Comparison between two antibiotic schemes in relation to surgical site infection in children: a randomized clinical trial

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Abstract

Background: There are few randomized clinical trials that prove the effectiveness of antibiotic prophylaxis (AP) to prevent pediatric surgical site infections (SSI). We undertook this study to determine the effectiveness of AP vs. traditional scheme of antibiotics.

Methods: We carried out a randomized clinical trial at the General Surgery Department of a Tertiary Care Children's Hospital in Mexico City. There were 187 consecutive patients, age 18 years or less, with clean or clean-contaminated procedures performed between January 2005 and December 2006. Exclusion criteria included previous scar on operated site, receiving antibiotics, or no informed consent. Cefalotin or clindamycin plus amikacin was administered 2 h before incision, continued for just 24 h in the experimental group (EG) vs. cefalotin or clindamycin plus amikacin administered just before, during or after incision and continuing for 5 days (control group, CG).

Results: Sixteen patients were excluded. EG included 26 clean and 54 clean-contaminated procedures, and in the CG there were 27 and 64 procedures, respectively. EG had a lower incidence of SSI (1/80 [1.2 %] vs. 10/91 [10.9 %], RR 9.7, (95% CI: 1.2-77.9, p = 0.009). The difference is based mainly on the clean-contaminated procedures.

Conclusions: AP administered 2 h before incision and continuing for 24 h significantly decreases the risk of SSI compared to CG in clean-contaminated procedures.

Key words: surgical site infection, prophylaxis, antibiotics, children.

Introduction

Current recommendations for the use of antibiotic prophylaxis (AP) in pediatric surgery are based on extrapolated patterns from studies on adults and indicated for clean and clean-contaminated surgeries.1-5

Surgical site infection (SSI) is a potentially preventable nosocomial disease. In our hospital SSI is considered the fifth leading cause of infection. In 1999, the frequency of SSI in our Department of General Surgery was 9.6% in clean surgeries and 25.8% in clean-contaminated surgeries,† figures that double the reported SSI rates in other international studies.7,8 Surgical prophylaxis is the most frequent reason for misuse of antibiotics in children and adults.9,10 Between 42 and 67% of the antibiotics are misused either by incorrect dose, pharmacy error, time of onset, or inappropriate duration or indication.5,11 Antibiotic prophylaxis is commonly used without robust evidence from research on pediatric surgical patients. In addition, misuse of antibiotics leads to toxicity, allergies, bacterial resistance and problems such as pseudomembranous colitis.4,12 There are no convincing studies in the literature that support the appropriate use of AP surgery in children. Current recommendations are extrapolated from adult studies, a situation supported by the American Academy of Pediatrics (AAP).1-5

Considering the shortage of prospective and randomized studies on AP to prevent SSI in the pediatric population and the percentages of infection in our hospital, we designed a controlled blinded, randomized clinical trial to assess the effectiveness of a
scheme of AP in children. Our intention was to test the hypothesis that administration of antibiotics 2 h prior to surgery and for no more than 24 h reduces the incidence of SSI compared with the administration immediately before, during or after surgery and for 5 days afterwards in pediatric patients with clean or clean-contaminated surgeries.

**Materials and Methods**

**Design**

We conducted a controlled, blinded, randomized clinical trial in pediatric patients with clean or clean-contaminated surgical procedures. We compared the effectiveness of a scheme of cefalotin or clindamycin and amikacin administered 2 h before surgery and for no more than 24 h with that of a scheme using the same antibiotics administered immediately before, during or after surgery and continuing for 5 days.

**Setting**

The study was carried out at the Department of General Surgery at the Hospital Infantil de México Federico Gómez in Mexico City.

**Patients**

Between January 2005 and December 2006, all patients <18 years of age who had a clean or clean-contaminated surgery were eligible for study inclusion. Exclusion criteria were as follows: patients who did not consent to the protocol, patients operated on outside of our hospital, patients who had a scar at the incision site, patients already receiving antibiotics for a prior or recurring problem before entering the operating room, those whose wound category changed to either contaminated or dirty at the time of surgery, and those patients who required reoperation at the same wound site.

**Procedures**

Experimental procedure consisted of IV administration of cefalotin for clean surgery and clindamycin along with amikacin for clean-contaminated surgery 2 h before surgery and for 24 h after surgery. Control group was administered these same medications IV in clean or clean-contaminated surgery but immediately before, during or after surgery and for 5 days afterwards (Table 1).

**Randomization**

Randomization was done by using a table of random numbers and allocation of each patient in sealed envelopes that were to be opened 2 h before surgery once inclusion criteria were met.

**Deployment**

One of the investigators (EB) generated the sequence of randomization and patients were enrolled in the study once the authorization form was signed by one of the other investigators (AG) who, in turn, verified that the antibiotic scheme was administered to each study group.

**SSI Surveillance**

A surgeon, independent of the group of researchers, assessed the presence of infection at the surgical site without knowing which group the patient belonged to. Evaluation of the surgical site was performed at 7 and 30 days postoperatively.

**Studied Variables and Operational Definitions**

Anesthetic risk was classified according to the American Association of Anesthesiologists’ ASA score. Nutritional status was classified as malnutrition according to Waterlow.

### Table 1. Differences between experimental and control groups

<table>
<thead>
<tr>
<th></th>
<th>Experimental group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP*</td>
<td>Cefalotin or clinda/amika</td>
<td>Cefalotin or clinda/amika</td>
</tr>
<tr>
<td>Time of first dose</td>
<td>2 h before skin incision</td>
<td>Immediately before, during or after surgery</td>
</tr>
<tr>
<td>Primary dose</td>
<td>Double normal BW/kg</td>
<td>Normal BW/kg</td>
</tr>
<tr>
<td>Intraoperative dose</td>
<td>If surgery is prolonged &gt;2.5 average lives of ABor bleeding &gt;15% of circulating volume</td>
<td>According to hourly scheme</td>
</tr>
<tr>
<td>Duration of AP</td>
<td>24 h</td>
<td>5 days</td>
</tr>
</tbody>
</table>

*AP, antibiotic prophylaxis: antibiotics used in both groups were clindamycin (40 mg/kg/day) and amikacin (15 mg/kg/day) in those procedures with clean-contaminated wound. In the remaining procedures, cefalotin was used (100 mg/kg/day). In neonates, dose was calculated on the basis of gestational age and body weight.
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defined urgent surgery as one that is done with the least loss of
time for a condition that immediately endangers an organ or the
life of the patient and elective surgery as one that is planned and
scheduled at least 24 h before surgery. Preoperative antibiotics
are defined as antibiotics used prior to the surgical incision.
Prophylactic antibiotics are defined as those administered
according to the requirements listed in Table 1. Intraoperative
antibiotics were those administered during surgery. Surgical time
was considered to be the time elapsed between the incision and
complete closure of the wound and was recorded in minutes.
Length of the wound was the wound size measured in cm (with
conventional tape) at the end of the surgery. Postoperative
antibiotics were those administered after surgery. Nosocomial
infection is that which is apparent after 48 h of hospitalization
and was not actively present or in an incubation period at the
time of admission.15

Criteria to Finalize the Study

The principal investigators of the study monitored the frequency
of SSI in each group. There were preliminary analyses of results
carried out for each group of the study every 3 months, and when
at least 1 month elapsed after completion of 75% of the projected
sample. Principal investigators, according to the Research
Committee of the Hospital, made the decision to discontinue
inclusion of patients after reviewing the preliminary results of
the frequency of SSI in each group after randomization of 182
patients. There was incontrovertible evidence of the benefit using
the prophylactic scheme: χ2 upon completion of the study was
<0.029 with an alpha level of 0.05 and statistical power of 80%
and was exceeded in this preliminary analysis according to the
method of Pocock.17

Statistical Analysis

Statistical analysis was carried out using Student’s t-test for
quantitative variables and χ2 for qualitative variables, obtaining
the relative risk for causing SSI. Prior to study initiation, it was
considered that there were the following confounding variables:
intraoperative bleeding, malnutrition, urgent surgery and drainage
at the surgical site. These variables were monitored prospectively
and, if there were statistically significant differences between
groups, a stratified analysis was conducted at the end of the study.

Results

In the preliminary analysis of the data of 187 patients (84.2% of
the projected total sample), we found a significant advantage for
the experimental group. Our Institutional Research Committee
concluded by consensus that prolonging the comparative study
had ethical implications in detriment of control group patients
and a decision was made to terminate the study.

Of the 187 patients, five were excluded (four had an infection
at a different site and one due to a change of injury type), leaving
182 patients. Eleven cases were considered as lost to follow-up. It
is noteworthy that these patients did not demonstrate SSI during
hospitalization or during the 7-day postoperative consultation,
but they did not attend the consultation at 30 days. Therefore, they
were excluded, leaving the sample for analysis in 171 patients (80
in the experimental group and 91 in the control group) (Figure 1).

Table 2 summarizes the epidemiological characteristics of both
groups, demonstrating that they were comparable except in the
preoperative hospital stay, duration of surgery and length of the
surgical wound. To determine whether these variables influenced
the presentation of SSI, they were analyzed along with those
variables prior to the study that were considered confounders
(urgency, bleeding and placement of drainage) as well as in the
group of SSI vs. those who had no infections. No significant
difference was found between these groups (Table 3). There were no significant differences in relation to the type of surgery performed in both groups, with the most common being closure of colostomy, posterior sagittal anorectoplasty, Nissen laparoscopy and laparoscopic pyloroplasty followed by tumor resection, resection of pulmonary metastases and opening of colostomy.

SSI

We had only one SSI in the experimental group (1.2%) vs. 10 SSI in the control group (10.9%), a difference that was statistically significant (p = 0.009, RR = 11.47, with 95% CI of 1.2-77.9, RAR = 9.7, RRR = 88.5, NNT = 11). Of the 11 infections, 10 were superficial incisional SSIs.

Incidence of SSI According to Type of Injury

We found that 3.7% of clean wounds had SSI vs. 7.6% of SSI in clean-contaminated wounds. There was no significant difference in the incidence of SSI related to the type of injury within each group. The rate of SSI in the experimental group was 0% for clean wounds and 1.9% for clean-contaminated wounds (p = 0.67). In the control group we found SSI in 7.4% of clean wounds and 12.5% in clean-contaminated wounds (p = 0.66).

Analysis of the Group with SSI

We proceeded to analyze exclusively the group of patients with SSI and found that there were no statistically significant differences between groups according to the type of injury (p = 0.81).

Analysis of Clean Surgeries

In this group there were no statistically significant differences in SSI between experimental and control groups (p = 0.25).

Table 2. Epidemiological characteristics of both groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Experimental (n = 80)</th>
<th>Control (n = 91)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>50 ± 56.3*</td>
<td>53.7 ± 59.8*</td>
<td>0.50</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>15.1 ± 14.7*</td>
<td>17 ± 14.6*</td>
<td>0.61</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>1.2</td>
<td>1.0</td>
<td>0.21</td>
</tr>
<tr>
<td>Preoperative stay (h)</td>
<td>255 ± 683*</td>
<td>98.9 ± 310*</td>
<td>0.002</td>
</tr>
<tr>
<td>Surgical time</td>
<td>109 ± 58*</td>
<td>150 ± 93*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clean surgeries</td>
<td>26 (30.5 %)</td>
<td>27 (27.8 %)</td>
<td>0.08</td>
</tr>
<tr>
<td>Wound length (cm)</td>
<td>6.8 ± 4.2*</td>
<td>8.5 ± 5.1*</td>
<td>0.01</td>
</tr>
<tr>
<td>Malnutrition (%)</td>
<td>47.1</td>
<td>34</td>
<td>0.05</td>
</tr>
<tr>
<td>Emergency (%)</td>
<td>17.6</td>
<td>12.4</td>
<td>0.21</td>
</tr>
<tr>
<td>Bleeding (ml)</td>
<td>55 ± 220*</td>
<td>62 ± 116*</td>
<td>0.86</td>
</tr>
<tr>
<td>Drainage (%)</td>
<td>8.2</td>
<td>12.4</td>
<td>0.25</td>
</tr>
<tr>
<td>SSI (%)</td>
<td>1.2</td>
<td>10.9</td>
<td>0.009</td>
</tr>
</tbody>
</table>

*Mean ± SD.

SSI, surgical site infection.
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Analysis of Clean-Contaminated Surgeries

In this group we did find a statistically significant difference in SSI, with a majority of the frequency in the control group with respect to the experimental group ($p = 0.03$, RR 7.5).

Surgical Complications

We had three surgical complications, one in the experimental group and two in the control group. One patient had an intestinal perforation and received a primary closure without any sequelae. Another patient had a liver laceration during a laparoscopic pyloroplasty. The laceration was sutured with good results. Finally, one patient had a bladder neck injury during a posterior sagittal anorectoplasty that was repaired and managed with bladder catheter, having a good evolution. None of the patients with complications presented SSI.

Discussion

SSI represents a frequent cause of nosocomial infection in children and prolongs the hospital stay, increasing the costs of surgical care. In adults, adequate AP has become a core element of strategies to improve the quality of surgical care. There are a large number of controlled clinical trials that demonstrate their usefulness among adults. In children, despite the lack of sufficient scientific support, different organizations recommend the use of AP in the same manner as adult patients. In our study we found SSI in 6.4% of all wounds but most were in the control group who received antibiotics for several days. However, during this study, the numbers were different from those previously reported in our hospital 8 years ago. They were very similar to those found in other studies outside of Mexico.

According to the results, the first important consideration was that SSI incidence was significantly higher in the control group than in the experimental group (10.9% vs. 1.2%, respectively), which showed a RR 9.7 times higher for SSI in the control group (95% CI = 1.2-77.9). Osuigwe et al. reported results of a randomized, double-blind comparison of 278 pediatric patients comparing AP with placebo in clean surgeries for inguinal hernioplasty without finding a difference in the incidence of SSI, even though all were clean surgeries. In our study, the proportion of clean surgeries was ~30% in both groups. However, the statistical power demonstrated the advantage of surgical prophylaxis in clean-contaminated surgery without being able to demonstrate this in clean surgeries. A much larger sample is necessary to demonstrate the usefulness of AP in inguinal hernia clean surgeries in children. In open inguinal surgery, a recent meta-analysis of 6705 adult patients found no difference between antibiotics and placebo. Therefore, in the case of clean surgeries, we must weigh the risk of SSI vs. the risk of antibiotic administration. Only when it is expected that the risk of SSI is higher would it be appropriate to administer AP. Because our hospital is a tertiary care center, the proportion of clean surgical wounds (30%) is low. These results may differ in first- or second-level centers where a higher proportion of clean surgeries is found.

Length of hospital stay may favor the presence of nosocomial infections and it was considered that this may occur between 48 and 72 h postoperatively. The presence of nosocomial bacteria within 24 h of admission has even been reported, especially in patients undergoing invasive procedures. A longer preoperative hospital stay may be associated with an increased frequency of SSI; however, our results showed that it was not a risk factor because patients from our experimental group had longer preoperative stay. Prolonged surgical time is a demonstrated risk factor for SSI in children. Because duration of surgery and wound length were higher in the control group, we had to stratify the analysis to assess whether these factors are related to SSI. There were no significant differences and, therefore, were not factors associated with SS in this study (Table 3). Moreover, the experimental group showed a higher number of malnourished patients but with less SSI, so the nutritional status of patients was not associated with SSI. Doig in his study of 277 patients, reported that emergency

<table>
<thead>
<tr>
<th>Variable</th>
<th>With SSI (n=11)</th>
<th>Without SSI (n=160)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative stay (h)</td>
<td>37.6±27*</td>
<td>185±55*</td>
<td>NS</td>
</tr>
<tr>
<td>Surgical time (min)</td>
<td>192±101*</td>
<td>130.1±8*</td>
<td>NS</td>
</tr>
<tr>
<td>Wound length (cm)</td>
<td>9.9±6.2*</td>
<td>7.6±4.7*</td>
<td>0.134</td>
</tr>
<tr>
<td>Malnutrition (%)</td>
<td>27.3</td>
<td>41.9</td>
<td>0.26</td>
</tr>
<tr>
<td>Emergency (%)</td>
<td>27.3</td>
<td>14.4</td>
<td>0.22</td>
</tr>
<tr>
<td>Bleeding (ml)</td>
<td>74±142*</td>
<td>54±180*</td>
<td>0.83</td>
</tr>
<tr>
<td>Drainage (%)</td>
<td>27.3</td>
<td>10</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*Mean ± SD.
SSI, surgical site infection.
surgery resulted in twice as many SSIs in relation to elective surgeries, but in our study it did not influence the presence of infection, surgical bleeding or use of drains.

The current recommendation for the optimal timing of AP administration is 60 min prior to surgery. However, as demonstrated by Classen in 1992, the time limit for administration is 2 h prior to surgery. In a study comparing SSI rates among 1313 pediatric patients in whom perioperative AP consistent with current recommendations was used, with SSI rates in 721 historical controls, Ichikawa et al. showed that the benefits of AP are maintained and the frequency of SSI is reduced, even if administered at the time of induction of IV anesthesia or at the time of endotracheal intubation, without the need for postoperative dosing. Anticipating that there may be delays in the implementation of the preoperative dose of antibiotic, we decided to administer AP 2 h preoperatively, as in the study by Classen. Our study demonstrates, in a comparative, prospective and randomized manner, that administering a correct dose of intravenous antibiotics during the 2 h prior to surgery and for no more than 24 h postoperatively, significantly reduces the incidence of SSI.

In pediatric patients, results of our study corroborate the following recommendations for AP in surgery:

- Suitable indication, that it is proven to be effective according to the microbial flora involved in the surgical procedure
- Use of only one antibiotic if possible, with low toxicity and low cost
- Preoperative dose is indicated between 1 and 2 h prior to surgery
- If the surgery lasts more than two half-lives of the antibiotic used or if there is bleeding of >15% of the estimated body volume, then the antibiotic dose should be repeated intraoperatively
- AP should not exceed the 24 h postoperative period
- The first preoperative dose should double the usual therapeutic dose except for newborns and should be administered intravenously. Subsequent doses should be the usual therapeutic dose for each antibiotic.

In relation to costs, although it was not the intent for the present study, it is obvious that reducing antibiotic administration to a fifth of what is traditionally used will yield significant savings of ~80% of the average cost of these medications in these types of surgeries.

In conclusion, in our study AP administered 2 h before surgery and continued for 24 h reduced SSI rates by almost 10-fold (RR = 9.7, CI 95% = 1.2-77.9) compared with antibiotics administered for 5 days in pediatric patients with clean-contaminated wounds.

References