Comparative Evaluation of Efficacy and Safety of “Septilin Syrup” with Prophylactic Antibiotics, in Preventing Postoperative Infections in Children

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ABSTRACT

Preoperative prophylactic antibiotic administration, for preventing postoperative infections in children has been a controversial issue. “Septilin syrup” is a polyherbal formulation recommended for anti-inflammatory, antimicrobial, immunomodulatory, and antioxidant actions. This study was planned for the comparative evaluation of efficacy and safety of “Septilin syrup” with prophylactic antibiotics in preventing postoperative infections during elective surgery in children.

This study was an open, randomized, comparative, phase III clinical trial. A total of 50 children admitted for various elective surgeries were enrolled in the study, and were randomly, allocated into “Septilin syrup” group and “other drugs” group. The children from the “Septilin syrup” group were administered 5 ml of “Septilin syrup” in the morning of the surgery and “Septilin syrup” was continued in the same dose, twice daily for the 1st postoperative week. In the “other drugs” group, patients were administered Inj. Ceftriaxone (50 mg/kg), at the time of induction of anesthesia, which was followed by oral antibiotics for the 1st postoperative week. Children from both the groups were monitored postoperatively, and laboratory investigations were repeated after 48 hours. Children from both the groups underwent Ig assay on day 0 and day 7. The predefined primary efficacy endpoint was incidence of postoperative surgical wound or systemic infection, while the secondary safety endpoints were the incidence of adverse events and patient compliance to therapy.

This study observed that no patient from both the groups developed surgical wound infection, and patients on Septilin therapy had smoother clinical recovery than the other drugs group. Also, there were no clinically significant adverse reactions, in Septilin group, which confirms the safety of Septilin. The observed beneficial effects might have been due to the synergistic activities of the ingredients, which include anti-inflammatory, antimicrobial, immunomodulatory, and antioxidant actions. Therefore, it may be concluded that, “Septilin syrup” is safe and equally effective alternative to prophylactic antibiotics in preventing postoperative infections, following elective surgery in children. (The Ind. Pract. 2005; 58(7): )

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INTRODUCTION

Children are vulnerable to postoperative infections, and prophylactic antibiotics are administered (at the induction of anaesthesia) to prevent postoperative infections, a practice which has remained controversial. Problems with compliance, adverse drug reactions (ADRs) and the development of antibiotic resistance can be significant with the use of broad spectrum prophylactic antibiotics.1,2

“Septilin syrup” is a polyherbal formulation with antimicrobial, anti-inflammatory, immunomodulatory, and antioxidant properties. “Septilin syrup” contains the powder of Balsamodendron mukul (80 mg), and extracts of Maharasnadi quath (30 mg), Rubia cordifolia (15 mg), Tinospora cordifolia (14 mg), Trikatu (13 mg), Saussurea lappa (13 mg), Emblica officinalis (8 mg) and Glycyrrhiza glabra (6 mg).

AIM OF STUDY

This study was planned for comparative evaluation of the safety and efficacy of “Septilin syrup” with prophylactic antibiotics, in preventing postoperative pediatric infections, during elective surgery in children.

STUDY DESIGN

This study was an open, randomized, comparative, phase III clinical trial conducted at the Department of Pediatric Surgery, University Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India, from June 2001 to September 2003, and was approved by the “Institutional Ethics Committee”.

MATERIAL AND METHODS

Inclusion criteria
A total of 50 children, of either sex, who had been admitted for elective surgery were enrolled in the study, and a written informed consent was obtained from the parents of all the children.

Exclusion criteria

Children with renal, hepatic or cardiac impairment, and those children whose parents refused to give written informed consent were excluded from the study.

STUDY PROCEDURE

The enrolled children were randomly allocated into two groups of 25 each (“Septilin syrup” group and “other drugs” group). All the children underwent preoperative clinical and laboratory investigations. All the children from the “Septilin syrup” group were administered 5 ml of “Septilin syrup” on the morning of surgery and “Septilin syrup” was continued in same dose, twice daily, during the 1st postoperative week. In the “other drugs” group, all the children were administered Inj. Ceftriaxone (50 mg/kg), at the time of induction of anaesthesia, which was followed by oral antibiotics during the 1st postoperative week.

Procedure of immunoglobulin (Ig) assay

5 ml of blood was collected by venupuncture and after clot formation the serum was transferred to a sterile test tube. The test tube was centrifuged at 3000 rpm for 5 minutes. Finally, the collected serum was kept at -20°C. Quantitative estimation of serum IgG was done by the method of Single Radial Immunodiffusion Technique and the preparation of agar antiserum solution was done (Table 2).

The agar antiserum solution was poured directly over dry slides before and after the gel had solidified, the plates were kept for 2 hours in the refrigerator. Subsequently, walls of 2 mm were cut at a distance of 14 mm from each other, and each plate contained a set of standard for each immunoglobulin with the serum samples to be quantitated. 5 µl of diluted serum was placed in each well with the help of a micropipette, and the set containing different dilutions of standard and serum samples were prepared with 0.03 M phosphate buffer saline (pH 8). Overt sera were applied for testing IgA and
IgM, whereas 1: 10 dilution sera were used for IgG estimation. The slides were kept in moist petridishes at 4°C, and the readings were recorded (after 24 hours for IgG and IgA and after 72 hours for IgM). The diameter of the precipitation rings was measured, and square of the ring diameters of the reference serum was plotted out against the concentration of immunoglobulins (mg/100 ml) in a graph, for estimating the quantity in test serum.

**Follow-up and assessment**

Children from both the groups were monitored postoperatively, and laboratory investigations were repeated after 48 hours. Children from both the groups underwent Ig assay on day 0 and day 7.

**Primary and secondary endpoints**

The predefined primary efficacy endpoint was the incidence of postoperative operation site, or systemic infection, while the secondary safety endpoints were the incidence of adverse events and patient compliance to therapy.

**Adverse events**

All the adverse events either reported or observed by the patients were recorded with information about severity, date of onset, duration and action taken regarding the study drug.

**Statistical analysis**

Statistical analysis was done according to intent-to-treat principles. A change in various parameters from baseline values was evaluated by “Two way ANOVA Test”. The minimum level of significance was fixed at 95% confidence limit and a 2-sided p value of <0.05 was considered significant.

**RESULTS**

The children in both the groups were comparable as regards age and body weight (Table 3). The male female ratio in both the groups was 1:1. The mean duration of both anesthetic and surgical stress in the “Septilin syrup” group and “other drugs” group children was 90 ± 14.23 and 88 ± 11.43 minutes, respectively (p>0.05; NS).

There was no incidence of postoperative surgical wound infection in both the groups. However, in 12 (48%) children from the “other drugs” group, there was postoperative high fever, while in comparison only 2 (8%) patients from the “Septilin syrup” group developed fever. Further, 3 (12%) children in “other drug” group developed URTI, while no patient from the “Septilin syrup” developed URTI. Also, 20 children from the “other drug” group (80%) complained of anorexia for a week and 14 (56%) children from the “other drug” group suffered from severe nausea and vomiting, while there were no such ADRs were observed in the “Septilin syrup” group. There was a significant increase in the immunoglobulin levels (IgG) the in “Septilin syrup” group at the end of the study (p<0.01; S), while there was no significant change in the other immunoglobulins (p>0.05; NS) in the other drugs group (Table 4 and Figure 1).

Overall, children on “Septilin syrup” therapy had smoother clinical recovery as compared to the children in the “other drugs” group. Also, there were no other clinically significant adverse reactions, either observed by investigators, or reported by patients, in the “Septilin syrup” group, till the end of the study.

**DISCUSSION**

Prophylactic antibiotic use in children, to prevent serious illness is successful only in certain specific circumstances. Antibiotic prophylaxis can be given to prevent infection caused by a specific pathogen, to prevent infection at an infection-prone site, or for the general protection of a vulnerable host. Prophylaxis directed towards a specific pathogen is usually more successful than the protection of infection-prone sites in highly susceptible children.1

Preoperative antibiotic usage and the effectiveness vary depending upon the procedure and background rate of postoperative infections. Prolonged use of antibiotics following surgical procedure generally has no benefit and may result in superinfection, which multiplies antibiotic-resistant bacteria or fungi.2
### Table 1
**Various type of surgeries performed in both the groups**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Type of operation</th>
<th>No. of patients</th>
<th>Septilin syrup group</th>
<th>Other drugs group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branchial cyst</td>
<td>Excision</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Parotid tumor</td>
<td>Superficial parotidectomy</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lipoma (back)</td>
<td>Excision</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hemangioma (trunk)</td>
<td>Excision</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Undescended testis</td>
<td>Orchidopexy</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Bilateral inguinal hernia</td>
<td>Herniotomy</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Meningomyeloce</td>
<td>Repair</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Duplication cyst of gut</td>
<td>Exploratory laparotomy</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Recurrent appendicitis</td>
<td>Interval appendicetomy</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>25</strong></td>
<td><strong>25</strong></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2
**Preparation of agar anti-serum solution**

<table>
<thead>
<tr>
<th>Name of antisera</th>
<th>Quantity (ml)</th>
<th>Antiserum</th>
<th>Buffer solution</th>
<th>3% agar solution</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>0.2</td>
<td>3</td>
<td>3.2</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>IgA</td>
<td>0.16</td>
<td>3.04</td>
<td>3.2</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td>0.16</td>
<td>3.04</td>
<td>3.2</td>
<td>6.4</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3
**Age and weight of the patients from both the groups**

<table>
<thead>
<tr>
<th></th>
<th>Septilin syrup group</th>
<th>Other drugs group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN</td>
<td>SEM</td>
</tr>
<tr>
<td>No. of patients</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>3.49</td>
<td>0.771</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>11.62</td>
<td>0.846</td>
</tr>
</tbody>
</table>

### Table 4
**IgG (mg/dl) levels in the “Septilin syrup” and “other drugs” groups**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Day 0</th>
<th>Day 7</th>
<th>Difference</th>
<th>95% of CI of diff.</th>
<th>t</th>
<th>p value</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septilin syrup</td>
<td>1105</td>
<td>1192</td>
<td>87</td>
<td>20.22 to 153.8</td>
<td>2.967</td>
<td>p&lt;0.01</td>
<td>S</td>
</tr>
<tr>
<td>Other drugs</td>
<td>1128</td>
<td>1120</td>
<td>-8</td>
<td>74.78 to 58.7</td>
<td>0.2728</td>
<td>p&gt;0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>
It is appropriate to protect a vulnerable host in only a few circumstances, and it is impossible to eliminate all the bacteria from a human host; often, attempts to do so result in a life-threatening infection with antibiotic-resistant microorganisms. However, the use of antimicrobial prophylaxis for children undergoing surgery has been documented to be very successful in both the prevention of infection, and the reduction in episodes of bacterial sepsis and/or invasive bacterial disease.4,5

This study observed that there was no incidence of postoperative surgical wound infection in both the groups. However, majority of children from the “other drugs” group had postoperative high fever, while in comparison only a few children from the “Septilin syrup” group. Further, some children from in the “other drugs” group developed URTI and nausea, and majority of children in the “other drugs” group had severe anorexia, while no child from “Septilin syrup” suffered from these disorders. There was remarkable increase in the IgG levels in the “Septilin syrup” group by the end of the study. Overall, children on “Septilin syrup” therapy had a smoother clinical recovery as compared to the children in the “other drug” group. Also, there were no clinically significant adverse reactions, in the “Septilin syrup” group, till the end of the study, which confirms the safety of “Septilin syrup”. These beneficial effects might have been due to the synergistic activities of the ingredients of “Septilin syrup”, which are well documented.

The principle ingredients of Balsamodendron mukul are triterpenes, flavanone, naringenin,6,7 guggulsterone, guggulsterols, myrrhanol-A, and myrrhanone-A.8 The principle ingredients of Rubia cordifolia are triterpene glycosides (rubianosides II, III, IV and rubianol-G) and anthraquinones (cordifoliol and corfifodiol).9,10 The active constituents of Saussurea lappa are lappadilactone, dehydrocostuslactone, costunolide,11 sesquiterpene conjugates (saussureamines),12 cynaropicrin,13 shikokiol,14 and jacesidi-n.15 The active constituents of Tinospora...
Tinospora cordifolia are diterpene glucosides (A-D), cordioside, cordifoliosides, cordiol, syringin, diterpene furanolactones tinosporide, and columbia. The active ingredients of Emblica officinalis are tannoids (emblicanin-A and -B, punigluconin, and pedunculagin), pyrogallol, non-sesquiterpenoids, phenolics, proanthocyanidins. The active ingredients of Glycyrrhiza glabra are tannoids (emblicanin-A and -B, punigluconin, and pedunculagin), pyrogallol, non-sesquiterpenoids, phenolics, proanthocyanidins. The active ingredients of Emblica officinalis are tannoids (emblicanin-A and -B, punigluconin, and pedunculagin), pyrogallol, non-sesquiterpenoids, phenolics, proanthocyanidins. The active ingredients of Glycyrrhiza glabra are tannoids (emblicanin-A and -B, punigluconin, and pedunculagin), pyrogallol, non-sesquiterpenoids, phenolics, proanthocyanidins. The active ingredients of Tinospora cordifolia are glyburin, glycerin, formononetin, isoflavonoids, glycosides, glyasperin-D, bioflavonoids (glabranin, pinocembrin, licoflavone, and wighteone), licoagrodin, prenylated retrochalcones, licoagrochalcone, licoagroaurone and flavonoids, licochalcone-C, kanzonol-Y, glycinflanin-B and glycyrrhizic acid. Septilin has antimicrobial, anti-inflammatory, immunomodulatory, and antioxidant actions. Tinospora cordifolia improves the phagocytic and intracellular bactericidal capacities of neutrophils. Glycyrrhizin from Glycyrrhiza glabra exhibits potent antimicrobial activity. Balsamodendron mukul, and Saussurea lappa have strong anti-inflammatory potential. The anti-inflammatory activity of Saussurea lappa is due to the stabilization of lysosomal membranes, antiproliferative effects and the inhibition of iNOS, and the dehydrocostus lactone from Saussurea lappa decreases the tumor necrosis factor-alpha (TNF-α) levels. Tinospora cordifolia has potent immunostimulatory activities, which increases levels of antibodies and activates macrophages. Emblica officinalis enhances cell survival, increases phagocytosis and (gamma-interferon) γ-IFN production. Glycyrrhizan from Glycyrrhiza glabra poten- tiates reticulo endothelial (RE) system and enhances immunostimulation. Glycyrrhiza glabra acts on macrophage function, leading to stimulation of macrophages de-novo, and beta-glycyrrhetinic acid from Glycyrrhiza glabra is a potent inhibitor of the classical complement pathway. Balsamodendron mukul has potent antioxidant actions. Rubia cordifolia inhibits the nitric oxide (NO) production in macrophages and induction of iNOS, and exhibits free radical scavenging effect. Saussurea lappa inhibits NO production, induction of iNOS and activation of nuclear factor kappa-B (NFk-B) in accordance with the induction of heat-shock protein. Emblica officinalis decreases the iNOS induction, decreases free radical production and increases antioxidant enzyme levels. Therefore, it may be summarized that, the observed beneficial effects of the “Septilin syrup” in this study might be due to synergistic actions of its ingredients, which include antimicrobial action (of Tinospora cordifolia and Glycyrrhiza glabra), anti-inflammatory action (of Balsamodendron mukul and Saussurea lappa), immunomodulatory action (of Tinospora cordifolia, Emblica officinalis, and Glycyrrhiza glabra), and antioxidant action (of Balsamodendron mukul, Rubia cordifolia, Saussurea lappa, Emblica officinalis, Glycyrrhiza glabra).

CONCLUSION

The practice of prophylactic antibiotic administration at the induction of anesthesia in order to prevent postoperative infections in children has been a point of debate. “Septilin syrup” is a polyherbal formulation recommended for immunomodulation, and this study was carried out to prevent this misuse of antibiotics and find a safe and equally effective alternate method to prevent postoperative infections during elective surgery in children. This study observed that no patients in both the groups developed wound infection and patients on “Septilin syrup” therapy had a much smoother clinical outcome in comparison to those children treated with antibi-
thetic therapy. Also, there were no clinically significant adverse reactions, in the "Septilin syrup" group, which confirms the safety of "Septilin syrup". These beneficial effects might have been due to the synergistic activities of the ingredients of "Septilin syrup", which include antimicrobial, anti-inflammatory, immunomodulatory, and antioxidant actions. Therefore, it may be concluded that, "Septilin syrup" is safe and equally effective alternate method to prophylactic antibiotic therapy to prevent postoperative infections during elective surgery in children.

REFERENCES


