CLINICAL POSTOPERATIVE RECOVERY AFTER ADENOTONSILLECTOMY IN PEDIATRIC AGE: ROLE OF PIDOTIMOD

AGOSTINO SERRA, LUIGI MAIOLINO, GIANLUCA CAMPIONE, ANGELO CONTI, PAOLA DI MAURO
ENT Department -University of Catania, Italy

ABSTRACT

***Introduction**: There are numerous relationships between behaviour and immune system. Is particularly useful to identify the possible role played by a specific molecule to immunostimulant, Pidotimod, on restoring and optimizing physical performance in pediatric patients undergoing adeno-tonsillectomy surgery.*

***Materials and methods**: The study was performed on 600 patients, 275 males and 325 females, aged between 5 and 12 years, all subjected to adeno-tonsillectomy surgery.*

➢ Group A: 300 patients treated with immunostimulant therapy (Pidotimod)

➢ Group B: 300 untreated patients with no therapy.

The treatment of patients in the A group with Pidotimod provided for the administration of the drug, which started soon after hospitalization Parents of all patients provided a specific questionnaire

The patient follow-up was divided into three phases:

- *Phase T0: one week after the adeno-tonsillectomy intervention*
- *Phase T1: three months after the adeno-tonsillectomy intervention*
- *Phase T2: six months after the adeno-tonsillectomy operation.*

***Results**: The analysis of the obtained data revealed in its "absolute" evaluation the presence of a difference, somewhat evident, expressed in mean values, between the total score obtained in group A and that in group B.*

PHASE T0: The analysis of "relative" values, related to each single symptom, identified as the most prevalent phenomena, in descending order of frequency, dysphagia, odinophagia and asthenia

PHASE T1: Reduction in the mean value of the mean score for the reference symptoms

PHASE T2: Further decrease in the mean score for the reference symptoms in the two different groups

***Conclusions**: The results of the study carried out, highlight the role that immunostimulants, specifically Pidotimod, can be used to optimize healing processes in pediatric patients undergoing adeno-tonsillectomy surgery.*

***Keywords**: adeno-tonsillectomy surgery; immune system; physical performance; dysphagia, odinophagia and asthenia.*

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Introduction

The complex functional system called as "whole" represents the immune organized set of multiple defense systems of the human body. Immune activity can be defined as the summary of a whole set of biological functions that you linked and interact with each other through the intervention of specific ways of "communication link".

The anatomic-functional set that realizes the above is made up of different systems:

- nervous system
- endocrine system
- immune system

The information interchange between the various systems uses complex modulators circuits which operate at different functional levels. This interaction is accomplished systemically throughout the body, by means of communication between different bodies, including at the level of cellular communication[1].

In this situation the encephalic system plays a “primary”, as well as in all regulatory activities of the human body, which in its generalization has taken since the most remote archetypal character: the brain was already considered the supreme coordination headquarters of the various functional activities of the human body in the 7th century BC, a time when Alcmaeon of Croton attributed to the brain the role of supporter of “isonomia” between the different components of the human body.

The activities of interaction of the nervous system with the endocrine and immune systems, are based on molecular mechanisms which are mediated by various factors, such as:

- neuromodulators
- cytokines
- receptor systems.

Neuromodulators, whose activity is performed through the organization and regulation of interneuronal communications. They exert various typologically different actions on the behavioural and emotional sphere as well as play an important endocrine function[2,3].

The receptor systems of several neuromodulators and neurotransmitters are distributed in various areas of the central nervous system, the peripheral nervous system, of different tissues as well as in the immune system cells.

The receptor elements have high species-specificity for each neuromodulator or neurotransmitter, although the effects that these may mediate differ generally in relation to their location, in the face of their clear anatomical and structural overlay.

Cytokines have multiple biological activities, such as:

➢ amplification of the response of lymphocytes to antigens

➢ communicative mediation between the different cells of the immune system

➢ immune cell differentiation and growth stimulation

➢ immune-hormonal action

➢ action influencing the behavioural sphere.

T lymphocytes are the major cytokine producers, in particular T helper (CD4) and Tc (CD8).

The encephalic region is one of the most important target organs for cytokines, a field in which they manifest their action through a nervous path and a bloodstream[5].

The nervous route, primarily mediated by the vagus nerve, is particularly relevant to the signals coming from the gastrointestinal tract. For blood borne, instead, some cytokines pass the blood-brain barrier and enter through the other circum-ventricular organs where the barrier is permeable.

In the brain, cytokines induce the production of inflammatory mediators, such as prostaglandin E2, and synthesis of other cytokines microglial cells and astrocytes. Cytokines are expressed at the level of the CNS, either in response to an activation of the immune system, and in the absence of peripheral signals by the latter[4].

In the normal brain, the population of macrophages, which includes the perivascular macrophages and microglia and meningeal is inactive, but not in the event of a local or systemic inflammatory process. Macrophages play a key role in the signal transduction from the periphery to the brain and the macrophage activation state that influences the size of this transduction[7].

On the basis of what above reported, it is deduced that the brain may respond to immune origin cytokines, it can produce cytokines that mimic the situation device and may initiate a communication with the immune system. The efferent branches of the vagus nerve, in fact, inhibit the release of inflammatory cytokines in the periphery through the α-7 nicotinic receptors located on peripheral immune cells[9].

Recent studies have found that the immune cells, as well as having specific receptors, are capable of producing neurotransmitters crucial, as well as hormones and active substances on the nervous system. That discovery has permitted to theorize that the two systems, the neuroendocrine and the immune systems, can communicate with each other and coordinate response even when the information is initially perceived by a single system and they can also influence mutually[6,13].

A typical example of the above is verifiable, for example, in the physiology of the thymus gland, controlled by hormones and neuropeptides that have as their main target thymic epithelial cells that produce cytokines, neuropeptides and thymic hormones[8].

Glucocorticoids induce the degeneration of thymocytes in the process of differentiation, while estrogen promotes the development and formation of CD4 lymphocytes and androgens that promote the development of limphocytes CD 8.

Gonadal and sexual steroids at high levels induce a thymic invasion while prolactin stimulates the proliferation of thymic cells by increasing the production of cytokine interleukin 2.

Melatonin induces activated T lymphocytes to release opioid peptides that stimulate the immune system and exert an anti-stress action; it also intervenes in the regulation of glucocorticoid receptor on thymic cells, it protects them from degeneration induced by glucocorticoids and rebalances zinc levels that tend to decrease with the age[15].

The secretion of timulina, whose production is increased by prolactin, thyroid hormones, GH, β-endorphin, leuenkefalina, from the zinc and melatonin, follows a circadian rhythm characterized by a nocturnal peak as melatonin. Melatonin is believed to be involved in regulating immunomodulatory functions by increasing the production of thymic hormones.

The "growth factors" play an important role in nervous system development and in the modulatory regulatory, in the endocrine system and in the immune system too. They are involved in many fundamental physiological processes affecting different aspects of cell proliferation and differentiation and they exercise stimulant effects or inhibitors depending on the target cells.

"Growth factors", however, are characterized by a wide range of actions both in terms of the location of target organs and in the category of activity they mediate.

Some have a very wide-ranging spectrum of action, others a high degree of specialization; some actions take place predominantly of the endocrine type and affect cells at a distance from the synthesis site, others act principally in the area of the site of synthesis[14,17,18].

The various growth factors are synthesized in the central nervous system and in many other tissues, even at the level of lymphocytes and activated macrophages. In this situation, play an important role the neurotrophins, such as NGF and IGF-1, which are involved in physiological situations and they affect the harmonious development of the nervous system, the endocrine system and the immune system. Their stimulating effects inhibitors, may also play an important pathogenic role in several diseases and being implicated in pathological proliferative processes[12,13].

There are numerous relationships between behaviour and immune system, as certain immune modifications activate specific behavioural responses and, following the change in the mental attitude, one can observe changes in the immune response[16].

The close connections between the different systems induces the hypothesis that the optimization of immune performance in patients subjected to psycho-physical stress, such as post surgical, physical status, as well as positively influence might also encourage the rebalancing of psychic status, according to actual modulation on the entire neuro-psycho endocrine-immunological complex[10,11].

Based on the above considerations is particularly useful to identify the possible role played by a specific molecule to immunostimulant, Pidotimod, on restoring and optimizing physical performance in pediatric patients undergoing adeno-tonsillectomy surgery.

The choice of that specific molecule is based on individual and multiple actions that it can execute in the dynamic immune responses, such as:

- modulation of HLA-DR expression
- modulating expression of CD83 and CD86 molecules
- promoting the maturation of dendritic cells
- stimulation of dendritic cells to release pro-inflammatory molecules, pro-activating on T lymphocytes
- increased expression of TLR-2 receptors.

The set of effects that are extrinsic with regard to immunomodulatory activities that this molecule exerts on the innate and adaptive immune system.

Materials and methods

The study was performed on 600 patients, of both sexes, 275 males and 325 females, aged between 5 and 12 years, All subjected to adeno-tonsillectomy surgery.

➢ The subjects were divided into two groups:

➢ Group A: 300 patients treated with immunostimulant therapy (Pidotimod)

➢ Group B: 300 untreated patients with no therapy.

The treatment of patients in the A group with Pidotimod provided for the administration of the drug, which started soon after hospitalization, to 400mg/day per os for 20 days per month for 3 consecutive months. Parents of all patients, Group A and Group B, provided a specific questionnaire for the discharge of the hospital, aiming at detecting the subjective clinical performance of the individual children at weekly intervals.

The instrumental methodology involved performing all three phases of:

• Oropharingoscopy

• Endoscopic evaluation

These examinations were aimed at the visualization of the morpho-structural characteristics of the oro-pharyngeal complex.

The patient follow-up was divided into three phases:

• Phase T0: one week after the adeno-tonsillectomy intervention

• Phase T1: three months after the adeno-tonsillectomy intervention

• Phase T2: six months after the adeno-tonsillectomy operation (Table 1).

A GROUP	B GROUP
134 MALES	141 MALES
166 FEMALES	159 FEMALES
MIDDLE AGE: 7, 3 YEARS	MIDDLE AGE: 7,1 YEARS

Table 1: subdivision of patients into two groups A and B.

SYMPTOMS	SCORE				
DYSPHONIA	0	1	2	3	4
HALITOSIS	0	1	2	3	4
ANOREXIA	0	1	2	3	4
ASTHENIA	0	1	2	3	4
DYSPHAGIA	0	1	2	3	4
ODYNOPHAGIA	0	1	2	3	4
HEARING LOSS	0	1	2	3	4
CACOSMIA	0	1	2	3	4
SNORING	0	1	2	3	4
INTENSE SALVATION	0	1	2	3	4
COUGH	0	1	2	3	4
RHINOLALIA	0	1	2	3	4
RHINORRHEA	0	1	2	3	4

Table 2: evaluative questionnaire for residual symptomatology after adeno-tonsillectomy.

The questionnaire was formulated taking into account thirteen symptoms related to possible suffering conditions of the oro-pharyngeal district, in order to identify not only the absence or presence, but also the relative quantification according to a variable score from 0 to 4, respectively indicating:

0 = no symptoms

1 = very mild symptomatology

2 = mild/light symptomatology

3 = moderate symptomatology

4 = severe symptomatology

The overall evaluation of the questionnaire was based on the sum of individual scores (Table 2).

Results

The analysis of the obtained data revealed in its "absolute" evaluation the presence of a difference, somewhat evident, expressed in mean values, between the total score obtained in group A, subjects treated with Pidotimod, and that in group B, subjects not treated. These differences in overall scores, albeit with different margins, have been highlighted both in T1 phase follow up, 3 months after surgery and in T2 follow-up, 6 months apart from the T1 phase, surgical intervention.

The "relative" rating was focused on each symptom and relate to the two different groups, both in T1 and T2 stages.

PHASE T0:

In phase T0, the overall score of all questionnaires reported an average value of 35.2 for Group A and 33.9 for Group B sample.

The analysis of "relative" values, related to each single symptom, identified as the most prevalent phenomena, in descending order of frequency, dysphagia, odinphagia and asthenia, which were used as parametric symptoms with the following scores of average value (Table 3)

	DYSPHAGIA	ODYNOPHAGIA	ASTHENIA
A GROUP	3,5	3,1	2,9
B GROUP	3,7	3,3	2,6

Table 3: mean values of the reference symptoms at phase T0.

PHASE T1:

The evaluation of the questionnaires showed at T1 a reduction in the mean value of the mean score for the reference symptoms in the two different groups, as listed below (Table 4):

PHASE T2:

The evaluation of the questionnaires showed in T2 a further decrease in the mean score for the reference symptoms in the two different groups, as shown below (Table 5):

The statistical evaluation of the data obtained from the survey was based on the calculation of the mean score in the questionnaires of all patients, Group A and Group B, in relation to specific reference symptoms, with a parametric value.

	DYSPHAGIA	ODYNOPHAGIA	ASTHENIA
A GROUP	2,20	1,60	1,46
B GROUP	2,66	1,96	1,80

Table 4: mean values of the reference symptoms at phase T1.

	DYSPHAGIA	ODYNOPHAGIA	ASTHENIA
A GROUP	0,46	0,70	0,46
B GROUP	2,10	1,13	0,83

Table 5: mean values of the reference symptoms at phase T2.

The standard deviation values in T1 and T2 are given in Tables 6 and 7.

DS	DYSPHAGIA	ODYNOPHAGIA	ASTHENIA
A GROUP	0,805	0,621	0,507
B GROUP	0,844	0,764	0,664

Table 6: Standard deviation values of the T1 phase reference symptoms.

DS	DYSPHAGIA	ODYNOPHAGIA	ASTHENIA
A GROUP	0,571	0,596	0,571
B GROUP	0,607	0,681	0,698

Table 7: Standard deviation values of the T2 phase reference symptom.

The relevance and the value of the numerical differences found in the above calculations have been elaborated by applying Student's Tests (Table 8, Table 9).

	T1 A group	T1 B group	P value
DYSPHAGIA	2.20 ± 0.805	2.66 ± 0.844	0.032
ODYNOPHAGIA	1.60 ± 0.621	1.96 ± 0.764	0.046
ASTHENIA	1.46 ± 0.507	1.80 ± 0.664	0.033

Table 8: Application of student T calculation at T1 stage.

	T1 A group	T1 B group	P value
DYSPHAGIA	2.20 ± 0.805	2.10 ± 0.607	0
ODYNOPHAGIA	0.70 ± 0.596	1.13 ± 0.681	0.011
ASTHENIA	0.46 ± 0.571	0.83 ± 0.698	0.03

Table 9: Application of student T calculation at T2 stage.

Conclusions

Recent evidence on the bio-functional aspects of the immune system has shown that this acts corally with other complexes of the human-psychic, endocrinological, neurological- organism, constituting a functional set of blocks that intervene in modulation of "defensive" responses that can be induced from noxae of various kinds and nature.

Among the factors that can most trigger a "stressful" action on both the physical compartment and the psychic compartment, surgery can not be included, especially if performed in pediatric age. Childhood is, in fact, a very lively life-time in the immune profile, precisely because of the chronobiological characteristics that regulate it.

In this context it is important to emphasize that, on one hand, the "in vitro" induced effects on immunostimulation by specific molecules, such as Pidotimod, have been extensively studied; on the other hand, studies have so far been conducted in vivo, which led to the evaluation of possible effects on pediatric patients undergoing adeno-tonsillectomy.

In addition to the light of the delicate role that the adeno-tonsillary complex plays in the immune system, in addition to the other factors considered, age and surgical insult, in the homeostasis of the defensive economy of the human organism.

The study, aimed at the before mentioned goals, was conducted on 600 children aged between 5 and 12 years, subjected to adeno-tonsillectomy surgery. Patients were divided into two groups, A and B, of which the first subject was treated with Pidotimod and the second with no treatment.

The overall analysis of the data obtained has highlighted the progressive improvement of the clinical "status" of patients, both in "global" and "parcel" order, of parametric symptoms such as dysphagia, odynophagia and asthenia, along different phases T0, T1 and T2.

The comparison between the two groups A and B showed that the improvement was more pronounced in Group A patients than in Group B, and in terms of faster post-intervention recovery time, and a clearer reduction in the symptomatic intensity.

The above numerical results were evaluated by comparative statistical analysis, with particular reference to the calculation of the average value of the ead responses with the Student-t test.

Group A patients throughout the three month period of therapeutic administration did not exhibit any adverse events or manifestations of poor tolerability of the product.

The overall results of the study, in the light of the evaluations carried out, highlight the role that immunostimulants, specifically Pidotimod, can be used to optimize healing processes in pediatric patients undergoing adeno-tonsillectomy surgery.

Accordingly, it is apparent that Pidotimod may be definitively useful and profitablely included as a supportive therapy in daily clinical practice in pediatric patients undergoing adeno-tonsillectomy surgery

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Corresponding author
Prof. Luigi Maiolino
University of Catania – ENT Department
Azienda Ospedaliera Universitaria "Policlinico – Vittorio Emanuele", University of Catania
Via Santa Sofia n. 78
95123 Catania
(Italy)