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Restores the immune balance

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Septilin SMS Meta-analysis Study

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Adults: **Syrup:** 2 teaspoonfuls three times daily.
Tablet: 2 tablets twice daily till the symptoms are relieved, followed by 1 tablet twice daily as maintenance therapy.

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Clinical Efficacy and Safety of Septilin Tablets in Respiratory Tract Infections: A Meta-analysis

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ABSTRACT

The aim of this study was to perform meta-analysis on the efficacy and short- and long-term safety of Septilin tablet in RTIs, as reported in 38 published studies conducted between 1958 and 2001 in 2,765 patients with RTI. Adults received one to two tablets, t.i.d. for 7 days to three months. Children were administered one-quarter tablets q.i.d. to one tablet t.i.d. for 7 days to three months. Duration of the treatment varied from 7 days to three months. Improvement in the symptoms, clinical recovery and immunoglobulins were taken into consideration. Results of the study showed statistically significant improvement in patients with RTI. Of the 1,613 patients with Upper RTI (URTI), 1,211 patients responded to the Septilin therapy and among the 838 patients with lower RTI, 720 patients responded to the therapy. In comparative control trials conducted with Septilin in RTIs, 74.42% of patients treated with Septilin improved as compared to the other treatment (52.86%). But with Septilin treatment, the improvement was better with minimal adverse effects. Immunoglobulin (IgG, IgA, IgM) levels showed significant improvement with Septilin. Adverse effects included gastrointestinal disturbances in 11 cases (0.39%), dry mouth in nine cases (0.32%), skin rashes in three patients (0.11%). Adverse effects were mild and no patient withdrew from the study on their account. Whereas patients in the comparative controlled drugs (antibiotics and anti-allergics), reported drowsiness and sedation in 21 cases (18%), dry mouth in seven patients (7.78%) and dizziness and incoordination of movements in three cases (3.33%). Therefore, it can be concluded that Septilin tablets are effective and safe in treating RTIs.

Key words: Meta-analysis, Septilin, respiratory tract infection

The term respiratory tract infection (RTI) describes acute infections involving the nose, paranasal sinuses, pharynx, larynx, trachea and bronchi. Viruses cause most upper RTIs (URTIs), with rhinovirus, parainfluenza virus, coronavirus, adenovirus, respiratory syncytial virus, coxsackie virus and influenza virus accounting for most cases.[1] In the United States, the common cold leads to 75-100 million physician visits annually at a conservative cost estimate of US $7.7 billion per year. Americans spend $ 2.9 billion on over-the-counter drugs and another US$ 400 million on prescription medicines for symptomatic relief.[2,3] More than one-third of patients, who saw a doctor, received an antibiotic prescription, which has implications for antibiotic resistance from overuse of such drugs.[3] An estimated 22-189 million school days are missed annually due to cold. As a result, parents missed 126 million workdays to stay home to care for their children. When added to the 150 million workdays missed by employees suffering from cold, the total economic impact of cold-related work loss exceeds US$ 20 billion per year.[2,3] This accounts for 40% of time lost from work.[4] Most URTIs occur more frequently during the cold winter months. Adults develop an average of two to four colds annually. Antigenic variation of hundreds of respiratory viruses results in repeated circulation in the community. Acute pharyngitis accounts for 1-2% of all visits to outpatient and emergency departments, resulting in 7 million annual visits by adults alone.[1] Acute bacterial sinusitis develops in 0.5-2% of cases of viral URTIs.[5] Approximately 20 million cases of acute sinusitis occur annually in the United States. About 12 million individuals are diagnosed with acute tracheobronchitis annually, accounting for one-third of patients presenting with acute cough, these infections are the leading cause of death.[6]

Transmission of organisms causing URTIs occurs by aerosol, droplet or direct hand-to-hand contact with infected secretions, with subsequent passage to the nares or eyes.[7] Thus, transmission occurs more

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commonly in crowded conditions. Direct invasion of the respiratory epithelium results in symptoms corresponding to the area(s) involved. On examination, patients with common colds may have low-grade fever, nasal vocal tone, macerated skin over the nostrils and inflamed nasal mucosa.[8] There is a need for an effective and safe formulation to manage respiratory infections. A number of herbs are claimed to be effective in the management of these frequent infections. Septilin is a multi-herbal formulation claimed for its efficacy due to the synergistic action of the ingredients. It provides immunomodulatory activity that enhances natural immunity. A number of clinical studies have been carried out to evaluate the efficacy and safety of Septilin in various respiratory ailments. Results of each clinical trial showed that Septilin with its immunomodulatory, antioxidant, anti-inflammatory, anti-allergic, and antimicrobial actions was effective in various RTIs, with excellent short- and long-term safety. These studies need to be meta-analyzed to know the clinical status of Septilin in respiratory ailments.

Meta-analysis is a two-stage process; first stage is the extraction of data from each study and calculation of the result for each. The second stage involves deciding whether it is appropriate to calculate a pooled average result across studies. This process gives greater weightage to the results from the studies that give more information because these are likely to be closer to the truth.[9] Advantages of meta-analysis include deriving and statistical testing of overall factors/effect size parameters in related studies, generalization to the population of studies, ability to control for between study variation, including moderators to explain variation. To cumulate the results of all the studies, a meta-analysis was carried out to analyze the efficacy and short- and long-term safety of Septilin in RTI.

Aim of the Study

The aim of the study was to perform a meta-analysis on the efficacy and short- and long-term safety of Septilin tablets in RTI.

Material and Methods

Study Design

This is a cumulative meta-analysis of 38 published clinical trials of Septilin tablets in RTIs. Out of the 38 trials, 32 were open, one was placebo-controlled, and five were comparative controlled trials. The details of clinical studies evaluated for meta-analysis are mentioned in Table 1.

Inclusion Criteria

All published studies, which evaluated the role of Septilin in RTIs, were included in the meta-analysis irrespective of the study design i.e. controlled studies or open clinical studies. There were no restrictions regarding sex, age or duration of the disease. The outcome variables included measurement data on changes in clinical symptoms and signs, laboratory results, and incidence of adverse events during/after the treatment and immunoglobulin levels.

Table 1. Details of Clinical Studies Included in the Meta-analysis

Investigators name	Year	No. of patients
Agarwal NK, Agrawal V[10]	1986	25
Gaunekar L, Pereira P[11]	1988	30
Gokhale SG, Wakharia PV[12]	1958	44
Koti ST[13]	1992	18
Mishra DN, Singh T[14]	1981	58
Miglani VP[15]	1983	24
Nigam P, Kapoor KK, Singh R, et al[16]	1985	125
Sheth SC, Tibrewala NS, Warerkar UR, et al[17]	1959	82
Bhasin RC[18]	1990	30
Sarkar SK, Singh A, Singh H, et al[19]	1986	50
Luley S, Kalbande V[20]	1984	75
Roy VD[21]	1989	785
Khan A, Mukherjee V[22]	1984	44
Mukherjee D[23]	1984	23
Tawde UJ[24]	1981	30
Garga MK[25]	1980	40
Cooper RAF, Merchant NR[26]	1958	27
Grewal DS, Sharma BK, Shah DD, et al[27]	1985	50
Roy S[28]	1992	100
Sharma SC, Singhal KC[29]	1990	100
Singh BPM[30]	1992	35
Chugh JS[31]	1984	30
Das MR, Rai D[32]	1988	50
De Sequeira PA[33]	1979	50
Gadre KC, Shah HA, Behnugara AP[34]	1964	46
Vishwakarma SK[35]	1979	243
Rastogi PK, Bhatia BPR, Kumar A[36]	1982	64
Bhatia BPR, Tayal VK[37]	1978	24
Banerjee D[38]	1988	20
Dass MR[39]	1988	27
Gadekar HA, Jyoti VA, Komawar V et al[40]	1986	50
Motwani VB, Joshi PD[41]	1982	41
Lumba SP, Parmar TL, Bali H, et al[42]	1983	110
Sasikumaran Nair S[43]	1981	68
Sarkar M[44]	1983	25
Tawde U, Tawde NU[45]	1987	60
Lakshmipathi G, Rao VB[46]	1962	37
Nehru V[47]	2001	25

Exclusion Criteria

Phase I studies were excluded from the meta-analysis.

Study Procedures

A meta-analysis of 38 clinical studies conducted between 1958 and 2001 in 2,765 patients with RTI (1,613 were with URTI and 838 were with lower RTI) at various reputed hospitals all over India was performed to evaluate the efficacy and short- and long-term safety of Septilin in RTIs. Duration of the treatment varied from 7 days to three months. Adults received one tablet q.i.d. to two tablets t.i.d. for 7 days to three months. Children one-quarter tablet q.i.d. to 1 tablet t.i.d. for 7 days to three months. Improvement in the symptoms, clinical recovery, and immunoglobulins were taken into consideration. Incidence of adverse events during the study period and compliance to the drug treatment were also evaluated.

Primary and Secondary Outcome Measure

Primary predefined outcomes were clinical recovery from RTIs. Secondary end points were safety and compliance to Septilin tablets.

Adverse Effects

All adverse events, either reported or observed by patients, were recorded with information about severity, duration and action taken regarding the study drug. Relation of adverse events to study medication was predefined as *'Unrelated'* (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), *'Possible'* (follows a known response pattern to the suspected drug, but could have been produced by the patient's clinical state or other modes of therapy administered to the patient), *'Probable'* (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient's clinical state), and *'Certain'* (the adverse events must have definitive relationship to the study drug, which cannot be explained by concurrent disease or any other agent).

Statistical Analysis

Statistical analysis was done according to the intention-to-treat principles. Changes in various parameters from baseline values and values at the end of the study were pooled and analyzed cumulatively using Chi-square test or paired 't' test. Values are expressed as mean ± SD or as incidences of patients with or without symptoms. The minimum level of significance was fixed at 95% confidence limit and a two-sided $p \leq 0.05$ was considered significant. Statistical analysis was performed using GraphPad Prism Version 4.03 for windows, GraphPad Software, San Diego, California, United States (www.graphpad.com).

Results

The break-ups for upper and lower RTIs are given in Table 2. Statistically significant improvement was seen in trials conducted in patients with RTI. Of the 1,613 patients with URTI, 1,211 patients responded to the treatment, with a statistical significance of $p < 0.0001$ and percent protection of 75.08% and among the 838 patients with lower RTI (LRTI), 720 patients responded to the treatment, with a statistical significance of $p < 0.0001$ and percent protection of 85.92% (Table 3).

Among the patients with URTI, in 565 patients of tonsillitis; 460 patients responded with 81.42% protection, in 599 pharyngitis patients, 411 responded showing 68.61% protection; in 25 patients of laryngitis 24 showed 96% protection in patients with sinusitis and rhinitis, 76.89% and 91.01% protection was

Table 2. Break-up of Patients with RTI (n = 2,765)

Indication	No. of patients	Indication	No. of patients
Upper RTI		Lower RTI	838
Tonsillitis	565	Persistent cough (COPD)	155
Pharyngitis	599		
Laryngitis	25	Bronchitis	683
Sinusitis	424		
Rhinitis	278		

Table 3. Meta-analysis of Septilin in RTIs
(32 open trials + one placebo-controlled trial + 5 comparative controlled trial = 38 clinical trials)

Indication	No. of patients	Improvement	% protection
RTIs	2,765	2,178*	78.77
Upper RTI	1,613	1,211*	75.08
Tonsillitis	565	460*	81.42
Pharyngitis	599	411*	68.61
Laryngitis	25	24*	96.00
Sinusitis	424	326*	76.89
Rhinitis	278	253*	91.01
Lower RTI	838	720*	85.92
Persistent cough (COPD)	155	131*	84.52
Bronchitis	683	589*	86.24

*$p < 0.0001$ compared to the total number of patients with RTI before treatment.

observed, respectively (Table 3). Similarly in LRTI out of 683 patients with bronchitis, 589 responded with 86.24% and persistent cough due to varied etiology there was 84.52% relief (Table 3). In the comparative control trial, 74.42% of patients treated with Septilin improved as compared to the control group (52.86%) treated with anti-allergics and antibiotics. The statistical significance was $p < 0.0001$ (Table 4) in both Septilin and control groups, but improvement was found to be better with Septilin treatment. The comparative drugs were anti-allergics (chlorpheniramine maleate) and antibiotics (cotrimoxazole and penicillins).

The immunoglobulin levels showed significant improvement, IgG from 1,456.00 ± 342.80 mg/dl at baseline to 1,715.00 ± 287.10 mg/dl after the treatment ($p < 0.009$), IgA from 200.80 ± 46.73 mg/dl before the treatment to 241.40 ± 43.26 mg/dl after the treatment ($p < 0.01$), and IgM levels from 167.80 ± 68.38 mg/dl before the treatment to 195.70 ± 63.21 mg/dl after the treatment ($p < 0.01$), in two open-label clinical trials (Table 5). These observations support the immunomodulatory effect of Septilin. Out of the 2,765 patients with RTI, in patients treated with Septilin, gastrointestinal disturbances in 11 cases (0.39%), dry mouth in nine cases (0.32%) and skin rashes in three patients (0.11%) were observed. In patients treated with comparative controlled drugs (antibiotics and anti-allergics) patients presented with adverse effects such as drowsiness and sedation in 21 cases (18%), dry mouth in seven patients (7.78%), and dizziness and incoordination of movements in three cases (3.33%). All adverse effects were mild in nature and did not necessitate withdrawal of study medication (Table 6). Majority of the adverse effects were seen in patients treated with comparative controlled drugs (140) such as antibiotics and anti-allergics with 28% as compared to <1% in Septilin-treated patients.

Table 4. Meta-analysis of Septilin in RTIs in Comparative Controlled Clinical Trials

Study	No. of patients			
	Septilin		Comparative control	
	Total no. of patients	Improvement	Total no. of patients	Improvement
1	50	47	50	44
2	30	21	30	18
3	40	40	10	0
4	27	3	25	2
5	25	17	25	10
Total	**172**	**128* (74.42%)**	**140**	**74* (52.86%)**

*p < 0.0001 compared to the total number of patients with RTI before treatment.

Discussion

The number of papers published on meta-analysis in medical research has increased sharply in the past decade; however, the merits and perils of the meta-analysis continue to be debated in the medical community.[48,49] A useful definition of meta-analysis was given by Huque as: 'A statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be combinable'.[50] A single study often cannot detect or exclude with certainty clinically relevant differences in the effects of two treatments. Cumulative meta-analysis is defined as the repeated performance of meta-analysis whenever a new trial becomes available for inclusion. Such cumulative meta-analysis can retrospectively identify the point in time when a treatment effect first reached conventional levels of significance.[51]

Meta-analysis thus not only consists of a combination of data but also includes the epidemiological exploration and evaluation of results ('epidemiology of results').[52] Therefore, new hypotheses that were not posed in single studies can be tested in meta-analyses.[53] The number of patients included in clinical trials is often inadequate, as in some cases the required sample size may be difficult to achieve.[54] Meta-analysis may, nevertheless, lead to the identification of the most promising or urgent research question and may permit a more accurate calculation of the sample sizes needed in future studies.[55] Goals of the meta-analysis are to enable the overall significance of an effect to be evaluated, based on the multiple studies available, to estimate an overall effect size by combining the individual estimates in multiple studies.[56]

Table 5. Meta-analysis of Septilin in Immunoglobulin Levels (total = 2 open trials) (n = 49) Immunoglobulin Levels (mean ± SD)

IgG (mg/dl)		IgM (mg/dl)		IgA (mg/dl)	
Before treatment	**After treatment**	**Before treatment**	**After treatment**	**Before treatment**	**After treatment**
1,456.00 ± 342.80	1,715.00 ± 287.10*	167.80 ± 68.38	195.70 ± 63.21**	200.80 ± 46.73	241.40 ± 43.26**

*p < 0.009 compared to the before treatment values; **p < 0.001 as compared to the before treatment values.

Table 6. Adverse Events

Treatment	Adverse effects	No. of patients	Incidences of occurrence (%)
Septilin (n = 2,765)	Gastrointestinal disturbances	11	0.39
	Dry mouth	09	0.32
	Skin rashes	03	0.11
Comparator control drugs (n = 140)	Drowsiness and sedation	21	18
	Dry mouth	07	7.78
	Dizziness and incoordination	03	3.3

In the present meta-analysis, clinical trials and their details were tabulated and analyzed statistically. The outcome of this analysis showed marked improvement with Septilin in patients with RTIs.

Septilin has immunomodulatory, antioxidant, anti-inflammatory, anti-allergic and antimicrobial actions. It has an excellent short- and long-term safety. Septilin is a multiherbal preparation and the effect of the formulation is due to the synergistic action of the ingredients. *Tinospora cordifolia* has potent immunomodulatory and immunostimulatory actions, which increase the levels of antibodies and activate macrophages.[57,58] *Emblica officinalis* enhances cell survival and increases phagocytosis and γ-IFN production.[59] Glycyrrhizin from *Glycyrrhiza glabra* potentiates the reticuloendothelial system,[60] enhances immunostimulation,[61] and acts on macrophage function *in vitro*, leading to stimulation of macrophages *de novo*,[62] β-glycyrrhetinic acid from *Glycyrrhiza glabra* is a potent inhibitor of the classical complement pathway.[63] *Balsamodendron mukul*,[64-66] *Rubia cordifolia*,[67] *Emblica officinalis*,[68] *Glycyrrhiza glabra*,[69] and *Moringa pterygosperma*[70] have potent antioxidant actions. *Balsamodendron mukul* has strong anti-inflammatory potential.[71] *Glycyrrhiza glabra*[72] and *Moringa pterygosperma*[73] have also been reported for its anti-inflammatory properties.

Tinospora cordifolia improves the phagocytic and intracellular bactericidal capacities of neutrophils.[74] Glycyrrhizin from *Glycyrrhiza glabra* has potent antiviral activity.[75] *Emblica officinalis* has antibacterial properties, especially against *Escherichia coli, Klebsiella pneumoniae, Klebsiella ozaenae, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella typhi, Salmonella paratyphi* A and B, and *Serratia marcescens*.[76] *Rubia cordifolia* has antibacterial properties.[77] *Moringa pterygosperma* possesses antibacterial and antiviral properties and inhibits the growth of gram-positive and gram-negative bacteria such as *E. coli, S. typhi* and *S. paratyphi*.[78] *Tinospora cordifolia*[79] and *Emblica officinalis*[80] have antipyretic properties. *Balsamodendron mukul* is beneficial in RTIs, including chronic tonsillitis, pharyngitis, chronic bronchitis, nasal catarrh, and laryngitis.[81] *Glycyrrhiza glabra* is an expectorant and hence is beneficial in asthma, acute or chronic bronchitis, and chronic cough.[82-84]

Conclusion

The outcome of this meta-analysis, which included 38 clinical studies, carried out between 1958 and 2001, in 2,765 patients with RTI indicated significant clinical efficacy and safety of Septilin tablets. The cumulative data analysis revealed significant clinical improvement with adequate symptomatic relief in Septilin-treated patients. Adverse events were negligible (<1%) in Septilin-treated patients and did not necessitate withdrawal of the drug. The overall drug compliance was very good. Therefore, it may be concluded that Septilin tablets are clinically effective and safe in patients with RTIs. Septilin, a multi-ingredient formula, has immunomodulatory activity and enhances natural immunity. It is also a safe and effective adjuvant to antimicrobials in the management of recurrent infections. When co-prescribed with antibiotics, Septilin ensures faster recovery, reduces the duration and cost of therapy, besides preventing reinfections.

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