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Can an oral supplement with Sambucus nigra, Zinc, Tyndallized Lactobacillus acidophilus (HA122), Arabinogalactans, vitamin D, vitamin E and vitamin C, improve post-surgery quality of recovery? Survey among adult and children to identify potential benefit.

Alessandro Maselli Del Giudice[⋆,†,1], Francesco Barbara[1], Francesco Cariti[1], Salvatore Dadduzio[1], Valentina De Robertis[1], Silvana Ciccarone[1], Michele Barbara[1], Francesca Cialdella[1]

Otolaryngology department - Monsignor Raffaele Dimiccoli Hospital, Barletta, Italy

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ABSTRACT

Abstract: Oral supplements have known abilities to stimulate immune-answer. In addition, some molecules, such as those extracted from Sambucus nigra, have a strong antibacterial and antiviral capacity. For these reasons, oral supplementation is used to improve the immune system. In this study we aim to investigate how an oral supplement with multi-element can support the recovery of patients who underwent surgery. To this aim we separately analyzed a sample of 130 patients under 17 years and 130 adults. All patients were treated by antibiotic therapy and assigned to group 1, 2, 3 or control (subgroups) based on the treatment with oral supplement performed. Each group followed a specific treatment by nutraceuticals (Difensil Immuno and/or Vitamin D). The health condition of the patients was investigated by looking at their blood test and using a validated questionnaire. All patients who underwent oral supplementation showed a higher percentage of positive answers to the questionnaire than control groups. Based on the results, our study shows that oral supplementation with selected and specific elements like Sambucus nigra, Zinc, Tyndallized Lactobacillus acidophilus (HA122), Arabinogalactans, vitamin D, vitamin E and vitamin C, can be a valid support to immune system, after surgery both in adults and children.

Key words: surgery–oral supplement–Sambucus nigra–Tyndallized Lactobacillus acidophilus–quality of life.

1 INTRODUCTION

Several clinical trials have shown that it is possible to use nutraceutical compounds to modulate and stimulate the immune-answer in patients affected by cancer [1], by acquired immune-deficiency [2] and in populations that have a good health but that could be overexposed to risk of viral infection [3].

The immune-answer can be stimulated by using single molecule [4] or a combination of elements [3,5]. The majority of these natural compounds improve immunity by increasing the efficiency of macrophages [6] and leucocytes [7] and by modulating the production of inflammatory cytokines [8] and reducing reactive oxygen species (ROS) [9].

Surgery determines a stress for human body [10] independently from the length and the aggressiveness of the procedure and it can expose patients to infection and difficulties to recover good health [11].

The oral supplements thank to their ability to stimulate and modulate the immune answer can support the recovery patients after different types of surgery [12,13].

To date, nobody investigated the effect of oral supplements with multi elements nor compared the effect of different oral supplement in patients who underwent otolaryngology procedure, both in adults and children.

⋆ Corresponding author.

† Email: ale.maselli@tiscali.it.

Aim of this study was to analyze the effect of oral supplementation with a multi-elements oral supplement on a sample of adults and children underwent surgery. To this aim we investigated the quality of life after surgery by a questionnaire.

2 MATERIALS AND METHODS

This case-control study was conducted in the Otolaryngology departments of hospital Monsignor Raffaele Dimiccoli from October 2019 to may 2020. All procedures were approved by the local Institutional Review Board committee and were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Adults participants signed a written informed consent document authorizing their enrollment in the study and same did children's parents of the ones that were included.

Inclusion criteria for adults were: age >18 years, no major neurological or psychological disease, elective surgery, known contraindications or allergies to one of the elements contained in the oral supplement, reduced compliance in participating due to surgical procedure performed.

Inclusion criteria for children were: age < 17, elective surgery, known contraindications or allergies to one of the elements contained in the oral supplement, absence of approval from parents.

Four groups were created: Group 1 (G1), Group 2 (G2), group 3 (G3) and control group (CG) and then divided in two subgroups based on the age <17, called junior (J) or >17 named senior (S).

All four groups performed standard antibiotic treatment (necessary for ethical reason).

CG performed only standard therapy.

Patients in group 1J underwent 10 ml of Difensil Immuno (DI) (Difensil® Immuno, Humana® Italia SpA e Ditrevit® 1000, Humana Italia SpA) corresponding to 122 mg of Sambucus nigra, 7.5 mg of Zinc, 1x109 Tyndallized Lactobacillus acidophilus (HA122), 10 mg of Arabinogalactans, 10 mcg (400 IU) of Vitamin D, 30 mg of Vitamin E and 90 mg of Vitamin C. Group 1S used 15 ml of DI which contains 183 mg of Sambucus nigra, 11.2 mg of Zinc, 1.5 x109 Tyndallized Lactobacillus acidophilus (HA122), 15 mg of Arabinogalactans, 15 mcg (600 IU) of Vitamin D , 45 mg of Vitamin E and 135 mg of Vitamin C.

Patients in group 2J were treated with 1000 UI of vitamin D and the ones in 2S with 1200 UI. Control group performed only antibiotic treatment.

Group 3J was treated with 10 ml of DI in addition to 600 UI of vitamin D and 3S with 15 ml of DI plus 600 UI of vitamin D.

All patients started using oral supplementation (single dose with breakfast) immediately after surgery and they continued oral supplementation for 30 consecutive days also after hospital discharge.

Antibiotic treatment was performed for 1 week after surgery using amoxicillin with two different posology based on age; patients under 14 based on their weight, while the one over this age used 1 mg x 3 (each 8 hours).

Subjects were randomly assigned by a computer to one of the four groups.

Patients were all interviewed by using approved health assessment questionnaire (HAQ) [Fries et al 1980] (table 1); patients over 13 years personally answered to the questions, while the ones under 13 were supported by their parents.

Table 1. The questions that we used to investigate patients' health conditions after surgery

1) I feel strong and well
yes no
2) I have no problem in my daily care (washing)
yes no
3) I have no problem in my daily care (wearing)
yes no
4) I am comfortable to walk more than 30 minutes
yes no
5) I can perform my daily activity without effort
yes no
6) I have difficulties to eat
yes no
7) I am not hungry at all
yes no
8) I feel comfortable to stay with others
yes no
9) I cannot sleep because of pain
yes no

The following blood parameters were evaluated and collected: red blood cells (RBC) count, white blood cells (WBC) count, hemoglobin concentration (Hb), polymerase chain reaction (PCR) value, Erythrocyte sedimentation rate (ESR), pro-calcitonin (PC).

Three time points were identified: T0=at the moment of hospitalization (baseline), T1=15 days after surgery, and T2=30 days after surgery; at each follow-up all outcome measures (questionnaire and blood test) were collected.

Children population included 130 subjects (age average 10,2 years; SD:3; CI 95%: 6-17) and same number of patients were included in the adults' group (age average 35,9 years; SD: 12; CI 95%: 18-66).

2.2 Statistical analysisThe statistical analysis was performed by using STATA®. One-way ANOVA was performed to evaluate the variation of blood parameters. Kruskal-Wallis was used for analyzing the questionnaire results. One-way ANOVA and Kruskal-Wallis were performed by considering the adults and children subgroups separately.

A p value < 0.05 was considered to be statistically significant.

3 RESULTS

3.1. Adults population (Senior)The 66 men and 64 women were divided between the four groups as follow, 32 subjects (15 men and 17 women) in the CG (age average 38,5; SD: 12,4), 31 patients (15 men and 16 women) in G1 (age average 34; SD:11,7), 34 people (17 men and 17 women) in G2 (age average 32,7; SD: 11,5) and the remain 32 (18 men and 14 women) were in G3 (age average:42,5; SD:12,3).

Figure 1 summarizes the different types of surgery performed in the adult population.

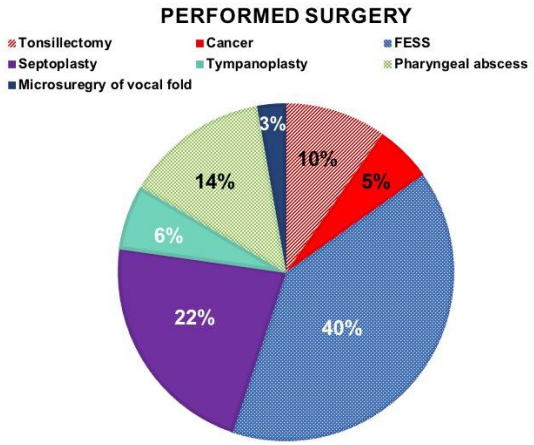

Figure 1. The graphic shows the different type of surgery performed by the adults included in the study.

None of the patients presented post-surgical complication. No statistically significant differences were observed on blood parameters between the four groups at the three follow-ups, specifically RBC (one-way ANOVA: p =0.9), WBC (one-way ANOVA: p =0.8), Hb (one-way ANOVA: p =0.9), PCR (one-way ANOVA: p =0.7), ESR (one-way ANOVA: p =0.9) and PC (one-way ANOVA: p =0.7).

3.2 Children population

The 72 males and 58 female were divided between the four groups as follow 32 subjects (17 boys and 15 girls) in the CG (age average 9.5; SD: 3.6), 32 patients (15 boys and 17 girl) in G1 (age average 8.4; SD:3.2), 33 people (17 males and 16 females) in G2 (age average 9.6; SD: 2.3) and the remain 33 (18 boys and 14 girls) were in G3 (age average 9; SD:4).

Figure 2 shows the distribution of performed surgery in children.

None of the patients presented post-surgical complication. No statistically significant differences were observed on blood parameters between the four groups at the three follow-ups, specifically RBC (one-way ANOVA: p =0.8), WBC (one-way ANOVA: p =0.7), Hb (one-way ANOVA:

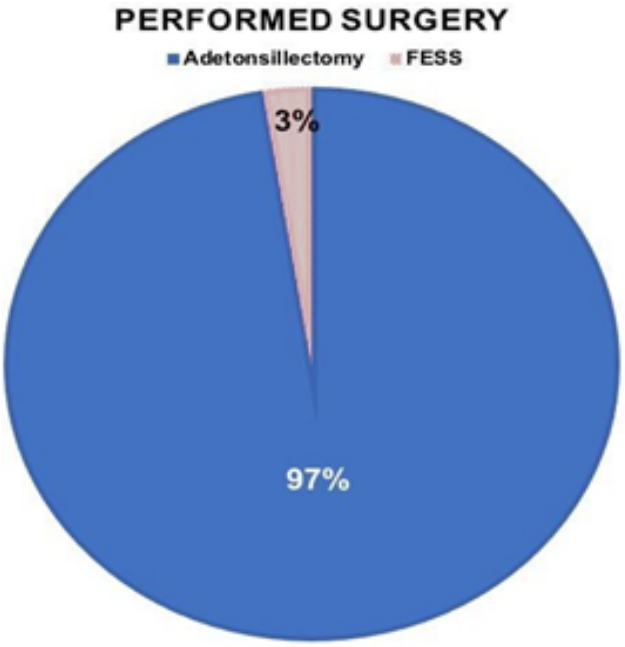

Figure 2. shows the type of surgery performed in children

p =0.8), PCR (one-way ANOVA: p =0.6), ESR (one-way ANOVA: p =0.6) and PC (one-way ANOVA: p =0.8).

4 DISCUSSION

Overall our results showed that the use of oral supplementation could positive impact on the health, both in adults and children as evidenced by the answers that we obtained by our questionnaire. The use of vitamin D alone was the less powerful compared to the use of multielement booster independently if it was administered as unique supplementation or in combination with vitamin D.

Patients who combined Difensil Immuno with vitamin D obtained better outcomes than using only the multielement booster and this result was confirmed both in adults and children.

Blood parameters did not show any significative changes underlining the safety of oral supplements.

Difensil Immuno contains a series of elements that modulate and stimulate the immune answer; the good state of the immune system is generally associated with better sensation of wellness. Each element acts differently on the immune-system.

Sambucus nigra (SN) is a plant extract is able to inhibit viral replication [14] and increases the production of inflammatory cytokines (IL-1 beta, TNF-alpha, IL-6, IL-8), in particular TNF- The latter has a pivotal role in the regulation of inflammatory cytokines production [17] and improves the macrophage answer to viral infection [18].

Vitamin C regulates cytokines production inducing adequate but not excessive immune answer to the viral infection [7], specifically it improves chemotaxis, stimulates prolifer-

Table 2. Summarizes the results of survey in adults

	Group	T0 P-value	T1 P-value	T2 P-value
	CG			
Question 1	G1	0.07	0.001	< 0.001
	G2		0.02	0.04
	G3		<0.0001	<0.0001
Question 2	GC			
	G1	0.08	0.003	<0.0001
	G2		0.03	0.04
	G3		<0.0001	<0.0001
Question 3	CG			
	G1		0.002	<0.001
	G2	0.09	0.02	0.04
	G3		<0.0001	<0.0001
Question 4	CG			
	G1		0.0003	<0.0001
	G2	0.08	0.02	0.04
	G3		<0.0001	<0.0001
Question 5	CG			
	G1		0.001	<0.0001
	G2	0.09	0.02	0.04
	G3		<0.0001	<0.0001
Question 6	CG			
	G1		0.003	<0.0001
	G2	0.06	0.02	0.04
	G3		<0.0001	<0.0001
Question 7	CG			
	G1		0.004	<0.0001
	G2	0.07	0.02	0.04
	G3		<0.0001	<0.0001
Question 8	CG			
	G1	0.08	0.002	<0.0001
	G2		0.02	0.04
	G3		<0.0001	<0.0001
Question 9	CG			
	G1	0.09	0.004	<0.0001
	G2		0.02	0.04
	G3		<0.0001	<0.0001

ation of leucocytes and increases the neutrophil phagocytic activity. Furthermore, Ascorbic acid increases production of α/β interferons and down- regulates the synthesis of pro-inflammatory cytokines [9].

Vitamin D showed same ability vitamin C to stimulate immune-answer, it promotes differentiation of monocytes/macrophages in their active form, and at the same time, increase the chemotactic and phagocytic capacity of these cells [19].

Zinc improves the macrophages phagocytosis ability, the capacity of antigen presentation and signal transmission between these cells and the other belonging to the immune-system. In addition, this element promotes the secretion on IL-6 and TNF- 8 which further contributes to improve the immune-answer [20].

Arabinogalactan enhances natural killer cells and macrophages and modulates the secretion of pro-inflammatory cytokines. Humans clinical studies have shown that arabinogalactan increases the immune answer to defend against common cold infection. In addition, this molecule stimulates the increase of IgG and IgE. The most plausible theory is that arabinogalactan improves the efficiency of B and T cells by protecting the host from viral and bacterial infection [21].

Lactobacillus is one of the most used probiotics, because it has shown excellent capacity to enhance the immune answer especially in case of infection of URT [22]. This probiotic regulates T-cell activation so to avoid an excessive immune-answer against the virus [23].

Probiotics in general reduce ROS production and induce an early release of proinflammatory cytokines such as IL-8, TNF-α, IL-12p70, and IL-6 and IL-1β. Literature showed that probiotics modulate the activity of macrophage in the beginning of the infection by determining an early immune-stimulating effect [24].

In particular, the heat-killed (tyndallized) strains, characterized by different bacterial components (lipoteichoic acids, peptidoglycans, and/or exopolysac charides) [25], supports immune-modulation, protects against pathogens, and fortifyies the mucosal barrier integrity [25, 26]. As additional effect, daily intake of heat-killed Lactobacillus plantarum L-137 (HK L-137) can improve inflammation and lipid metabolism in subjects at risk of inflammation [27].

All these molecules through the modulation of the immune system reduce the systemic inflammation [4, 28] and improve the wellness sensation in patients who have underwent surgery.

Table 3. Summary of questionnaire results in children

	Group	T0 P-value	T1 P-value	T2 P-value
	CG			
Question 1	G1	0.09	0.001	< 0.001
	G2		0.02	0.02
	G3		<0.001	<0.0001
Question 2	GC			
	G1	0.06	0.003	0.001
	G2		0.03	0.02
	G3		0.004	0.0001
Question 3	CG			
	G1		0.002	<0.001
	G2	0.07	0.03	0.03
	G3		<0.0001	<0.0001
Question 4	CG			
	G1		0.003	<0.001
	G2	0.08	0.02	0.04
	G3		0.0001	<0.0001
Question 5	CG			
	G1		0.001	<0.0001
	G2	0.09	0.02	0.04
	G3		<0.0001	<0.0001
Question 6	CG			
	G1		0.003	<0.0001
	G2	0.08	0.02	0.04
	G3		<0.0001	<0.0001
Question 7	CG			
	G1		0.004	<0.0001
	G2	0.06	0.04	0.02
	G3		<0.0001	<0.0001
Question 8	CG			
	G1	0.07	0.002	<0.0001
	G2		0.02	0.04
	G3		<0.0001	<0.0001
Question 9	CG			
	G1	0.06	0.003	<0.0001
	G2		0.04	0.02
	G3		<0.0001	<0.0001

5 CONCLUSIONS

Our study shows that oral supplementation with selected and specific e lements l ike S ambucus n igra, Z inc, Tyndallized Lactobacillus acidophilus (HA122), Arabinogalactans, vitamin D, vitamin E and vitamin C, can be a valid support to immune system, after surgery both in adults and children.

The group treated with vitamin D alone had the least response of all, while the combination of Difensil Immuno + vitamin D immediately followed by Difensil Immuno group gave the best result. Based on these results we think that due to the safety of the products currently available on the market an immune support with nutraceuticals should be always considered after surgery independently from patient's age.

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AUTHOR BIOGRAPHY

Alessandro Maselli Del Giudice Otolaryngology department - Monsignor Raffaele Dimiccoli Hospital, Barletta, Italy

Francesco Barbara Otolaryngology department - Monsignor Raffaele Dimiccoli Hospital, Barletta, Italy

Francesco Cariti Otolaryngology department - Monsignor Raffaele Dimiccoli Hospital, Barletta, Italy

Salvatore Dadduzio Otolaryngology department - Monsignor Raffaele Dimiccoli Hospital, Barletta, Italy

Valentina De Robertis Otolaryngology department - Monsignor Raffaele Dimiccoli Hospital, Barletta, Italy

Silvana Ciccarone Otolaryngology department - Mon-signor Raffaele Dimiccoli Hospital, Barletta, Italy

Michele Barbara Otolaryngology department - Mon-signor Raffaele Dimiccoli Hospital, Barletta, Italy

Cialdella Francesca Otolaryngology department - Monsignor Raffaele Dimiccoli Hospital, Barletta, Italy