Evaluation of efficacy and safety of Septilin Junior tablets in recurrent upper respiratory tract infections in children

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ABSTRACT

Recurrent infections remain a common presentation in ENT practice, and recurrent upper respiratory tract infections (URTIs) not responding to antibiotics should alert the doctor to a possible underlying immunodeficiency. Recent studies have demonstrated the crucial role played by the immune defence mechanism of the host and it has been hypothesized that immunomodulation may have a favorable impact in treating recurrent URTIs. This study was planned to evaluate the efficacy and safety of Septilin Junior tablets in recurrent URTIs.

The study was an open, non-comparative clinical trial approved by the Institutional Ethics Committee of B.J. Medical College, Ahmedabad. Hundred children aged 5 to 14 years with history and evidence of recurrent URTIs, of both sexes, were included in the study. Children having concomitant severe illness necessitating other treatment, severe malnutrition and associated high-grade fever, genetic and endocrine disorders and those whose parents refused to give informed consent, were excluded from the study. A baseline history was obtained in order to determine the child’s eligibility for enrolment in the trial. A thorough ENT examination was done for current evidence of URTI. All children were subjected to laboratory examinations, throat swabs for microbial culture and sensitivity, radiograph of paranasal sinuses and nasal endoscopy. All children consumed Septilin Junior tablets for 4 weeks, the dose predetermined by the age of each child. The children were followed up every week for a total period of 4 weeks and during each follow-up visit, ENT examination was done and observations recorded in the structured case record sheets. All local and systemic adverse events reported by children/parents or observed during clinical examination were recorded with information about severity, time of onset, duration and action taken regarding the study drug. An analysis was done according to intention-to-treat principles.

One hundred children with a history of recurrent URTIs, were enrolled in the study, the mean age being 7.99 years. Symptomatic relief was evident after 2 weeks and a majority of children were clinically cured after 3 weeks of treatment. At the end of the study, almost all children were found clinically asymptomatic. The total leukocyte count, ESR, eosinophil count, and absolute eosinophil count significantly decreased from baseline values. Elevated ASO titer, CRP levels and IgE levels significantly decreased from baseline values. All the children, whose throat swabs were positive at the time of enrollment, had throat swabs with negative results at the end of the study. The overall compliance to the treatment was excellent and no clinically significant adverse events were either reported or observed during the entire period of study.

This study observed significant improvement in clinical, hematological and immunological parameters in children suffering from recurrent URTIs, and it can be concluded that Septilin Junior tablets are effective and safe for treatment and prevention of recurrent URTIs in children.
INTRODUCTION

Recurrent infection remains a common presentation in ENT practice despite the decrease in frequency of pyogenic infections with new generation antimicrobials. It has been suggested that persistent or recurrent URT infections that do not respond to antibiotics should alert the doctor to a possible underlying immunodeficiency\(^1,2\). It has been documented that the majority of patients with a primary immunodeficiency have a history of recurrent ENT infections\(^3,5\). Although primary immunodeficiency is uncommon, most patients have no demonstrable immunodeficiency even after exhaustive immunological testing. Spickett et al. observed that a large proportion of patients with antibody deficiency were ENT outpatients without the underlying diagnosis being made\(^2,4\). The same report found that the average delay from onset of recognizable symptoms of antibody deficiency to diagnosis was 6.26 years\(^2,5\).

It is important to remember that primary immune deficiencies, especially antibody deficiencies, can present at any age. The incidence of Common Variable Immunodeficiency is bimodal, with the first peak in the first 5 years of life and the second peak in the second decade, but it should still be a considerable for the elderly\(^2,6\).

A triad of rhinorrhoea, cough and fever characterize recurrent upper respiratory infections (URTIs). Most of these conditions are self-limiting and invariably have a viral etiology. Recurrent attacks of URTIs may lead to distinct morbidity. Repeated attacks of tonsillitis may lead to complications like rheumatic heart disease or post streptococcal glomerulonephritis, untreated otitis media may lead to devastations such as perforation of the tympanic membrane, labyrinthitis, sensory neural hearing loss and facial nerve palsy, and rhinitis may lead to complications such as laryngotracheobronchitis, pharyngitis and mucocele.

The detection of important clinical signs is critical for the diagnosis of these conditions. Sore throat is the cardinal feature of tonsillitis while rhinorrhea characterizes rhinitis. In pharyngitis, jugulodigastric adenitis is commonly present, while there is marked tenderness over nasal sinuses in sinusitis and chronic recurrent otitis media is characterized by ear discharge.

Clinically, URTIs can be classified into three groups as benign (rhinitis), potentially serious (pharyngitis, tonsillitis, otitis media and sinusitis) and serious (retropharyngeal abscess, epiglotitis, croup and diphtheria). Presence of respiratory distress, drooling of saliva, hoarse voice, strider, high fever, patch in throat and altered consciousness suggest serious URTIs. The hallmark of upper respiratory tract infection is lack of lower respiratory signs and absence of any radiographic changes in the chest.

Recent studies have demonstrated the crucial role played by the host immunity defence mechanism and it had been hypothesized that immunomodulation may have favourable impact in treating recurrent URTIs. Most children suffering from recurrent URTIs, receive antimicrobials, which are seldom necessary. These antimicrobials are associated with risk of various short- and long-term adverse events and furthermore, there is always the inherent risk of emergence of microbial resistance to these antimicrobials\(^\).

Septilin Junior tablet is a polyherbal formulation with *Commiphora wightii*, Shankh bhasma and extracts of Maharasnadi quath, *Tinospora cordifolia*, *Rubia cordifolia*, *Emblica officinalis*, *Moringa pterygosperma*, *Glycyrrhiza glabra* and Trikatu. Various clinical studies have observed the beneficial immunomodulation offered by Septilin Junior tablets in various disorders. This study was planned to evaluate the efficacy and safety of Septilin Junior tablets in recurrent URTIs.
MATERIAL AND METHODS

Aim of the study
This study was aimed to evaluate the clinical efficacy, short- and long-term safety of Septilin Junior tablets in treatment and prevention of recurrent URTIs.

Study design
The study was an open, non-comparative clinical trial conducted from January 2002 to December 2004, at the Department of Pediatrics, approved by the Institutional Ethics Committee of B. J. Medical College, Ahmedabad, India.

Inclusion criteria
One hundred children, aged 5 to 14 years, of both sexes with a history and evidence of recurrent URTIs (tonsillitis, pharyngitis, rhinitis, sinusitis and otitis media), attending the outpatient clinic, of the Department of Pediatrics, B.J. Medical College, Ahmedabad, were included in the study. A written informed consent was obtained from parents.

Exclusion criteria
Children having concomitant severe illness necessitating other treatment, severe malnutrition and associated high-grade fever, genetic and endocrinial disorders and those whose parents refused to give informed consent were excluded from the study.

Study procedures
A baseline history was obtained in order to determine the child’s eligibility for enrolment in the trial. The baseline assessment included personal data, a description of symptoms and details of past medical history. Thereafter all children underwent a clinical examination. A thorough ENT examination was done for current evidence of URTI. All children were subjected to laboratory tests for routine blood examination, presence of C reactive protein (CRP), ASO titer, serum IgE levels, throat swabs for microbial culture and sensitivity, radiograph of paranasal sinuses and nasal endoscopy.
All children consumed Septilin Junior tablets for 4 weeks, the dose predetermined according to the child’s age (for the age group of 5-7 years: 1 tablet, twice daily, 8-10 years: 1 tablet, three daily and 11-14 years: 2 tablets, twice daily). All children were followed up every week for 4 weeks and during each follow-up visit, ENT examination was done and observations recorded in the structured case record sheet. All patients were reviewed clinically and laboratory investigations repeated at the end of 4 weeks.

Primary and secondary outcome measures
The predefined primary outcome measures were symptomatic improvement, and reduction in the upper respiratory tract inflammation. The predefined secondary outcome measures were reduction in number of recurrent episodes of URTI, incidence of adverse events and compliance to treatment.

Adverse events
All local and systemic adverse events reported by children/parents or observed during clinical examination were recorded with information about severity, time of onset, duration and action taken regarding the study drug. Children were allowed to voluntarily withdraw from the study, if they had experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment.

Statistical analysis
An analysis was done according to intention-to-treat principles. Changes in various parameters from baseline values to the values after the 4th week were analyzed by using
"paired t test". The minimum level of significance was fixed at a 95% confidence limit and a 2-sided p value of <0.05 was considered significant.

RESULTS
One hundred children with a history of recurrent URTIs were enrolled in the study, the mean age being 7.99 years (range: 4–12 years). Out of 100 children, 27 had recurrent tonsillitis, 27 had recurrent pharyngitis, 22 had recurrent rhinitis, 9 had recurrent sinusitis and 15 had recurrent otitis media.

The symptomatic relief was evident after 2 weeks and a majority of children were clinically cured after 3 weeks treatment. At the end of the study, almost all children were found clinically asymptomatic. The total leukocyte count significantly decreased from baseline value of 8467 cells/cumm to 7136 cells/cumm at the end of study ($t=5.965$, $p<0.0001$). The ESR significantly decreased from baseline value of 23.26 mm/hr to 11.49 mm/hr at the end of study ($t=9.209$, $p<0.0001$). There was significantly decrease in the elevated eosinophil count from baseline value of 2.704% to 1.789% at the end of study ($t=2.766$). The absolute eosinophil count significantly decreased from baseline value of 23.26 cells/cumm to 11.49 cells/cumm at the end of study ($t=9.209$, $p<0.0001$) (Figure 1).

ASO titer was found raised in 6 children with tonsillitis and 4 children with otitis media. The ASO titer significantly decreased from baseline values of 264.7 IU/ml to 97.01 IU/ml at the end of study ($t=8.300$, $p<0.0001$). CRP was also found raised in 10 children at the time of enrollment and these elevated CRP levels significantly decreased from baseline value of 6.656 mg/ml to 1.408 mg/ml at the end of study ($t=9.408$, $p<0.0001$) (Figure 2). It was observed that, in 96 children, serum IgE level was significantly raised and these elevated IgE levels significantly decreased from baseline value of 422.4 IU/ml to 122.4 IU/ml at the end of study ($t=6.656$, $p<0.0001$) (Figure 3).
Throat swab culture examination was done for children suffering from recurrent tonsillitis, pharyngitis and otitis media. Out of 27 (39.13%) children suffering from pharyngitis, 19 (27.54%) were positive for throat culture and 8 (11.59%) had a negative throat swab, at the beginning of the study. Out of 27 (39.13%) children suffering from tonsillitis, 16 (23.19%) were positive for throat culture and 11 (15.94%) had negative throat swabs. Out of 15 (21.74%) children suffering from otitis media, 3 (4.35%) were positive for throat culture and 12 (17.39%) had negative throat swabs. All children with a positive throat swab at the time of enrollment had negative throat swabs at the end of the study.

The overall compliance to the treatment was excellent and no clinically significant adverse events were either reported or observed during the entire period of the study.

**DISCUSSION**

Pharyngitis often has a bacterial etiology and Group A β-hemolytic streptococci are the common isolated bacteria. Throat culture is now recognized as the gold standard diagnose Group A β-hemolytic streptococcal infection. The ASO titre is a special serologic test, known as anti-streptolysin O, which measures the quantity of antibody against a component of streptococcal bacteria and is a useful diagnostic test for streptococcal disease.

Though rhinitis is an acute self-limiting viral illness, recurrence is very common, either because of repeat infections by same type of virus or infection by another virus of a different serotype (e.g. rhinovirus, adenovirus, influenza and parainfluenza virus, enterovirus and coxsackie virus). Some researchers have suggested that in rhinitis, the host response to the viral infection, which leads to release of chemomediators of inflammation, and proinflammatory cytokines are responsible for the clinical symptoms and signs, rather than mucosal drainage or viral colonization. Chronic rhinitis has been shown to be associated with allergy, chronic sinusitis, nasal polyps, foreign body impaction, deviated nasal septum, cystic fibrosis and nasal diphtheria. It is estimated that 5-10% of URTIs are complicated by bacterial infection of sinus and *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Morexella catarrhalis* are the important bacterial pathogens responsible.

Otitis media is an infection ascending from the upper respiratory tract via the eustachian tube and in a majority of cases, pathogens involved are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Morexella catarrhalis*, and recurrent otitis media is associated with allergy, eustachian tube abnormality and cleft palate.

Tonsils play a crucial role in immunoprotection and both cell mediated immunity and tonsils, mediate the immune surveillance mechanism. Various studies shown that there is increased B cell induction by tonsils as a response to specific antigen and recurrent tonsillitis may lead to alternation in serum immunological parameters.
Antibody deficiencies are the commonest primary immunodeficiencies and also most likely to present with recurrent ENT infections. Primary defects of cell-mediated immunity, neutrophil function, or complement activity are relatively rare. The commoner immunodeficiencies are easy to exclude with a simple panel of blood tests. It is essential that the differential white cell count be examined closely, for neutropenia (may contribute to infection), lymphocyte count (can be reduced in severe combined immune deficiency), thrombocytopenia (associated with immunodeficiency) and eosinophilia (suggestive of atopy or vasculitis as a contributing factor to recurrent infection). It is important that the ‘normal values’ used as reference ranges are age-specific for the patient. Reduced immunoglobulin levels characterize the majority of primary antibody deficiencies. Patients with common variable immunodeficiency will usually have low levels of antibodies, and often have recurrent pyogenic URTIs related to Pneumococcus, streptococcus and Haemophilus.

The generation of antibodies to specific antigen demonstrates an intact humoral immune system. Antibodies to commonly available vaccines such as Haemophilus influenzae type b, pneumococcus and tetanus toxoid have been observed in patients with otitis media. Immunoglobulin E (IgE) is one of the five classes of immunoglobulins (the others being IgA, IgD, IgG and IgM), its main functions being to protect the host against invading parasites via the antigen-specific IgE interaction with mast cells and eosinophils. However, the same antibody-cell combination is also responsible for the typical allergy, or immediate hypersensitivity, reactions. There are two major types of receptors for the Fc portion of the IgE molecule on cells (a high affinity receptor found primarily on mast cells and basophils, and a low affinity receptor found on CD23 cells). Though IgE immunoglobulins are distributed throughout the body, cells synthesizing IgE are found predominantly in association with mucosal tissues.

C Reactive Protein (CRP) is a test that measures the concentration of a protein in serum that indicates acute inflammation. CRP is detected with the use of antiserum in several tests that measure the protein and protein-bound molecules. C-reactive protein is a special type of protein produced by the liver during episodes of acute inflammation. The most important role of CRP is its interaction with the complement system, which is one of the body's immunologic defense mechanisms. While this is not a specific test, it does give a general indication of acute inflammation. This test is a useful check for inflammatory flare-ups and the test is also useful to monitor response to therapy. Normally, there is no CRP in the blood serum.

In the present study, all children had a history of recurrent upper respiratory tract infections and there was a rapid symptomatic relief and clinical cure. There was significant decrease in the total leukocyte, eosinophil and absolute eosinophil count, ESR, ASO titer, CRP levels and IgE levels at the end of the study. All children with a positive throat swab result at the time of enrollment had a negative throat swab result at the end of the study. These favorable results of Septilin Junior tablets might be due to the synergistic actions of the ingredients.

Commiphora wightii is well known for its antimicrobial activity. Historically, Ashry et al. reviewed the occurrence, constituents and medicinal use of myrrh, obtained from the stem of Commiphora myrrha (Commiphora myrrha produces gum resin called myrrh) and they observed that Commiphora wightii has considerable antimicrobial activity and is medicinally used in a variety of diseases. Manguro et al. fractionized a steam-distilled residue of Commiphora resin that yielded four novel dammarane triterpenes, their structures determined by using spectroscopic, physical, and chemical methods. Fatope et al. identified and isolated a new...
antifungal flavanone, muscanone, and along with known naringenin from Commiphora wightii. Meselhy et al. demonstrated significant in vitro inhibition of NO formation in lipopolysaccharide activated murine macrophages and when compared, Z- and E-Guggulsterones were the most potent inhibitors of NO production, followed by myrrhanol A and myrrhanone A. El Zhu et al. observed that bioactivity-directed fractionation and purification of Commiphora wightii afforded a fraction, which showed moderate scavenging effect.

_Tinospora cordifolia_ had been studied extensively for its immunomodulating activities. The active principles of _Tinospora cordifolia_ were found to possess immunomodulatory activities and caused significant increases in IgG antibodies in serum, along with macrophage activation. Thatte et al. reported the potent immunostimulation by _Tinospora cordifolia_, with effects comparable to lithium and glucan. Bishayi et al. demonstrated the effect of _Tinospora cordifolia_ extract on immunostimulatory functions in carbon tetrachloride intoxicated mature rats and the results suggested that treatment by _Tinospora cordifolia_ extract might be beneficial for improving immune functions. Sohni et al. studied the activity of _Tinospora cordifolia_ formulation in immunomodulation and recorded an enhancement in humoral immunity evidenced by the hemagglutination titre along with stimulation of cell-mediated immunity as observed in the leukocyte migration inhibition tests. Diwanay et al. observed that extracts prepared from _Tinospora cordifolia_ exhibited various immunopharmacological activities in cyclophosphamide-treated mouse ascitic sarcoma and it offered protection towards cyclophosphamide-induced myelo and immunoprotection as evident by significant increase in white cell counts, hemagglutinating and hemolytic antibody titers. Manjrekar et al. studied the effect of _Tinospora cordifolia_ in inhibition of immunosuppression produced by cyclophosphamide and observed that ethanol extracts of leaf stems inhibit cyclophosphamide-induced anemia. Chintalwar et al. isolated an arabinogalactan from _Tinospora cordifolia_ and reported a polyclonal mitogenic activity against B-cells, while their proliferation did not require macrophages activation. Rege et al. evaluated the immunomodulatory property of _Tinospora cordifolia_ on surgical outcome in patients of malignant obstructive jaundice, and reported improvement in surgical outcome by a strengthening of host defenses. The protective effects of _Tinospora cordifolia_ have been studied and a significant improvement in improved phagocytic and intracellular bactericidal capacities of neutrophils in the _Tinospora cordifolia_-treated group has been noted.

In a clinical study by Rege et al. immunosuppression induced by cholestasis was favorably immunomodulated in patients with obstructive jaundice by _Tinospora cordifolia_, probably via consolidating host defence mechanism. In another study, the immunobiological activity of _Tinospora cordifolia_ appeared to improve the phagocytic function without affecting the humoral or cell-mediated immune system. Goel et al. observed direct and indirect antioxidant actions of _Tinospora cordifolia_.

The n-hexane-dichloromethane extract of the roots of Rubia cordifolia were tested in vitro for antioxidant and antimicrobial activities and a high antioxidant activity was observed. The ethyl acetate and chloroform fractions of Rubia cordifolia were effective on _S. aureus_ and _E. coli_, respectively. Five arborinane-type triterpene glycosides (rubianosides II, III, IV, rubianol-g and rubianthraquinone) have been isolated from the roots of Rubia cordifolia. The inhibitory effects of the isolated constituents on nitric oxide production in lipopolysaccharide-activated macrophages were examined and it was observed that the cyclic peptide constituents potently inhibited overproduction of nitric oxide and induction of inducible nitric oxide synthase. In addition, an anthraquinone constituent, 2-methyl-1, 3,6-trihydroxy-9, 10-anthraquinone, was found to show inhibitory effects on the release of beta-hexosaminidase in RBL-2H3 cells.
The immunomodulatory properties of *Emblica officinalis* were evaluated *in vitro* and it was demonstrated that there was a significant decrease in the nitric oxide synthase induction and the effect was attributed to the immunosuppression caused by *Emblica officinalis*. Nosal'ova *et al.* evaluated the antitussive activity of *Emblica officinalis* *in vitro* and reported a dose dependent suppression of the number of cough efforts, frequency of cough, and intensity of cough attacks in inspirium and expirium. The antitussive activity of *Emblica officinalis* was more effective than the non-narcotic antitussive agent dropropizine and it was hypothesized that the antitussive activity of the dry extract of *Emblica officinalis* might be due not only to antiphlogistic, antispasmodic and antioxidant efficacy effects, but also to its effect on mucus secretion in the airways.

The cytoprotective and immunomodulating properties of *Emblica officinalis* against oxidative damage have been well documented. In one study, it was observed that the presence of *Emblica officinalis* resulted in an enhanced cell survival, decreased free radical production, higher antioxidant levels, and increased phagocytosis and gamma-interferon production. In another study, the immunomodulatory activity of a polyherbal formulation, containing extract of *Emblica officinalis* and *Tinospora cordifolia* was studied and reported of significantly increased leukocyte proliferation and NK cell activity. These results indicated that pretreatment with the formulation selectively increased the proliferation of splenic leukocyte as well as B cell mitogen, lipopolysaccharide and cytotoxic activity. Another study determined the anti-oxidant and immunomodulatory properties of *Emblica officinalis* and there was a significant inhibition of both lipopolysaccharide and concanavalin-A-stimulated lymphocyte proliferation. *Emblica officinalis* significantly inhibited Cr-induced free radical production, restored antioxidant status back to control level, and inhibited apoptosis and DNA fragmentation induced by Cr. Interestingly, *Emblica officinalis* relieved the immunosuppressive effects of Cr on lymphocyte proliferation and even restored the IL-2 and gamma-IFN production considerably. Arora *et al.* had reported *Emblica officinalis* for their antimutagenic activities.

*Glycyrrhiza glabra* had been investigated for its immunomodulating effects in various research studies. An isolated compound from the stolon of *Glycyrrhiza glabra* (an acidic polysaccharide glycyrrhizan GA) has displayed remarkable reticuloendothelial system potentiating activity. Wagner *et al.* have reported the potential immunostimulating effect of an extract of *Glycyrrhiza glabra* root. Nose *et al.* observed the effects of polysaccharide fractions obtained from *Glycyrrhiza glabra* on macrophage function *in vitro*, leading to stimulation of macrophages de novo.

The protective effect of *Moringa pterygosperma* on hepatic marker enzymes, lipid peroxidation, and antioxidants was investigated during antitubercular drug-induced toxicity in vitro. Administration of *Moringa* extract significantly decreased hepatic marker enzymes and lipid peroxidation with a simultaneous increase in the level of antioxidants. The authors attributed to *Moringa pterygosperma* extract a protective effect that works by decreasing liver lipid peroxides and enhancing antioxidants. In an *in vitro* study, the modulatory effects of extract of *Moringa pterygosperma* were investigated with reference to drug metabolizing Phase I and II and anti-oxidant enzymes, glutathione content and lipid peroxidation in the liver and it was reported that *Moringa pterygosperma* extracts were capable of scavenging peroxyl and superoxyl radicals.

In various research studies, Septilin Junior tablets had been shown beneficial and it was hypothesized that Septilin Junior tablets might have immunomodulatory and anti-inflammatory properties, which potentiate the non-specific immune responses of the body.
These effects might be due to stimulation of phagocytosis by macrophage activation, increase in the polymorphonuclear cells, augmentation of granulocyte-macrophage differentiation, natural killer cell activity, antibody-dependent cytotoxicity and enhancing the secretion of antibodies into the circulation. Septilin Junior tablets has marked anti-inflammatory and antiexudative activity as demonstrated by the granuloma pouch method in experimental rats. It also has a sterilizing effect on the organisms associated with acute rhinosinusitis.

The overall compliance and absence of any clinically significant adverse events indicate the excellent long-term safety profile of Septilin Junior tablets.

CONCLUSION
Potent immunostimulation is an important factor in treatment and prevention of recurrent URTIs in children. This study observed the favorable significant improvement in clinical, hematological and immunological parameters in children suffering from recurrent URTIs and it can be concluded that, Septilin Junior tablets is an effective and safe drug for treatment and prevention of recurrent URTIs in children.

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