Title: Prospective outcomes of management of third molar extractions via a large multicenter study

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1.0 Abstract. The outcomes of the surgical management of impacted third molars are known to be influenced by many factors including the complexity of the extraction, age of the patient and underlying health of the patient. Although individual reports of complications have been published, a prospective and large scale review has not been reported. Since there is significant variability in practice patterns, particularly the use of antibiotics of various regimens, collating the results of a large numbers may provide a better understanding of what the true risks are and which antibiotic strategies are associated with improved outcomes. A Practice Based Research Network (PBRN) recruiting up to 100 practitioners and each prospectively reporting up to 50 cases to generate a significant amount of prospective data on relevant clinical research questions. It is expected that there is not uniformity in practice of antibiosis related to surgical management of third molars and this data may provide some information on trends that positively or negatively influence outcomes, both short and long term.

2.0 Purpose of the study. The objective of this study is to determine the clinical outcomes of the currently varying practices in antibiotic management of patients undergoing surgical extraction of third molars by prospectively collecting data through a Practice-based Research Network (PBRN). We plan to conduct a prospective study on patients with diagnosis of soft tissue or partial or full bony third molar impaction. By analyzing this data, we will determine the outcomes of the various antibiotic therapies used in patients with third molar impaction surgical and identify factors which predict successful outcomes of different treatment regimens in specific sub-groups of those patients with these conditions.

Initial analysis of the data collected will focus on the underlying diagnoses, antibiotic type, regimen, duration antibiotic-related complications, and third molar surgical extraction-related complications. We plan to assess all data by comparison of antibiotic therapies by CDT codes and chart review between all patients who met inclusion criteria for the study. We anticipate that future studies will be developed from this data base with specific possibilities including patient quality of life and more detailed analysis of impacted third molars management clinical outcomes using other methods to prevent infections and related complications.

3.0 Background and rationale. In 2012 it was reported by Adde and Calvo, respectively, that antibiotic therapy was needed after third molar surgical extraction. In 2011 Dodson et al. recommended the use of a
single-dose of intravenous penicillin or clindamycin or oral systemic antibiotic therapy preoperatively and continued postoperatively for 2 to 7 days to prevent postoperative surgical site infections. Based on these studies, it was concluded that third molar surgical extraction providers and clinicians needed to understand how best to achieve prophylactic therapies for infections following surgical and simple extractions of third molars. As a direct result, other surgeons and investigators have published their outcomes on trends of antibiotic therapy. Siddiqi and Zafar publish their outcomes on antibiotic prophylaxis in third molar surgery, that led to the additional conclusion that use of antibiotic prophylaxis should not be routinely administered when third molars are removed in a healthy patient. Collectively, this information established the fact that there is likely to be a direct relationship between patient complications, interdisciplinary confusion, antibiotic resistance, patient outcomes, and the use of antibiotic in the antibiotic therapy in the surgical and simple management of third molars. The evidence mentioned above has led oral and maxillofacial surgery providers to appreciate that clinical outcome studies need to be developed to assess the practices of antibiotic usage among them. The most recent findings in this area support and extent this concept by the use of antibiotic therapy for management of third molar extractions lead to increased healthcare costs and antibiotic prescription is unnecessary after third molar surgical and simple extractions when preoperative infections are not presented.

4.0 Design

4.1 Selection of Participants/Interventions

4.1.1 Inclusion criteria:

- Patients age range 15-35 years
- Patients receive surgical extraction of at least one mandibular third molar
- ASA I or II
- Signed Consent of Patient/Parent
- Patient not on an antibiotic for other reason within 14 days
- Patient scheduled for follow up 7-14 days postoperatively

4.1.2 Exclusion criteria:

- Patients who receive other interventions: socket grafting, hemostatic agents in sockets
- Preexisting infection in one of the surgical sites
- Lack of follow up reporting

4.2.0. Other sites investigator recruitments. The University of Cincinnati will lead this multicenter study. This study will be performed with the collaboration with a Practice Based Research Network recruited by the American Association of Oral and Maxillofacial Surgery (AAOMS) that involves up to 100 investigators throughout the US. The PIs will retain copies of the following documents in the protocol regulatory binder:

a. Sites must maintain documentation that facilities and equipment at the outside site are adequate to conduct the research, including a plan to provide emergency care to participant. This documentation may not be filed in regulatory binder but available upon request.
4.2 **Subject Recruitment.** Ongoing recruitment of patients with partial and full bony third molar impaction will take place through the practice for each site of the PBRN. Potential subjects will be recruited during clinical evaluations by third molar surgery provider team (OMS) members in each site of the PBRN. Clinical investigators will screen potential subjects and determine if the patient is interested in participating in the study. The clinical investigator will explain the purpose of the study and review the consents with the subject. It will be explained that participation is optional and that either choice will not alter patient care. Because participation in the study is minimal risk, subject consent will be obtained at enrollment visit. No additional attempts will be made to obtain consent from the patient. Any individual request to withdraw from participation will be accepted.

4.3 **Duration.** The proposed study would involve data collection from up to 50 patients from each site of the PBRN. The sponsor Institution at the University of Cincinnati is expecting to partner with 60-100 researchers through the PBRN. Recruitment of patients with partial and full bony third molar impaction who have been seen at the Oral and Maxillofacial Surgery (OMS) outpatient clinic of each site of PBRN. Data collection and analysis is expected to take approximately 2 months to complete per subject. Overall study data collection is anticipated to be completed one year from the first subject enrolled.

5.0 **Study interventions and data collection**

5.1 **Prospective Chart Review:** Once an investigator has screened a potential subject for inclusion and exclusion criteria the subject’s records will be reviewed and data collected will be entered into a database.

5.2 **Data Collection.** Data collection categories include demographics, diagnostic information, (i.e., diagnosis identification, laboratory results, and other medical problems), details of treatment(s), antibiotic therapies, regimens, antibiotic-related complications, charges and fees for outpatient clinic and hospital, and other related-evaluations.

6.0 **Potential benefits.** There is no direct benefit to the patient for participation in this study.

7.0 **Potential risks, discomforts, and inconveniences.** Potential risks are minimal. Prospective data are collected and measured, without involving further patient care or interaction or involving protected health information. No treatment is prescribed or withheld on an experimental basis. No additional radiographs are required to be a part of the study. There are no financial risks to patients participating in this study.
Patient confidentiality will be maintained by identifiable information being viewed by only direct
care providers. Security of the database system will be maintained by limiting data analysis to a
core group of investigators. These include: Deepak G. Krishnan (PI) and Stuart Lieblich (co-PI),
and other related staff of the American Association of Oral & Maxillofacial Surgeons (AAOMS)
for this study. The remaining investigators including the participants in the PBRN will not have
the ability to analyze or download information from the database.

A separate consent will be utilized to obtain consent for publication and educational use of any
identifiable patient studies or images. We will use the approved/current UCHealth authorization
form for consent. Photographs will only be used if a consent form has been signed. Photos will
be maintained for the length of the study. Other photographs may be obtained in the course of
clinical care and used only for clinical management and diagnostic feature recognition. No
means will be used to attempt to de-identify the individual as facial structures and placement are
necessary for content of research/publication. The ability to download digital information will be
restricted by the password protected database to the core investigators to minimize the
possibility of unapproved use. If an image is stored by an investigator it will be on a locked
secured form of memory. Images that are retained by individual investigators for clinical
purposes are not covered under this study’s content.

7.1 Data Safety Monitoring Plan (and/or DSMB). This is a prospective observational study.
This project does not require a medical monitoring and/or DSMB. Our alternative mechanism for
this study is ongoing data will be monitored at the time of entry by AAOMS staff and reported to
the PI in a timely manner.

8.0 Risk/benefit analysis. There are no direct benefits to the subject. There are minimal
risks to the subjects in this study and substantial benefits to patients undergoing clinical
treatment for third molar impaction in the future.

9.0 Methods
This multicenter research project is expected to involve 100 investigators recruited by the
American Association of Oral Maxillofacial Surgeons (AAOMS) in a PBRN. Oral maxillofacial
surgery practitioners; with an active dental license, who graduated from an accredited OMS
residency programs, prospectively report data related to antibiotic management associated with
surgical management of third molars.

Each doctor collects up to 50 unique numbered subject identifiers, to attach to patient chart
along with a spreadsheet to match unique subject identifier to their patient chart number. Only
the co-PI’s will have a list of which doctors received which set of unique subject identifier
numbers.

At least one follow up visit must be completed for the results to be entered along with at least
one telephone contact 60 days postoperatively to see if any later complications occurred.
Practitioners will use their own standard protocols for antibiotic administration, anesthesia,
surgical technique, postoperative analgesics, etc. Data will be collected and analyzed based on antibiotic used, early postoperative infections (days 2-12) and late postoperative infection (days 12-60 days). Data point entering via a standardized web based means will be utilized and hosted by a single site housed at the AAOMS headquarters. Patient identifiers other than age and sex will not be transmitted to the central data collection base. Each site will maintain patient records per usual protocol.

9.1 Data Analysis: Data analysis will take place once the prospective chart review is completed. Data to be collected on each case:

Practitioner coded identifier # (include years of practice post residency)
Patient age:
Sex:
Patient BMI:
ASA status: If not ASA I, then enter disease(s)
Drop down menu of teeth by type of impaction:
    (Numbering of supernumerary teeth using 7 series)

Planned Antibiotic regimen at time of surgery:
    1. No oral or parenteral antibiotic
    2. Antiseptic rinses preoperative
       a. Chlorhexidine
       b. Listerine/OTC
    3. Antiseptic rinse post-operative
       a. Chlorhexidine
       b. Listerine/OTC
    4. Topical in socket
       a. Doxycycline
       b. Clindamycin
       c. Other
    5. Preoperative (PO)
       a. Amoxicillin
       b. Penicillin
       c. Clindamycin
       d. Cephalexin/other cephalosporin
       e. Azithromycin/other macrolides
       f. Other
    6. Perioperative (IV)
       a. Ampicillin
       b. Penicillin
       c. Clindamycin
       d. Cephalexin
       e. Combination agent, e.g. Unasyn
       f. Other
7. 1-3 days postoperative
   a. Amoxicillin
   b. Penicillin
   c. Clindamycin
   d. Cephalexin/other cephalosporin
   e. Azithromycin/other macrolides
   f. Other

8. 4-7 days postoperative
   a. Amoxicillin
   b. Penicillin
   c. Clindamycin
   d. Cephalexin/other cephalosporin
   e. Azithromycin/other macrolides
   f. Other

Therefore can analyze based on antibiotic regimen, i.e. does protocol #8 lead to different outcome than #4, etc.

Postoperative reporting:
1. No complications
2. Treatment for alveolar osteitis
3. Rx for postoperative infection
4. Management of postoperative infection by irrigation
5. Management of postoperative infection by incision and drainage (office)
6. Management of postoperative infection by I&D in hospital
7. A combination of any of the above

A.) Trends in the usage of antibiotics for surgical extraction of impacted third molars and the effects these trends have on outcomes. We will test development of antibiotic related-complications during postoperative period and need for other therapies.
B.) Related antibiotic usage cost analysis. Based on preliminary data collected for this study, we will test our alternative hypothesis that the use of pre- and postoperative antibiotic therapies creates higher costs and charges to patients, hospitals and clinics.

For the above hypotheses, we will perform a logistic regression to test the association of what type of antibiotic use with the development of antibiotic-related complications. The impact of different interventions will also be tested. As a secondary goal, we will also collect information on the time needed to initiate antibiotic therapy when the information is available. The time to event data will be examined using survival curves and tested using Kaplan Meier log rank tests. Data will then be analyzed using Cox proportional hazard models to identify important factors associated with the time to initiate antibiotic therapy postoperatively. For the first hypothesis (A), the effect of antibiotic usage on the need for higher hospital-related charges will be tested using a logistic model. The effects of medical comorbidities (such as other conditions presented
at the time of intervention), other specific diagnosis, gender, and age of initial surgical intervention will be assessed as covariates. Covariates that show significant effects on the outcomes will then be included in the models. Model fit will be evaluated, and residuals will be examined. The analyses will be performed using Statistical Analysis Software (SPSS, or SAS, SAS Institute, Cary, NC). Effects will be considered significant if p<=0.05.

9.1 Sample Size Justification: Our primary goal is to test the association between the practice of antibiotic usage and its outcomes and related morbidities. To achieve 80% power to detect differences in outcomes based on the different antibiotic regimens with 5% error rate, we need at least 1800 subjects with diagnosis of third molar impaction that requires surgical extraction. While the overall results may not be able to identify specific associations between an outcome and a regimen, we are hoping that our large sample size will at least provide us with information on the general trends in the practice of antibiosis in third molar surgery.

10.0 Security

Patient information will be collected and maintained in a password computer and will be housed within the Division of Oral and Maxillofacial Surgery at UC. A person must have UC system access to login. Additional security for the patient database restricts access to only those persons specifically granted authorization by the Principle Investigator. Sensitive data (such as PHI) will be further restricted with access granted only to the core research group.

It is possible for data to be downloaded from password protected database. Individuals who lack authority to see confidential data can download reports with non-identifiable data only. The core research group will have the ability to download sensitive fields and if such a download occurs, the core investigators maintains a record of who, what, when, and to where copies of the database were imported.

As this Project involves only minimal risk to participants, a Data and Safety Monitoring Plan is not outlined, other than above.

The detailed data security plan was will be in accordance with the recently released UC policy that requires all data must be housed in the Secure Data Center although the Division or OMS can have an administrator manage it.

11.0 Process to be used for obtaining consent

11.1 Prospective Chart Review: Patient consent is requested for the prospective portion of this study. This study is minimal risk. There are interactions planned for this portion of the research. Adequate safeguards are in place to protect confidentiality. There is an ongoing relationship with many of the subjects. Thus, this study would be not possible if consent were not required.
11.2 Registry of future patients: Patient consent will be sought from patients with that require surgery for removal of impacted third molars seen in the offices of the participating OMSs. The major elements of the study will be described in the consent form, including examples of the type of data we will extract from charts and how the data will be stored in a safe and confidential location. If a participant declines to participate and retrospective data exists for that participant, the participant will be asked if we may continue to use their information which was obtained previously. If the participant declines, their information will be removed from the database.

11.3 Consent process for photographic data: Should photographs be deemed beneficial for publication, patient Consent, as applicable, will be sought from those subjects. Direct care providers will call the subject and ask permission for use of the photograph. If the subject agrees, the consent form will be mailed to the subject’s home along with a self-addressed envelope. The investigator or her designee will again call the subject in order to describe the study and the use of the photograph using the consent form as a discussion guide. If the subject agrees to participate, the consent will be signed by all appropriate parties and will be returned to the investigator.

References


