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

Dr. Hauk Øyri DDS , Dr. Olga Jonsdottir DDS ,
Professor Janicke Liaaen Jensen DDS, Dr. odont ,
Professor Tore Bjørnland DDS, Dr. odont

PII: S2212-4403(18)31300-2
DOI: https://doi.org/10.1016/j.oooo.2018.12.004
Reference: OOOO 4053

To appear in: *Oral Surg Oral Med Oral Pathol Oral Radiol*

Received date: 11 May 2018
Revised date: 3 October 2018
Accepted date: 7 December 2018

Please cite this article as: Dr. Hauk Øyri DDS , Dr. Olga Jonsdottir DDS , Professor Janicke Liaaen Jensen DDS, Dr. odont , Professor Tore Bjørnland DDS, Dr. odont , The use of a tetracycline drain reduces alveolar osteitis: a randomized prospective trial of third molar surgery under local anaesthetics and without the use of systemic antibiotics, *Oral Surg Oral Med Oral Pathol Oral Radiol* (2018), doi: https://doi.org/10.1016/j.oooo.2018.12.004

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Authors: HAUK ØYRI, [a] OLGA JONSDOTTIR, [b] JANICKE LIAAEN JENSEN, [c] TORE BJØRNLAND. [d]

[a] Dr. Hauk Øyri, DDS. Department of Oral Surgery and Oral Medicine, Institute of Clinical Dentistry, Faculty of Dentistry, University of Oslo, Norway
E-mail: hauk.oyri@odont.uio.no

[b] Dr. Olga Jonsdottir, DDS. Department of Oral Surgery and Oral Medicine, Institute of Clinical Dentistry, Faculty of Dentistry, University of Oslo, Norway.
E-mail: olgahronn@gmail.com

[c] Professor Janicke Liaaen Jensen, DDS, Dr. odont. Department of Oral Surgery and Oral Medicine, Institute of Clinical Dentistry, Faculty of Dentistry, University of Oslo, Norway.
E-mail: j.c.l.jensen@odont.uio.no

[d] Professor Tore Bjørnland, DDS, Dr. odont. Department of Oral Surgery and Oral Medicine, Institute of Clinical Dentistry, Faculty of Dentistry, University of Oslo, Norway.
E-mail: tore.bjornland@odont.uio.no

Corresponding author:
Dr. Hauk Øyri, DDS
Department of Oral Surgery and Oral Medicine, Institute of Clinical Dentistry, Faculty of Dentistry, University of Oslo. P.O. Box 1109 Blindern, 0317 Oslo, Norway.
Phone: +4722852233 Fax : +4722852341
E-mail: hauk.oyri@odont.uio.no

Key words: dry socket, complications, oral surgery, morbidity, pain, analgesics, antibiotics

Disclosures: There is no conflict of interest related to the individual author's commitments. Janicke Liaaen Jensen has been involved in the development of the University Health

Network, but has no financial interests in this. None of the authors has received any grants related to this project or to its publication. The present paper has not been reviewed by other journals or published previously, neither have the results been presented at any conferences or congresses.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abstract word count: 200
Statement of Clinical Relevance word count: 40
Total word count: 3456
Number of references: 23
Number of figures: 1
Number of tables: 3

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 tetracyclin-impregnated drain is a simple and effective way to reduce the incidence of alveolar osteitis and overall postoperative morbidity.

ABSTRACT

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 anaesthesia were randomized into a drain group (n=100), with an oxytetracycline 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 ($p<0.001$). The risk of developing AO was approximately six times higher in the control group, and females had a 2.5 times higher risk than males. Patients in the control group had significantly more pain at the day of surgery and days 4-7. Presence of AO was associated with continued use of analgesics ($p<0.001$). No patients experienced postoperative infections or had complications requirering hospitalisation.

Conclusion

The present study showed that an oxytetracycline drain drastically 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.

Clinical trial registration number: NCT03494972 (ClinicalTrials.gov)

INTRODUCTION

Third molar surgery is one of the most frequent procedures in oral and maxillofacial surgery. In the country of Norway, with 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 1.0 to 37.5%.[2]

Blum (2002) 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. (2012), and is the definition of AO used in the present study.[4]

Systemic antibiotics (SAB) in 3MS have been shown to reduce postoperative infection and AO, but unnecessary use of SAB in otherwise healthy patients is controversial due to the increasing number of resistant bacteria.[5] It is therefore important to utilize an effective treatment strategy in 3MS avoiding SAB, and still decreasing the risk for AO.
In our department, there is a long tradition of placing a tetracycline impregnated gauze drain in the socket after 3MS to prevent AO. Akota et al. (1998) investigated this practice in a randomized split-mouth study of 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 one-year quality assessment showed the incidence of AO after 3MS to be as low as 3.5%.[7]

Aim

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 one week postoperatively. 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. Patients were randomized into two groups by a sealed envelope system: a drain group and a control group. The study population comprised patients undergoing surgical removal of one or both mandibular third molars (3M) 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 signing a detailed informed consent form.

The inclusion criteria were: age ≥18 years; indications for removal of one or both 3M, ASA I-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 available to attend a postoperative examination after one week. Exclusion criteria were: age <18 years, no indications for removal of 3M, ASA III or higher, pregnancy or breastfeeding, need for sedatives or systemic antibiotics, does not possess a smartphone and unable to attend a postoperative examination after one 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 two 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 (2015/2168/REK sør-øst B).

Study variables

Demographic variables (age, gender, smoking habits and occupation) were obtained from the patients' electronic charts. Physical status was classified as ASA I or II according to the inclusion criteria. Clinical variables and postoperative complications were registered. An 11-point scale (NRS-11) was used for self-reporting of pain twice daily (8 AM and 8 PM). 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 operations utilizing a standardized surgical protocol previously described Øyri et al. (2015).[7] All patients performed a one minute mouth rinse with 0.12% chlorhexidine (Flux PRO Klorhexidin, Actavis Norway AS, Oslo, Norway) preoperatively. Injection of regional and local anaesthetics (Xylocaine Dental Adrenaline, Dentsply Ltd., Surrey, England) were done five minutes prior to incision and elevation of a full-thickness mucoperiosteal envelope flap. Ostectomy was carried out at the buccodistal aspect of the tooth 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 non-absorbable sutures (Supramid 3-0, B. Braun Melsungen AG, Melsungen, Germany). Sterile drapes blinded the procedure towards the patient. Duration of surgery was recorded from the incision until suturing was completed. 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 manoeuvre" was performed in the control group. Over-the-counter analgesics (paracetamol 500 mg and ibuprofen 400 mg) with dosages according to body weight were 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. Chlorhexidine 0.12% mouthwash (CHX) twice daily for 1 week was advocated. Verbal and written postoperative instructions were provided. All patients were scheduled for removal of sutures and drain if placed, after one week and were encouraged to initiate contact earlier if necessary.

Data collection methods and statistical analysis

All study parameters were recorded in a questionnaire both created and accessed through University Health Network (UHN) as previously described by Øyri et al. (2015).[7] Pain scores (NSR-11) and self-reported intake of analgesics (yes/no) were monitored on a day-to-day basis and recorded for seven days. A digital questionnaire accessed through an encrypted link sent by SMS to the patients' cell phones twice daily was utilized, starting in the evening of the day of surgery. All data were consolidated and imported from the UHN and SMS databases to SPSS (version 17.0, IBM Corp., Armonk, NY). The data were analysed using chi-square, 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. We experienced no dropouts during the study period, yielding an inclusion rate of 100%. Demographic characteristics are presented in Table 1 and treatment characteristics and outcomes in Table 2.

The incidence of AO was 23% in the control group and 5% in the drain group. This finding was statistically highly significant ($p<0.001$). Gender, use of contraceptives, age, smoking, postoperative use of CHX, postoperative use of antibiotics (two patients in the control group), indications for surgery, surgical time, tooth angulation and surgical complexity were adjusted for and the difference with regards to AO between the two groups was still statistically highly significant ($p<0.001$).

The risk of developing AO in the drain group was shown by logistic regression to be reduced as compared to the control group (OR 0.176). The risk of developing AO was almost six times higher in the control group (OR 5.7). Women had a 2.5 times higher risk than men of developing AO (OR 2.5). The variables age, use of contraceptives (females), smoking, or 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 ($p<0.001$) 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 seven-day postoperative period. In the drain group, 43.5% of patients scored no pain, 53.5% mild pain, 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 to the drain group in the evening the day of surgery and, over at postoperative days 4-7 (Table 3). We found no significant differences in pain scores one week postoperatively related 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 following three days, the reported use of analgesics dropped from 70% to 45% of patients and there was no significant difference between the groups. At the fifth postoperative day, 49% of patients in the control group reported use of analgesics, versus 31% in the treatment group ($p=0.018$). At day seven, the corresponding numbers were 43% and 24% ($p=0.07$). Overall, 33.5% of all patients reported to be using analgesics one week after surgery. Presence of AO was strongly associated with continued use of analgesics ($p<0.001$).

Absence from work or school

Close to two-thirds of the patients (64%) in both groups did not absent themselves from work or school after surgery. Thirty-six patients (36%) in each group reported being absent from work or school for 1-4 days, with an average of 0.57 days (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 or the control group, age, smokers/non-smokers, or in patients with or without AO. Regarding pain scores, patients scoring mild, moderate and severe levels of pain, reported more days absent compared with patients reporting no pain ($p=0.003$). Patients reporting severe pain had the highest mean number of days absent (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, respectively (p=0.118) had returned to normal activities.

DISCUSSION

The main finding in this study is the significantly lower rate of AO in patients where a drain had been placed in the socket after 3MS. In the drain group, only 5% of patients were diagnosed with AO versus 23% of patients in the control group. This is in accordance with results in a previous smaller study by Akota et al. (1998).[6] The present study includes a larger study population, and an even distribution of patients in the two 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 ($p<0.001$). Comparing our results with reported AO incidence in other studies (Blum 2002, Coulthard et al. 2014), the incidence of AO in the drain group is very low, and within the reported range in the control group (Kolokythas et al. 2010).[3, 10, 2]

To the best of our knowledge, apart from Akota et al. (1998), no other study has evaluated the effect of a tetracycline impregnated drain in 3MS, or local application of tetracycline without the addition of SAB.[6] In a clinical study in which a tetracycline compound was placed in the alveolus after 3MS and Amoxicillin 500 mg/8 hours was given four days postoperatively, the authors found no additional effect on the incidence of AO of the tetracycline compound (Sanchis et al. 2004).[11]

Several systematic reviews and meta-analyses have shown that the use of SAB in 3MS reduces the rate of AO and postoperative infection. Lodi et al. (2012) found that 12 patients needed to be treated with SAB to prevent one case of infection. In light of the rampant development of resistant bacteria, the authors concluded that use of SAB in 3MS is likely to do more harm than good (Lodi et al. 2012).[5, 12, 13] Cautious use of SAB in 3MS seems to be a reasonable treatment strategy and may be considered a valuable contribution in the dental community in the attempt to combat global development of antimicrobial resistance.

As opposed to SAB, local administration of tetracycline for a short period of time is unlikely to cause antimicrobial resistance.[14] Local application of tetracycline in the extraction socket has been used to prevent AO in 3MS surgery 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 due to its availability, low cost, low grade of adverse effect, and safe intraoral use. Terramycin-Polymyxin B is a broad spectrum antibiotic effective on both gram-negative and gram-positive bacteria. It is labelled for treatment of superficial skin infections, but has successfully been used in different oral and maxillofacial procedures in our department for the past decade, e.g. as an intra- and extra-oral 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 antibiotics covering the drain.

There are many factors that may affect healing after 3MS, thus making comparison of the different incidence of post-operative AO obtained in various studies difficult. Our results indicate that use of an oxytetracycline-impregnated drain may be one factor that possibly can reduce post-operative AO. Reduction of postoperative morbidity in third molar surgery has previously been thoroughly investigated. For review, see Coulthard et al. (2014), Taberner-Vallerdú et al. (2017), and Rodríguez Sánchez et al. (2017). Various local measures have been applied and tested, but the majority of studies included in these reviews have used SAB in conjunction with surgery, thus highly biasing the results.[10, 17, 18] The results from our study, in which no SAB was used, show a very low incidence of AO and a low overall postoperative morbidity. Rodríguez Sánchez et al. (2017) concluded that 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. (2014) concluded that there is insufficient evidence from single studies on irrigation method or irrigation volume regarding AO.[10]

Increased postoperative pain is one of the parameters in 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 4-7 (Table 3).

Significantly more 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 ($p<0.001$).

Over-the-counter analgesics were advocated as first-line analgesic therapy. In a time when abuse of opioid analgesics is frequently reported, this seems like a reasonable strategy in postoperative pain management after 3MS (Keith et al. 2017).[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, with an 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 (1997), Bienstock et al. (2011), and Pogrel (2012). [21, 22, 23] It may imply that the drain may have an effect on pain and secondarily on absence from work or school. Compared with the results presented in the previously mentioned studies, patients in our study seemed to return to work and school faster. Less downtime after surgery is considered beneficial both for the individual patient as well as socioeconomically.

The 3MS treatment protocol in our department includes a post-operative visit one week after surgery for all patients. The post-operative visit consists of suture and drain removal, alongside with clinical evaluation of the initial wound healing. This procedure is, in our opinion, not more time-consuming than suture removal alone. We do not want to exclude other methods, or surgical techniques, that are shown to reduce AO, but our method, using an oxytetracycline impregnated drain, works well in our department. We therefore suggest that this method may be considered to reduce AO. Whether our choice of method is superior to any other method or technique has to be explored in future studies comparing drains with and without antibiotics.

In conclusion, in the present study comprising 200 patients, the use of an oxytetracycline drain in 3MS drastically reduced the incidence of AO postoperatively. The described treatment strategy, without the use of SAB, seems to be efficient in lowering overall postoperative morbidity in 3MS. Strategies to reduce postoperative morbidity are important,

as 3MS will continue to be a common surgical procedure in the future. We propose that the described treatment strategy in the present study should be considered when performing 3MS.

ACKNOWLEDGMENTS

The authors would like to thank Professor Per-Erik Isberg for valuable assistance with the statistical analyses. We thank the company Tise for creating an encrypted system to report pain scores. Furthermore, we are grateful to the staff at our department for help with patient logistics, and Write2Publish (www.correction-home.fr) for English language corrections.

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FIGURE LEGENDS

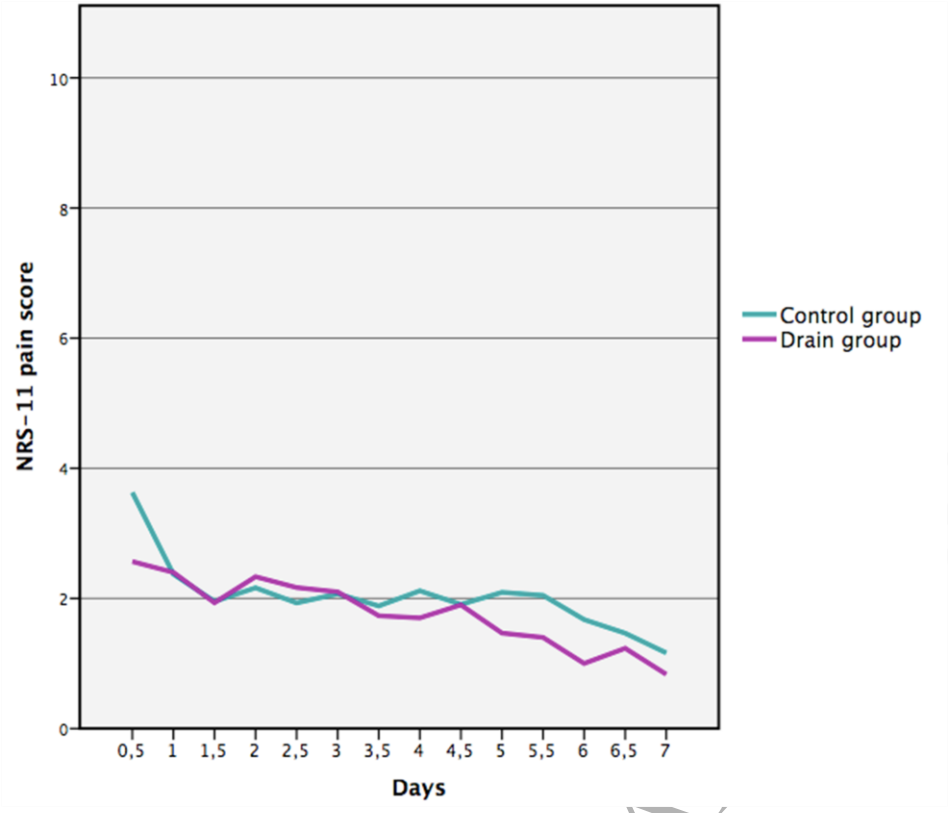

Figure 1. Change in postoperative pain scores (NRS-11) on a day-to day basis for the control and drain groups, using a self-reported numeric scale from 0-10 (NRS-11). Mean pain scores during the first postoperative week were comparable for the control group and drain group.

Table 1. Demographic characteristics of the 200 consecutive patients included in the present study. Patients were allocated to two 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.

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

n: Number; SD: Standard deviation; NS: Not significant

Table 2. Treatment characteristics and outcome of the 200 consecutive patients included in the present study. Patients were allocated to one of two groups. Surgical complexity was defined by the surgeon immediately postoperatively based on surgical time: straightforward (<10 min), medium (11-15 min), complex (>15 min). Regarding 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 ($p<0.001$). No patients experienced complications that required hospitalisation. No postoperative infections were recorded. Minor complications other than AO were reported by four patients (4/2%): bleeding >24 hours (2/1%), allergic reaction (1/0.5%) and neurosensory disturbance of the inferior alveolar nerve (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 three months after completion of the 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<0.001
Postoperatively	42.02 (SD 7.99)	44.48 (SD 8.02)	p<0.001
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<0.001
Other complications			
Bleeding >24 hours	0	2 (2%)	
Allergic reaction	0	1 (1%)	
NSD IAN	1 (1%)	0	NS

** 1 patient missing in the control group; ** 2 patients missing in the drain group; n: Number; NS: Not significant; ROM: Range of motion; CHX: Chlorhexidine mouth wash; SAB: Systemic antibiotics; NSD: Neurosensory disturbance; IAN: Inferior alveolar nerve*

Table 3. Mean pain scores (NRS-11) reported postoperatively starting at 8 PM on the day of surgery (Day 0.5), and then at 8 AM and 8 PM on day one (Day 1, Day 1.5), on day three (Day 3, Day 3.5), on day six (Day 6, Day 6.5) and at postoperative control (Day 7). The highest mean pain score was at 8 PM 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=0.008). Statistical differences between the groups were also seen ~~at~~ 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 day 1.5, 3.5 and day 7. The difference between patients with and without AO in the drain group was not statistically significant. This might be explained by the low number of patients (n=5) with AO in the drain group.

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[a]	Total (n=100)	SD	With AO (n=5)	SD	No AO (n=95)	SD	P value[a]	Total (n=100)	SD	P value[b] Control vs. Drain
Day 0.5	3.48	2.379	3.27	2.197	0.461	3.32	2.228	4.60	1.140	2.83	1.844	0.383	2.93	1.852	0.008*
Day 1	2.74	1.727	2.24	1.637	0.346	2.35	1.660	2.40	1.673	2.46	1.841	0.636	2.46	1.823	0.129
Day 1.5	2.26	1.839	1.84	1.414	0.045*	1.94	1.527	2.80	0.447	2.09	1.670	0.066	2.12	1.637	0.584
Day 3	3.12	1.453	1.89	1.644	0.614	2.15	1.674	3.50	1.291	1.76	1.719	0.569	1.84	1.735	0.723
Day 3.5	3.00	2.160	1.41	1.154	0.001*	1.74	1.555	3.60	1.140	1.56	1.372	0.527	1.67	1.429	0.591
Day 6	2.82	1.704	1.43	1.244	0.225	1.75	1.471	1.75	1.500	1.15	1.134	0.334	1.18	1.151	0.037*
Day 6.5	2.22	1.927	1.48	1.568	0.290	1.65	1.674	1.75	1.258	1.24	1.363	0.484	1.27	1.355	0.274
Day 7	3.00	2.256	1.03	1.102	0.000*	1.49	1.670	3.00	1.581	0.77	0.888	0.054	0.88	1.042	0.000*

NRS-11: Numeric Rating Scale; AO: Alveolar osteitis; SD: Standard Deviation

[a]*Levene´s t-test. Difference in mean pain score between patients with and without AO in the control group and the drain group respectively*
[b]*Levene´s t-test. Difference in mean pain score between the control group and drain group*
** Statistically significant ($p<0.05$)*