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Nodolase™: A Review of Efficacy

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Review Article

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ABSTRACT

NODOLASE™ it's a new dietary supplement formulated with natural active and characterized by anti-inflammatory, anti-edema, analgesic and anti-oxidant effects. The aim of this review was to report the efficacy of NODOLASE™ in several patients. NODOLASE™ has been studied in patients with joint, tendons and muscle diseases, acute exacerbations of COPD and dental disease. In patients with wrist, ankle and knee sprain or with muscle strain as well as after plaster cast removal, NODOLASE™ resulted in a good efficacy in reducing pain and swelling. Furthermore, NODOLASE™ was able to significantly improve the joint function by a significant reduction of stiffness of at least 30% in all studies.

In patients with mild to moderate acute exacerbations of COPD, NODOLASE™ has been added to the antibiotic therapy. However, compared to the broad-spectrum antibiotic therapy alone, the combination with NODOLASE™ has resulted in a faster improvement of cough and dyspnea. The results of this study showed that the antibiotic association with NODOLASE™ was able to improve better the respiratory function (FEV1) compared to antibiotic monotherapy. Also extremely important the addition of NODOLASE™ has determined a higher impact on the inflammatory pattern and in particular on IL-6, IL-8 and TNF-alpha in comparison to the antibiotic alone. NODOLASE™ in combination with analgesic in patients undergoing wisdom teeth has been investigated in a randomized study. In comparison with a traditional analgesic for 7 days the group treated with the combination NODOLASE™+analgesic achieved better results in terms of efficacy with a lower incidence of pain local recurrence as well as a better recovery of the mandibular function.

No adverse effects due to the administration of NODOLASE™ were reported. Treatment with NODOLASE™ was evaluated safe in all studies both by clinicians and patients.

INTRODUCTION

The term "dietary supplement" is widely used to designate formulations that are also called nutraceuticals, but it would be better restricted to individual compounds used to treat or prevent deficiencies.

Dietary supplements [1] are widely used and offer the potential to improve health if appropriately targeted to those in need. Inadequate nutrition and micronutrient deficiencies are prevalent conditions that adversely affect global health. Although improvements in diet quality are essential to address these issues, dietary supplements and/or food fortification could help meet requirements for individuals at risk of deficiencies.

We conducted a systematic review to estimate the efficacy of NODOLASE™.

NODOLASE™

It's a new dietary supplement formulated with natural active and characterized by anti-inflammatory, anti-edema, analgesic and anti-oxidant effects. The main mechanism of action of NODOLASE™ consists in the stabilization of cell membranes, slowing or reducing the intracellular content loss of damaged cells and removing the radical oxygen species that cause inflammation.

These actions are due to the presence in the formulation of NODOLASE™ of Bromelain, Curcuma longa and Methyl-sulfonyl-

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methane (MSM).

Bromelain it's one of the active ingredients which attributed the anti-inflammatory action of proteolytic enzymes extracted from pineapples [2]; it exhibits anti-inflammatory action due to inhibition of thromboxane synthetase, the enzyme that leads to the formation of pro-inflammatory prostaglandins and thromboxanes [3].

Chemokines and inflammatory cytokines (IL-1, IL-6, IL-8, TNF-alpha) play an important role in sustaining the local inflammatory response [4].

Curcumin is a spice commonly used for a long time as a coloring agent (yellow) in many kinds of curry powder in food [5]. Evidence from in vitro studies revealed that curcumin has an inhibitory effect on substances involved in the inflammatory pathway, including lipoxygenase, cyclooxygenase (COX), phospholipase, collagenase, elastase and hyaluronidase. Furthermore, curcumin was found to inhibit the activation of free radical activated transcription factors such as nuclear factor kappa B and nitric oxide synthase. It also reduces the pro-inflammatory cytokines: as tumor necrosis factor alpha, interleukin (IL)-1 beta, IL-8 and the matrix metalloproteinase. All of these substances have a major role in the inflammatory joint process. Jackson et al. [6] reported that curcumin strongly inhibited collagenase and stromelysin expression, suggesting its therapeutic potential for the treatment of arthritis. Concerning safety profiles, curcumin was demonstrated to be safe, even after high-dose ingestion of up to 8,000 mg/day for 3 months. In various chronic illnesses in which inflammation is known to play a major role, curcumin has been shown to exhibit therapeutic potential. These diseases include Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis, epilepsy, cerebral injury, CVDs, cancer, allergy, asthma, bronchitis, colitis, rheumatoid arthritis, renal ischemia, psoriasis, diabetes, obesity, depression, fatigue and AIDS.

The Methylsulfonylmethane (MSM) is the natural form of organic sulfur [7] and a therapeutic agent used worldwide for treat many inflammatory disorders and painful. Sulphur it's an essential element for all of our cells function. In fact, in the case of sulfur deficiency the body is unable to build healthy cells, especially flexible and permeable [8].

MATERIALS AND METHODS

To date there is scarce information from clinical trials of dietary supplements in patients with joint, tendons and muscle disease. The purpose of this systematic review is to summarize the findings of recent trials investigating the impact of NODOLASE™ [9] a dietary supplement in adults affected by different inflammatory diseases.

NODOLASE™ it's a new dietary supplement with anti-inflammatory, anti-edema, analgesic and anti-oxidant effects. In tendon, bone and joint diseases has led high percentages of reduction of pain, swelling and edema and inflammation was usually resolved completely.

Eligible studies were prospective, randomized, comparative, open label, multicenter. Seven articles met our inclusion criteria for the systematic review (N=542) and were analyzed. Five studies have been conducted in patients with wrist, ankle and knee sprain and in patients with muscle strain or after plaster cast removal.

One study involved patients undergoing wisdom teeth extraction and another one has been conducted in patients with acute exacerbations of COPD. Outcomes included the pain VAS Scale [10] evaluation and the WOMAC Score for joint stiffness [11]. NSAIDs use "on demand" was also obtained in order to define the real need in the clinical practice. In all studies data were expressed as averages. The composite scores were analyzed with ANOVA test. An independent Student's T test assessed the comparison of scores. Significance was placed at $p<0.05$.

RESULTS

NODOLASE™ in Patients with Knee Sprain

The knee joint is stabilized by four major ligaments; the anterior cruciate ligament (ACL), the posterior cruciate ligament (PCL), the medial collateral ligament (MCL) and lateral collateral ligament (LCL) [12].

The first study [12] evaluated the efficacy and safety of NODOLASE™ in grade 1-2 adult patients suffering distortion in the knee during non-competitive sport. 84 patients were randomized into two treatment group: Tecartherapy+NODOLASE™ 4.5 g one sachet daily for 14 days or Tecartherapy alone [13] with a total of 6 sessions lasting an average of 20 min. All subjects were evaluated at baseline, after 2 (T1) and 4 weeks (T2). Parameters evaluated were:

- Pain
- Swelling
- Hematoma
- Joint Stiffness

The assessment of efficacy included the effects of treatments on painful symptoms assessed by the VAS Scale and the

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evaluation of post-traumatic functional joint limitation through the WOMAC Score for the joint stiffness and the reduction of swelling and of hematoma if present. In this study It has been also evaluated the use on demand of NSAIDs in the two groups of treatment. In **Table 1**, are summarized the patient's characteristics.

Table 1. The study sample.

	GroupA/Tecar (n=42)	Control Group B/Tecar.+NODOLASE™ (n=42)
Males/Females	27/15	31/11
Ligament involved		
MLC	18	19
LCL	14	12
ACL	6	5
PCL	4	6
Entity of distortion		
Grade 1	6	8
Grade 2	34	36
WOMAC score		
Pain (Likert 0-4)	7,9 +/- 1,6	8,4 +/- 1,3
Joint function	42,4 +/- 4,2	43,2 +/- 3,7
Stiffness	3,8 +/- 0,3	3,4 +/- 1,2
Total	**54,1 +/- 6,1**	**55,0 +/- 6,2**
Pain		
VAS 0-100 mm	70 +/- 2,1	68+/- 3,3

Results showed that pain and swelling in the knee improved in both groups. However, compared to Tecartherapy alone (group B) ($p<0.05$) the association of Tecartherapy with NODOLASE™ (group A) resulted in a more marked effect on the pain both at the T1 and T2 ($p<0.01$) **(Figure 1)**.

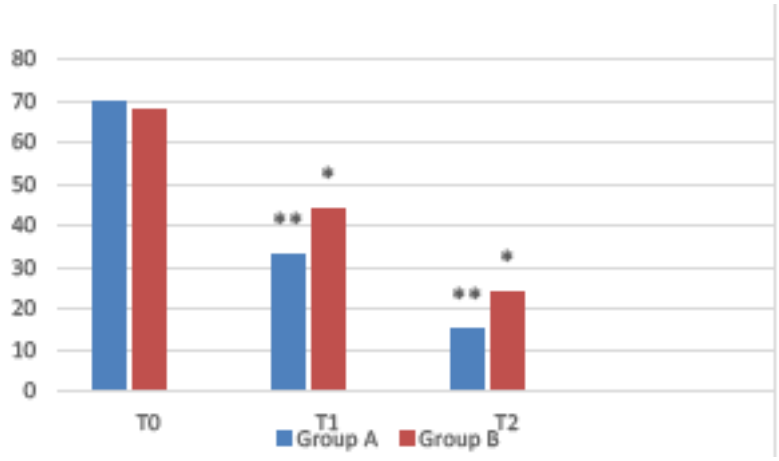

Figure 1. Effects of treatments on pain (VAS scale).

Legend: *p<0,05 vs. basal **p<0, 01 vs. basal
Group A: Tecartherapy+NODOLASETM 4.5 g one sachet daily for 14 days
Group B: Tecartherapy alone

The same trend occurred with regard to the effects on the function of knee joint. In fact, the treatment with NODOLASE™ in combination with Tecartherapy resulted more effective ($p<002$) with respect to the Tecartherapy alone ($p<0.05$) at both T1 and T2 **(Figure 2)**.

e-ISSN:2319-9865
p-ISSN:2322-0104

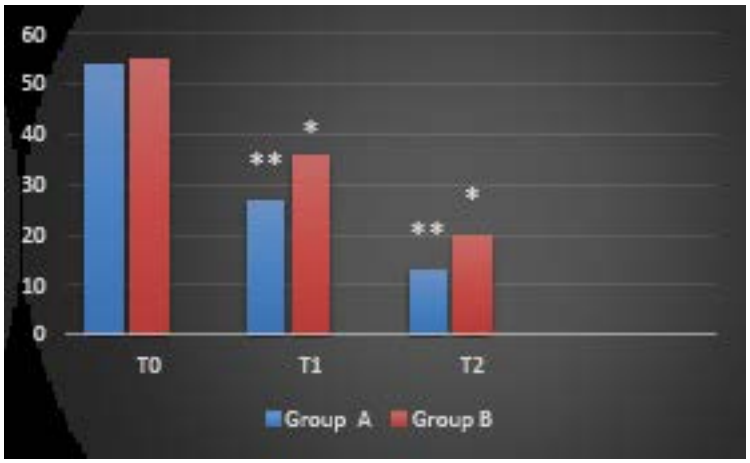

Figure 2. WOMAC score during treatment.

Legend: *p<0,05 vs. basal **p<0,02 vs. basal
Group A: Tecartherapy+NODOLASETM 4.5 g one sachet daily for 14 days
Group B: Tecartherapy alone

NODOLASE™ in Patients with Ankle Sprain [14]

The second study was a randomized comparative in "real practice trial" and reported the administration of NODOLASE™ in the treatment of post-traumatic edema in patients with contusion and ankle sprain.

The trials enrolled 74 subjects of age between 30 and 60 years practicing non-competitive sports which has been underwent to a X-RAY 2 Projections and an ultrasound evaluation due to a traumatic event.

To all was applied the R.I.C.E. protocol (Rest, Ice, Compression and Elevation) [15]. No one requested the application of a plaster cast for the immobilization of the ankle.

The subjects were divided into 2 groups: Group A (n=37) supplemented with Bromelain for 14 days 2 cpr 50 mg/day and Group B (n=37) treated with NODOLASE™ one sachet 4.5 g per day for 14 days. In group A there were 21 patients with contusion and 16 subjects with distortion. In group B 23 patients were with contusion and 14 subjects with distortion. All subjects were evaluated at baseline, after 7 days (T7) and after two weeks (T14).

The efficacy evaluation on edema and inflammation was estimated by measuring the ankle circumference. The symptomatology was assessed by a Visual Analogue Scale (VAS) for pain while for the assessment of post traumatic functional limitation of the ankle the Authors used the WOMAC score for stiffness joint.

The results showed that both groups have been proven effective in determining a significant clinical improvement.

However, NODOLASE™ showed respect to Bromelain alone a higher efficacy in inducing the reduction of the edema measured at malleolar level together with a speeder action **(Table 2)**.

Table 2. Malleolar medium circumferences (cm) in the two groups at T0, T7 and T14.

	T0	T7	T14
Group A: (Bromelain)	28,7	27,1	26,4 *
Group B: (NODOLASETM)	29,1	26,1*§	24,9**

NODOLASE™ in Patients with Wrist Sprain [16]

In this Open Label efficacy study of NODOLASE™ in patients affected by wrist sprain during non-competitive sport, the Authors included 48 consecutive adult subjects of both sex (32 men and 16 women) suffering from distortion of the 1st and 2nd grade at the wrist. (12 patients with grade 1 and 36 patients with grade 2). They excluded patients with a fracture of the wrist, patients who had taken anti-inflammatories in 12-24 h prior to the traumatic event or with a history of peptic ulcer or bleeding. The positivity at pregnancy test was a further condition of exclusion.

All patients were subjected to an X-ray evaluation of the wrist, in order to rule out a fracture, and an application of ice, a bandaging tight and a lower limb elevation in the first 24 h after the trauma. No patient experienced the need of surgery and all patients were treated with a conservative approach. The following parameters were evaluated:

- Pain depending on the severity of the distortion

- Swelling

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- Reduced wrist mobility

- Stiffness of the wrist

- Joint instability

In all patients the degree of distortion, the ligaments involved, the VAS score (0-100 mm) the pain and the WOMAC score of joint involvement (including, pain Likert 0-4 scale) joint function and stiffness have been assessed before the treatment and after 1 (T1) and 3 weeks (T2). Patients have been treated with NODOLASE™ 4,5 g one sachet/daily for 21 days. It was allowed the use of NSAIDs on demand.

Patients was given a diary and clinician asked them to report it after one week with the indication of note any painful relapses and especially the time to return to normal activities of the traumatized wrist. An overall judgment was also asked about the treatment efficacy (very good-good-poor) and its tolerability.

Primary objective of the study was the evaluation of NODOLASE™ on pain and swelling of the wrist. For the assessment of pain a Visual Analog Scale (VAS) with a score from 0 (no pain) to 100 (maximum pain) was used. Secondary objective of the study draws an assessment of improvement in WOMAC score from baseline in reference to pain, joint stiffness and joint function in patients with major symptoms. The total score could range from 0 to 96 points. Both the VAS and WOMAC score were measured at T0 (baseline), T1 (after 1 week) and T2 (after 3 weeks). In addition, also in this study the use of NSAIDs was permitted on "demand". The consumption of these drugs was reported in order to assess the real need. Further the return to manual activities and use of traumatized wrist by patients was rated. Pain and swelling of the wrist improved significantly with NODOLASE™ after 1 week and this improvement lasted until T2 (3 weeks) ($p<0.04$) **(Figure 3)**.

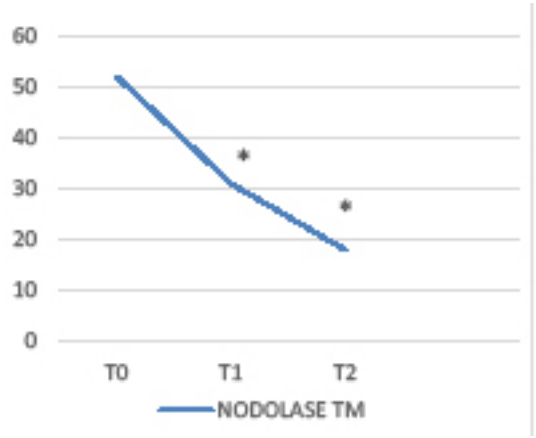

Figure 3. Effects of NODOLASETM on pain (VAS scale).

Legend: *p<0,04 vs. basal

The same result was obtained regarding the effects on the wrist joint **(Figure 4)**. In fact, treatment with NODOLASE™ was significantly effective in improving the joint function by a reduction of stiffness starting after 1 week ($p<0.05$) and continued up to 3 weeks ($p<0.02$).

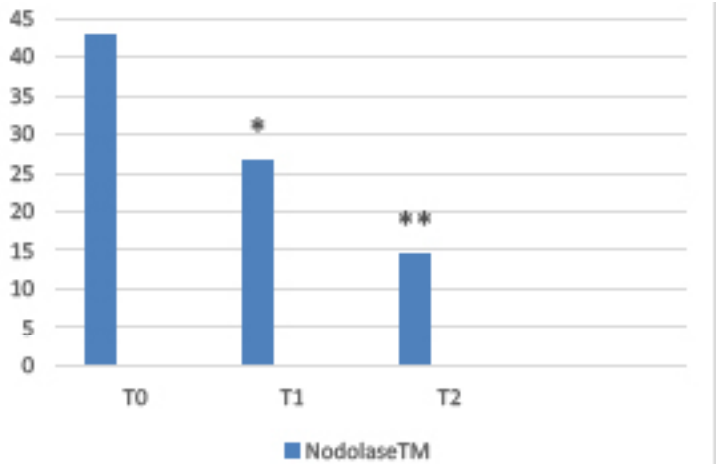

Figure 4. Effects of treatment (WOMAC score) with NODOLASETM on wrist joint stiffness.

Legend: *p<0,05 vs. basal **p<0,02 vs. basal

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p-ISSN:2322-0104

All patients completed their diary in order to express an opinion regarding the efficacy and tolerability of NODOLASE™ treatment **(Figure 5)**.

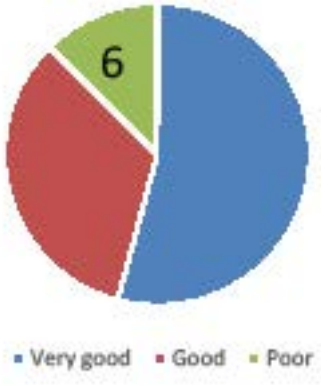

Figure 5. Efficacy and tolerability of NODOLASETM by patient evaluation.

NODOLASE™ in Patients with Muscle Strain [17]

The objective of the study was to evaluate the efficacy and safety of NODOLASE™ in non- agonistic sports practitioners suffering from muscle strain. In this prospective randomized study of "real practice" were included 78 consecutive adult outpatients of both sexes (49 men and 29 women) suffering from muscle strain (42 patients with a calf strain and 36 patients with strained quadriceps).

Patients with a muscle injury or a tear, patients who had taken anti-inflammatories in 12-24 h preceding the traumatic event or a history with a history of peptic ulcer or bleeding were excluded. The positivity of pregnancy test was a further condition of exclusion.

Patients were randomized into two groups:

Group A: n=39 treated with R.I.C.E Protocol plus NODOLASE™ 4.5 g one sachet daily for 14 days.

Group B: n=39 treated with R.I.C.E. Protocol alone.

All patients underwent an ultrasound echocardiography in order to rule out the presence of distractions or of a muscle tears and treated with ice, rest, bandaging tight and leg elevation (R.I.C.E Protocol).

The parameters evaluated were:

- pain according to the severity of the stretch
- swelling
- inflammation
- muscle stiffness
- movement restriction

For all patients the pain was evaluated with a Visual Analogue Scale (VAS 0-100 mm) **(Table 3)**.

Table 3. Patients characteristics.

	Group A/R.I.C.E.+NODOLASE (n=39)	Control Group B//R.I.C.E (n=39)
Males/Females	23/16	24/15
Muscle involved		
Calf	22	20
Quadriceps femoris	17	19
Practiced sports		
Football	17	18
Athletics	13	12
Tennis	4	3
Basket	5	6
PAIN		
Score (VAS 0-100 mm)	64 +/- 2,1	58 +/- 3,3

Primary objective of the study was to evaluate the efficacy of NODOLASE™ in patients with muscle strain in addition to R.IC.E. Protocol towards the only R.I.C.E. Protocol application. For the assessment of the pain a visual analog scale was used (VAS) with a score from 0 (no pain) to 100 (maximum pain).

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p-ISSN:2322-0104

To all patients has been suggested to report any painful relapses and to express a judgment on the recovery times and an overall evaluation of NODOLASE™ efficacy and tolerability. Secondary objectives of the study were the evaluation of any painful relapses and the recovery time to return to sport activity by patients. Also it is allowed the eventual use of NSAID drugs on "demand" and the consumption of these drugs have been reported by the patients in order to assess the real use of these drugs.

Pain significantly improved in Group A with the addition of NODOLASE™ at time T1 (after 1 week) ($p<0.02$) and at T2 (2 weeks) ($p<0.02$); even with the application of the R.I.C.E protocol in Group B pain improved ($p<0.05$) but with the addition of TM NODOLASE this effect was more intense **(Figure 6)**.

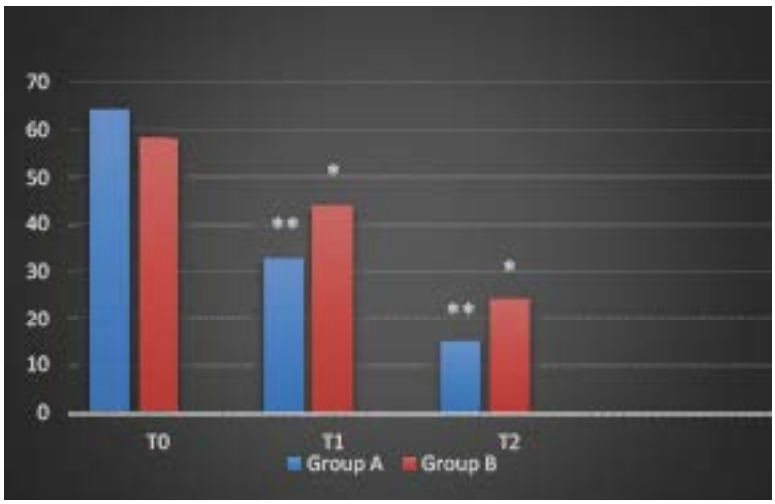

Figure 6. Treatment effects on pain (VAS scale).

Legend: *p<0,05 vs. basal **p<0,02 vs. basal
Group A: n=60: 7 days of a broad spectrum antibiotic
Group B: n=60: 7 days of a broad spectrum antibiotic+NODOLASETM for 14 days

NODOLASE™ in Patients after Plaster Cast Removal [18]

The authors conducted a Prospective Observational study in clinical practice in subjects with ankle sprain presenting residual swelling, pain and long-term joint stiffness after plaster cast removal.

They enrolled 54 consecutive subjects of both sexes suffering from an episode of ankle sprain treated with pinstriped ankle and having a residual component of edema and pain as well as a residual joint stiffness after the plaster cast removal. All individuals of age between 30 and 50 years were non-competitive sport practitioners and have been submitted to X-RAY 2 projections and at an ultrasound evaluation. The R.I.C.E. protocol was applied to all.

All patients received NODOLASE™ 4.5 g one sachet per day for 28 days. The efficacy evaluation on edema and inflammation was assessed by measuring the ankle circumference **(Figure 1)** at T0 and T28.

The effect on pain has been assessed by a visual analogue scale (VAS), while for the assessment of post - removal functional limitation the WOMAC stiffness score for joint (12) both at T0 and T28 has been used.

NODOLASE™ was effective in reducing the residual edema plaster removal as evidenced by reducing the ankle circumference and improving joint function through a reduction effect of the stiffness.

Also NODOLASE™ resulted in a significant improvement in pain symptoms **(Table 4)**.

Table 4. NODOLASETM effects.

Malleolar circumference (mean)	**T0** 24,5	**T28** 20.3	p<0.05 vs. T0
Pain VAS scale (mean)	**T0** 7.3	**T28** 4,2	p<0.01 vs. T0
Joint stiffness (WOMAC R.A.)		**T28** 39%	p<002 vs. T0

NODOLASE ™ in Patients with Cute Exacerbations of COPD [19]

Chronic Obstructive Pulmonary Disease is a condition characterized by a chronic lung airway obstruction, with airflow limitation at all or only partially reversible, slowly progressive and caused by a chronic inflammation of the airways and of lung parenchyma.

The exacerbation of COPD [20] is defined as "a prolonged deterioration in the patient's condition with respect to the stable state and beyond normal daily variation, which occurs acutely and requires a modification of the treatment in a patient suffering from COPD."

Many inflammatory mediators, including IL-6, IL-8 and TNF-α, are capable of damaging lung structures and/or to maintain the neutrophil inflammation.

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This randomized, comparative study evaluated the efficacy and safety of NODOLASE™ in subjects with COPD exacerbation of mild to moderate grade (<=2 previous episodes of exacerbation history in the last year on basic bronchodilator therapy and FEV1 between 50% and 80%) in combination with broad spectrum antibiotic vs. broad-spectrum antibiotic monotherapy.

The study included 120 subjects (42 Gold Stage I and 78 Gold Stage II) of both sexes (68 men and 52 women) suffering from acute exacerbation of COPD mild/moderate characterized by the presence of symptoms and/or signs such as:

- increased cough
- increase in sputum volume
- purulent sputum
- sputum color change
- increased dyspnea
- fever ≥ 37 °
- peripheral edema
- increased respiratory rate
- pathological rumors increase

The following parameters were evaluated:

- Sputum: Color, Quantity/germs isolated
- Cough (mild-moderate-severe)
- Dyspnea (mild-moderate-severe)
- FEV1 (ml)
- Inflammatory Pattern: IL-6 IL-8 and TNF-alpha
- Bronchodilators: doses

All parameters were evaluated in the two groups at T0, T7 and T14. Cough and dyspnea were assessed by a modified VAS scale. The pattern of inflammation was measured in plasma by ELISA and Spectrophotometric analysis. FEV1 was assessed by Spirometry.

The comparison between groups was performed using an independent t-test of Student and a Mann-Whitney U test. Significance was at $p<0.05$.

Patients received: Group A n=60: 7 days of a broad spectrum antibiotic. Group B n=60: 7 days of a broad spectrum antibiotic+NODOLASE™ for 14 days.

**Both groups taken as therapy for the underlying disease a bronchodilator

Coughing and dyspnea improved in both groups. However, compared to the broad-spectrum antibiotic therapy alone [21] the combination with NODOLASE™ has resulted in significant improvement of both parameters after two weeks and particularly of the dyspnea **(Figure 7)**.

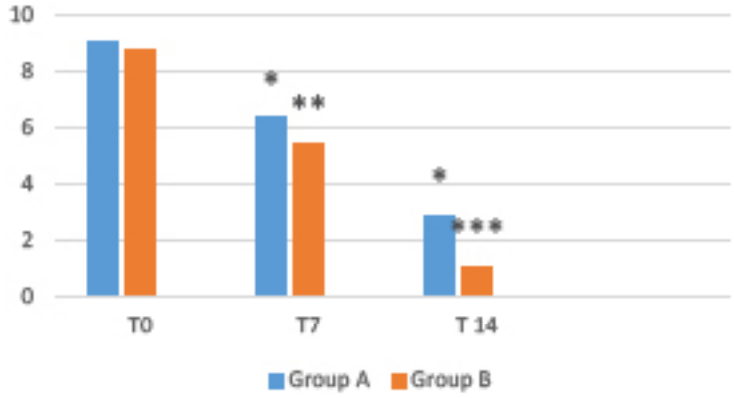

Figure 7. Effect of treatments on dyspnea (VAS modified.

Legend: *P<0,05 vs. T0 **p<002 vs. T0 ***p<0,01 vs. T0
Group A n=60: 7 days of a broad spectrum antibiotic
Group B n=60: 7 days of a broad spectrum antibiotic+NODOLASETM for 14 days

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p-ISSN:2322-0104

Concerning sputum reduction or the aspect change from purulent to normal for the underlying disease the effects were similar in the two groups with a higher trend of efficacy for the association antibiotic broad-spectrum plus NODOLASE™ after 1 and 2 weeks.

Particularly important were the effects of treatments on respiratory function measured by FEV1 **(Table 5)** and the evaluation of the pattern of inflammation of cytokines involved in the exacerbation episode (IL - 6, IL- 8 and TNF -alpha) [22] **(Tables 6-8)**.

Table 5. FEV1 (L).

	Gruppo A FEV1 (ml)	Gruppo B FEV1 (ml)
T0	1,28	1,34
T7	1,42	1,81 **
T14	1,58 *	2.01 ***

Legend: * p<0,05 vs. T0 ** p<0,03 vs. T0 *** p<0,01 vs. T0

Table 6. IL-6 plasma concentrations (pg/ml).

	Gruppo A: 7 days of a broad spectrum antibiotic	Gruppo B: 7 days of a broad spectrum antibiotic + NODOLASE™
T0	7,38	8,98
T7	6,21	4,3**
T14	4,9*	1,5***

Legend: * p<0,05 vs. T0 ** p<0,03 vs. T0 *** p<0,01 vs. T0

Table 7. IL-8 plasma concentrations (pg/ml).

	Gruppo A n=60 7 days of a broad spectrum antibiotic	Gruppo B n=60 7 days of a broad spectrum antibiotic+NODOLASE™
T0	10,37	11,44
T7	8,48	5,31 **
T14	6,53*	2,26 ***

Legend: * p<0,05 vs. T0 **P< 0,02 vs. T0 ***p<0,01 vs. T0

Table 8. TNF-alfa plasma concentrations (pg/ml).

	Gruppo A n=60 7 days of a broad spectrum antibiotic	Gruppo B n=60 7 days of a broad spectrum antibiotic+NODOLASE™
T0	13,8	14,5
T7	11,6	7,8**
T14	7,9 *	2,5***

Legend: * p<0,05 vs. T0 ** p<0,02 vs. T0 *** p<0,01 vs. T0

The results of this study show that the antibiotic association with NODOLASE™ was able to improve more efficiently the respiratory function (FEV1) compared to antibiotic monotherapy. Also extremely important the addition of NODOLASE™ has determined a higher impact on the inflammatory pattern and in particular on IL-6, IL-8 and TNF-alpha with respect to the antibiotic treatment alone.

NODOLASE™ in Patients Undergoing Wisdom Teeth Extraction [23]

The efficacy and safety of NODOLASE™ in combination with analgesic in patients undergoing wisdom teeth extraction presenting edema, swelling, pain and mandibular contraction in the long term, has been investigated in this randomized, comparative study that included 84 subjects of both sexes (48 men and 36 women) and age between 25 and 40 years.

The following parameters were evaluated:

- Edema, swelling and local pain

- Facial pain

- Paresthesia at lip

- Mandibular contraction with difficult chewing

Patient was randomized in two groups: Group A=Synflex 550 (7day) and Group B=Synflex 550 (7day) plus NODOLASE™ 4,5 gr/die (14 day). Evaluation of pain was made by the VAS scale while mandibular contraction by the MTA tests **(Figure 8)**. Test was considered positive if there was a problem at the MTA and the patient touched the temporo-mandibular joint. Further the number of painful relapses locally between T7 and T14 in the 2 groups was recorded.

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Figure 8. MTA test execution.

Both groups showed a significant analgesic and anti-edema effects respect to baseline. However, after a week the addition of NODOLASE™ to analgesic improved significantly the efficacy of treatment **(Figure 9)**.

After an additional week of NODOLASE™ treatment a lower incidence of symptoms and/or signs, due to a decreased occurrence of painful relapses, was documented **(Table 9)**.

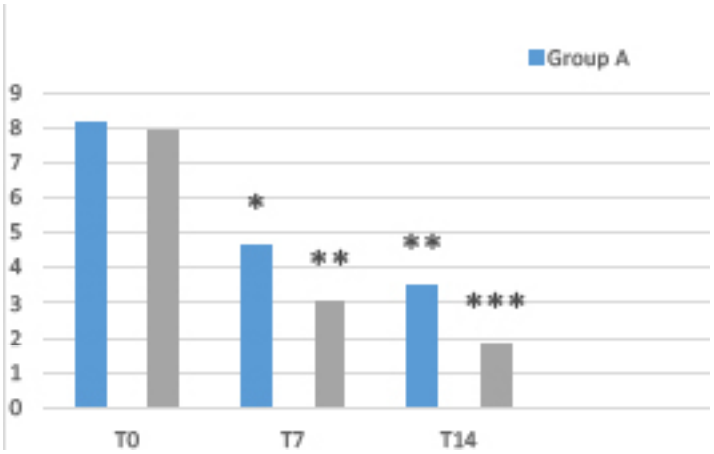

Figure 9. Pain improvement (VAS scale) [23].

Legend: * p<0,05 vs. T0 ** p<003 vs. T0 *** p<0,01 vs. T0
Group A=Synflex 550 (7day)
Group B=Synflex 550 (7day) plus NODOLASETM 4,5 gr/die (14 day).

Table 9. Comparison between the two groups (recurrent local pain).

	Group A (n=42) Synflex 550 (7day)	**N=10**
Patients with local relapse during interval T7-T14		B vs. A **-33%**
	Group B (n=42) Synflex 550 (7day) plus NODOLASE™ 4,5 gr/die (14 day)	N=3

In comparison with a traditional analgesic for 7 days the group treated with the combination NODOLASE™+analgesic achieved better results in terms of efficacy with a lower incidence of pain local recurrence with a better recovery of the mandibular function.

Both treatments showed a good safety profile together with an optimal compliance. All patients have completed the treatment.

DISCUSSION

Tendon, muscle and joint diseases are characterized by a strong inflammatory component. The same applies to the exacerbations of chronic bronchitis and tooth extractions of wisdom teeth. In particular, pain is a common symptom but in the case of sprains and contusion of ligaments all the functional alterations that affect the normal daily activities are very important.

NODOLASE™ has been studied in patients with joint, tendons and muscle diseases. In patients with wrist, ankle and knee sprain or with muscle strain as well as after plaster cast removal, NODOLASE™ resulted in a good efficacy in reducing pain and swelling. Furthermore, NODOLASE™ was able to significantly improve the joint function by a significant reduction of stiffness in all studies.

In patients with mild to moderate acute exacerbations of COPD, NODOLASE™ has been added to the antibiotic therapy. However, the combination with NODOLASE™ has resulted in a faster improvement of cough and dyspnea and has been able to improve better the respiratory function (FEV1) compared to antibiotic mono-therapy. Also extremely important the addition of NODOLASE™ has determined a higher efficacy on the inflammatory pattern and in particular on IL-6, IL-8 and TNF-alpha in comparison to the antibiotic alone.

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NODOLASE™ in combination with analgesic in patients undergoing wisdom teeth achieved better results in terms of efficacy in comparison with a traditional analgesic for 7 days with a lower incidence of pain local recurrence, as well as a better recovery of the mandibular function.

No adverse effects due to the administration of NODOLASE™ were reported. Treatment with NODOLASE™ was evaluated safe in all studies both by clinicians and patients.

CONCLUSION

NODOLASE™ as supplement should be considered as a viable alternative in cases of traumatic events characterized by edema, pain, joint and muscles functional limitations as well as an additional treatment for acute exacerbations of COPD and dental diseases.

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