The use of a tetracycline drain reduces alveolar osteitis: a randomized prospective trial of third molar surgery under local anesthetics and without the use of systemic antibiotics

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Objectives. Our aim was to investigate the effect of an oxytetracycline-impregnated gauze drain on the incidence of alveolar osteitis (AO) and postoperative pain during the first week after mandibular third molar surgery.

Study Design. Two hundred consecutive patients undergoing third molar surgery under local anesthesia were randomized into a drain group (n = 100), with an oxytetracycline-impregnated drain placed in the extraction socket, and a control group (n = 100). An experienced surgeon performed the surgery. Systemic antibiotics were not used.

Results. The incidence of AO was 23% in the control group and 5% in the drain group ($P < .001$). The risk of developing AO was approximately 6 times higher in the control group, and females had a 2.5 times higher risk compared with males. Patients in the control group had significantly more pain on the day of surgery and on days 4 to 7. The presence of AO was associated with continued use of analgesics ($P < .001$). No patients experienced postoperative infections or had complications requiring hospitalization.

Conclusions. The present study showed that an oxytetracycline-impregnated drain significantly reduced the incidence of AO after third molar surgery. The described treatment strategy, without the use of systemic antibiotics, seemed efficient in lowering overall postoperative morbidity and downtime after third molar surgery. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:205–212)

Third molar surgery is one of the most frequent procedures in oral and maxillofacial surgery. In Norway, which has a population of about 5 million, some 75,000 third molars are estimated to be removed annually.[1] Alveolar osteitis (AO) is a well-known complication in mandibular third molar surgery (3MS), and the prevalence is reported to range from 1% to 37.5%.[2]

Blum defined AO as "postoperative pain inside and around the extraction site, which increases in severity at any time between the first and third day after the extraction, accompanied by a partially or totally disintegrated blood clot within the alveolar socket with or without halitosis."[3] This is supported in a more recent Cochrane review by Daly et al., and this definition of AO was used in the present study.[4]

Systemic antibiotics (SABs) in 3MS have been shown to reduce postoperative infection and AO, but unnecessary use of SABs in otherwise healthy patients is controversial because of the increase in the number of resistant bacteria.[5] It is, therefore, important to utilize an effective treatment strategy in 3MS, with avoidance of SAB while still decreasing the risk of AO.

In our department, the practice of placing a tetracycline impregnated gauze drain in the socket after 3MS to prevent AO has been in existence for a long time. Akota et al. investigated this practice in a randomized split-mouth study in 50 patients undergoing bilateral 3MS. The rate of AO was significantly lower in the drain group (4%) compared with the control group (35%).[6] Accordingly, the practice has been continued in our department, and a recent 1-year quality assessment showed the incidence of AO after 3MS to be as low as 3.5%.[7]

The primary aim of the present randomized controlled clinical study was to investigate the effect of an oxytetracycline-impregnated gauze drain in 3MS on the incidence of AO 1 week after surgery. A secondary aim was to further explore postoperative morbidity after 3MS.

MATERIAL AND METHODS

Study design

The study was designed as a single-blind randomized controlled trial. Using a sealed envelope system, patients were randomized into 2 groups: a drain group and a control group. The study population comprised patients undergoing surgical removal of one or both

Statement of Clinical Relevance

Decreasing morbidity after mandibular third molar surgery is of great clinical importance. In our study, we showed that use of a tetracycline-impregnated drain is a simple and effective way to reduce the incidence of alveolar osteitis and overall postoperative morbidity.

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mandibular third molars (3Ms) from January 2016 until March 2017. Patients referred to our department, who fulfilled the inclusion criteria, were asked to participate in the study. Patients were prospectively included after they signed a detailed informed consent form.

The inclusion criteria were age 18 years or greater; indications for removal of 1 or both 3Ms, American Society of Anesthesiologists (ASA) classes I and II; no need for sedatives; possession of a smartphone with Internet access (to be able to register pain score and use of analgesics (see "Data collection methods and statistical analysis"); and availability to attend a postoperative examination after 1 week. Exclusion criteria were age less than 18 years; no indications for removal of 3Ms; ASA class III or higher; pregnancy or breastfeeding; need for sedatives or SABs; not possessing a smartphone; and inability to attend a postoperative examination after 1 week. The National Institutes of Health's Consensus Statement (1979), and the American Association of Oral and Maxillofacial Surgeons' White Paper on Third Molar Data (2007) served as guidelines when evaluating indications for 3M removal.[8,9]

Study population (n = 200) and group size (n = 100) were determined through power analysis: 90% power, 5% significance level and an expected difference of up to 10% between the 2 groups.

Ethical approval

The study was performed in accordance with the principles of the Declaration of Helsinki. The Regional Committee for Medical and Health Research Ethics approved the study (No. 2015/2168/REK sør-øst B).

Study variables

Demographic data (age, gender, smoking habits, and occupation) were obtained from the patients' electronic charts. Physical status was classified as ASA class I or II according to the inclusion criteria. Clinical variables and postoperative complications were recorded. An 11-point scale (numeric rating scale [NRS]-11) was used for self-reporting of pain twice daily (8 a.m. and 8 p.m.). Self-reported consumption of analgesics at these time points was also registered. Pain scores were categorized as no pain (score 0), mild pain (score 1−3), moderate pain (score 4−6) and severe pain (score 7−10) according to NRS-11.

Surgical procedure and medication

An experienced oral surgeon performed all of the operations utilizing a standardized surgical protocol previously described by Øyri et al.[7] All patients performed a 1-minute mouth rinse with 0.12% chlorhexidine (CHX) (Flux PRO Klorhexidin, Actavis Norway AS, Oslo, Norway) preoperatively. Injection of regional and local anesthetics (Xylocaine Dental Adrenaline, Dentsply Ltd., Surrey, England) were performed 5 minutes prior to incision and elevation of a full-thickness mucoperiosteal envelope flap. Ostectomy was carried out at the buccodistal aspect of the tooth by utilizing a high-speed surgical bur under sterile saline irrigation. Tooth sectioning was performed, if necessary. All teeth were completely removed. The wound was irrigated with 20 mL of sterile saline, the soft tissue was reapproximated and fixated with interrupted nonabsorbable sutures (Supramid 3-0, B. Braun Melsungen AG, Melsungen, Germany). The patient was blinded to the procedure with the use of sterile drapes. The duration of surgery, from the incision until suturing was completed, was recorded. The surgeon had no knowledge of the group to which the patient had been allocated until completion of surgery. According to previous randomization, 100 patients had a drain saturated with Terramycin-Polymyxin B (Pfizer, Pfizer Inc., New York, NY) placed in the extraction socket, hereafter referred to as "drain." A "sham drain-placement maneuver" was performed in the control group. Use of over-the-counter analgesics (paracetamol 500 mg and ibuprofen 400 mg), with dosages according to body weight, was recommended for pain control. Two tablets of Pinex Forte (Actavis Group, Hafnafjordur, Iceland), 500 mg paracetamol/30 mg codeine, were provided for optional use if severe pain was experienced. Use of CHX twice daily for 1 week was recommended. Verbal and written postoperative instructions were provided. All patients were scheduled for removal of sutures and drain, if placed, after 1 week and were encouraged to initiate contact earlier, if necessary.

Data collection methods and statistical analysis

All study parameters were recorded in a questionnaire, created and accessed through the University Health Network, as previously described by Øyri et al.[7] Pain scores (NSR-11) and self-reported intake of analgesics (yes/no) were monitored on a day-to-day basis and recorded for 7 days. A digital questionnaire, accessed through an encrypted link sent by Short Message Service to the patients' cell phones twice daily, was utilized, starting on the evening of the day of surgery. All data were consolidated and imported from the University Health Network and Short Message Service databases to SPSS version 17.0 (SPSS Inc., Chicago, IL). The data were analyzed by using χ^2, independent t test, Levene's t test, and regression analysis. The significance level was set to 5%.

RESULTS

The material comprised anamnestic and clinical recordings from 200 patients during the first postoperative week after 3MS. There were no dropouts during

the study period, and thus, we achieved an inclusion rate of 100%. Demographic characteristics are presented in Table I, and treatment characteristics and outcomes are provided in Table II.

The incidence of AO was 23% in the control group and 5% in the drain group. This finding was statistically highly significant ($P < .001$). Gender, use of contraceptives, age, smoking, postoperative use of CHX, postoperative use of antibiotics (2 patients in the control group), indications for surgery, surgical time, tooth angulation, and surgical complexity were adjusted for and the difference with regard to AO between the 2 groups was still statistically highly significant ($P < .001$).

The risk of developing AO in the drain group was shown by logistic regression to be less compared with the control group (odds ratio [OR] 0.176). The risk of developing AO was almost 6 times higher in the control group (OR 5.7). Women had a 2.5 times higher risk of developing AO compared with men (OR 2.5). The variables age, use of contraceptives (females), smoking, and postoperative use of CHX were not associated with a significantly higher risk of AO. We found a slightly higher risk of AO associated with increasing surgical complexity, increased surgical time, and angulated tooth position, but this risk was not statistically significant. Self-reported pain score (NRS-11) was significantly associated with AO ($P < .001$), and the risk of having AO increased with a higher pain score.

Pain and analgesics

In the control group, 33% of patients scored no pain, 54% mild pain, 11% moderate pain, and 2% severe pain during the 7-day postoperative period. In the drain group, 43.5% of patients scored no pain, 53.5% mild pain, and 3% moderate pain, and no patients reported severe pain. The mean postoperative pain scores are shown in Figure 1. Patients in the control group scored significantly higher levels of pain compared with those in the drain group on the evening of the day of surgery and over postoperative days 4 to 7 (Table III). We found no significant differences in pain scores 1 week postoperatively in relation to gender or age.

Self-reported use of analgesics was similar in both groups on the day of surgery. During the first postoperative day, 93% of patients reported using analgesics. The reported use of analgesics dropped during the following 3 days, from 70% to 45% of patients, and there was no significant difference between the groups. At postoperative day 5, 49% of patients in the control group reported use of analgesics vs 31% in the treatment group ($P = .018$). At day 7, the corresponding numbers were 43% and 24% ($P = .07$). Overall, 33.5% of all patients reported to be using analgesics one week after surgery. The presence of AO was strongly associated with continued use of analgesics ($P < .001$).

Absence from work or school

Close to two-thirds of the patients (64%) in both groups did not miss work or school after surgery. Thirty-six patients (36%) in each group reported being absent from work or school for 1 to 4 days, with an average of 0.57 days (standard deviation [SD] 0.856) in the drain group, and 0.69 days (SD 1.061) in the control group. There was no significant difference between the drain and control groups or in association with age, smoking/not smoking, and presence/absence of AO. With regard to pain scores, patients scored mild, moderate, and severe levels of pain and reported more days of absence from work or school compared with patients reporting no pain ($P = .003$). Patients reporting severe

Table I. Demographic characteristics of the 200 consecutive patients included in the present study*

Variable	*Drain group (n = 100)*	*Control group (n = 100)*	*P value*
Gender			
Female	64 (64%)	63 (63%)	
Male	36 (36%)	37 (37%)	NS
Age (mean)	24.7 (SD 3.9)	25.7 (SD 4.2)	NS
Age groups			
<25 years	56 (56%)	47 (47%)	
>25 years	44 (44%)	53 (53%)	NS
ASA classification			
ASA I	96 (96%)	93 (93%)	
ASA II	4 (4%)	7 (7%)	NS
Smoking	3 (3%)	7 (7%)	NS
Work status			
Student	67 (69.8%)	66 (66%)	
Employee	29 (30.2%)	30 (30%)	
Other	0 (0%)	4 (4%)	NS

*Patients were allocated to 1 of 2 groups, a drain group and a control group. In the drain group, a gauze drain saturated with oxytetracycline ointment was placed in the socket after removal of the mandibular third molar.
N, number; *SD,* standard deviation; *NS,* not significant.

Table II. Treatment characteristics and outcome of the 200 consecutive patients included in the present study*

Variable	*Drain group (n = 100)*	*Control group (n = 100)*	P value
Indication for surgery			
Prophylactic	41 (41%)	29 (29.3%)	
Pericoronitis	51 (51%)	58 (58.6%)	
Caries	6 (6%)	11 (11.1%)	
Resorption	1 (1%)	0	
Periodontitis	0	1 (1%)	
Cyst	1 (1%)	0	NS
Tooth angulation			
Vertical	18 (18%)	13 (13%)	
Mesioangular	32 (32%)	27 (27%)	
Horizontal	11 (11%)	16 (16%)	
Distoangular	39 (39%)	44 (44%)	NS
Local analgesics (mL)	5.23 (SD 0.30)	5.24 (SD 0.34)	NS
Surgical time (min)	9.46 (SD 3.41)	9.21 (SD 4.22)	NS
Surgical complexity†			
Straightforward	25 (25.3%)	37 (37%)	
Medium	64 (64.6%)	51 (51%)	
Complex	10 (10.1%)	12 (12%)	NS
ROM (mm)			
Preoperatively‡	47.27 (SD 5.29)	49.07 (SD 5.35)	$P < .001$
Postoperatively	42.02 (SD 7.99)	44.48 (SD 8.02)	$P < .001$
Use of CHX mouthwash			
postoperatively	99 (99%)	94 (94%)	NS
Use of SAB postoperatively	0	2 (2%)	NS
Alveolar osteitis	5 (5%)	23 (23%)	$P < .001$
Other complications			
Bleeding >24 hours	0	2 (2%)	
Allergic reaction	0	1 (1%)	
NSD IAN	1 (1%)	0	NS

*Patients were allocated to 1 of 2 groups. Surgical complexity was defined by the surgeon immediately postoperatively on the basis of surgical time: straightforward (<10 min), medium (11−15 min), complex (>15 min). With regard to indications for surgery, tooth angulation, local analgesics, surgical time, and surgical complexity, there were no statistically significant differences between patients in the drain and control groups. In the drain group, more teeth were removed for prophylactic reasons, but this finding was not statistically significant. There was a significant reduction in ROM postoperatively of approximately 5 mm in both groups ($P < .001$). No patients experienced complications that required hospitalization. No postoperative infections were recorded. Minor complications other than AO were reported by 4 patients (2%): bleeding for greater than 24 hours by 2 (1%), allergic reaction by 1 (0.5%), and neurosensory disturbance of the inferior alveolar nerve by 1 (0.5%). The assumed allergic reaction was found to be oral soreness after rigorous use of CHX. The NSD of the IAN resolved within 3 months after completion of the study.
†1 patient missing in the control group.
‡2 patients missing in the drain group.
CHX, chlorhexidine mouth wash; *IAN,* inferior alveolar nerve; *n,* number; *NS,* not significant; *NSD,* neurosensory disturbance; *ROM,* range of motion; *SAB,* systemic antibiotic.

pain had the highest mean number of days of absence from work or school (2.5). Surgical complexity and surgical time did not affect absence from work or school. One week after surgery, 94% in the control group and 99% in the drain group ($P = .118$) had returned to normal activities.

DISCUSSION

The main finding in this study is the significantly lower rate of AO when a drain had been placed in the socket after 3MS. In the drain group, only 5% of patients were diagnosed with AO vs 23% of patients in the control group. This is in accordance with the results in a previous smaller study by Akota et al.[6] The present study included a larger study population and an even distribution of patients in the 2 groups. After statistical analysis and appropriate adjustments, the difference in AO between the drain and control groups could not be explained by any other factor than the drain itself ($P < .001$). In comparing our results with reported AO incidences in other studies,[3,10] we found the incidence of AO in the drain group to be very low and to be within the reported range in the control group.[2,3,10]

To the best of our knowledge, besides the study by Akota et al.[6], no other study has evaluated the effect of a tetracycline-impregnated drain in 3MS or the local application of tetracycline without the addition of SAB. In a clinical study by Sanchis et al.,[11] in which a tetracycline compound was placed in the alveolus after 3MS and amoxicillin 500 mg/8 hours was given 4 days postoperatively, the authors found no additional effect on the incidence of AO of the tetracycline compound.

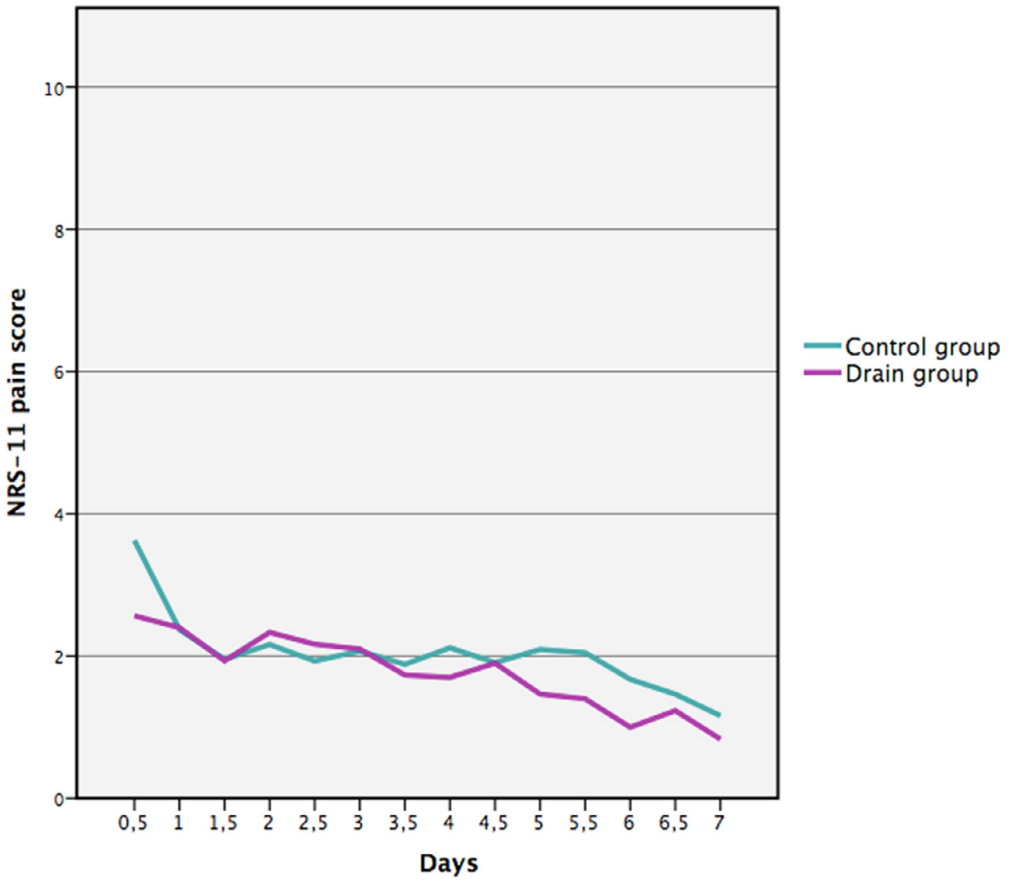

Fig. 1. Change in postoperative pain scores (NRS-11) on a day-to day basis for the control and drain groups, using a self-reported numeric scale from 0-10 (NRS-11). Mean pain scores during the first postoperative week were comparable for the control group and drain group.

Several systematic reviews and meta-analyses have shown that the use of SABs in 3MS reduces the rate of AO and postoperative infection. Lodi et al.[5] found that 12 patients needed to be treated with SABs to prevent 1 case of infection. In light of the increase in the numbers of resistant bacteria, studies have concluded that use of SABs in 3MS is likely to do more harm than good.[5,12,13] Cautious use of SABs in 3MS seems to be a reasonable treatment strategy and may be considered a valuable contribution by the dental community toward the attempt to combat global development of antimicrobial drug resistance.

As opposed to use of SABs, local administration of tetracycline for a short period is unlikely to cause antimicrobial drug resistance.[14] Local application of tetracycline in the extraction socket has been used to prevent AO in 3MS for many decades.[15,16] At the time of the present study, no ”pure” tetracycline ointment was commercially available in Norway. An oxytetracycline ointment was chosen because of its availability, low cost, low grade of adverse effects, and safe intraoral use. Terramycin-Polymyxin B is a broad-spectrum antibiotic effective against both gram-negative and gram-positive bacteria. It is labeled for treatment of superficial skin infections but has been used successfully in different oral and maxillofacial procedures in our department for the past decade (e.g., as an intraoral and extraoral wound dressing). Several mechanisms may explain the pronounced effect of the type of drain used in the present study: the “drain effect,” aiding in evacuation of blood and wound fluids; “protection” of the extraction socket by covering exposed bone and keeping debris from direct wound contact; or a local effect of the antibiotic covering the drain.

Many factors may affect healing after 3MS, and this makes it difficult to compare the different incidence rates of postoperative AO obtained in various studies. Our results indicate that use of an oxytetracycline-impregnated drain may be a factor that could reduce the incidence of postoperative AO. Reduction of postoperative morbidity in 3MS has previously been thoroughly investigated (for review, see Coulthard et al., Taberner-Vallerdú et al., and Rodríguez Sánchez et al.).[10,17,18] Various local measures have been applied and tested, but most studies included in these reviews have used SABs in conjunction with surgery, thus

Table III. Mean pain scores (NRS-11)*

Pain score days postoperatively, mean NRS-11	*Control group (n = 100)*							*Drain group (n = 100)*							*Control vs. Drain*
	With AO (n = 23)	*SD*	*No AO (n = 77)*	*SD*	*P value*†	*Total (n = 100)*	*SD*	*With AO (n = 5)*	*SD*	*No AO (n = 95)*	*SD*	*P value*†	*Total (n = 100)*	*SD*	*P value*‡ *Control vs. Drain*
Day 0.5	3.48	2.379	3.27	2.197	.461	3.32	2.228	4.60	1.140	2.83	1.844	.383	2.93	1.852	.008§
Day 1	2.74	1.727	2.24	1.637	.346	2.35	1.660	2.40	1.673	2.46	1.841	.636	2.46	1.823	.129
Day 1.5	2.26	1.839	1.84	1.414	.045§	1.94	1.527	2.80	0.447	2.09	1.670	.066	2.12	1.637	.584
Day 3	3.12	1.453	1.89	1.644	.614	2.15	1.674	3.50	1.291	1.76	1.719	.569	1.84	1.735	.723
Day 3.5	3.00	2.160	1.41	1.154	.001§	1.74	1.555	3.60	1.140	1.56	1.372	.527	1.67	1.429	.591
Day 6	2.82	1.704	1.43	1.244	.225	1.75	1.471	1.75	1.500	1.15	1.134	.334	1.18	1.151	.037§
Day 6.5	2.22	1.927	1.48	1.568	.290	1.65	1.674	1.75	1.258	1.24	1.363	.484	1.27	1.355	.274
Day 7	3.00	2.256	1.03	1.102	.000§	1.49	1.670	3.00	1.581	0.77	0.888	.054	0.88	1.042	0.000§

*Reported postoperatively starting at 8 p.m. on the day of surgery (day 0.5), and then at 8 a.m. and 8 p.m. on day 1 (day 1, day 1.5), on day 3 (day 3, day 3.5), on day 6 (day 6, day 6.5), and at postoperative control (day 7). The highest mean pain score was at 8 p.m. on the day of surgery. In the control group, mean pain score was 3.32 (SD 2.28) and in the drain group 2.93 (SD 1.85), and the difference was statistically significant ($P = .008$). Statistical differences between the groups were also seen on day 6 and day 7. Mean pain score was higher in the control group at both times. A statistically significant difference in mean pain scores between patients with and without AO in the control group was seen at days 1.5, 3.5, and 7. The difference between patients with AO and those without AO in the drain group was not statistically significant. This might be explained by the low number of patients with AO (n = 5) in the drain group.

†Levene's *t* test. Difference in mean pain scores between patients with AO and those without AO in the control group and the drain group, respectively.

‡Levene's *t* test. Difference in mean pain scores between the control group and drain group.

§Statistically significant ($P < .05$)

AO, alveolar osteitis; *NRS-11,* numeric rating scale; *SD,* standard deviation.

highly biasing the results.[10,17,18] The results from our study, in which SABs were not used at all, show a very low incidence of AO and low overall postoperative morbidity. Rodríguez Sánchez et al. concluded that the use of CHX, regardless of formulation, concentration, or regimen, was effective in reducing AO after 3MS.[18] In our study, all patients performed a preoperative mouth rinse with CHX, and the majority of patients reported using CHX in the postoperative period. Accordingly, the use of CHX cannot explain the differences in AO incidence found in our study. In addition, the volume and intensity of irrigation of the extraction sockets may influence the development of AO. In the present study, 20 mL of sterile saline was used. However, in a Cochrane Review, Coulthard et al. concluded that there is insufficient evidence from single-center studies on the association between irrigation method or volume and AO.[10]

Increased postoperative pain is one of the parameters for the definition of AO. Increasing self-reported pain scores during the postoperative period may alert the surgeon that the patient may have or is about to develop AO. Patients in the control group reported significantly higher levels of pain compared with the drain group at postoperative days 4 to 7 (see Table III). A significantly higher number of patients in the control group developed AO, and self-reported use of analgesics was significantly higher in the control group at postoperative days 5 and 7. These findings indicate higher pain levels. Furthermore, the presence of AO was naturally associated with continued use of analgesics ($P < .001$).

Over-the-counter analgesics were advocated as the first-line analgesic therapy. With frequent reports of abuse of opioid analgesics at the present time, this seems like a reasonable strategy in postoperative pain management after 3MS.[19] These recommendations are also in accordance with the American Association of Oral and Maxillofacial Surgeons White Paper on Opioid Prescribing (2017).[20]

In the present study, only 36% of patients reported absence from work or school after 3MS (average 0.57 day in the drain group and 0.69 day in the control group). This is low compared with the results reported by Berge, Bienstock et al., and Pogrel.[21-23] This implies that the drain may have an effect on pain and, secondarily, on absence from work or school. Compared with the results from the previously mentioned studies, patients in our study seemed to return to work and school earlier. Less downtime after surgery is considered beneficial both for the individual patient as well as socioeconomically.

The 3MS protocol in our department includes a postoperative visit 1 week after surgery for all patients. During the postoperative visit, suture and drain removal is performed, along with clinical evaluation of the initial wound healing. This, in our opinion, is not more time-consuming than performance of suture removal alone. We do not want to exclude other methods or surgical techniques that are shown to reduce AO, but our method, which involves use of an oxytetracycline-impregnated drain, works well in our department. We, therefore, suggest that this method be considered in attempts to reduce AO. Whether our method is superior to any other method or technique has to be explored in future studies comparing use of drains with and without antibiotics.

CONCLUSIONS

In the present study, which included 200 patients, the use of an oxytetracycline-impregnated drain in 3MS significantly reduced the incidence of postoperative AO. The described treatment strategy, without the use of SABs, seems to be efficient in lowering overall postoperative morbidity in 3MS. Strategies to reduce postoperative morbidity are important because 3MS will continue to be a common surgical procedure in the future. We recommend that the treatment strategy described here be considered when performing 3MS.

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