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Atlas Oral Maxillofacial Surg Clin N Am 20 (2012) 225–232

Atlas of the Oral and Maxillofacial Surgery Clinics

Perioperative Strategies for Third Molar Surgery

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Introduction

The removal of third molar teeth is one of the most common procedures performed by oral and maxillofacial surgeons. Third molar extraction is associated with undesirable sequelae and complication. Morbidity is related to pain, swelling, trismus, infection, alveolar osteitis, bleeding, nerve injury, dental injury, jaw fracture, temporomandibular joint dysfunction, lost workdays, and general inconvenience. Many factors and strategies have been studied to minimize the morbidity associated with third molar removal. This article focuses on perioperative strategies that have been suggested to influence the postoperative course after third molar extraction. These include the effect of smoking, chlorhexidine rinses, topical and systemic antibiotic use, and preemptive pharmacotherapies, including corticosteroids, analgesics, and muscle relaxants. Additional factors that may play a role, such as microbial contamination, surgical difficulty, surgeon experience, flap design, extent and closure, presurgical pathology, age, gender, and oral contraceptive use, are not addressed.

Tobacco smoking

The influence of smoking on postsurgical complications is well appreciated. The direct and indirect effects of cigarette smoke have been well described in relation to multiple soft tissue reconstructive procedures, including facelifts, abdominoplasty, breast reconstruction, free tissue transfer, and digit replantation (Table 1) [1]. The dental literature has also shown the detrimental effects of tobacco smoking on the immune response, alveolar bone loss, oral wound healing, and response to therapy (Table 2) [2]. Additionally, a recent systematic review showed that longer durations of perioperative smoking cessation seem to be beneficial, but the ideal period of tobacco cessation could not be specified. Outcome variables such as overall postoperative complications, mortality, pulmonary and respiratory complications, and wound infections were examined. A variety of general surgery procedures and onlay bone grafts and sinus lifts were evaluated, but dental extractions were not reviewed.

The literature relating smoking and third molar extraction is minimal. Al-Belasy [3] investigated the effect of smoking on incidence dry socket after mandibular third molar removal in men, comparing nonsmokers with cigarette and "shisha" smokers. They showed an incidence of 7% in nonsmokers, 31.6% in smokers who refrained the day of surgery, 17.9% in smokers who ceased tobacco use until the second day after surgery, and 10.5% when tobacco cessation continued until the third postoperative day or longer. A statistically significant difference was found between smokers and nonsmokers, but the difference between cigarette and shisha smokers was not found to be statistically significant. Further discussion provides support against the influence of the negative pressure effect of smoking on clot dislodgement and subsequent dry socket, favoring a systemic and local tissue pathogenesis. This finding agrees with the research of Meechan and colleagues [4], who

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http://dx.doi.org/10.1016/j.cxom.2012.06.001

Table 1
Effects of cigarette smoke

Substance	Action	Effect
Nicotine	• Direct vasoconstriction • Indirect catecholamine release • ↑ Red blood cells, fibrinogen, and platelet adhesiveness • Thromboxane A2 stimulation • Prostacyclin inhibition	• ↑ Oxygen demand and tissue hypoxia • Tunica media fibrosis and calcification • Thrombogenic state
Carbon monoxide	• ↑ Carboxyhemoglobin	• ↑ Oxygen-binding affinity and tissue hypoxia • Thrombogenic state

showed significant differences in immediate socket filling and postoperative pain in smokers over nonsmokers, especially female heavy smokers. Conversely, reports have shown no significant difference between smokers and nonsmokers in postoperative pain and wound healing.

Additional dental research evaluating periodontal regenerative therapy with an allograft has shown significant differences between smokers and nonsmokers. Rosen and colleagues [5] found that smokers had a 29% improvement in clinical attachment level, whereas nonsmokers had a 42% improvement at 1-year follow-up. This trend persisted long-term, with improvement of 31% and 42% for smokers and nonsmokers at 2 to 5 years, respectively. The adverse effects of tobacco smoking should encourage perioperative tobacco cessation. Grossi and colleagues [6] showed that tobacco cessation improved their patient population's healing response to equate that of nonsmokers, with similar observations on periodontal microbial content. The systemic and local influences of tobacco use are well-known. However, the relationship of smoking and postoperative course in relation to third molar surgery is not completely understood and has not been clearly proven to be causal in nature. Further studies are necessary to elucidate the mechanisms that make smoking a significant risk factor for dry socket. Preoperative and a minimum of two postoperative days of tobacco cessation is recommended for third molar dry socket prevention.

Table 2
Dentoalveolar effects of cigarette smoke

Alveolar bone loss	↑ Amount and severity of destruction (dose-related) ↓ Estrogen in women leads to ↑ IL-1, IL-6, TNF-α
Immune response	↓ Hemorrhagic responsiveness of the periodontium ↓ Gingival blood flow ↓ Neutrophil chemotaxis, phagocytosis, and adherence with ↑ oxidative bursts (direct toxicity) ↓ IgG, IgG2, T-cell proliferation
Healing and response to therapy	↓ Regenerative potential ↓ Fibroblast production of fibronectin and collagen ↑ Collagenase production ↓ Reduction in probing depth and clinical attachment gain

Abbreviations: IL, interleukin; TNF-α, tumor necrosis factor α.

Chlorhexidine

Chlorhexidine digluconate (CHX) is a commonly used topical antimicrobial agent used in dentistry. It has been shown to be effective in treatment and maintenance for periodontal disease and caries. CHX acts on gram-positive and gram-negative aerobes and anaerobes through membrane disruption. The therapeutic action of CHX is further enhanced by its substantivity, the ability to have a continued effect between dosages. Resistance and pathogen selection have not been shown to occur with use of CHX. Additionally, the adverse effects of CHX are minimal, including allergy, dental staining, increased calculus formation, and mucosal and taste alterations. The role of CHX rinses in prevention of alveolar osteitis (AO) and surgical site infection has also been extensively studied, with evidence for and against its use. The main arguments against CHX use is that a lack of evidence exists to prove its efficacy, failing to justify the associated expense.

In 1991, Larsen [7] performed a prospective, randomized, double-blind, placebo-controlled trial showing a 60% overall reduction of AO with the use of 0.12% CHX 1 week before and after M3

removal. This trial was based on a microbiologic explanation of the fibrinolysis related to AO. In 2005, in a meta-analysis review of human clinical trials involving mandibular third molar extractions only, Caso and colleagues [8] compared a preoperative rinse, preoperative and postoperative rinsing regimen, and control groups. The results showed that the benefit of CHX on the day of surgery alone did not reach statistical significance. However, they did find that an extended rinse period of several postoperative days may reduce AO incidence. In a similar meta-analysis, Minguez-Sera and colleagues [9] concluded that application of a 0.2% CHX paste every 12 hours for a week after mandibular third molar extraction reduced AO incidence. Overall, the studies investigating the efficacy of CHX in reducing third molar extraction postoperative pain and infection have mixed designs and possible cofounders. However, strong support exists for the use of chlorhexidine rinse and intra-alveolar application. Currently, the use of chlorhexidine should be considered in the context of a cost-benefit analysis, and directed by clinical judgment.

Preemptive analgesia

Much of the undesirable nature of third molar surgery is based on patient discomfort and decreased quality of life. Palliation through pharmacologic agents can significantly improve a patient's condition after surgery. Additionally, a proactive strategy to reduce the amount of discomfort has been investigated. Much of the literature is based on preventative or preemptive analgesia for obstetrics, thoracic surgery, and orthopedics. Evidence in relation to third molar surgery is sparse. Preemptive analgesia, defined as a "pharmacologic intervention initiated before a painful stimulus to inhibit nociceptive mechanisms before they are triggered," is a common practice. Attributes of an ideal preemptive analgesia regimen include [10,11]

1. Initiation before surgical trauma
2. Prevention of central sensitization secondary to surgical trauma
3. Prevention of central sensitization secondary to inflammation
4. Palliation throughout the perioperative period
5. Therapeutic effect lasting up to or greater than 10 weeks

Local anesthetic medications and nonsteroidal antiinflammatory drugs (NSAIDs) were shown to be more effective than opioids in a meta-analysis by Cliff [12] investigating the influence of preemptive analgesia on acute postoperative pain after major general surgery. A randomized controlled trial by Nayyar and colleagues [13] showed the preemptive effects of bupivacaine 0.5% with epinephrine 1/200,000 to significantly reduce pain at 6, 12, and 72 hours and 7 days. The effects of tramadol and ketoprofen for M3 surgery have been shown to be beneficial, but only data from 24 hours or less are presented, and postoperative dosing may be better for pain intensity, timing of onset, and degree of opioid requirement.

Santos and colleagues [14] investigated the muscle relaxant cyclobenzaprine as a postoperative medicament in a well-designed prospective, randomized, double-blind, placebo controlled, split-mouth study. They concluded that cyclobenzaprine is not useful in treating pain, swelling, or trismus after third molar removal. Currently, local anesthesia is the only pharmacotherapy that has proven efficacy for preemptive analgesia for third molar extractions. The effect of NSAIDs requires greater research to establish longer-term effects and appropriate timing of administration.

Antibiotic prophylaxis

Antibiotics have changed the influence of microbes on the human condition and infectious and inflammatory pathology. Historically, the fatal conditions are the infectious and inflammatory pathology secondary to microbes before the antibiotic era are now routinely and curatively treated with a combination of directed surgical intervention and antibiotics. The morbidity associated with infectious postoperative complications is also greatly reduced. The concept of prophylactic antibiotics is well accepted in the general surgery literature and in relation to specific postoperative conditions, such as total joint replacement and infective endocarditis. However, the clinical application in relation to third molar surgery, specifically, is not as clear. A plethora of research exists for and against preoperative administration of antibiotics for third molar surgery (Table 3). In

addition, the literature available is riddled with study design flaws and errors in conclusion, making critical appraisal difficult. Finally, the type and delivery of the antibiotic are also important to consider. Oral, intravenous, and topical antibiotic administrations have been studied, in addition to differences in specific antibiotic choice and dose. The benefit of any intervention must be examined in relation to societal impact, quality of life, cost, and adverse effects, and not merely statistical efficacy.

Table 3
Mandibular infections with and without antibiotics

Treatment	Number of third molars	Number without infection	Early infection	Late infection	Infection rate number (%)
No antibiotic	332	283	45	4	49 (14.8)
Systemic	1242	1114	96	32	128 (10.3)
Topical TC	1597	1555	28	14	42 (2.6)
Systemic + TC	250	244	3	3	6 (2.4)
Postoperative systemic	9	8	0	1	1 (11.1)
TC + postoperative systemic	13	13	0	0	0 (0.0)
TOTAL	3443	3217	172	54	226 (6.6)

Abbreviation: TC, tetracycline.

Data from Piecuch JF, Arzadon J, Lieblich SE. Prophylactic antibiotics for third molar surgery: a supportive opinion. J Oral Maxillofac Surg 1995;53:53–60.

Research in favor of antibiotic prophylaxis

In 2009 Monaco and colleagues [15] investigated the effect of 2 g of amoxicillin before removal of lower third molars in 59 patients aged 12 to 19 years. This study was randomized and controlled, and showed a statistically significant difference in postoperative pain, fever, wound infection, and consumption of analgesics in the test group. In 2007, Halpern and Dodson [16] published a placebo-controlled, double-blind, randomized clinical trial dividing 118 subjects into two arms investigating the efficacy of penicillin or clindamycin in preventing postoperative inflammatory complications. They found that 8.5% of the control subjects had a surgical site infection, and no infections were seen in the experimental group. Additionally, none of the experimental or control subjects experienced an AO. The results, although statistically significant, must be interpreted with caution, given an unusually low incidence of AO. In a meta-analysis by Ren and Mamstrom [17] also published in 2007, 16 clinical trials comprising 2932 patients found that preoperative antibiotic administration reduced the incidence of AO and wound infection from 6.1% to 4%, with 25 patients needing to be treated to avoid one such complication. Although these data provide statistical support for use of antibiotic prophylaxis, other factors, such as cost and adverse reactions, must be considered for the 24 of 25 patients who theoretically do not gain benefit from the intervention.

In 2004, Foy and colleagues [18] evaluated the Health Related Quality of Life (HRQOL) in 54 experimental and 60 control subjects having four third molars removed. They investigated the impact of preoperative intravenous antibiotics and did not find a statistical difference in HRQOL between the groups. However, they did show a significant difference in the number of postoperative visits requiring treatment; 4% of the experimental group had one postoperative visit with intervention, whereas 28% and 13% of the control group had one and at least two postoperative visits with intervention, respectively. A similar study in 2006 by Stavropoulous and colleagues [19] used the same control group and investigated the impact of topical minocycline. They found their experimental group had a 10% rate of postoperative delayed recovery, requiring one postoperative intervention. This group did, however, show a statistically significant improvement of HRQOL in time to recovery of chewing and mouth opening. The use of systemic versus topical antibiotic administration for prophylaxis is a subject of controversy and debate. The efficacy of each has been studied separately and compared, but not directly investigated in separate arms of a single study. Multiple additional studies have shown efficacy for intrasocket antibiotic administration, including tetracycline, metronidazole, and neomycin-bacitracin. However, concern has been expressed regarding tetracycline-induced neuropathy when used in proximity to the inferior alveolar nerve.

Research against use of antibiotic prophylaxis

In a split-mouth, double-blind, randomized, placebo-controlled trial with detailed evaluation of surgical and patient variables, Bezerra and colleagues [20] found no difference in postoperative inflammatory or infectious complications after third molar removal when 34 patients were given 500 mg of amoxicillin preoperatively or a placebo. One can argue that this study lacks power, and a larger study population is required to establish a clinically applicable conclusion. This argument is supported by the overall decreased rate of complications the patients experienced. Additionally, the dosage of 500 mg may not have been adequate to provide significant prophylaxis, limiting the impact of their study variable. A split-mouth, double-blind study by Siddiqi and colleagues [21] that randomly assigned 100 patients to receive 1 g of amoxicillin preoperatively, 1 g of amoxicillin preoperatively followed by 500 mg of amoxicillin every 8 hours for 2 days postoperatively, or placebo, separated by 3 weeks, failed to show any statistical significance. Finally, in 2007, Kaczmarzyk and colleagues [22] also evaluated 100 subjects, divided into three groups. Their prospective, randomized, double-blind, placebo-controlled trial did not show any prevention of postoperative inflammatory complications with either single-dose preoperative clindamycin or preoperative plus 5-day postoperative administration of clindamycin. These reports provide evidence that antibiotic prophylaxis does not limit postoperative complications of third molar extraction. However, their conclusions can be questioned given weaknesses in study designs.

Piecuch and colleagues [23] performed a retrospective analysis of 2134 patients in a group practice who underwent extraction of 6713 third molar teeth over a 9-year period. Of these patients, 2031 had a postoperative clinical examination documented an average of 7 to 10 days after surgery. The remaining had clear documentation of telephone calls at 48 hours and at 7 days.

The infection rate for maxillary third molars was 9 of 3270, or 0.3%; the infection rate for mandibular third molars was 6.6%. No cases of severe infection, hospitalization, need for intravenous antibiotics, or external incision and drainage occurred. Considering mandibular third molars alone, extraction without antibiotics resulted in a 14.8% infection rate, whereas systemic (generally oral) antibiotics decreased the infection rate to 10.8%, and topical tetracycline reduced the infection rate to 2.6%. Patients who received tetracycline topically and systemic antibiotics had an infection rate of 2.4% (Table 4).

Systemic antibiotics did not benefit patients undergoing maxillary third molar surgery alone. However, topical tetracycline significantly decreased the infection rate for erupted mandibular third molars. Systemic antibiotics and topical tetracycline reduced postoperative infections for mandibular partial and full bony third molars, but topical tetracycline was more effective. Clinical judgment was recommended for antibiotic use with soft tissue–impacted mandibular third molars.

Zuniga and Leist [24] raised the issue of tetracycline-induced neuritis, occurring after tetracycline contacts an exposed nerve. Subsequently, the same authors performed a prospective study in rats, showing that a nerve with an intact epineurium does not develop an inflammatory response to tetracycline; rather, an intense inflammatory response occurs only when the epineurium is damaged [25]. Gelfoam may protect the damaged nerve from the topical effects of tetracycline, without additional risk.

Table 4
Recent articles: do antibiotics provide benefit or not?

Year	Author	Journal	Method	Benefit	Preoperative Antibiotic
1999	Monaco [37]	Eur J Oral Sci	Oral	No	No
2004	Poeschl [38]	JOMS	Oral	No	No
2004	Foy et al [16]	JOMS	IV	Yes	Yes
2006	Stavropoulous et al [17]	JOMS	Topical	Yes	Yes
2007	Kaczmarzyk et al [19]	IJOMS	Oral	No	Yes
2007	Halpern & Dodson [14]	JOMS	IV	Yes	Yes
2009	Monaco et al [13]	JOMS	Oral	Yes	Yes
2010	Siddiqi et al [18]	IJOMS	Oral	No	Yes
2011	Pasupathy [39]	J Craniofac Surg	Oral	No	Yes
2011	Bezerra et al [11]	JOMS	Oral	No	Yes

Abbreviations: EUR J Oral Sci, European Journal of Oral Sciences; IJOMS, International Journal of Oral and Maxillofacial Surgery; IV, intravenous; J Craniofac Surg, The Journal of Craniofacial Surgery; JOMS, Journal of Oral and Maxillofacial Surgery.

In conclusion, despite some conflicting evidence, antibiotic prophylaxis clearly significantly decreases the occurrence of postoperative AO and SSI. However, surgeons must also consider issues regarding antibiotic resistance and systemic toxicity raised by Kaczmarzyk [26]. The use of antibiotics in cases of active infection; medical compromise that specifically requires systemic antibiotic prophylaxis, such as total joint prostheses; or specific cardiac conditions are completely different situations requiring dedicated research and investigation.

Corticosteroids

A plethora of literature is available on the role of corticosteroids in preventing postoperative morbidity.

In the dental field, Shafer [27] studied the effects of cortisone on postextraction wound healing in the rat model. Thirty-five experimental animals were given 2.5 mg of cortisone on the day of extraction of an upper molar, and 2.0 mg/d afterward. Histologically, no difference was seen in healing versus nonmedicated controls at 2, 4, 5, and 7 days. However at 10 days, soft tissue healing was impaired in the experimental animals. Clearly the exogenous steroid should not be continued for long periods. Although the use of steroids to decrease edema after oral surgery became common, it was not until the early 1970s that Hooley and colleagues [28] showed that a short course of corticosteroids only temporarily depressed endogenous steroid production in humans. In 1980, using a metapyrone test, Williamson and colleagues [29] noted that the hypothalamic-pituitary-adrenal axis returned to normal in 7 days in 10 consecutive patients who received 8 mg of dexamethasone intravenously immediately after oral surgery procedures.

Ross and White [30] presented the results of their randomized controlled trial in which 39 oral surgery patients were given 40 mg of hydrocortisone twice daily the day before, four times daily the day of surgery, and twice daily for 2 days postsurgery, compared with 22 placebo-controlled subjects. The authors noted a statistically significant decrease in edema and trismus in the experimental group. Pain was also less in the experimental group, but the difference was not statistically significant.

In 1964, Nathanson and Seifert [31] reported on the effects of betamethasone with various surgical procedures in their prospective randomized controlled trial in which 110 patients received 0.6 mg of betamethasone four times daily for 4 days, beginning immediately postoperatively, and 100 control patients received placebo. All subjects were examined by one of the authors daily for 5 days. The experimental group showed a significant reduction in edema and a trend toward decreased pain, with no difference in trismus. Because edema presented before the first dose was given, and resolved after that dose, their recommendation was modified to initiate therapy before the surgery and to continue 3 days postoperatively. Hooley and Francis [32] used Nathanson and Seifert's [31] dose recommendations for their split-mouth, self-controlled prospective randomized controlled trial of 476 patients undergoing removal of impacted mandibular third molars. They compared 1.2 mg of betamethasone orally the evening before surgery, then 1.2 mg four times daily the day of and 2 days after surgery. Tetracycline cones were placed into each extraction socket. These authors were the first to use cephalometric-positioned photographs for objective measurement of edema. Their findings showed that the controls had six times as much edema and twice as much trismus, and required twice as much pain medication as the experimental group. These authors additionally commented that they had used betamethasone for more than 2000 patients in the previous 8 years without any systemic complications. Numerous articles compare various steroids with placebo, including triamcinolone, dexamethasone, prednisone, methylprednisolone, and betamethasone. The details of these studies are thoroughly discussed in Gersema and Baker's 1992 review [33] of this topic. Although almost all of these studies were prospective randomized controlled trials, many also suffered from low subject numbers, inconsistent procedures, and subjective observation of results. Nevertheless, Gersema and Baker [33] concluded that "based on these studies, the use of perioperative corticosteroids appears to be a safe and rational method of reducing postoperative complications of edema, and possibly trismus and pain, following the removal of impacted third molars." These authors recommended a single preoperative 125-mg dose of methylprednisolone, given either intravenously or intramuscularly.

In a prospective randomized controlled trial, Buyyukurt and colleagues [34] compared 25 mg of prednisolone intramuscularly, 25 mg of prednisolone plus diclofenac intramuscularly, and control,

given immediately after third molar surgery. Each group had 15 patients. Pain intensity was measured on a visual analogue scale (VAS) and edema was measured objectively on the patient on days two and seven. These authors found significantly decreased edema and trismus at both day two and seven in the prednisolone and prednisolone-diclofenac groups compared with controls. Pain was studied only on the day of surgery and was significantly decreased in both the prednisolone and prednisolone-diclofenac groups, with the prednisolone-diclofenac combination more effective. These authors recommended a steroid/NSAID combination as more effective than steroid alone.

Dionne and colleagues [35] investigated this potentially synergistic effect of steroid plus NSAID versus control in a model of acute inflammation. This prospective randomized controlled trial had three groups: (1) preoperative dexamethasone/postoperative ketorolac, (2) preoperative dexamethasone/postoperative saline placebo, and (3) preoperative saline placebo/postoperative saline placebo.

The steroid was administered at 4 mg orally 12 hours before surgery and 4 mg intravenously 1 hour presurgery. The postoperative dose of 30 mg of ketorolac or saline placebo was given at pain onset, usually approximately 2 hours after the procedure. No difference was seen in pain onset in the dexamethasone or control groups. Pain reduction was significant in the dexamethasone/ketorolac group only. No difference was seen in pain between the steroid/placebo and placebo/placebo groups. Unfortunately, these authors did not compare the dexamethasone/ketorolac group with another group of placebo/ketorolac. Markiewicz and colleagues [36] published their study in 2008, titled "Corticosteroids Reduce Postoperative Morbidity After Third Molar Surgery: A Systematic Review and Meta-Analysis." The authors asked one simple question: "Among patients undergoing [third molar] removal, does peri-operative corticosteroid administration, when compared with similar control, decrease postoperative edema, trismus, and pain in the early (1–3 days) and late (>3 days) postoperative periods?" Twelve articles met their inclusion criteria. Their data confirmed that corticosteroids reduce edema and trismus in the early and late postoperative periods. In terms of pain, even fewer papers qualified for analysis because most papers focused on number of analgesic doses and analgesic dosage rather than on VAS scale. Consequently, the reduction of pain by corticosteroids in the early postoperative period is not statistically significant.

Summary

In conclusion, despite a plethora of papers on the various topics covered in this paper, actually very little definitive information is available. There does seem to be consensus that tobacco cessation, use of chlorhexidine, prophylactic antibiotics, and corticosteroids are of benefit in reducing complications and improving the postoperative quality of life after third molar surgery. However, the specifics of their implementation into patient care protocols remains to be specified. The most interesting area for future research is preemptive analgesia.

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