Prophylactic vs Postoperative Antibiotic Use in Complex Septorhinoplasty Surgery

A Prospective, Randomized, Single-blind Trial Comparing Efficacy

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Objective: To compare the efficacy of prophylactic vs postoperative antibiotic use in complex septorhinoplasty and strengthen the evidence base for antibiotic use in nasal surgery.

Design: A randomized, prospective, single-blinded trial.
One hundred sixty-four patients requiring complex septorhinoplasty surgery were recruited sequentially from the waiting lists of the 2 senior authors. Power was calculated at 80% at the 5% significance level. Patients randomized to the prophylactic arm of the study received three 1200-mg intravenous doses of amoxicillin-clavulanate, given at induction of anesthesia and at 6 and 12 hours postoperatively. Patients in the postoperative antibiotic arm received a 7-day course of 375 mg of amoxicillin-clavulanate 3 times a day. Patients allergic to penicillin were given erythromycin. Clinical and microbiological evidence of infection on the 10th postoperative day was categorized as either minor (vestibulitis) or major (nasal or septal cellulitis, septal abscess, secondary hemorrhage, or donor-site infection) infections.

Results: At follow-up, 6 (7%) of 82 patients in the prophylactic arm and 9 (11%) of 82 of patients in the postoperative arm showed evidence of infection. Most (80%) of infections were minor. There was no significant difference in infection rates between the prophylactic and postoperative arms on analysis (P = .42). All 164 patients completed the study on an intention-to-treat basis.

Conclusion: We recommend the use of prophylactic antibiotics rather than empirical postoperative antibiotics for patients undergoing complex septorhinoplasty.

Arch Facial Plast Surg. 2006;8:84-87

The nasal vestibule is lined with stratified squamous epithelium, whereas the nasal cavity is lined with ciliated columnar epithelium. There is a distinction between the normal flora of the nasal vestibule and those of the nasal cavity with regard to potential infectious pathogens (PIPs), in particular, Staphylococcus aureus. Staphylococcus aureus resides predominately in the nasal vestibule and facial skin but is also present in 18% to 50% of microbiologic cultures from nasal mucosal smears of healthy subjects and is considered to be the most important PIP. Gluck and Gebbers identified PIPs residing in 77% of healthy men, and in one third of cases there was a difference in the percentage of PIPs between the flora in the nasal vestibule and in the cavity. Common PIPs found included S aureus and gram-negative rods such as Klebsiella species, Escherichia coli, Enterobacteria species, and Haemophilus influenzae.

Staphylococcus aureus in the form of methicillin-resistant S aureus can cause life-threatening infections and has a carrier rate of 46%. In 10% to 30% of cases of S aureus infections, the organism can also produce toxic shock syndrome toxin as well as other enterotoxins. The incidence of toxic shock syndrome is, however, generally associated with the use of nasal packing. It has been estimated that 30% of methicillin-resistant S aureus wound infections originate in the patient's nose. Pirsig and Schafer demonstrated that the healthy nasal flora change after revision surgery; the number of potentially infectious pathogens increases from 5.5% to 24%.

Operations can be classified as clean, infected, or contaminated. Nasal procedures are contaminated owing to the unavoidable contact with PIPs. Many factors influence whether a contaminated wound becomes infected. It is generally thought that the normal defense mechanisms of the host destroy invading bacteria during routine nasal surgery, but this is not the case in complex nasal surgery.

Current evidence does not support the need for prophylactic or postoperative antibiotics in routine nasal surgery; however, the need for their use in complex na-
nal surgery remains unclear, as evidence is limited. Routine nasal surgery is defined as primary septoplasty or septorhinoplasty without grafting. Complex nasal surgery, by definition, includes nasal grafting and revision surgery. The postoperative infection rate in routine nasal surgery is approximately 2.5%. Two studies have comparatively compared the effectiveness of antibiotics with that of placebo in routine nasal surgery, and both have failed to show a reduction in infection rates. Although there is no evidence to support the use of antibiotics in routine nasal surgery, they are still prescribed to prevent infection. This fact has been highlighted by a recent survey by the American Rhinological Society, which found that 66% of its members still use antibiotics in routine nasal surgery.

In complex nasal surgery, available evidence does support antibiotic use owing to higher postoperative infection rates encountered, which are as high as 27%. The only prospective study, performed by Pirsig and Schafer, compared the efficacy of antibiotics with that of placebo in complex nasal surgery and showed a reduction in postoperative infection rates with the use of postoperative antibiotics. Their study found a total infection rate of 18% (18 of 100 patients), which included both mild and severe infections. The infection rate was 27% in the placebo arm of their study and 8% in the postoperative antibiotic arm. Their study did not evaluate the use of antibiotic prophylaxis.

The need for prophylactic antibiotic use in head and neck surgery is well documented owing to its high incidence of contaminated wounds, but to our knowledge there is no evidence regarding the efficacy of prophylactic antibiotic use in complex nasal surgery.

METHODS

OBJECTIVES

In accordance to the Consort guidelines, the aim of this study is to compare the efficacy of prophylactic vs postoperative antibiotic use in complex septorhinoplasty surgery and strengthen the evidence base for antibiotic use in nasal surgery. The null hypothesis assumed no difference in efficacy between prophylactic and postoperative use.

PARTICIPANTS

We obtained full approval from the ethics review committee of the Royal Free Hospitals Trust. All patients requiring complex septorhinoplasty (grafting and/or revision surgery) on the 2 senior authors’ (C.A.E. and L.B.) waiting lists at the Royal National Throat, Nose and Ear Hospital, London, England, were eligible for this study. One hundred sixty-four consecutive patients who needed complex septorhinoplasty were recruited without further selection. Patients requiring routine primary nasal surgery and patients who had taken oral antibiotics within 2 weeks of the operation date were excluded.

INTERVENTION

The patients randomized to receive prophylactic antibiotics (hereafter, the prophylactic arm) received three 1200-mg doses of intravenous amoxicillin-clavulanate based on the advice of a microbiologist. The first dose was given at induction of anesthesia, the second and third at 6 and 12 hours after surgery, respectively. Patients receiving postoperative antibiotics (hereafter, postoperative arm) received 375 mg of oral amoxicillin-clavulanate 3 times a day for 7 days, starting after surgery. Patients allergic to amoxicillin-clavulanate in the prophylactic arm were given 3 doses of 1000 mg of erythromycin at induction, at 6 hours postoperatively, and at 12 hours postoperatively; and 500 mg 4 times a day in the postoperative arm. A specimen from each patient’s nasal vestibule was obtained for a microbiologic swab before surgery.

OUTCOME MEASURES

At follow-up, on the 10th postoperative day each patient was examined by a physician for evidence of infection as the primary outcome measurement, and specimens were obtained for microbiologic swabs to check for the presence of pus as the secondary outcome measurement. Infection was categorized as either minor (vestibular cellulites) or major (nasal or septal cellulitis, secondary hemorrhage, or donor-site infection) depending on the clinical findings and microbiological analysis. In this study, a diagnosis of nasal vestibulitis required the presence of erythema, induration, and suppuration on clinical examination and was graded according to severity using a scoring system similar to that employed by Johnson et al and Parelli. All assessors were trained by the senior authors to reduce interobserver variability.

RANDOMIZATION AND STATISTICAL ANALYSIS

Power was calculated at 80% at the 5% significance level using a total of 164 patients. Power was determined using statistical tables and was based on expected infection rates of 40% in the prophylactic arm and 20% in the postoperative arm.

The first author used a computerized random number generator to produce the random allocation sequence, which was sealed in 164 consecutively numbered identical envelopes. Patients were allocated sequentially, and the corresponding envelope was opened at anesthetic induction to allocate the patient to receive either prophylactic or postoperative antibiotics.

This study was a single-blind study. Postoperative assessment on day 10 was performed by blinded assessors, who forwarded their findings to the first author. The χ² test was used for statistical analysis to compare the results of the treatment arms.

RESULTS

All 164 patients completed the study on an intention-to-treat basis. Eighty-two patients were allocated to each arm of the study. Patient recruitment started in 2001, and the study was completed in 2004.

The types and percentages of complex septorhinoplasty procedures performed in the study are as follows:

Table 1 shows the infection rates in the postoperative and prophylactic arms. We found no significant difference in the rate of infection between the 2 arms (Table 1) of the study (P = .42, χ² test). A P value of .42 in the χ² test indicates that there is no evidence to reject the null hypothesis. The relative risk of infection for those treated with prophylaxis was 0.67 (95% confidence interval [CI], 0.25-1.79).

[Table 1: Infection rates for postoperative and prophylactic arms]
Table 2 provides the demographics of surgical procedures performed with associated infection rates and the infection rate associated with each type of procedure. Table 3 shows the grade of infection (minor or major). We defined minor nasal infection as localized vestibulitis and major infection as more widespread cellulitis, abscess formation, and secondary hemorrhage. Donor-site infection was not encountered from either auricle or temporalis fascia site (Table 3). In our study, the total infection rate was 9% (15 of 164 patients), with a major infection rate of 1.8% (3 of 164 patients), which compares favorably with the rates in the literature.

Table 3 lists the types of bacteria found in specimens obtained for microbiologic swabs. The patients who developed postoperative infection had similar findings on nasal speci-mens from preoperative and postoperative microbiologic swabs. The patients who developed postoperative infection had similar findings on nasal specimens from preoperative and postoperative microbiologic swabs. No adverse effects were noted.

Table 1. Infection Rates in the Postoperative and Prophylactic Study Arms

<table>
<thead>
<tr>
<th>Infection</th>
<th>Postoperative Arm</th>
<th>Prophylactic Arm</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, No.</td>
<td>9</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>No, No.</td>
<td>73</td>
<td>76</td>
<td>149</td>
</tr>
<tr>
<td>Total, No.</td>
<td>82</td>
<td>82</td>
<td>164</td>
</tr>
<tr>
<td>Infection rate, %</td>
<td>11</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 2. Type of Surgery Performed With Associated Infection Rate*

<table>
<thead>
<tr>
<th>Type of Operation Performed</th>
<th>Prophylactic Arm</th>
<th>Postoperative Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal perforation repair</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>SRP (revision and/or graft)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>External</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Internal</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

Abbreviation: SRP, septorhinoplasty.
*Data are given as number of infections.

Table 3. Grade of Infection

<table>
<thead>
<tr>
<th>Infection</th>
<th>Minor</th>
<th>Major</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestibulitis</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Septal or nasal cellulitis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Secondary hemorrhage</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Septal abscess</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 4. Types of Bacteria Found in Specimens Obtained for Microbiologic Swabs

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Staphylococcus aureus</th>
<th>Klebsiella and Proteus Species</th>
<th>Salmonella</th>
<th>Morganella morganii</th>
<th>Mixed Anaerobes</th>
<th>Mixed Normal Flora</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic, No.</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative, No.</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total, No.</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

This prospective randomized study did not show a significant increase in infection rate among patients taking prophylactic antibiotics compared with those taking postoperative antibiotics during complex septorhinoplasty surgery. The relative risk of infection for those treated with prophylactic antibiotics was 0.67 (95% CI, 0.25-1.79). At best, the infection rate might be only 0.25 times as frequent if prophylactic antibiotics were used (75% risk reduction), or at worst, it could be 1.79 times as frequent (79% risk increase).

Power calculation was based on the assumption that the infection rate in patients receiving the standard 5-day dosage of postoperative antibiotics would be approximately 20% with an anticipated increase in infection of 40% in the prophylactic arm. As a result, the difference between the 2 groups would be detectable with 80% power at the 5% significance level with an allocation of 82 patients per group. Predicted infection rates were based on the evidence available in 2001. This included only 1 prospective trial that evaluated postoperative antibiotics in complex nasal surgery, which was performed by Pirsig and Schafer, and there was no available evidence with regard to the role of prophylaxis.

Pirsig and Schafer performed a comprehensive study to evaluate the role of postoperative antibiotics in complex nasal surgery and encountered an overall infection rate of 18%. This ranged from 27% in the placebo arm to 8% in the postoperative antibiotic arm. On the basis of their results, we used the postoperative antibiotic arm as the gold standard with the anticipation of finding higher infection rates in the prophylactic arm. We noted that in Pirsig and Schafer’s study, all patients, including those in the placebo arm, were treated with postoperative nasal packing that was impregnated with antibiotics and left in place for 6 days. Because we were not using antibiotic-impregnated nasal packing, we expected even higher rates of infection in both our prophylactic and postoperative arms and therefore adjusted our power calculation. We also thought it unethical to include a placebo arm in our study owing to the high infection rates quoted by others.

Interestingly, the infection rates in the prophylactic arm were found to be lower than anticipated and lower than that in the postoperative arm. The infection rate in the postoperative arm was comparable to that encountered by Pirsig and Schafer. In retrospect, the predicted overestimation of infection rates could have been avoided if an initial pilot trial was undertaken.

Our inclusion and exclusion criteria were stringent; however, other confounding variables, such as age, comorbidity, and smoking habits, were not taken into account. Overall, we had a similar case mix in each trial arm and therefore avoided an obvious treatment bias. The results from this study have certainly shed more light on the infection rates...
encountered in complex nasal surgery. Up to now, data have been scanty owing to the large numbers of patients required for recruitment to perform such a study.

*Staphylococcus aureus* was the most common pathogen isolated; we did not, however, encounter the methicillin-resistant variety. Most (80%) of the postoperative infections were minor. Two of the 3 major infections were in the postoperative arm, and 1 was in the prophylactic arm. Nasal vestibulitis was the most common type of infection. One of the most important objectives of this study was to quantify the definition of wound infection because this was the primary outcome measurement. It was the opinion of both senior authors that isolated mild erythema around the wound margin without evidence of induration and suppuration did not signify infection. Johnson et al also documented this observation in their study, in which antibiotic prophylaxis was evaluated in head and neck surgery. The erythema encountered probably represents venous and lymphatic engorgement and not infection.

Complex nasal surgery encompasses both revision and grafting surgery. An inherent variation of complexity exists within this group, and 10 of 15 nasal infections involved more complex nasal procedures. Such procedures included septal perforation repair and revision external surgery, where, owing to the length of surgery and greater tissue exposure, a higher contaminant exposure was encountered.

The antibiotic chosen for this study possesses good sensitivity against the organisms most likely to contaminate the operative site, and, on recommendation by a microbiologist, a prophylactic antibiotic regime of 3 intravenous doses of amoxicillin-clavulanate was used. However, current evidence suggests that there is no statistical advantage of multiple-dose vs single-dose prophylaxis using the same antimicrobial agent.

The advantages of prophylactic antibiotic use compared with postoperative antibiotic use are both microbiological and financial. Prophylactic antibiotic use discourages antibiotic resistance and superinfection and by definition should optimize prevention of infection. Although it would be difficult to prove, it is unlikely that a postoperative course of antibiotics would optimize tissue penetration in complex surgery. The question arises as to which factors determine whether a contaminated wound becomes infected. Generally, it is thought that the patient’s host defenses rapidly destroy microorganisms that are contaminating a wound. It could be argued that prophylaxis prevents the wound from becoming infected because the tissue concentration of antibiotic is optimum at the time of surgery. This is not necessarily the case with postoperative antibiotic use, when by definition you are treating a suspected infection. Infection rates in complex nasal surgery are higher because of larger PIP colonization and also because increased fibrosis found at revision surgery reduces antibiotic tissue penetration.

Various methods of introducing antibiotic cover have been investigated but only 1 study evaluated the in vivo efficacy of using nasal packing containing an antibiotic substance to inhibit PIPs after routine nasal surgery. The authors of that study found that nasal packing containing antibiotics effectively inhibits PIPs in the nasal flora, but the question remains as to whether this would be effective in complex nasal surgery. The problem with the use of topically applied antibiotics on nasal packing is 2-fold. First, it is a postoperative antibiotic application and not a true prophylaxis; second, doubt remains as to the extent of tissue penetration, particularly with respect to grafting.

As for any formal surgical skin incision, we recommend cleaning the skin with an appropriate antiseptic and discouraging shaving hairs with a surgical knife because this may promote infection. There are also proponents of soaking grafts in an antibiotic solution prior to insertion, which would certainly optimize tissue penetration; however, we did not employ this technique, and its efficacy has not been quantified.

In conclusion, to our knowledge this is the first prospective randomized study of the role of prophylactic antibiotic use in complex nasal surgery, and its results are in keeping with those of other studies that demonstrate the benefits of antibiotic prophylaxis in surgery. Therefore, we would recommend prophylactic antibiotic use in the form of three 1200-mg intravenous doses of amoxicillin-clavulanate before complex nasal surgery, and we concur with current evidence that antibiotics are not required in primary septorhinoplasty without grafting.

Accepted for Publication: April 27, 2005.

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Acknowledgment: We thank Andrew Simpson, MD, and Richard Morris, MD, of the Royal Free Hospital.

**REFERENCES**