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Original Article

Comparative study of two cefazolin prophylactic protocols in oncologic surgery of the larynx: A randomized trial

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Abstract

Objective Patients who need major head and neck surgery like laryngectomy are at risk of postoperative wound infection. Although the role of antibiotics in prophylaxis of clean contaminated head and neck surgery has been well documented, controversy exists in the optimal antibiotic regimen.

Methods In two tertiary referral hospitals (Imam Khomeini and Amir Alam hospital), 90 patients undergoing laryngectomy were prospectively randomized into two groups receiving cefazolin perioperative prophylaxis either for 2 days or for 5 days from June 2004 to March 2006. Then patients were blindly examined for the development of wound infection.

Results No wound infection was detected in either group. Two (4.4%) mucocutaneous fistula occurred in the 2-day group, and 3 (6.7%) in the 5-day group. There was no statistically significant difference in the infection rate between two groups.

Conclusion We conclude that a 2-day perioperative cefazolin prophylaxis is equally effective as longer therapies. The increased morbidity and cost of the latter are in favor of the 2-day prophylactic regimen.

Keywords Clean contaminated · Laryngeal cancer · Head and neck surgery · Wound infection · Antibiotic

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Introduction

Patients undergoing laryngeal oncologic surgery are at relatively high risk of developing complications. Among them, the incidence of wound infection is relatively high and varies from 3.5 to 87% [1]. Patients diagnosed with laryngeal cancer often have associated significant co-morbidity and present a high anesthetic and surgical risk. The development of wound infection in patients undergoing laryngeal cancer surgery can have devastating effects such as wound breakdown, the development of mucocutaneous fistulae, distant sepsis and death. It can also prolong hospital stay and costs, and may delay the administration of radiotherapy following surgery, which will increase the risk of tumor recurrence [2].

Risk factors for high wound infection rates following surgery include diabetes mellitus, nutritional deficiency, excessive tobacco and alcohol consumption, poor oral hygiene, preoperative radiotherapy and/or chemotherapy, preoperative tracheostomy, major resections with flap reconstruction, duration of the surgery, advanced tumor stage, duration of preoperative hospitalization, and hypopharyngeal and laryngeal cancers. Some of these factors, however, will increase the severity of the sepsis but they may only be significant in a small proportion of patients and therefore controversy exists regarding the true risk to these patients [3–5].

One major progress in head and neck oncological surgery during the last decades was the introduction of prophylactic antibiotics to prevent wound infection. Despite antibiotic usage the risk of infection can be as high as 41.8 [6, 7]. The use of prophylactic antibiotics in head and neck surgery has been well reviewed and accepted in the surgical articles [2, 8]. Prospective, randomized, trials have uniformly accepted that perioperative antibiotic prophylaxis has a key role in patients undergoing clean-contaminated or contaminated head and neck surgery, because without receiving antibiotics, the infection rate approaches 80–100% [3, 9]

Some of these studies have shown a significant reduction in the wound infection rate to <10% by using appropriate perioperative antibiotic regimes [2, 8]. Controversy, however, exists over the length and type of antibiotics [10, 11].

The efficacy of cefazolin as a prophylactic antibiotic in head and neck surgery has been reviewed in many studies [3, 12], but considering the costs and morbidities of a prolonged antibiotic regimen, we designed a prospective randomized study on 90 patients to compare the efficacy of two different protocols.

Materials and methods

A prospective, randomized, partially blind clinical trial of patients was conducted at the Department of Otolaryngology and Head and Neck Surgery of Tehran University, in two tertiary referral Hospitals of Amir Alam and Imam Khomainey, from June 2004 to March 2006. The protocol had been reviewed and approved by the Tehran University Ethics Committee (IRB) and all patients enrolled in the study reviewed and signed the informed consents.

Patients eligible to be included in this trial were those who had a histologically confirmed squamous cell carcinoma of the larynx and hypopharynx and were undergoing total or partial laryngectomy with or without neck dissection. None had a history of neck or laryngeal radiation.

Exclusion criteria were a history of recurrence or other primary tumors, tracheostomy, or reconstruction surgery with a flap, because these patients had been submitted to prolonged antibiotic administration. Also, cases with diabetes mellitus, immune suppression or tumor types other than squamous cell carcinoma were excluded from the study. In addition, the following exclusion criteria were taken into account: pregnancy, hypersensitivity to penicillins or cephalosporins, systemic antibiotic use within one week prior to the planned procedure, clinical or laboratory evidence of a preexisting infection or serious systemic renal disease.

On the basis of the examination data, patients were divided into four clinical disease stages according to the American Joint Committee on Cancer (AJCC) criteria [13]. Tumor characteristics at clinical examination were used to group them according to the tumor staging classification. Then they were staged into two groups (stage III or less, and stage IV). Finally, based on a computer-generated randomization code, patients were assigned into two groups. Group A patients received cefazolin 2.0 g preoperatively (extra dose if surgery was longer than 4 hours) and additional 6 intravenous cefazolin doses every 8 hours postoperatively. Group B patients received cefazolin 2.0 g preoperatively (extra dose if surgery was longer than 4 hours) which was continued postoperatively for 5 days. The two groups were matched for confounding factors such as suture material (vicril 3.0), type of neopharynx repair (3 layer), NG tube use, prep and drape process, and postoperative dressing and non-antibiotic orders. The hospital pharmacist maintained the randomization codes and dispensed all study drug supplies. The clinical investigators and coordinators were blinded to drug assignment. After surgery, patients continued to receive their assigned medications at 8-hour intervals for a total of three doses. Patients were examined daily for signs and symptoms of infection during their hospital stay. Based on a grading system of 0 for no erythema, 1+ for <1°cm of erythema, 2 + for <5°cm of erythema and induration, 3 + for >5°cm of erythema and induration, 4 + for purulent drainage, and 5 + for wound breakdown with mucocutaneous fistula. Any wound graded 3 + or more was considered infected. Grade five was analyzed independently.

One objective was to document all postoperative wound and non-wound infections after appropriate cultures. Specimens for aerobic and anaerobic cultures were obtained from open wound drainage, aspirated seromas and suction drainage as well. Non-wound infections were defined as infections of the tracheobronchial tree, urinary tract or blood as proven by the isolation of pathogenic organisms from relevant sources in a clinical setting of fever, leukocytosis, purulent sputum, pyuria or sepsis.

A sample size of 90 patients (45 patients in each group) was calculated to detect a difference of 80% (p1) in short course antibiotic group and 40% (p2) in longer antibiotic group [2, 3, 5, 9] for an alpha error of 5% and a beta error 10%.

Statistical analysis of the data was performed using chi square, Fisher, Mann-Whitney and tests. For all comparisons, the level of statistical significance was defined as a p value < 0.05. Results are reported as mean ± standard deviation.

Results

During the study period, 107 laryngectomy procedures were performed at these two centers on 107 patients, among which, 90 patients were eligible to enter our study and were randomized into the two abovementioned treatment groups, the number of patients in each group was equal. As the study was completed during their hospitalization, there was no loss to follow up.

All patients were male. Their mean age was 58 ± 11 years and their mean weight was 58.1 ± 9.8 kg. There was a positive history of smoking in 82% of patients, 30% used opium, and 9.0% consumed alcohol.

Tables 1 and 2 summarize the distribution of tumor stage and choice of surgical procedure, respectively. The mean duration of operation was 4.6 ± 1.4 hours and the mean hospitalization time was 7.7 ± 2.2 days.

Table 1 Tumor staging

Stage	Frequency
Stage I	6.7% (6)
Stage II	18.9% (17)
Stage III	50% (45)
Stage IV	24% (22)

Table 2 Types of surgery

Type of procedure	Frequency
Total laryngectomy without neck dissection	62.2% (56)
Total laryngectomy with neck dissection	16.7% (15)
Hemilaryngectomy	15.6% (14)
Supraglotic laryngectomy with or without neck dissection	5.6% (5)

The distribution of wound grades in the two groups is demonstrated in Fig. 1. According to the bar chart, none of the patients in either group had wound infection (Grade 3 or more). There was no statistical significant difference between two groups in wound infection rate with the chi square test. Also, there were no significant differences in weight, age, operation length, and hospitalization time. The fistula rate was 5.6% (5) in both groups; 2 (4.4%) patients in Group A and 3 (5.6%) patients in Group B. In terms of tumor stage, 6.7% of stage 3 patients (N = 3) and 9.1% of stage 4 patients (N = 2) were afflicted with this complication. There were no statistical differences in fistula rate among different staging groups. No antibiotic toxicity or infection at other sites was identified.

Discussion

It has clearly been known that the so-called clean-contaminated head and neck surgical procedure bears great risk of postoperative infections, the incidence of which, without the administration of perioperative antibiotics, ranges from 80 to 100% [3, 9]. This stems primarily from the gross and often extensive and prolonged contamination of the neck wound with oropharyngeal secretions. But the use of perioperative antibiotics has been shown to significantly reduce the postoperative wound infection and decrease it to the range of about 14–40% [2, 5]. However, even the best surgical techniques and most widespread antibiotics have not completely eradicated this problem [12, 13].

Studies on different types of antibiotics have demonstrated similar effects in preventing postoperative infections following major clean-contaminated head and neck surgical procedures [13]. All these antibiotic regimes have in common an activity against normal flora found on the mucosa of the upper aerodigestive tract. Wound infection rate after surgery is mainly correlated with the degree of wound contamination. In clean head and neck surgeries, usually the surgical site remains sterile, unless the area is contaminated accidentally, and it is generally accepted that perioperative antibiotic coverage is not necessary [3, 14]. Nonetheless, for clean-contaminated head and neck surgery, the necessity of perioperative antibiotic prophylaxis has been well demonstrated in many trials, the application of different antibiotics for variable periods resulted in differences in postoperative wound infection rates [15, 16]. Reviewing these trials, it can be stated that the ideal antibiotic prophylaxis for clean-contaminated

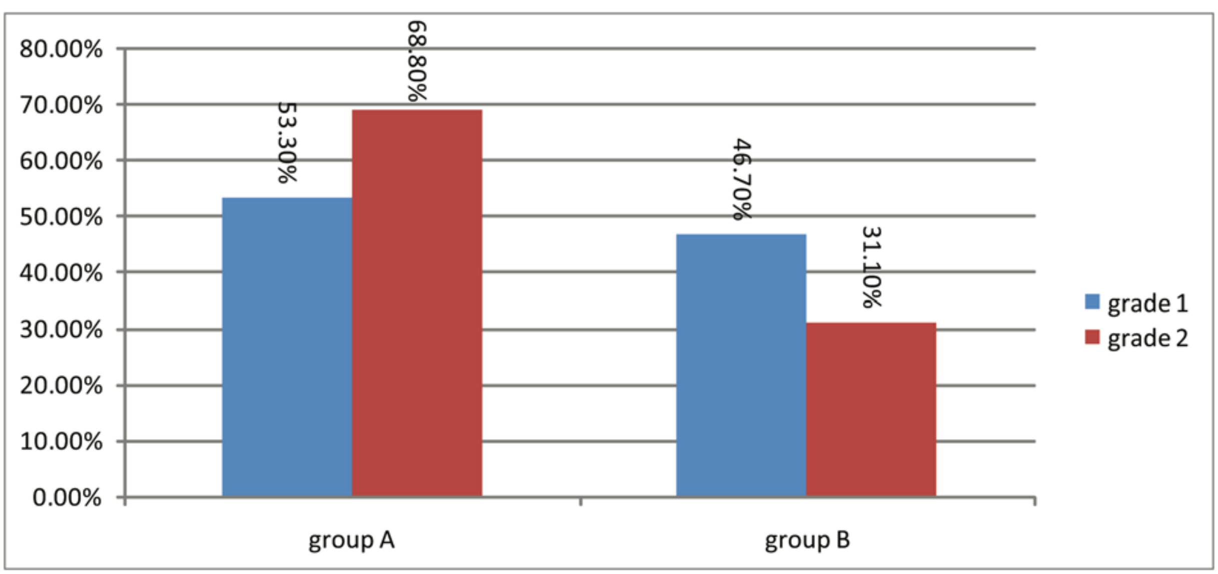

Fig. 1 Distribution of wound grades in the two studied groups

head and neck surgery should cover gram-positive and anaerobic bacteria, and the application of antibiotics beyond 48 hours after the operation time is not necessary [2, 3]. The need for gram negative coverage is still under debate [3, 17]. Cefazolin is one of the most commonly used antibiotics which has good coverage on bacteria in laryngectomy patients and comparing other antibiotics are cheaper, so we chose it in this study.

Laryngectomy, as a clean-contaminated surgical procedure, has a risk of postoperative infection as well, but the risk is lower [16]. In this study, only laryngectomy patients with no major risk factor were included, and two protocols of prophylactic cefazolin were compared. Surgical technique was accepted to be the standard because the same technique of drainage, hemostasis and wound closure was used in all cases, we apply vicril 3–0 to mucosal repairing, in all patients neo pharynx repaired in 3 layers, and usage of NG Tube, hemovace drain, the way of packing and the non-antibiotic orders were the same for all patients, therefore these factors can be excluded. Results showed that there were no significant differences in postoperative wound infection rate between these regimens and there was no infection if we exclude pharyngocotaneus fistula. This indicates there is no need for long term prophylaxis, and cefazolin alone is an effective prevention tool for clean-contaminated head and neck surgery.

Findings in the two groups with 2-day and prolonged antimicrobial prophylaxis were compared with each other for many risk factors including weight, age, postoperative hospitalization time ('t'–test) and surgery duration (Mann-Whitney Test). No statistical difference could be demonstrated between results of the two antibiotic regimens for any of these factors ($p > 0.05$ for all factors). This supports the finding that 5 days of cefazolin prophylaxis or more is not superior to a 2-day cefazolin prophylaxis regimen. In comparison to 1-day prophylaxis approaches, however, the infection rates were lower in our study, but this matter should be examined in larger studies [3, 7]. In terms of the choice of antibiotic, we used cefazolin in contrast to other studies that administered other more widespread antibiotics [15, 18]. Our results show that cefazolin prophylaxis can be adequate in low risk laryngectomy patients.

Several factors are suspected to increase the risk of postoperative infections [1, 3, 8]. For instance, the influence of prior radiotherapy on postoperative wound infection rate has long been an area of controversy. Some authors [3, 19, 20] stated that prior radiotherapy increases the postoperative infection rate. But many studies [2, 3, 5] have failed to demonstrate this relationship.

Prior tracheotomy is another factor that may be responsible for higher postoperative wound infection rates. Some authors have demonstrated that prior tracheotomy increases the risk of postoperative wound infection [2, 3] although other studies in the literature failed to demonstrate a statistically significant relationship, and only some increase in postoperative wound infection rates were detected [3].

Coexisting systemic diseases may interfere with patients' immunologic states and may increase postoperative wound infection rates. Diabetes mellitus may be responsible for higher wound infection rates, but no effect of this disease on postoperative wound infection rates have been demonstrated. [1, 13]

Besides poor prognosis, advanced tumors are reported to have higher rates of postoperative wound infection when compared with lower stages [1, 3, 7]. In our study, postoperative wound infection and fistula rates did not increase with tumor stage. This finding is not supported by literature, possibly due to the small number of studied cases in our study.

The risk of mucocutaneous fistula and wound infection increases with closure of the mucosal suture lines under tension, the inability to achieve a water-tight closure, or application of complex reconstructions (e.g. myocutaneous flaps). Some studies [3] have reported that wound infection rates rise after supraglotic laryngectomy or total laryngectomy if more mucosa than suspected is resected, probably due to high tension at the mucosal suture line. All these facts were considered in our study design.

Conclusions

Prolonged and 2-day antimicrobial prophylaxis for clean-contaminated procedures was shown to be of similar efficacy. Prolonged antimicrobial prophylaxis is therefore not considered necessary for laryngeal cancer surgery. In clean-contaminated procedures, like laryngectomy, cefazolin can be a good choice with no need to add another antibiotic.

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