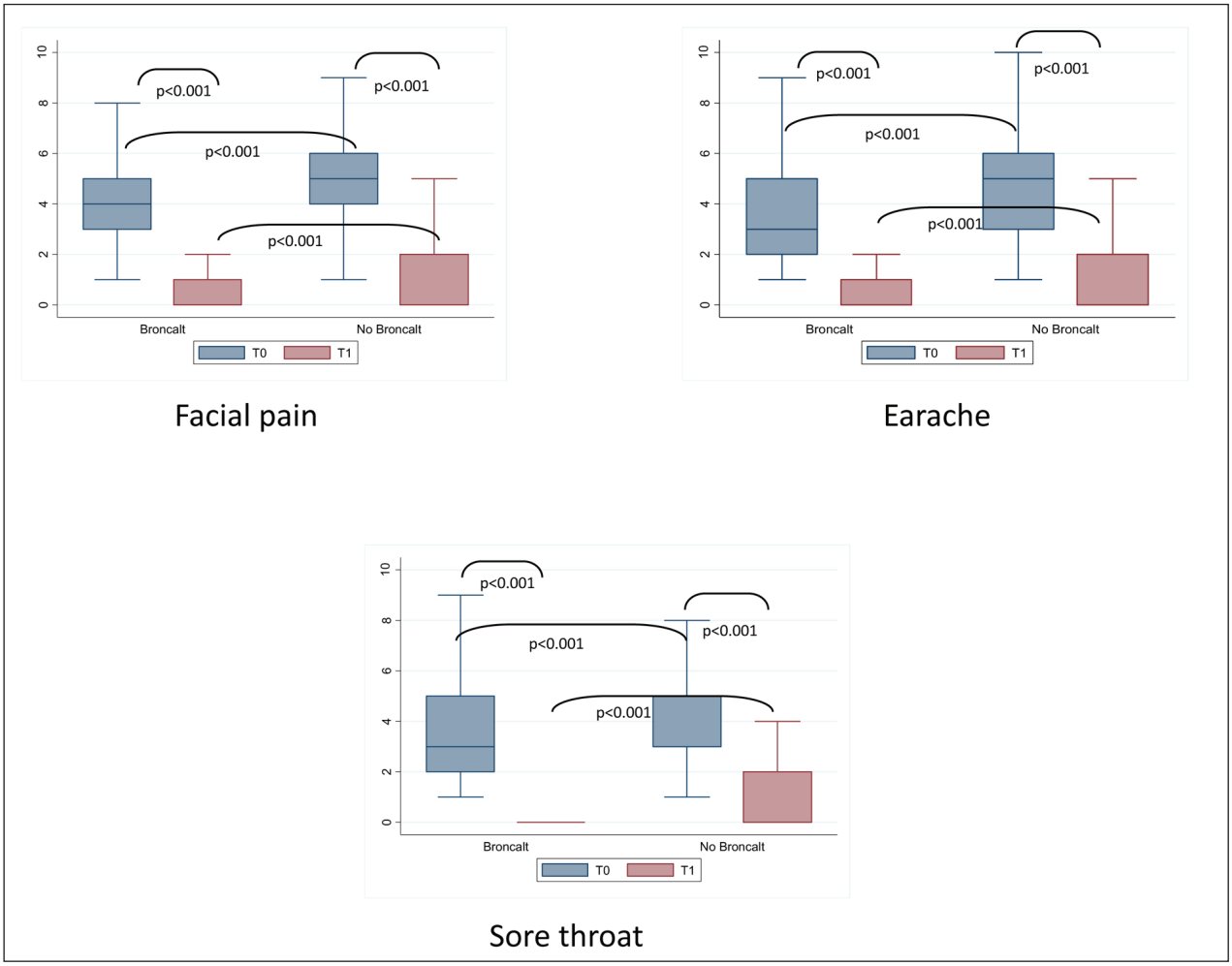

Figure 1. Visual Analogue Scale scores at T0 and T1 in patients treated with or without Broncalt concerning facial pain, earache, and sore throat

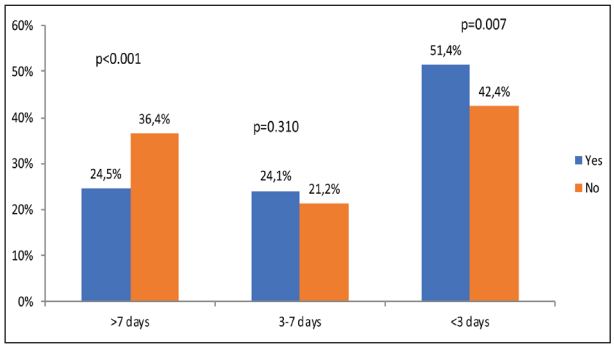

Figure 2. Percentages of patients treated with or without Broncalt with symptom disappearance within 3 days, between 3 and 7 days, and over 7 days

Discussion

At present, there is great interest in the complementary medicine to improve human diseases, including inflammatory/infectious diseases.

Chronic inflammation entails the accumulation of cells and exudates in involved tissues. Inflammation has been studied since thousands of years with the aim of contrasting its effects on the body. In AD 30, Celsius described the 4 classic signs of inflammation (*rubor, calor, dolor,* and *tumor*) and used extracts of willow leaves to relieve them. For many years, salicylate-containing plants were applied therapeutically and lead to the production of a major anti-inflammatory

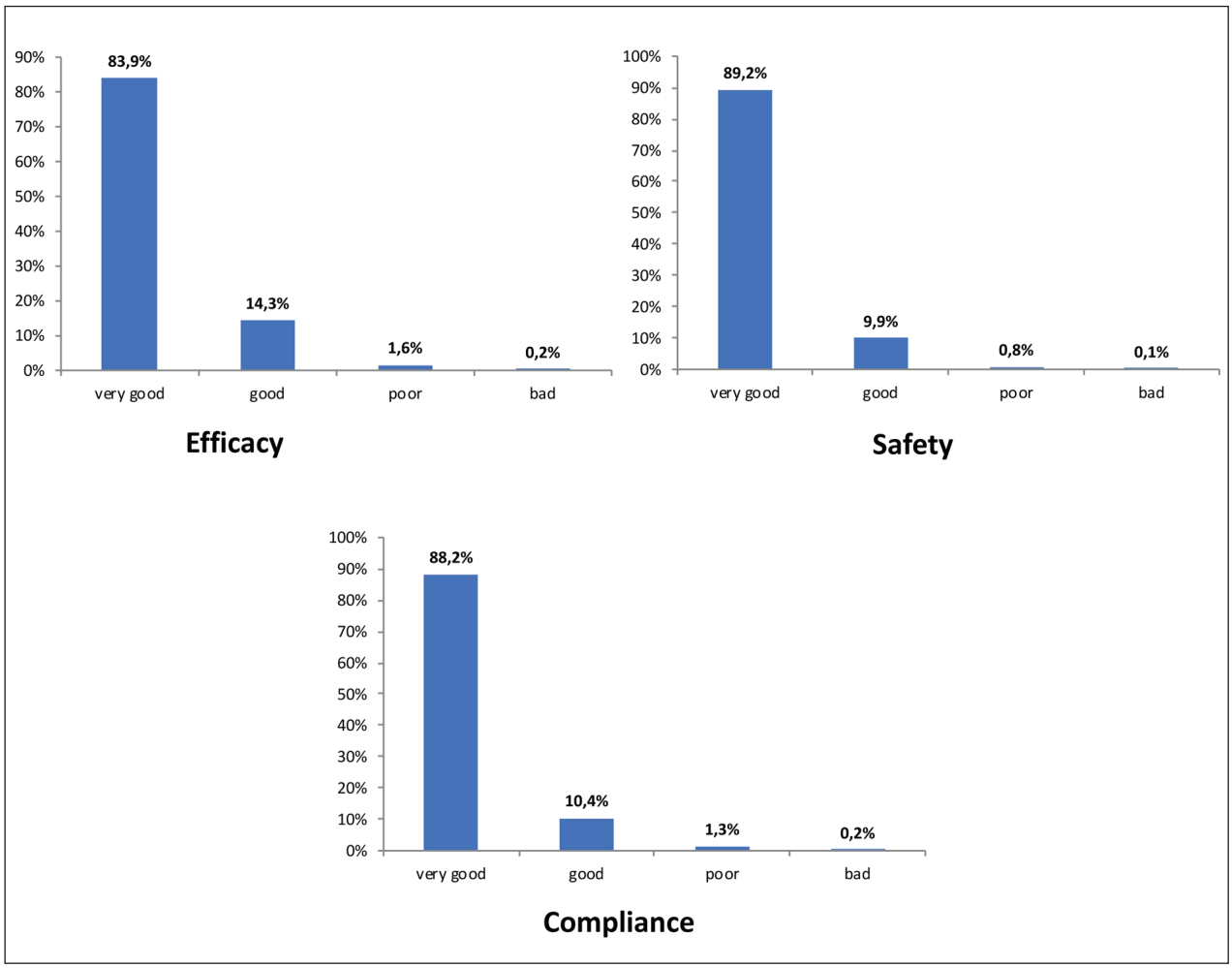

Figure 3. A= Patients' perception of Broncalt efficacy; B= Patients' perception of Broncalt tolerability; C= Patients' perception of Broncalt Compliance

drug (acetylsalicylate). Acetylsalicylate, an agent with anti-inflammatory activity, is derived from natural sources, and is used extensively in current clinical practice. It represents the paradigmatic example of the use of plant-derived compounds in medicine. Many other salicylate-like drugs are now available including the non-steroid anti-inflammatory drugs (NSAIDs). However, a long-lasting use of these compounds may commonly induce adverse events, even severe.

Natural products with anti-inflammatory activity have long been used as a folk remedy for inflammatory conditions such as fevers, pain, migraine and arthritis. As the inflammatory basis of disease becomes clear, anti-inflammatory food products become of greater interest. In this regard, the medical device Broncalt® contains extracts of grapefruit, HA, and thermal water of Medesano.

Currently, the mechanisms of action of these molecules have been identified and examined in depth, thus, their clinical use is no longer empirical but based also on solid scientific grounds. In particular, Broncalt® may exert a relevant anti-inflammatory-antimicrobial activity.

The current survey demonstrated that Broncalt® significantly improved the clinical feature in chronic respiratory ORL disorders in clinical practice. Interestingly, the effectiveness was quick as many symptoms disappeared in Broncalt-treated patients within 3 days. Moreover, it has to be noted that most of Broncalt-treated patients did not take any other medication, and in any case took less antibiotics and anti-inflammatory drugs.

The present findings are consistent with a previous study that explored the therapeutic effects of similar multi-component nutraceuticals in the treatment of chronic ORL diseases (6).

Therefore, the present survey confirms that Broncalt® was able to significantly reduce clinical features in patients with chronic ORL disorders characterized by an inflammatory reaction. However, the current experience has some limitations, mainly concerning the open design and the lack of objective functional data. On the other hand, the strength of this survey is the high number of enrolled patients and the real-world setting, so the findings may mirror what occurs in the daily practice.

In conclusion, the present survey evidenced that Broncalt® may induce a safe and quick control of respiratory complaints in chronic ORL disorders.

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Original article

Broncalt®, class II medical device, in patients with chronic relapsed upper airways disease: a survey in clinical practice

*Gian Franco Cupido[1], Matteo Gelardi[2], Ignazio La Mantia[3], Salvo Emanuele Aragona[4], Claudio Vicini[5], Giorgio Ciprandi[6], and Italian Study Group on inflammatory otorhinolaryngological disorders**

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Summary. Chronic respiratory otorhinolaryngological (ORL) diseases may exacerbate. Broncalt® is a class II Medical Device containing: thermal water (Medesano, PR, Italy), hyaluronic acid, and grapefruit seed extract. It could exert a safe and effective anti-inflammatory, washing, and antimicrobial activity. The current survey, conducted in clinical practice of 84 Italian ORL centers, evaluated its safety and efficacy in the treatment of patients with exacerbated chronic upper airways disease. The 459 (254 males, mean age 44.7 years) patients were evaluated at baseline (T0) and after a 2-week treatment (T1), treated or not-treated with Broncalt®. Signs and symptoms severity were measured by visual analogue scale. Broncalt® significantly, quickly, and safely diminished the clinical features in all sub-groups ($p<0.001$ for all). In conclusion, Broncalt® is a class II Medical Device able to exert a safe, quick, and effective activity in patients with relapsed chronic ORL disorders. (www.actabiomedica.it)

Key words: upper airways, exacerbated chronic disease, thermal water, hyaluronic acid, grapefruit seed extract

Introduction

Airways disorders are very common in clinical otorhinolaryngological (ORL) practice. Chronic upper airways diseases may relapse usually because of infections.

Respiratory exacerbations may be commonly caused by bacterial, viral or fungal aetiology, even though non-infectious cause might also be implied. However, infection is the most frequent reason for exacerbated chronic ORL disease. The treatment of relapsed chronic airways diseases is targeted to fight

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both infection and inflammation using antibiotics and anti-inflammatory drugs. Pharmacological therapy is usually effective, but there is increasing interest to consider complementary medicine as alternative option (1-3).

In this regard, Broncalt® is a new class II medical device containing salso-bromo-iodine thermal water (spring of Medesano, PR, Italy) 8%, hyaluronic acid (HA) 0.1%, and grapefruit seed extract 0.35%.

Recently, it has been reported that Broncalt® was effective in the treatment of postnasal drip-related cough in children with upper respiratory tract infections (4).

On the basis of this background, an Italian survey explored the pragmatic approach of a group of otolaryngologists in the management of relapsed chronic upper-airways disorders in clinical practice. Therefore, the aim of the current survey was to evaluate the efficacy and safety of Broncalt® in outpatients with exacerbated chronic respiratory ORL diseases.

Materials and Methods

The current survey was conducted in 84 Italian ORL centers, distributed in the whole Italy, so assuring a wide and complete national coverage. Otolaryngologists were asked to recruit all consecutive patients visited because of exacerbated chronic ORL disease.

Patients were consecutively recruited during the specialist visit. The inclusion criteria were: to have a diagnosis of relapse of chronic ORL disease, both genders, and adulthood. Exclusion criteria were to have comorbidities and concomitant medications able to interfere the evaluation of outcomes. As this survey was based on a real-world practice, the doctors had the complete liberty of choosing the preferred medications on the basis of the best practice. Actually, patients were subdivided in 2 sub-groups: i) patients treated with standard therapy plus Broncalt® (active group), and ii) patients treated with standard therapy alone (control group).

All patients signed an informed consent. All the procedures were conducted in a real-world setting.

The treatment course lasted 2 weeks. The medical device Broncalt® (Aurora Biofarma, Milan, Italy) was taken following the specific indications, such as two tablets/daily. Patients were visited at baseline (T0), after 1-week treatment (T1), and after 2-week treatment (T2).

Clinical examination and fiber-endoscopy were evaluated in all patients at all visits.

All clinical data were inserted in an internet-platform that guaranteed the patients' anonymity and the findings' recording accuracy.

The following clinical parameters were evaluated: nasal obstruction, mucosal edema, hyperemia, earache, swelling, sore throat, dysphagia, dysphonia, and cough. These issues were considered both as the quote of patients having them and their perceived severity. Symptom severity was assessed by a visual analogue scale (VAS). VAS is a psychometric test widely used to measure the patient's perception of symptom severity, emotions, pain, etc. Currently, VAS is a reliable and valid tool to assess the perception of symptoms and signs (16). The VAS consisted of one ruler asking for signs and symptoms severity perception. In this study, the VAS was a 10-cm horizontal line on which 0 implied the absence of sing or symptom, while 10 corresponded to maximal severity. VAS is considered a routine and validated parameter to assess disease severity in clinical practice and inflammatory markers are closely related with nasal obstruction perception (17).

In addition, the symptom disappearance duration was also considered, such as 3 period were established for symptom receding: by 3 days, between 4-7 days, and beyond 7 days.

Doctors also evaluated: the effectiveness (scored as very effective, effective, scarcely effective, and ineffective), the tolerability (scored as very good, quite good, poorly good, no good), and the compliance (very good, good, scarcely good, and no good).

Safety was measured by reporting the occurrence of adverse events.

The paired T-test was used. Statistical significance was set at $p < 0.05$. Data are expressed as medians and 1th and 3rd quartiles. The analysis was performed using STATA, College Station, Texas, USA.

Results

Globally, 459 (254 males, mean age 44.7 years) patients were visited and completed the treatment course.

The demographic characteristics and type of chronic respiratory disease are reported in Table 1.

In particular, the two subgroups were similar concerning the gender and the age.

The distribution of chronic relapsed respiratory diseases was significantly different about some types, i.e. patients not-treated with Broncalt had more frequently recurrent otitis an chronic tonsillitis, whereas Broncalt-treated patients suffered more commonly from chronic pharyngitis. Subgroup treated with Broncalt took significantly less antibiotics, but more anti-inflammatory drugs than the other subgroup; interestingly Broncalt-treated subgroups did not take any medication more frequently (51% versus 6.3%).

Considering the frequency of patients without symptoms or signs after the treatment, Broncalt treatment induced higher percentages of symptomless patients for nasal obstruction, rhinorrhea, dysphonia, and edema (Table 2).

The percentages of patients treated with or without Broncalt with global symptom disappearance within 3 days, and over 7 days were significantly different between groups (Figure 1). In particular, 44.7% of Broncalt-treated patients and 14.3% of patients without Broncalt treatment had no more symptoms within 3 days (p=0.007). On the contrary, 27% of patients without Broncalt treatment and 66.7% of Broncalt-treated patients still present symptoms over one week (p<0.001).

In patients treated with Broncalt, the perception of efficacy was very good in 74.2% and good in 21.2% (Figure 2A); the tolerability was very good in 83.7% and good in 15.2% (Figure 2B); the compliance was very good in 82.6% and good in 16.3% (Figure 2C).

The treatment was well tolerated by all patients and no relevant adverse event was reported.

Table 1. Demographic and clinical characteristics of patients, treated with or without Borncalt

	Broncalt N=396		No Broncalt N=63		p-value
Characteristic					
Male gender, n(%)	223	56.3%	31	49.2%	0.292
Mean age, (SD)	44.5	22.2	45.5	19.2	0.960
Relapsed disease					
Recurrent Otitis, n(%)	74	18.7%	8	12.7%	0.249
Chronic Tonsillitis, n(%)	**17**	**4.3%**	**9**	**14.3%**	**0.001**
Chronic Laryngitis, n(%)	40	10.1%	5	7.9%	0.592
Chronic Rhinopharyngitis, n(%)	112	28.3%	14	22.2%	0.317
Chronic Pharyngitis, n(%)	74	18.7%	13	20.6%	0.714
Dysphonia, n(%)	51	12.9%	8	12.7%	0.968
Concomitant treatments					
Antibiotics	**26**	**6.6%**	**5**	**7.9%**	
Cefalosporins	13	3.3%	3	4.8%	
Chinolones	4	1.0%	0	0%	
Macrolides	3	0.8%	0	0%	
Other	6	1.5%	2	1.1%	
Anti-inflammatory	**115**	**29.0%**	**23**	**3.2%**	
Antipyretics	3	0.8%	0	0%	
Corticosteroids	95	24.0%	18	28.6%	
FANS	10	1.3%	4	6.3%	
Other	7	2.5%	1	1.6%	
Anti-inflammatory+antibiotics	**53**	**13.4%**	**31**	**49.2%**	
No drug	**202**	**51.0%**	**4**	**6.3%**	

Table 2. Proportion of patients without symptoms and signs after treatment in the two subgroups: treated with or without Broncalt, evaluated at T1

Symptom	Broncalt	No Broncalt	P
Facial pain	21.2%	11.1%	0.062
Nasal Obstruction	**51.8%**	**31.8%**	**0.003**
Rhinorrea	**39.7%**	**22.2%**	**0.008**
Post nasal drip	30.8%	25.4%	0.384
Earache	21.7%	15.9%	0.289
Nose swelling	34.9%	30.2%	0.466
Sore thorat	23.7%	27.0%	0.576
Dysphonia	**25.8%**	**14.3%**	**0.048**
Cough	39.4%	27.0%	0.059
Hyperaemia	59.1%	47.6%	0.087
Edema	**41.2%**	**20.6%**	**0.002**

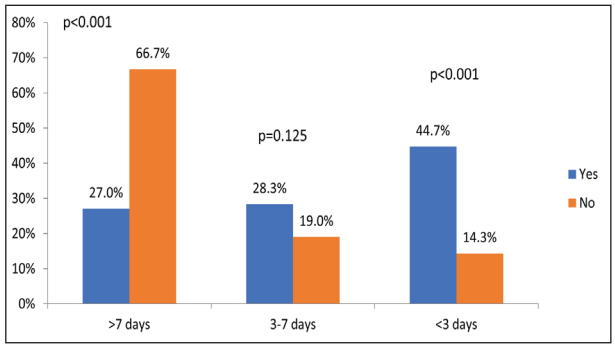

Figure 1. Percentages of patients treated with or without Broncalt with symptom disappearance within 3 days, between 3 and 7 days, and over 7 days.

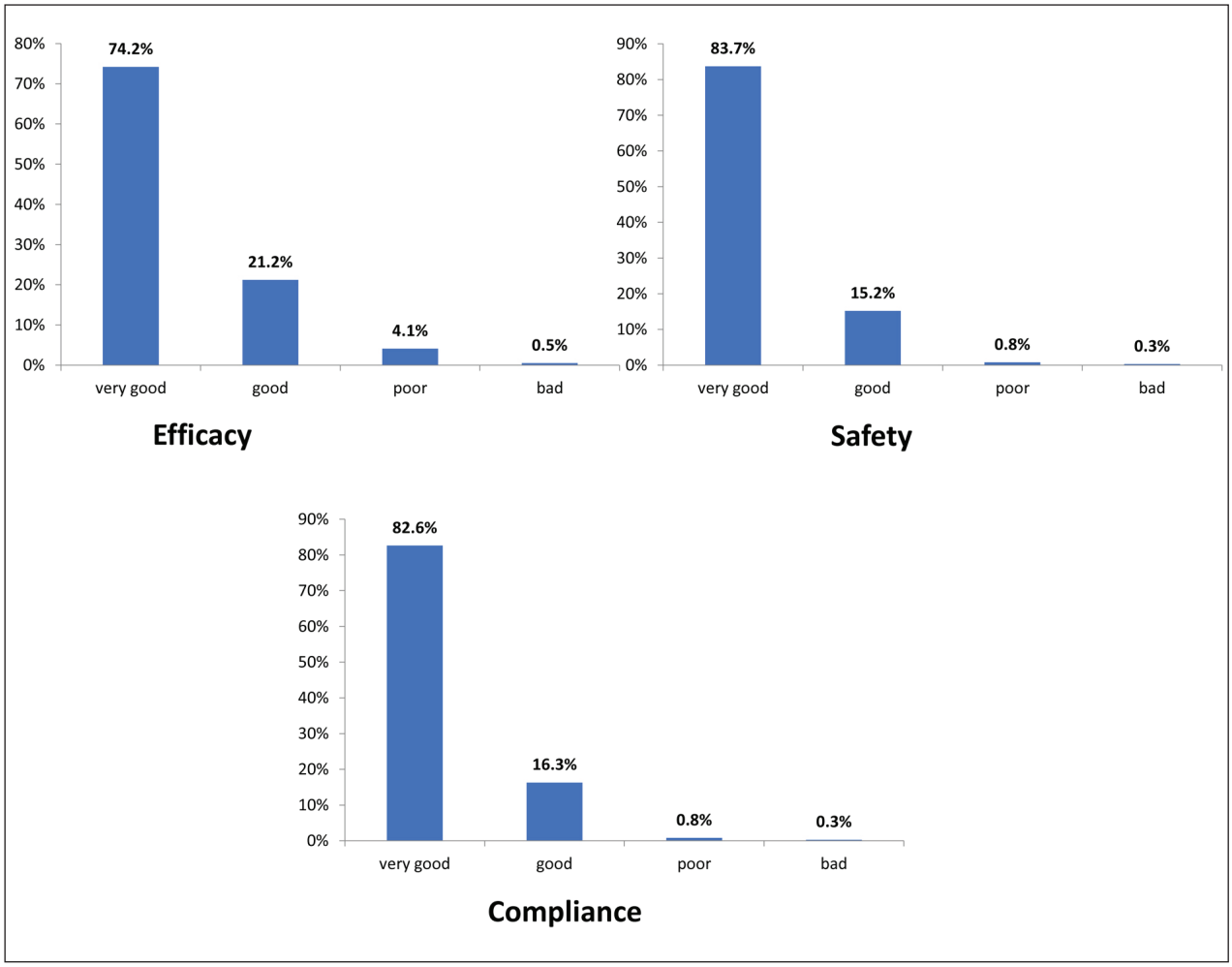

Figure 2. A= Patients' perception of Broncalt efficacy; B= Patients' perception of Broncalt tolerability; C= Patients' perception of Broncalt Compliance.

Discussion

The current survey demonstrated that Broncalt® significantly improved the clinical feature in relapsed chronic upper airways disorders in ORL clinical practice. In particular, the clinical effectiveness of Broncalt was quick as about 50% of treated patients achieved a symptom disappearance just within 3 days. Notably, patients in Broncalt subgroup more frequently did not assume any medication. The present findings are consistent with a previous study that explored the therapeutic effects of this medical device in the treatment of children with ORL infections (4).

The use of non-pharmacological treatment represents a challenging option. The present survey supports the concept that complementary medicine may have a role in clinical practice also in patients with respiratory exacerbation. In fact, previous systematic reviews evidenced that herbal medicines could be beneficial in the treatment of rhinosinusitis and othe ORL disorders (1-3). Therefore, the present survey confirms that a medical device, such as Broncalt®, may significantly reduce clinical features in chronic ORL disorders characterized by an exacerbation.

However, the current experience has some limitations, mainly concerning the open design and the lack of objective functional data. On the other hand, the strength of this survey is the high number of enrolled patients and the real-world setting, so the findings may mirror what occurs in the daily practice.

In conclusion, the present survey evidenced that Broncalt® may induce a safe and quick control of respiratory complaints in inflammatory exacerbated chronic ORL disorders.

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Original article

VAS for assessing the perception of antihistamines use in allergic rhinitis

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Summary. The quantification of the antihistamines' consumption is particularly relevant in clinical practice, since their remarkable use is usually associated with severe symptoms. The aim of the study was to measure the visual analogue scale (VAS) for assessing the patient's perception about antihistamines use in patients with allergic rhinitis. 103 patients (49 males, mean age 35.9 years) with allergic rhinitis due to Parietaria pollen were evaluated retrospectively. They recorded monthly the number of antihistamine tables they took during the pollen season (lasting for about 5 months). There was a strong relationship (r= 0.921 Pearson; p<0.0001) between the number of tablets and the VAS score. The assessment of the perception of the antihistamines use by VAS could be an easy and quick tool in the management of patients with allergic rhinitis in clinical practice. (www.actabiomedica.it)

Key words: allergic rhinitis, antihistamines, visual analogue scale, medication use, perception

Introduction

Antihistamines are commonly prescribed in the management of allergic disorders as first-line choice for allergic rhinitis and urticaria. They are widely used as histamine is the main mediator of allergic reaction and quickly relieve allergic symptoms. Thus, antihistamines are a first-line choice for allergic rhinitis and urticaria (1,2).

The quantification of their consumption may be particularly relevant in clinical practice, since their remarkable use is usually associated with severe symptoms (3). In addition, symptomatic use of antihistamines is a useful parameter for evaluating allergen immunotherapy effectiveness (4,5).

The antihistamines use is commonly evaluated asking directly to the patient the amount, but it can be bothersome and the patients often forget the actual quantity of the tablets taken. Therefore, a diary may be supplied for recording the number of tablets, but patients may be negligent frequently.

Visual analogue scale (VAS) is a psychometric test widely used to measure the patient's perception of symptom severity, emotions, pain, etc. Currently, VAS is a reliable and valid tool to assess allergic control (6). Recently, it has been reported that VAS is a fruitful measure also on smartphone screens at the population level (7). Moreover, combined symptoms severity and medication use assessment by VAS was considered for evaluating AIT response (8). Therefore, VAS may be considered a routine and validated parameter to assess allergic symptom severity in clinical practice (9).

Recently, it has been reported that VAS is a fruitful measure also on smartphone screens at the population level (7). Moreover, combined symptoms severity and medication use assessment by VAS was considered for evaluating AIT response (8). Therefore, VAS may be considered a routine and validated parameter to assess allergic symptom severity in clinical practice (9,10).

That's why we tested the hypothesis that VAS could be a good tool to measure also patient's perception about medication use, specifically concerning anti-

histamines, in clinical practice. The advantage might be the simplicity and mainly the evaluation of the patient's point of view considering her/his own perception of antihistamines taken. Therefore, the aim of the study was to measure the visual analogue scale (VAS) for assessing the patient's perception about antihistamines use in patients with allergic rhinitis (AR).

Materials and Methods

Globally, 103 patients (49 males, mean age 35.9 years) with allergic rhinitis due to Parietaria pollen were evaluated retrospectively.

Allergic rhinitis was diagnosed according to validated criteria, such as on the consistency between history and sensitization (1). In other words, the exposure to the sensitizing allergen should induce the symptom occurrence.

We gave them a diary where they recorded monthly the number of antihistamine tables they took during the pollen season (lasting for about 5 months). Subsequently, they were visited and their perception of antihistaminic use was evaluated by a VAS.

The VAS consisted of one 10-cm ruler asking for antihistamines use perception. In this study, the VAS was a horizontal 10-cm line on which 10 implied the highest medications use, while 0 corresponded to no medications use.

Initially, patients were instructed to a mark on the line indicating their perception at that moment. Thus, the lower was the numerical score marked by the patient, the lower was the perceived medications use. With a movable marker, the subject could mark any point on the 10-cm segment which best described his/her perception. No interval marker was visible on the line.

In addition, patients were asked to withhold the packs of the antihistamines used. Later, the patients were interviewed to verify the consistency between what had been reported in the diary and the real medication consumption.

All patients gave an informed written consent. The internal Review Board approved the procedure.

The relationship between tablets number and VAS was calculated by the Pearson test. We labelled the strength of the association as follows: for absolute values of r, 0 to 0.19 is regarded as very weak, 0.2 to 0.39 as weak, 0.40 to 0.59 as moderate, 0.6 to 0.79 as strong and 0.8 to 1 as very strong correlation (11).

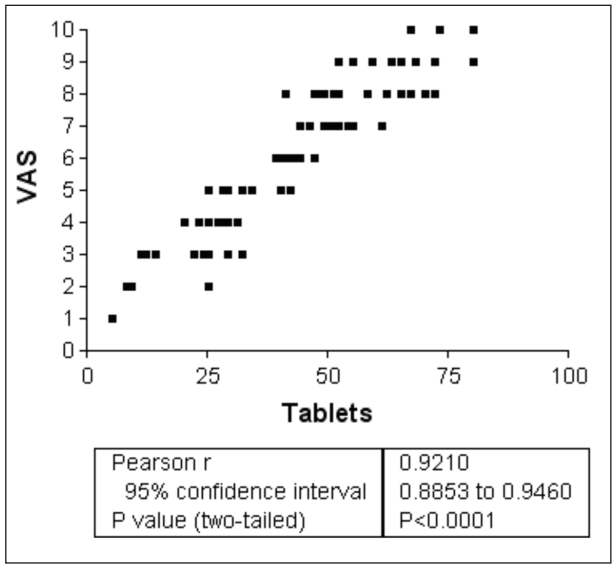

Figure 1. Relationship between number of taken tablets and VAS score assessing the perception of their use

Statistica software 9.0 (StatSoft Corp., Tulsa, OK, USA) was used for all the analyses.

Results

All patients were re-visited and reported the diary and performed VAS.

There was a strong relationship (r= 0.921 Pearson; p<0.0001) between the number of tablets and the VAS score (Figure 1).

In addition, the comparison between diary recorded data and the number of tablets used was very high (>95%).

Discussion

The main outcome is the possibility of using VAS to estimate the patient's perception of antihistamines use in clinical practice. Indeed, the patients' perception measured by VAS correlated well with the quantity of antihistamines taken recorded in the diary. Actu-

ally, the results are not surprising, as good correlation should be expected between two self-reported tools in the same patient. Furthermore, the VAS was completed after the medication diary was kept for 5 months. The act of documenting medication use will likely raise self-awareness of medication use and may help in recall of use when completing the VAS. Thus, the two tools are not independent of each other. Also, the VAS medication use likely closely mirrors allergic rhinitis symptom scores. However, the assessment of the patient perception of medication use should be always associated with the symptom scoring to correctly tailor management strategies. The symptom scoring could be measured by the traditional 4-point scale (such as 0= absent, 1=mild, 2= moderate, 3= severe) or even by VAS itself (4). In this regard, a combined VAS (i.e. to measure the patient perception of both symptom severity and medication use) has been proposed recently to evaluate the response to allergen immunotherapy (5).

The clinical relevance of the present study also concerns the widespread use of antihistamines as they exert an antagonism of histaminic activities and an anti-allergic activity (12-15).

This study has some possible limitations: the open design and the relative awareness of patients as they kept the diary. However, it was conducted in a real-world setting, therefore the findings may be translated to the clinical practice.

In addition, it has to be noted that antihistamines exert a mere symptomatic effect, as when they are suspended, allergic inflammation and symptoms restart. Moreover, as allergic inflammation is frequently a chronic condition, it may be useful to combine antihistamine treatment with non-pharmacological strategy, including thermal water and food supplements. In this regard, it has been recently reported that thermal water associated with hyaluronic acid and grapefruit seed extract significantly improved respiratory symptoms (16).

In conclusion, antihistamine use may be assessed also by the measurement of patient perception by VAS in clinical practice.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Original article

Influence of cigarette smoking on allergic rhinitis: a comparative study on smokers and non-smokers

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Summary. It has been described that exposure to tobacco smoke causes worsening of allergic rhinitis symptoms. Otherwise, some studies have demonstrated a negative association between cigarette smoke and allergic rhinitis (AR). Given this inconsistency, this study evaluated the quality of life and immuno-inflammatory parameters in current smokers and nonsmokers suffering from AR. A comparative cross-sectional study was conducted in patients who presented symptoms of AR. Patients were categorized into two groups: current smokers and non-smokers based on salivary cotinine measurements. Primary outcomes were the levels of immuno-inflammatory biomarkers (IgE, IL-4, IL-5, IL-13, IL-17, and IL-33) in serum and nasal lavage and the quality of life assessed by the Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ). Secondary outcomes included salivary cotinine levels, and pulmonary function parameters, such as forced vital capacity (FVC), forced expiratory volume in 1s (FEV_1), and FEV_1/FVC ratio. Twenty-two patients per group were included in the analysis, with no significant difference regarding demographic characteristics. Statistically significant higher values in salivary cotinine levels ($p<0.001$) and lower lung function FEV_1 ($p=0.044$) and FEV_1/FVC ($p=0.047$) were found in smokers than in nonsmokers. Only serum IL-33 was significantly different in the 2 groups ($p<0.001$): smokers had higher values compared to non-smokers. There were no significant differences in MiniRQLQ parameters. Although cigarette smoking was not associated with more severe symptoms, smoking could be associated with increased risk of developing airway remodeling and decreased lung function in AR patients, thus appropriate treatment should be prescribed if smoke avoidance is unfeasible. (www.actabiomedica.it)

Key words: cigarette smoking, allergic rhinitis, quality of life

Introduction

Allergic rhinitis (AR) is a common and chronic IgE-mediated respiratory inflammatory disease, AR affects between 10 and 25% of the worldwide general population (1).

Although AR has different degrees of severity, it impairs quality of life (QoL), sleep, daily activities, and school or work performance (2). It is frequently ignored, misdiagnosed, and mistreated, which not only is detrimental to health but also has societal costs (3). The clinical expression of AR has been reported in relation to environmental allergen exposure in genetically predisposed individuals (4).

Environmental factors, such as exposure to indoor and outdoor air pollution, changed lifestyle, bacterial/viral infections, geographic variations, socioeconomic conditions, and infant feeding, are frequently quoted as adjuvant factors for allergic sensitization and clinical expression variability (5). Indoor air pollution includes

the combustion products of biomass for domestic energy (6), the endotoxins, a component of the cell wall of gram-negative bacteria, which is a potent pro-inflammatory agent commonly found in house dust (7), and the cigarette smoke exposure which can be divided into primary smoking exposure and secondary 'passive' or 'second-hand' smoking exposure (8, 9).

Previous studies have provided conflicting results regarding the potential correlation between tobacco smoke and AR. A study on 155 adolescents demonstrated a significantly higher prevalence of AR in current smokers compared to nonsmokers and an even greater difference in passive smokers as opposed to nonsmokers (10). Conversely, a cross-sectional study found a higher prevalence of allergic nasal symptoms in nonsmokers, in contrast, an increased prevalence of nasal congestion and chronic rhinitis no-AR correlated was associated with a positive smoking history (11). Moreover, in a cross-sectional study in adult patients with AR, symptoms severity and quality of life in smokers were not significantly different from non-smokers (12). Previous studies have documented a significant difference of goblet cell density and thickening of the nasal mucosa epithelium in smokers compared to nonsmokers, with a significant increase of neutrophils and T-helper 2 (Th2) lymphocyte subsets (13), as well as in total and specific IgE levels that were significantly higher in smokers compared with nonsmokers (14).

On the contrary, another study found that exposure to tobacco smoke caused a decrease in cytokines involved in IgE-mediated mechanisms (IL-4, IL-5, IL-13, IL-25), suggesting that smokers could have less expression of allergy than non-smokers (15).

Given the little consensus regarding the current evidence, the aim of the study was to evaluate the quality of life, nasal function, and immuno-inflammatory parameters in current smokers and nonsmokers suffering from AR.

Materials and Methods

A comparative cross-sectional study was conducted at the Otolaryngology Unit of the Santa Marta e Santa Venera Hospital in Acireale, Catania, Italy, between 2018 and 2019 in smokers and nonsmokers who presented symptoms of AR.

Investigations were performed according to the Declaration of Helsinki on Biomedical Studies Involving Human Subjects. The study design was approved by the local ethics committee. All subjects were informed about the procedures and aims of the study and provided written informed consent.

Inclusion criteria were: adulthood, both genders, and presence of AR symptoms.

Patients were excluded if they had AR diagnosed less than a year, who were receiving nasal or systemic corticosteroids in the 3 months before the examination, who took antihistamines longer than 15 continuous days in the last 30 days, or who received allergen immunotherapy in the last 3 years. Patients with a history of respiratory tract infections in the last 4 weeks were also excluded.

The diagnostic criteria used for AR were those defined by the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (16), in combination with positive skin test reactions to suspected allergens, according to a procedure previously described (17).

Status of current smoking was assessed measuring the salivary cotinine levels. Cotinine is a biomarker of nicotine exposure and can be measured in blood, urine, and saliva; in all three matrices, it has a half-life of approximately 17 h, allowing time for detection of recent nicotine exposure (18). Salivary cotinine was biochemically analyzed using Enzyme-Linked ImmunoSorbent Assay (ELISA) kit from Salimetrics, USA according to a procedure previously described (19). Cotinine value of 15 ng/ml was used as the cut-point, as recommended by the Society for Nicotine and Tobacco Research (20). Patients were categorized into two groups as current smokers if reporting a value > 15 ng/ml of salivary cotinine and nonsmokers if lower than that value.

The primary outcome of the study was the difference between current smokers and nonsmokers patients regarding the levels of immuno-inflammatory biomarkers in serum and nasal lavage, and the quality of life parameters assessed using the Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) (21). Nasal lavage was performed inserting 5 ml of sterile isotonic saline into each nostril with a slightly

reclined position of the head during occlusion of the soft palate and aspirated subsequently from each nasal cavity three times before the sample was collected. Samples were centrifuged at 1200 × g for 10 min at 4°C and supernatants were extracted and aliquoted in 0.5 mL and stored at -80°C for subsequent measurement. To obtain serum, venous blood was collected into EDTA containing vials and centrifuged at 1200 × g for 10 min at 4 °C. All samples were stored at -80°C until cytokine analysis.

Levels of IgE, IL-4, IL-5, IL-13, IL-17, and IL-33 in nasal lavages were determined using Multiplex assays (FlowCytomix, eBioscience) according to the manufacturer's instructions. Levels of IgE, IL-4, IL-5, IL-13, IL-17 and IL-33 in serum were assessed by enzyme-linked immunosorbent assay (ELISA) using commercially available assays.

Secondary outcomes included differences in salivary cotinine levels, inhalant allergens sensitivity, and pulmonary function. This last has been evaluated by using a dry spirometer (MasterscreensBody, Viasys, Hoechberg, Germany) and performed according to the ATS recommendations (22). The best values of FEV_1, FVC, FEV_1/FVC were taken for the study analysis.

Statistical analysis

Data were analyzed by using the Statistical Package for Social Sciences program (SPSS for Windows 20.0 Chicago, USA). Groups were compared using the Student t test for normally distributed quantitative data. Data not showing normal distribution were analyzed using the Mann-Whitney U-test. Results were presented as frequency, mean ± standard deviation and median (min-max). Values of $p<0.05$ were considered significant.

Results

Of the 49 patients invited to participate, 44 patients (89.8%), who met the inclusion and exclusion criteria, agreed to participate, 22 current smokers (cases) and 22 non-smokers (controls). The two groups were similar in relation to age, gender, duration of AR disease, and types of sensitization to allergens (Table 1).

In nasal lavages, only IgE, IL-4, IL-17, and IL-33 levels could be detected, but no significant differences were found between the two study groups. Otherwise,

Table 1. Demographic characteristics of study participants with diagnosed AR

Characteristics	Current smokers N=22	Non-smokers N=22	p-value
Age, (years)			
Mean ± SD	36.4 ± 11.3	32.5 ± 10.4	0.102
Median	38	36	-
Range	20-64	19-62	-
Gender, n (%)			
Male	13 (59.1)	11 (50)	0.484
Female	9 (40.9)	11 (50)	
Duration of AR, (years)			
Mean ± SD	5.3 ± 1.8	4.8 ± 1.4	0.357
Median	3	3	-
Range	1-6	1-7	-
Types of sensitization to allergens, n (%)			
Monosensitized	7 (31.8)	9 (40.9)	0.305
Polysensitized	15 (68.2)	13 (59.1)	

AR: Allergic Rhinitis; SD: standard deviation
*$p < 0.05$

levels of IgE, IL-4, IL-5, IL-13, IL-17, and IL-3 were detectable in the serum of all patients, but only IL-33 levels were significantly higher in current smoker patients compared with non-smokers (586.8±23.7 pg/mL vs. 203.1±21.4 pg/mL, respectively, p<0.001) (Table 2).

Current smoker patients presented a significantly higher concentration of cotinine in saliva than non-smokers (285.7±52.3 ng/mL vs. 1.9±0.6 ng/mL, respectively, p<0.001). In current smoker group, a significantly lower FEV_1 (p=0.044) and FEV_1/FVC ratio (p=0.047) were found when compared to non-smokers values. However, no differences were observed between the two study groups regarding FVC values. The overall mean score for MiniRQLQ showed no significant differences between the two study groups (p=0.386) (Table 3).

Discussion

Nowadays, it is clear that the severity of allergic airway diseases, such as AR and asthma, is a consequence of the interaction between genes and the environment (23,24).

Cigarette smoke is probably the most common environmental factor that has been associated with

Table 2. Nasal and serum immuno-inflammatory markers in study patient groups

Characteristics	Current smokers N=22	Non-smokers N=22	p-value
Nasal immuno-inflammatory biomarkers, mean ± SD			
IgE, (kU/L)	3.9 ± 0.7	4.6 ± 0.5	0.318
IL-4, (pg/mL)	14.3 ± 2.1	13.7 ± 1.9	0.287
IL-5, (pg/mL)	No detected	No detected	/
IL-13, (pg/mL)	No detected	No detected	/
IL-17, (pg/mL)	29.2 ± 3.2	33.2 ± 3.6	0.347
IL-33, (pg/mL)	85.7 ± 14.8	105.1 ± 13.7	0.092
Serum immuno-inflammatory biomarkers, mean ± SD			
IgE, (kU/L)	189.4 ± 32.7	197.6 ± 31.5	0.288
IL-4, (pg/mL)	34.2 ± 16.3	24.3 ± 12.2	0.402
IL-5, (pg/mL)	0.5 ± 0.3	0.4 ± 0.2	0.721
IL-13, (pg/mL)	0.6 ± 0.1	0.5 ± 0.1	0.074
IL-17, (pg/mL)	0.5 ± 0.2	0.6 ± 0.2	0.619
IL-33, (pg/mL)	586.8 ± 23.7	203.1 ± 21.4	< 0.001*

pg/mL: picogram/milliliter; kU/L: Kilo unit/Liter; SD: standard deviation
*p < 0.05

Table 3. Salivary cotinine levels, pulmonary function outcomes, and MiniRQLQ overall in study patient groups

Characteristics	Current smokers N=22	Non-smokers N=22	p-value
Salivary cotinine levels (ng/mL), mean ± SD	285.7 ± 52.3	1.9 ± 0.6	< 0.001*
Pulmonary function outcomes, mean ± SD			
FEV_1 (L)	2.2 ± 0.8	3.3 ± 0.8	0.044*
FVC (L)	3.1 ± 0.9	3.6 ± 0.8	0.175
FEV_1/FVC	70.8 ± 4.8	89.4 ± 9.7	0.047*
MiniRQLQ overall, mean ± SD	1.48 ± 0.29	1.51 ± 0.22	0.386

ng/mL: nanogram/milliliter; FEV_1: forced expiratory volume in 1s; FVC: forced vital capacity; L: Liter; MiniRQLQ: Mini Rhinoconjunctivitis Quality of Life Questionnaire; SD: standard deviation
*p < 0.05

various airway diseases, including rhinosinusitis, bronchitis, and pneumonia in children (25-27). However, previous population-based studies have provided conflicting information regarding the potential correlation between tobacco smoke and AR. A study recruiting 200 patients demonstrated that both past and current SHS exposure were significant risk factor for AR (28). Contrariwise, other studies showed a negative association between cigarette smoke and AR (11).

In the present cross-sectional study, we examined the impact of cigarette smoking on immuno-inflammatory parameters and quality of life in current smokers and nonsmokers suffering from AR. Immuno-inflammatory biomarkers were measured on nasal lavage fluid and serum because it was an easy and non-invasive method for detecting and characterizing biochemical alterations associated with allergic inflammation (29, 8).

This study showed that current smoker AR patients had no worsening in both quality of life and immuno-inflammatory parameters, compared to non-smokers. These findings were in contrast to a previous study where cigarette smoke exposure resulted in a noticeable increase in nasal levels of IL-4, IL-5, and IL-13 causing a shift to a Th2-dominated local cytokine milieu and supposing an enhancement of allergic response (30).

Other works supported the notion that cigarette smoke is an adjuvant factor for AR showing an association between smoke and increased serum IgE and skin test reactivity, presumably because of heightened histamine release (30, 31). However, other studies, including the present, did not report any association (32).

Although the similarity between current smokers and non-smokers found in our investigation is striking, there nevertheless are other aspects of divergence, such as the serum level of the cytokine IL-33 and lung function. There are recent studies reporting the involvement of IL-33 in Th2-mediated inflammatory responses in allergic diseases, such as asthma, atopic dermatitis, and AR (33). Moreover, the elevated level of this cytokine was correlated with the severity of rhinitis symptoms, suggesting a role in the pathophysiology of this disorder (34). IL-33 may be released by epithelial cells during injury or necrosis caused by exogenous triggers, such as mechanical trauma, viruses, smoke, airborne allergens, or endogenous triggers, suggesting that IL-33 may act as an endogenous danger signal; thus, it has been termed an "alarmin" (34, 35).

Our study confirmed these findings, emphasized by much more higher serum IL-33 levels in smokers compared to non-smokers. Moreover, this study also present data that further support the concept of the role of IL-33 as a promoter of airway remodeling by acting on lung fibroblasts (36). This assumption arises mainly from the fact that, in our study, current smokers had impaired lung function, provided by low values of FEV_1 and FEV_1/FVC ratio, typical markers for bronchial obstruction.

In addition, increasing cotinine levels in smokers have been shown to be associated, as in our study, with worse pulmonary function test results in a dose-dependent manner (37).

There are some limitations to this study. First, regarding the failure to identify all cytokines chosen as the object of the study despite we performed all procedures (serum and nasal lavage collections) according to previously described techniques. This issue could be due to the limited half-life of the cytokines or patients not completely symptomatic at the time of the examination.

Another limitation to this study is the inability to prove the airway remodeling from a histological point of view; bronchial mucosa biopsy specimens should be obtained to corroborate this assertion

This study shows no differences in quality of life and immuno-inflammatory parameters between current smokers and non-smokers suffering from AR, suggesting that the effect of cigarette smoke exposure may have a distinct mechanism of action in allergic disease. Indeed, there is evidence of an increased signal alarm (IL-33) in smokers, which results in harmful consequences, such as decreased lung function, and its inexorable progression if the consumption of tobacco is maintained. The observed findings reinforce the need for any existing preventive action, on the avoidance of tobacco use. However, it is well known that smoke avoidance is frequently infeasible, thus there is the need to prescribe appropriate treatments able to reduce the smoke damage on respiratory airways. As tobacco smoke induces a chronic depend-

ence, prolonged pharmacological therapy could be adequately integrated with nutraceuticals. In this regard, bromelain is an effective and safe anti-inflammatory agent, particularly indicated in upper airways disorders (38).

In conclusion, tobacco smoke may significantly affect airways in patients with AR; consequently, careful evaluation and management of smokers should be performed.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Original article

Oral health in children with sleep-disordered breathing: a cross-sectional study

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Summary. Sleep-disordered breathing (SDB) is associated with a wide range of oral manifestations, including adeno-tonsillar hypertrophy, narrow dentoalveolar width, increased overjet, reduced overbite, and malocclusion. There are no studies about the relationship between SDB and poor oral health in the pediatric population. The aim of this study was to investigate oral health status and oral health-related quality of life (OHRQoL) in children at risk of SDB (SDB+), compared with a control group, not at risk for SDB (SDB). The current cross-sectional study recruited consecutive children, aged between 8 and 17 years, from a university-based dental clinic. Caregivers completed the Pediatric Sleep Questionnaire (PSQ) to stratify risk of SDB. Both children and caregivers completed the Child Oral Health Impact Profile (COHIP) to measure the OHRQoL. A dental exam was conducted to evaluate dental caries, periodontal status, oropharyngeal characteristics, and dental occlusion. DMFS (decay-missing-filled for permanent teeth), dmfs (for primary teeth), PPD (pocket probing depth), parent COHIP score, child COHIP score, and BOP (bleeding on probing) were compared between children SDB+ and SDB-. In this study, 122 children were enrolled and divided into two equal subgroups (61 each). There was a significant association between SDB and all six outcomes (all $p < 0.05$) with higher values in SDB+ children. SDB+ was associated with a poorer OHRQoL, and a greater COHIP score for both parents and children. In conclusion, the current study suggests that the impact of SDB on oral health and OHRQoL in children is relevant and far-reaching. Therefore, it is necessary to closely monitor the oral health of SDB+ children, and, if appropriate, to use gentle non-pharmacological treatments able to reduce nasal congestion. (www.actabiomedica.it)

Key words: sleep-disordered breathing, oral health, quality of life, children

Introduction

Sleep-disordered breathing (SDB) is a common breathing disorder in the paediatric population; it is characterized by the disruption of normal respiratory patterns and ventilation during sleep (1).

SDB can manifest itself in a variety of conditions from the simple snoring to the upper airway resistance syndrome until the obstructive sleep apnoea (OSA) with secondary growth impairment, neurocognitive deficits, and less often cardiovascular sequelae (2,3). The prevalence of SDB has been estimated in several studies and varies from 0.7% to 13.0%, depending on the populations studied, the methods used for assessment, and the diagnostic criteria (4). Commonly, 1-5% are diagnosed with OSA (5), with a peak prevalence at

2-5 years of age, when the lymphoid tissue of the tonsils and adenoid is largest in relation to airway size (6). SDB is associated with reduced sleep quality, resulting in behavioural issues, cognitive deficits, poor school performance, chronic respiratory diseases, and craniofacial deformation (7-9). In addition, children with SDB often show a wide range of oral manifestations, including adenoid hypertrophy, tonsillar hypertrophy, macroglossia, thick soft palate, reduced posterior airway space, reduced sagittal nasopharyngeal and oropharyngeal dimensions, narrow dentoalveolar width, increased overjet, reduced overbite, and malocclusion (10-12). Many of these oral manifestations are associated with several oral diseases, including dental caries and periodontal disease (13). Compounding this issue, many SDB children are mouth breathers, which leads to xerostomia leading to an increase in caries susceptibility (14). Therefore, it can be deduced that oral manifestations found in children with SDB likely have significant and far-reaching consequences on their oral health, but actually, there are no studies linking SDB with poor oral health in the paediatric population. Therefore, the aim of this study was to investigate both the oral health status and oral health-related quality of life (OHRQoL) in children at risk of SDB (SDB+) compared with a control group not at risk for SDB (SDB-).

Materials and Methods

The current cross-sectional study was conducted between November 2018 and March 2019 in paediatric patients who attended routine dental check-up at the dental clinic of the Catania University. Inclusion criteria were: age between 8 and 17 years at the time of enrolment, to be in good overall health, and to not have active orthodontic treatment within the last year.

The study was approved by the local Institutional Review Board and written informed consent was obtained from all parents or guardians of the participating children.

Caregivers were asked to complete the Paediatric Sleep Questionnaire (PSQ) to stratify the risk of SDB (15). PSQ is a 22-item questionnaire comprising three symptom complexes: snoring, excessive daytime sleepiness, and inattentive or hyperactive behaviour, an overall score of ≥8 indicate SDB.

In order to evaluate oral health, the measurement of OHRQoL was assessed considering the answers given by the children and their caregivers to the Child Oral Health Impact Profile (COHIP) questionnaire (16). The COHIP questionnaire consists of 35 items representing 5 conceptually distinct domains: oral health (oral symptoms such as teeth pain, sensitivity, and oral sores), functional wellbeing (child's ability to perform specific everyday activities), social/emotional wellbeing (peer interactions and mood states), school environment (assignments associated with the school environment), and self-image (positive feelings about self). Responses were scored on a scale ranging from 0 (never) to 4 (almost all the time). For some items, the scale was reversed so that higher scores consistently indicated poor oral health. A sub-score for each of the five COHIP domains and an overall total COHIP score were calculated. For the overall scores, higher scores reflect worsened OHRQoL.

The clinical examinations were carried out by a trained dental doctor, not involved in the study and blinded to results of the PSQ, using a dental mirror and a ball-ended periodontal probe. Craniofacial features and dental occlusion were recorded. Soft palate morphology was classified according to the Mallampati classification (17). Tonsil size was classified according to the Brodsky score (18). Dental occlusion was evaluated using Angle's malocclusion classification (19). The diagnosis of dental caries was based on the detection of carious lesions at the cavitation stage, as recommended by the World Health Organization (WHO). DMFS and dmfs indices (decayed, missing, and filled surfaces; lower-case letters for primary teeth, upper-case for permanent teeth) were used (20).

The periodontal examination was performed for the Ramfjord index teeth (teeth number: 3, 9/F, 12/I, 19, 25/P, 28/S), separate recordings were made for the four smooth surfaces of these teeth, and an average tooth score was then recorded (21).

Two periodontal indices were measured to assess periodontal status: 1) Bleeding on probing (BOP) recorded after stimulating the region where gingiva and teeth come to contact each other by a periodontal probe; and 2) Probing pocket depth (PPD) is defined

as the distance between the gingival margin and the bottom end of the periodontal pocket (22).

Statistical analysis

Descriptive and inferential statistics were used for analysis. Continuous variables were presented as mean ± SD, or median as appropriate, while categorical variables were expressed as frequencies and percentages. Statistical analyses were performed as follows: Descriptive and inferential statistics were used for analysis. Continuous variables were presented as mean ± SD, while categorical variables were expressed as frequencies and percentages. Statistical analyses were performed using the chi-square test of homogeneity and non-parametric Mann-Whitney's test for qualitative variables and T-Student test for quantitative variables. For all six outcomes, a regression analysis was used to adjust for confounders (gender, caregiver's education, family social class, obesity, Mallampati classification, Brodsky score, and Angle's malocclusion classification). All statistical tests were performed with the MedCalc Statistical Software, v. 9.2.1.0 (MedCalc Software, Belgium) and p values of less than 0.05 were regarded as statistically significant.

Results

A total of 122 patients was enrolled and divided into two equal subgroups (61 each) dichotomized into children at risk for SDB (SDB+ group) and children, not at risk for SDB (SDB- group).

The demographic details of the two study populations are outlined in Table 1.

There was a significant difference between the two study subgroups considering DMFS, dmfs, CO-HIP, PPD and BOP (all $p < 0.05$) with higher values among SDB+ children when compared to the other subgroup (Table 2).

A regression analysis was performed adjusting for the following confounders: gender, caregiver's education, family social class, weight, Mallampati classification, Brodsky score, and class of malocclusion. In the regression analysis, age was calculated using groups that differ in age by 1 year. Caregiver's education was

Table 1. Demographic characteristics of study participants with diagnosed AR

Characteristics	SDB+ N=61	SDB- N=61	p-value
Age (in years), mean ± SD	12.4 ± 3.1	11.9 ± 2.8	0.475
Gender, n(%)			
Male	33 (54.1)	31 (50.8)	0.254
Female	28 (45.9)	30 (49.2)	
Homes with smoking, n(%)	10 (16.4)	11 (18)	
Caregiver's education, n(%)			
Upper secondary school	12 (19.7)	9 (14.8)	0.231
Bachelor's degree	49 (80.3)	52 (85.2)	
Family social class, n(%)			
Middle class	36 (59)	37 (60.7)	0.467
Upper class	25 (41)	24 (39.3)	
Weight, n(%)			
Normal	55 (90.2)	57 (93.4)	0.766
Obese	6 (9.8)	4 (6.6)	
Pediatric Sleep Questionnaire, mean ± SD	12.7 ± 3.1	5.5 ± 2.4	0.006*

SDB: Sleep-disordered breathing; SD: standard deviation
*$p < 0.05$

Table 2. DMFS, dmfs, Parent and Child COHIP, PPD, and BOP between the two study groups

Outcomes	SDB+ N=61	SDB- N=61	p-value
DMFS index, mean ± SD	13.6 ± 4.7	3.5 ± 2.2	< 0.001
dmfs index, mean ± SD	8.5 ± 2.3	2.7 ± 1.1	< 0.001
COHIP (overall) parent, mean ± SD	24.5 ± 5.6	16.7 ± 4.3	0.003*
COHIP (overall) child, mean ± SD	23.2 ± 4.6	15.9 ± 3.8	0.004*
PPD (mm), mean ± SD	2.4 ± 0.5	0.8 ± 0.3	< 0.001
BOP proportion of bleeding ± SD	0.9 ± 0.2	0.3 ± 0.2	0.004*

SDB: Sleep-disordered breathing; SD: standard deviation; DMFS: decayed, missing, and filled surfaces (for permanent teeth); dmfs: decayed, missing, and filled surfaces (for primary teeth); COHIP: Child Oral Health Impact Profile; PPD: probing pocket depth; BOP: bleeding on probing
*$p < 0.05$

categorized as upper secondary school, and bachelor's degree, with the upper secondary school serving as the reference group. Social class was categorized as middle class, and upper class, with the middle class serving as the reference group. Weight was categorized as normal, and obese, with normal serving as the reference group. Mallampati classification was categorized as class I, class II, and class III, with class I serving as the reference group. Brodsky score was categorized as grade 0, grade I, grade II, and grade III, with grade 0 serving as the reference group. Malocclusion was categorized as normal (Class I), postnormal (Class II) and prenormal (Class III) occlusion, with Class I serving as the reference group. As for DMFS regression analysis, there was a significant association between DMFS and SDB, family social class, and malocclusion. Regarding dmfs regression analysis, it has been shown a significant association between dmfs and SDB, caregiver's education, weight, Mallampati classification, and Brodsky score. The PPD regression analysis demonstrated a significant association between PPD and SDB, gender, and Brodsky score (Table 3). Table 4 shows the results of COHIP Parent regression analysis where it was noted a significant association between parent COHIP score and SBD, weight, and Mallampati classification. Moreover, the COHIP Child regression analysis showed a significant association regarding child COHIP score and SDB, weight, Mallampati classification, and malocclusion. The BOP regression analysis highlighted a significant association between BOP and SDB and weight.

Discussion

There is evidence that SDB correlates with poor systemic health in children (23-25). Despite this, there is a lack of investigation concerning the relationship between SDB and oral health in children. This is a critical question that needs to be answered and our study is likely to provide important insights into this association. We hypothesized that SDB has a profound negative impact on oral health in children. As anticipated, SDB was associated with six outcomes: DMFS, dmfs, PPD, BOP, and a child COHIP and parent COHIP questionnaire.

The OHRQoL was measured by the child and parent COHIP scores, with the higher the score the poorer the OHRQoL. SDB was found to have a significant impact on the OHRQoL for children and adults (higher child and parent COHIP scores). Given that SDB is associated with dental caries, PPD, and BOP, this comes as no surprise and further validates the association of SDB and poor oral health. In the regression analysis, both child and parent COHIP scores were associated with weight. We found a close relationship between them, indeed obesity is likely a contributing factor for adverse health outcomes and therefore increased risk of SDB (26). Obesity and caries have been shown to coexist in children of low socioeconomic status (27). Surprisingly, there was no association between the child and parent COHIP scores and caregiver's education or family social class. We were anticipating that low education and social class

Table 3. DMFS, dmfs and PPD Regression Analysis

Predictor/Confounder	Differences in means	95%CI (Lower/Upper)	p-value
DMFS Regression Analysis			
Intercept	41.54	12.65/70.43	0.004
SDB	9.74	3.77/13.83	< 0.001
Male gender	1.24	-2.36/4.84	0.240
bachelor's degree vs. upper secondary school	-9.07	-19.68/1.55	0.082
upper class vs. middle class	-5.66	-10.65/-0.67	0.043*
Obese vs. normal	2.18	-5.39/9.74	0.064
Mallampati class II vs. class I	0.86	-4.52/6.23	0.383
Mallampati class III vs. class I	-1.33	-10.64/7.98	0.287
Brodsky grade I vs. grade 0	-11.59	-23.52/0.35	0.072
Brodsky grade II vs. grade 0	-10.85	-24.53/2.84	0.073
Brodsky grade III vs. grade 0	-8.63	-22.67/5.42	0.096
Malocclusion class II vs. class I	-27.69	-43.18/-12.21	< 0.001
Malocclusion class III vs. class I	-26.93	-42.12/-11.75	< 0.001
dmfs Regression Analysis			
Intercept	-0.23	-15.32/14.87	0.856
SDB	5.76	3.47/8.04	< 0.001
Male gender	1.57	-1.13/4.27	0.238
bachelor's degree vs. upper secondary school	7.28	-1.02/15.59	0.045*
upper class vs. middle class	0.22	-3.62/4.06	0.376
Obese vs. normal	-4.01	-7.14/-0.87	0.023*
Mallampati class II vs. class I	0.84	-2.56/4.23	0.288
Mallampati class III vs. class I	7.98	2.45/13.51	0.002*
Brodsky grade I vs. grade 0	5.07	0.88/9.25	0.018*
Brodsky grade II vs. grade 0	3.69	-0.36/7.73	0.049*
Brodsky grade III vs. grade 0	11.98	4.87/19.12	< 0.001
Malocclusion class II vs. class I	2.11	-6.32/10.54	0.097
Malocclusion class III vs. class I	5.71	-1.08/12.48	0.074
PPD Regression Analysis			
Intercept	1.95	-0.62/4.53	0.052
SDB	2.56	1.53/3.59	< 0.001
Male gender	0.83	0.67/0.98	0.010*
bachelor's degree vs. upper secondary school	-1.04	-3.15/1.07	0.075
upper class vs. middle class	-0.29	-0.78/0.21	0.188
Obese vs. normal	-0.31	-1.05/0.43	0.128
Mallampati class II vs. class I	-0.29	-0.76/0.19	0.347
Mallampati class III vs. class I	0.23	-0.29/0.74	0.322
Brodsky grade I vs. grade 0	-0.63	-1.43/0.18	0.048*
Brodsky grade II vs. grade 0	-0.76	-1.43/-0.08	0.033*
Brodsky grade III vs. grade 0	-0.40	-1.56/0.76	0.047*
Malocclusion class II vs. class I	-0.96	-2.43/0.51	0.088
Malocclusion class III vs. class I	-0.83	-2.13/0.47	0.164

SDB: Sleep-disordered breathing; SD: standard deviation; DMFS: decayed, missing, and filled surfaces (for permanent teeth); dmfs: decayed, missing, and filled surfaces (for primary teeth); PPD: probing pocket depth.
*$p < 0.05$

would be associated with higher COHIP scores, but no such relationship was noted. A possible explanation for this could be our study sample. There were limited numbers of children in each of the respective categories, insufficient to draw definitive conclusions. A final remarkable association was found between child and

Table 4. COHIP Parent, COHIP Child, and BOP Regression Analysis

Predictor/Confounder	Differences in means (or Odds Ratio)	95%CI (Lower/Upper)	p-value
COHIP Parent Regression Analysis			
Intercept	26.39	-3.56/56.33	0.073
SDB	8.34	3.87/12.92	< 0.001
Male gender	2.04	-1.56/5.64	0.265
bachelor's degree vs. upper secondary school	-9.35	-21.63/2.94	0.143
upper class vs. middle class	0.93	-4.42/6.28	0.347
Obese vs. normal	2.18	-7.16/8.03	0.029*
Mallampati class II vs. class I	0.44	-2.01/6.54	0.056
Mallampati class III vs. class I	23.08	10.54/35.62	< 0.001
Brodsky grade I vs. grade 0	-5.03	-17.34/7.28	0.423
Brodsky grade II vs. grade 0	-10.85	-11.32/15.33	0.539
Brodsky grade III vs. grade 0	2.05	-22.67/5.42	0.756
Malocclusion class II vs. class I	-13.52	-33.15/6.11	0.073
Malocclusion class III vs. class I	-16.82	-34.88/1.25	0.057
COHIP Child Regression Analysis			
Intercept	3.87	-18.42/26.15	0.642
SDB	8.72	4.17/13.27	< 0.001
Male gender	0.57	-2.33/3.47	0.536
bachelor's degree vs. upper secondary school	-7.83	-18.05/2.39	0.097
upper class vs. middle class	2.87	-2.52/8.26	0.126
Obese vs. normal	-3.04	-7.64/1.57	0.035*
Mallampati class II vs. class I	2.64	-1.46/6.73	0.047*
Mallampati class III vs. class I	16.28	6.35/26.21	< 0.001
Brodsky grade I vs. grade 0	-1.67	-8.58/5.25	0.443
Brodsky grade II vs. grade 0	-1.05	-6.32/4.23	0.412
Brodsky grade III vs. grade 0	-4.75	-13.83/4.34	0.137
Malocclusion class II vs. class I	8.45	-2.62/19.53	0.025*
Malocclusion class III vs. class I	8.11	-2.08/18.28	0.044*
BOP Regression Analysis			
Intercept	31.45	0/4238.53	0.378
SDB	246.66	12.57/8543.52	< 0.001
Male gender	7.88	0.57/76.88	0.109
bachelor's degree vs. upper secondary school	0.07	0/97.57	0.421
upper class vs. middle class	0.35	0.78/5.31	0.359
Obese vs. normal	0.02	0/0.56	0.005*
Mallampati class II vs. class I	0.07	0.06/1.19	0.077
Mallampati class III vs. class I	13.83	1.59/188.44	0.063
Brodsky grade I vs. grade 0	1.53	0/265.18	0.603
Brodsky grade II vs. grade 0	3.56	0.03/5832.79	0.735
Brodsky grade III vs. grade 0	2568.30	870.45/7834.53	0.087
Malocclusion class II vs. class I	1.93	0.47/7.43	0.327
Malocclusion class III vs. class I	0.14	0.03/5.31	0.153

SDB: Sleep-disordered breathing; SD: standard deviation; COHIP: Child Oral Health Impact Profile; BOP: bleeding on probing
*$p < 0.05$

parent COHIP scores and Mallampati classification. Higher scores (poorer OHRQoL) were associated with higher Mallampati classification. This is perhaps due to these patients being at increased risk for SDB, which in turn puts them at greater risk for oral health complications (28). Our analysis showed that there is

a significant association between SDB and dental caries in the primary and permanent dentitions. The relationship between SDB and dental caries, although not clearly understood, may be secondary to sharing common risk factors. For example, it is well established in the literature that dry mouth is associated with dental caries and OSA (29). A study showed that the incidence of dry mouth upon awakening is much higher in OSA patients versus primary snorers and increases linearly from mild, moderate, to severe OSA (30). Given the increased degree of dry mouth that accompanies the severity of OSA, the association noted between SDB and dental caries comes as no surprise. Future studies should compare the association between pediatric dental caries and mild, moderate, and severe OSA respectively. Another important finding of our study was that SDB is associated with periodontal status (BOP and PPD). As with dental caries, this relationship is likely the result of shared risk factors. In addition to dental caries, dry mouth is associated with the gingival disease. A study reported that xerostomia was related to gingival disease in young adults via the accumulation of dental plaque (31). Gingival inflammation secondary to xerostomia may explain our findings that children with SDB have greater BOP and PPD. As well, all of the SDB patients in our study were mouth-breathers, and chronic gingivitis and periodontitis are frequently found in mouth-breathers (32,33). Notably, we found only an association between low socioeconomic status and dental caries in the permanent dentition. Based on previous studies that concretely show the relationship between low socioeconomic status and dental caries in the primary dentition, we speculate our findings are related to a small study sample (34).

The present results showed strong associations between SDB and all six outcomes. However, future studies need to be properly designed and carried out to definitively determine causality. Our hope from this study is that medical and dental practitioners will be alerted to pay careful attention to the oral health of their SDB patients, understanding that they are at an increased risk for a number of oral health problems. As the oral health consequences of SDB become more commonly recognized by the medical community, diagnosis and appropriate interventions can begin earlier, minimizing social, financial, systemic, and oral health complications. In addition, it may be fruitful to use, if appropriate, gentle non-pharmacological treatments able to reduce nasal congestion and sequelae of respiratory infections that frequently may be associated with SDB. In this regard, a recent study reported a successful treatment with thermal water, hyaluronic acid, and grapefruit seed extract in reducing nasal congestion and airways hyperreactivity in children with upper respiratory infections (35).

In conclusion, SDB should be thoroughly managed in childhood to prevent chronic and potentially irreversible damage.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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