Special Contribution: Third Molar Clinical Trials Annotated Bibliography

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Purpose: To provide clinicians with an annotated bibliography of published articles from research funded externally by the Oral and Maxillofacial Surgery Foundation, spanning 1996 to 2015, addressing the topic of third molar management.

Materials and Methods: A brief summary for each article was generated by the respective authors.

Results: The complete annotated bibliography generated by the authors is included in the Appendix.

Conclusion: The annotated bibliography provides clinicians and other interested individuals with a summary of current literature emanating from clinical studies on third molar topics.

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After a comprehensive review of the literature sponsored by the American Association of Oral and Maxillofacial Surgeons (AAOMS; J Oral Maxillofac Surg 52:1104, 1994), it became obvious that more data must be generated to evolve data-based decision making for third molar management. Wisely, the AAOMS Board of Trustees sought a comprehensive set of clinical studies to assess the risks of retaining third molars and data on recovery after third molar removal. Based on productive experience with the longitudinal trial involving orthognathic surgical patients, faculty at the University of North Carolina at Chapel Hill (UNC) were asked to design and lead the project. Funding was provided jointly by the Oral and Maxillofacial Surgery Foundation, the AAOMS, and the oral and maxillofacial departments at the University of Kentucky and the UNC. The umbrella project became known as Third Molar Clinical Trials.

A unique aspect of the clinical studies was a prospective, longitudinal study of patients retaining third molars, those with third molar symptoms, and those without symptoms. Although the time frame required to generate adequate data was projected by some to be quite lengthy, the initial trial was planned for 5 years. Because this “exploratory trial” led to meaningful clinical data, the study was extended through 2014. The prospective, longitudinal design with primary data collection involving investigators from multiple disciplines and surgeons has led to a rich set of data about third molar pathology and management.

Concurrently, prospective, multisite clinical trials were implemented addressing clinical and health-related quality of life recovery after third molar surgery. In addition, data on third molars were analyzed from patients enrolled in population or clinical studies implemented for other purposes.

This Special Contribution to the Journal of Oral and Maxillofacial Surgery is designed to provide clinicians with an annotated summary of published articles spanning 1996 to 2015 from research sponsored by the Oral and Maxillofacial Surgery Foundation.
Materials and Methods

All cited articles have been published in peer-reviewed journals. All data are from studies approved by the UNC institutional review board. The principal author (R.P.W.) grouped the articles by topic chronologically. Each author briefly summarized the findings from the respective articles in his or her assigned group: recovery after third molar surgery (O.A. and B.N.), clinical and population studies (C.S.), symptomatic periodontal pathology (C.B.L.M.), asymptomatic periodontal pathology (J.P.), and occlusal caries (E.L.F.). Their annotations are in italic text in the Appendix.

Discussion

The collective clinical studies and the published data expand knowledge about third molar management for clinicians and the public. Although conclusions are many, the collective data confirm that most, but not all, individuals will have pathology with retained third molars over time. Few pathologic conditions are symptomatic. The differences in pathologic conditions between third molars and first or second molars are likely related to the eruption into the mouth of third molars after jaw growth is complete. In consequence, for most individuals with a full complement of molars, insufficient space exists for a healthy clinical environment around third molars.

The cited studies have limitations, including demographic characteristics of patients retaining third molars in the longitudinal trial (most were Caucasian and more highly educated than the US population), enrolled study patients retaining third molars over time might be unique because half the US population in the patients' age range have had all third molars removed, and outcomes of surgery to remove third molars were limited to procedures by trained surgeons. However, until further research is reported, these are the only data available to clinicians on most of the covered topics.

The data on clinical and quality-of-life outcomes on recovery after third molar removal and pathology with retained third molars confirm what clinicians might surmise. However, the published data allow clinicians to better understand and predict outcomes for individual patients.

Appendix

Third Molar Management Annotated Bibliography

The following citations with related comments summarize the content of the respective articles from published literature on the topic for clinicians and others. In addition, a series of seminars discussing the data are available by subscription at www.watchseminars.com.

RECOVERY AFTER THIRD MOLAR SURGERY


This study was a validation of the condition-specific Health-Related Quality Of Life (HRQOL) questionnaire, designed to capture patients' perception of recovery after third molar surgery for 14 days after surgery. This study evaluated the recovery of 20 patients for oral function, lifestyle, pain, and other symptoms. The HRQOL instrument is appropriate to evaluate recovery from third molar surgery.


HRQOL recovery after third molar surgery for 200 patients from 2 academic centers, including average pain swelling and interference with oral function, showed substantial improvement in all groups by day 6 after surgery. Prolonged recovery was noted in patients with a surgery time longer than 30 minutes and in female patients.


HRQOL and clinical recovery after third molar surgery were analyzed for 630 patients from 9 community practices across 5 states and 5 academic centers. Recovery for most HRQOL measurements occurred within 5 days after surgery.


Predictors of delayed recovery from third molar removal were identified by multivariate analyses from 547 patients with clinical and HRQOL data assessed for 14 days after surgery. Age older than 18 years, female gender, and 2 lower third molars below the occlusal plane increased the odds of delayed HRQOL recovery. Prior third molar symptoms, female gender, and the surgeon's higher estimate of difficulty at surgery increased the odds of delayed clinical recovery.


In a targeted study of healthy patients with 4 third molars below the occlusal plane, those who were not given intravenous (IV) antibiotics before
surgery had a higher incidence of delayed clinical recovery compared with the group that did receive IV antibiotics before surgery. No statistically meaningful differences in HRQOL outcomes were detected between the 2 groups after surgery.


In a targeted study of high-risk patients, IV corticosteroids before surgery with no accompanying antibiotics had a minimal but positive impact on HRQOL measurements, without a delay in clinical recovery. Administration of IV corticosteroids at surgery also decreased patient reports of postsurgical nausea.


When clinical recovery was delayed, a meaningful increase was detected for HRQOL outcomes for the domains of lifestyle, oral function, and pain.


The continued use of postsurgical pain medication over time after third molar surgery, including nonsteroidal anti-inflammatory drugs or opioids, was associated with delayed recovery for HRQOL outcomes such as lifestyle and oral function. This association suggests that using a patient's pain medication regimen might be a more sensitive behavioral indicator of the overall recovery for pain than using pain scales alone.


For targeted high-risk patients, topical antibiotics at surgery, specifically minocycline in slow-release polylactic-co-glycolic acid microspheres placed in lower third molar surgery sites, showed substantial improvements in clinical recovery and HRQOL outcomes for oral function. Clinical outcomes with topical antibiotics could be differentiated from clinical outcomes with IV antibiotics; presurgical IV antibiotics lowered the risk of postsurgical alveolar osteitis and wound infection, whereas topical antibiotics lowered the risk of alveolar osteitis only.


A lower third molar radiographically close to the inferior alveolar canal was associated with prolonged HRQOL recovery for oral function and pain. No meaningful delay was found for clinical recovery. Postsurgical data were from 579 patients with at least 1 mandibular third molar below the occlusal plane.


The Oral Health Impact Profile (OHIP-14), a global oral health questionnaire, developed by Slade et al (J Oral Maxillofac Surg 62:1118, 2004) has been used to measure how different oral health conditions affect quality of life. A more targeted and condition-specific instrument developed by Shugars et al uses HRQOL after third molar surgery. The 2 questionnaires were completed by patients after having 4 third molars removed. Quality-of-life recovery after third molar surgery was rapid when assessed by any of the patient-reported indicators. OHIP-14 and the condition-specific HRQOL instrument were complementary tools to measure quality-of-life outcomes. Each instrument addresses important outcomes uniquely, better defining recovery after third molar surgery.


This prospective clinical study suggested presurgical incomplete mandibular third molar root formation alone was not associated with clinical or HRQOL recovery after surgery. However, clinical and HRQOL recovery were not prolonged when mandibular third molar roots were not complete, although the third molars below the occlusal plane required more bone removal.


After assessing data from 974 healthy patients after third molar surgery, HRQOL recovery for the oldest cohort considerably lagged behind recovery for younger patients, including all lifestyle measurements, oral function measurements of chewing and eating, and pain. Recovery for female patients substantially lagged behind male patients for usual daily activity, social interaction, recreation, all oral function measurements, and pain.

This prospective, nonrandomized study suggested that topical minocycline placed in third molar extraction sites during surgery or passively applied as a cold wrap after surgery could be effective as adjunctive methods to prescribed analgesic medications to decrease the highest reported pain levels after surgery.


Removal of third molars with minor pericoronitis symptoms improved quality of life of affected patients, particularly outcomes for pain and oral function.

CLINICAL AND POPULATION STUDIES


In a representative sample of the US population of 5,831 patients 18 to 34 years old from the Third National Health and Nutrition Examination Survey (NHANES), the presence of a visible third molar increased the risk of finding a periodontal probing depth (PD) of at least 5 mm on the adjacent second molar (odds ratio [OR] = 2.1; 95% confidence interval [CI], 1.6 to 2.8).


In a sample of the US population, the Atherosclerosis Risk in Communities (ARIC) study of 6,793 men and women 52 to 64 years old being studied over time for cardiovascular disease, the presence of a visible third molar increased the risk of finding a periodontal PD of at least 5 mm on the adjacent second molar (OR = 2.5; 95% CI, 2.5 to 3.5).


In a population of 360 obstetric patients from the OCAP study analyzed with multivariable models, a third molar PD of at least 4 mm at enrollment (risk ratio [RR] = 1.4; 95% CI, 1.1 to 2.0) or third molar bleeding on probing at enrollment (RR = 1.7; 95% CI, 1.3 to 2.3) was associated with periodontal disease progression between enrollment (<24 weeks of pregnancy) and postpartum (≥72 hours postpartum).


For elderly patients from the Piedmont 65 study (mean age, 73 yr), most (79%) who reached the eighth decade of life had evidence of third molar caries or periodontal pathology. Overall, third molar caries and periodontal pathology were associated with those of non-third molars. Few patients (17%) had evidence of caries and periodontal pathology affecting third molars. This elderly population, no periodontal pathology or caries was detected in only 21% of patients.


For elderly patients from the Piedmont 65 study (mean age, 73 yr), African Americans had more retained third molars and were more likely than Caucasians to have periodontal pathology with third molars. Caucasians were more likely to have third molar caries.
In a study of pregnant patients after mechanical debridement of biofilm during the second trimester, pathogen counts were not decreased postpartum in those with a visible third molar. If no visible third molars were present, then mechanical debridement alone lowered pathogen counts postpartum for all pathogens studied.


Very few third molars were retained in 372 patients having orthognathic surgery. Retained third molars after surgery tended to be erupted to the occlusal plane in quadrants with missing premolars.


Two thousand thirty-five of 6,793 men and women 52 to 64 years old in the ARIC study had a visible third molar. A visible third molar was associated with more severe periodontal pathology in teeth more anterior in the mouth (increased periodontal PD and clinical attachment loss) compared with those with no visible third molar.


In 2,003 of 6,793 men and women 52 to 64 years old in the ARIC study, coronal caries on visible third molars were statistically associated with caries on non-third molar teeth.


In a summary analysis of 4 reports that included periodontal probing data, patients with a visible third molar were more likely to have greater periodontal PDs overall, particularly on second molars, and higher periodontal extent scores, suggesting a larger biofilm gingival interface surface area on molars with an environment conducive to anaerobic pathogens compared with those with no visible third molar.


Fewer than 2% of 2,035 patients in the ARIC study with a visible third molar were free of coronal caries and periodontal pathology. Conversely, 68% of patients had clinical evidence of third molar caries and periodontal pathology. Periodontal pathology was more prevalent on third molars than caries. Patients with caries or periodontal pathology on third molars were more likely to have similar findings on teeth more anterior in the mouth.


Based on data from 3 population studies and the Third Molar Clinical Trials of young adults, asymptomatic third molars were associated with increased periodontal disease on second molars and progression of periodontal disease after 2 years. Data from this summary report also showed that retained third molars in the presence of periodontal inflammation were associated with substantial increases in levels of serum inflammatory markers such as interleukin (IL)-6, soluble intercellular adhesion molecule-1, and CRP.


Although second premolar removal compared with first premolar or no premolar removal increased the number of patients with upright third molars that were more likely to erupt over time, outcomes were not statistically important. Clinicians cannot reliably advise patients to retain or remove third molars at the end of orthodontic treatment based on premolar removal or no removal. Changes in third molar angulation during orthodontic treatment were not predictable based on premolar removal because of the wide range of angulations and changes within each group over time.


In a study of 1,798 obstetric patients in the Maternal Oral Therapy to Reduce Obstetric Risks study at enrollment, clinical indicators of more severe periodontal inflammatory disease for first and second molars, assessed by periodontal PDs, clinical attachment levels, and bleeding on probing, were detected more often in those with at least 1 third molar visible compared with patients with no visible third molars. Patients with at least 1 visible third molar were more likely to have moderate or severe periodontal disease compared with those with no visible third molars. Most Caucasian patients were Latino, a population with limited third molar data in the English-language literature.

Third molar prevalence was similar in the first decade of the 21st century, suggesting that patterns of care were similar during that time frame. NHANES population data for 2011 through 2012 differed by jaw, gender, ethnicity, and education levels.

RETAIN THIRD MOLARS: PERICORONITIS, SYMPTOMATIC PERIODONTAL PATHOLOGY


Higher levels of "orange complex" bacteria and elevated gingival crevicular fluid (GCF) II-1β inflammatory mediators distinguished pericoronitis from periodontitis. Removal of third molars resulted in elimination of detectable "orange complex" bacteria from the patients' biofilm.


Thirty-seven percent of 480 patients bad pain or swelling in the 3 months before third molar surgery that was sufficient to prompt them to seek removal of third molars before symptoms occurred again. One fourth of symptomatic patients reported on the OHIP-14 that their lifestyle measures were affected "fairly often" or "very often" before surgery. Difficulty relaxing, feeling irritable, feeling tense, and interruptions to meals were reported most frequently.


The impact on quality of life of symptomatic pericoronitis is comparable to that of postsurgical after following third molar surgery.


The study compared the prevalence and severity of periodontal inflammatory disease in patients with (n = 56) and those without (n = 195) pericoronitis symptoms. Thirty-one percent of patients with pericoronitis had incipient and 55% had early disease in the third molar region compared with 25% with incipient and 38% with early disease in patients without pericoronitis (P = .003). The median number of PDs of at least 4 mm for all teeth differed statistically for patients with pericoronitis (median, 5; interquartile range [IQR], 3 to 9) and without pericoronitis (median, 3; IQR, 0 to 8; P = .03).


Significantly more patients (88%) had at least 1 distal second molar (D2M) periodontal PD of at least 4 mm at enrollment compared with after surgery (46%; P < .01). Significantly more patients (61%) had at least 1 PD of at least 4 mm anterior to D2M at enrollment compared with after surgery (29%; P < .01).


Most patients (70%) with mild pericoronitis symptoms elected third molar removal an average of 3 months after enrollment. Having problems with lifestyle and oral function, which are outcomes not often considered by clinicians, were meaningfully associated with patients' decision to proceed with early third molar removal.


All pain outcomes with pericoronitis were significantly associated with items in the lifestyle and oral function domains (P < .01). Clinically important correlations were seen for pain outcomes and daily routine, social life, eating a regular diet, chewing food, and talking (P < .01).

RETAIN THIRD MOLARS: ASYMPTOMATIC PERIODONTAL PATHOLOGY


At baseline one fourth of 329 asymptomatic patients enrolled in a longitudinal clinical study bad at least 1 periodontal PD of least 5 mm in the third molar region (distal of second molars or around third molars) with at least 2 mm of attachment loss. A PD of at least 5 mm was found in a larger proportion of patients at least 25 years old compared with those younger than 25 years (33% vs 17%). Third molars at the occlusal plane and in a vertical or dis-

In 295 asymptomatic patients, subgingival biofilm samples were taken from the distal of second molars before periodontal probing. In patients with PD of at least 5 mm in the third molar region, "orange and red complex" periodontal bacteria were detected greater than $10^3$ in 80% and greater than $10^5$ in 44% (vs 66 and 36%, respectively, in those with PD <5 mm). "Red complex" pathogens were not detected without "orange complex" pathogens.


GCF samples were taken from the mesial of all first molars and distal of all second molars in 316 asymptomatic patients. Periodontal inflammatory mediator levels of IL-1β and prostaglandin E2 were assayed. GCF IL-1β was substantially elevated with a PD of at least 5 mm in the third molar region compared with patients with a PD shallower than 5 mm. GCF prostaglandin E2 was not substantially elevated. Increased PD and GCF IL-1β were suggestive of early periodontitis in affected patients.


Of 254 patients at enrollment, 59% bad at least 1 PD of at least 4 mm in the third molar region. The same patients were followed for a median of 2.2 years, 38% of those with an initial PD of at least 4 mm had an increase in PD of at least 2 mm compared with only 3% of those with an initial PD shallower than 4 mm.


For 237 patients (median age, 25.9 yr; median follow-up, 2.2 yr), 44% of maxillary third molars and 26% of mandibular third molars below the occlusal plane changed angulation or position. Of all third molars with at least 1 PD of at least 4 mm in the third molar region, half were mandibular at the occlusal plane with a vertical or distal angulation. One third consisted of mandibular third molars below the occlusal plane with a mesial or horizontal angulation.


For 195 patients with 4 asymptomatic third molars, the presence of periodontal pathology in the third molar region at baseline was predictive of periodontal pathology in third molars and teeth more anterior (median follow-up, 5.9 yr). Having at least 1 PD of at least 4 mm in the third molar region (incipient disease) at enrollment increased the odds 12-fold that at least 4 PDs of at least 4 mm (early disease) would be found at 6-year follow-up. Having incipient disease in the third molar region...
at enrollment also increased the odds almost 5-fold that at least 4 PDs of at least 4 mm would be found on teeth more anterior at follow-up.


Sixty-nine patients with 4 asymptomatic third molars were followed for a median of 2.4 years before removal of third molars (median postsurgical follow-up, 9 months). Patients with all PDs shallower than 4 mm at the D2M at postsurgical follow-up increased (71%) compared with before surgery (41%).


Of 106 patients with all PDs shallower than 4 mm at enrollment, 38% had a change in third molar region periodontal status, with at least 1 third molar region PD of at least 4 mm detected at a median follow-up of 4 years.


Of 411 patients with 4 asymptomatic third molars, 83% bad at least 1 visible third molar. The visible presence of third molar in young adults was meaningfully associated with periodontal inflammatory disease (PD ≥4 mm) on non-third molars compared with those with no visible third molars (59 to 35%). If at least 1 third molar was visible, then there was a 2.5-fold increase in the presence of a PD of at least 4 mm on teeth more anterior.


In 75 patients, D2M PD of at least 4 mm was detected much less often when measured after removal of all third molars compared with before surgery (23 vs 71%). None of the demographic or surgical variables examined except for presurgical of D2M PD of at least 4 mm were meaningfully associated with postsurgical D2M outcomes.


This study was a review of the biologic basis for third molar pathology and prevalence based on patients enrolled in longitudinal studies.


Few longitudinal data exist on changes over time of third molars below the level of the occlusal plane, an inherently unstable position in the jaw. Unerupted teeth that remain static with no changes in position over time are rare. Estimating the frequency of third molar eruption to the occlusal plane for a population appears to be difficult; predicting the event for an individual might not be possible.


In 409 healthy young adult patients, periodontal pathology was detected more frequently in the third molar region (third molars and distal of second molars) compared with remaining first and second molar probing sites (65 vs 40%). Caries was detected more frequently on first and second molars compared with third molars (75 vs 24%). A PD of at least 4 mm was detected more often when all patients' third molars were at the occlusal plane compared with those with at least 1 below the occlusal plane (72 vs 33%). Sixteen percent of patients with 4 asymptomatic third molars at the occlusal plane were free of periodontal pathology and caries.


For 179 patients with 4 asymptomatic third molars, the prevalence of third molar caries and third molar periodontal pathology increased from baseline to follow-up 7 years later. At follow-up, prevalence of caries was greater on first or second molars compared with third molars (85 vs 50%), and periodontal pathology was greater on third molars compared with probing sites more anterior to the distal of second molars. Third molars with PD of at least 4 mm and occlusal caries increased from enrollment to follow-up (18 to 34%).


Yearly dental prophylaxis treatments for removal of subgingival biofilm in 262 healthy young adult patients with 4 asymptomatic third molars and 2-year follow-up had minimal or no impact on decreasing deeper PDs.

Of 129 patients with all third molar PDs shallower than 4 mm in the third molar region at enrollment followed for 6 years, 47% had elective third molar removal and 21% had developed at least 1 PD of at least 4 mm in the third molar region. In patients retaining asymptomatic third molars over time, 32% had no detected PD of at least 4 mm in the third molar region.

RETAIN THIRD MOLARS

Occlusal Caries


At baseline 28% of 303 asymptomatic patients had at least 1 third molar at the occlusal plane with occlusal caries. Patients older than 25 years were more likely than those younger than 25 to have occlusal caries on a third molar (39 vs 11%). Fewer than 2% of third molars had occlusal caries if first and second molars were free of caries.


For 211 patients with median 2.9-year follow-up, the presence of caries in the first and second molars at baseline was strongly predictive of the development of third molar caries over time. At baseline, older patients were more likely to have third molar caries than those younger than 25 years; however, patients who were younger at baseline were more likely to develop third molar caries at follow-up (9 vs 19%). Only 1% of third molars had occlusal caries if first and second molars were free of caries.


For 49 patients with 5-year follow-up, periodontal pathology was more prevalent than occlusal caries for those with third molars erupted to the occlusal plane (61 vs 27%). Only 37% had neither third molar occlusal caries nor a PD of at least 4 mm in a third molar region.


Younger patients from lower socioeconomic strata, smokers, and those with poor oral hygiene are at increased risk of occlusal caries development on retained third molars. Patients with any first or second molar caries at baseline were 80% more likely to have a new third molar caries lesion at the end of follow-up compared with those with caries-free molars. Favorable oral hygiene behaviors and better socioeconomic status were associated with decreased caries risk, whereas independent of other covariates, smoking increased third molar caries risk 2-fold.