The efficacy of antibiotic prophylaxis for impacted and semi-impacted third molar surgery: A prospective randomized double-blind clinical trial

Eficácia da profilaxia antibiótica em terceiros molares inclusos e semi-inclusos: Ensaio clínico prospectivo, randomizado e duplo cego

Eficacia de la profilaxis con antibióticos en terceros molares impactados y semi impactados: Ensayo clínico prospectivo, aleatorizado y doble ciego

Ana Paula Silva Gangá
ORCID: https://orcid.org/0000-0003-4784-1328
Escola Superior São Francisco de Assis, Brazil
E-mail: anapaula_sgangar@hotmail.com

Henrique Augusto Pautz Tarantino
ORCID: https://orcid.org/0000-0001-7861-3200
Escola Superior São Francisco de Assis, Brazil
E-mail: henrique_tarantino@hotmail.com

Natália Bermond Arpini
ORCID: https://orcid.org/0000-0002-9485-3770
Escola Superior São Francisco de Assis, Brazil
E-mail: natarpini@hotmail.com

Tatiany Pimentel Ferreira
ORCID: https://orcid.org/0000-0003-2835-2553
Escola Superior São Francisco de Assis, Brazil
E-mail: taty_pf@hotmail.com

Paula Sampaio de Mello
ORCID: https://orcid.org/0000-0002-7972-6896
Escola Superior São Francisco de Assis, Brazil
E-mail: paulasampaomello@gmail.com

Raphael Castiglioni Coser
ORCID: https://orcid.org/0000-0001-6754-9629
Escola Superior São Francisco de Assis, Brazil
E-mail: raphaelscor@vixface.com.br

Abstract
Impacted and semi-impacted third molar surgery is a frequent dental procedure. Due to potentially major tissue manipulation during surgery, antibiotic prophylaxis may be indicated to prevent infection of the surgical wound. This study evaluated the surgical conditions of patients following extraction of impacted and semi-impacted third molars with or without prior antibiotic prophylaxis. Signs of infection and inflammation, postoperative pain level and efficacy of the prescribed drugs were recorded. This was a prospective, randomized, double blind clinical trial with split-mouth design. A total of 23 healthy (ASA I) volunteers with indication for bilateral mandibular third molar extraction were recruited, totaling 46 surgical procedures. One hour prior to the procedure, volunteers received 1g of amoxicillin or placebo and a drug for pain prevention and control. The surgical acts were performed by last-year dental students. Postoperative pain was assessed using a visual analogue scale and an 11-point box scale at selected postoperative intervals of 4 h, 12 h, and 24 h. After seven postoperative days, study volunteers were examined for clinical signs of infection and/or inflammation, such as pus, intra and extraoral swelling, trismus, heat, flushing and temperature change. There were only two cases of postoperative complications, one of intraoral edema (placebo group) and one of trismus (antibiotic prophylaxis group). There were no statistically significant differences for any of the indicative signs of infection. The pain scales revealed no differences between pain levels in both groups at all times evaluated, regardless of the pain scale used ($P > 0.05$). To conclude, the low infection rate observed in our study does not reflect any need for antibiotic prescription in systemically healthy patients. The adverse effects of antibiotics in addition to selection for resistant bacteria outweigh the benefits of antibiotic prophylaxis in healthy (ASA I) patients.

Keywords: Antibiotic prophylaxis; Oral surgery; Third molar.
1. Introduction

Impacted and semi-impacted third molar surgery is a frequent dental procedure. Third molars erupt between 15 and 18 years of age and may be indicated for extraction in cases of risk or discomfort to the patient. For instance, pericoronitis is the leading reason for extraction of third molars (Normando, 2015; Sarica, et al., 2019), followed by preventive extraction to avoid oral complications, such as periodontal disease in the second molars, tooth resorption, dental caries and the development of cysts and tumors (Santosh, 2015).
The terms impacted or semi-impacted teeth correspond to the dental elements which have failed to fully overcome the physical barrier and reach their correct positioning in the dental arch within the expected time, or have done so partially, either due to bone and soft tissue covering, obstruction by adjacent teeth or a genetic abnormality (Seguro & Oliveira, 2014). In these cases, treatment planning is critical to avoid transoperative issues, to assess the need for preoperative and postoperative drug prescription (antibiotics, anti-inflammatory drugs and analgesics) and to minimize postoperative complications (Santosh, 2015; Roy, et al., 2015). Due to potentially major tissue manipulation during impacted and semi-impacted third molar surgery, antibiotic prophylaxis may be indicated to prevent infection of the surgical wound. Antibiotic administration should preferably be performed prior to the surgical procedure so that the drug plasma concentration is high during tissue manipulation (Gill, et al., 2018). In addition, some authors point out that antibiotic prophylaxis should be maintained for 24 h following the procedure (Blatt & Al-Nawas, 2019).

To date, there remains no consensus on the most effective drug protocol and whether there is a need for routine antibiotic prophylaxis for extraction of impacted third molars (Siddiqi, et al., 2010). According to Cubas-Jaeger and Asmat-Abanto (2016), postoperative complications are caused by surgical trauma and are of inflammatory origin, which does not justify the need for antibiotic use. The indiscriminate prescription of antibiotics may result in the selection of resistant microorganisms and impact antibiotic therapy for other purposes (Gill, et al., 2018; Brigantini, et al., 2016). Another worrisome factor is the possible development of intestinal dysbiosis, which consists of a permanent imbalance between benign bacteria and pathogens of the intestinal microbiota, thus decreasing one’s ability to absorb nutrients and causing lack of vitamins (Conrado, et al., 2018).

Since the current literature on antibiotic prophylaxis for third molar extraction is conflicting, the aim of the present study was to evaluate the efficacy of single-dose antibiotic use prior to extraction of impacted and semi-impacted mandibular third molars by comparing postoperative oral conditions.

2. Methodology

This study was carried out in the oral surgery center of the Escola Superior São Francisco de Assis – ESFA, Espírito Santo state, Brazil, and had prior approval by the Research Ethics Committee of the Centro Universitário Católico de Vitória, Espírito Santo state, Brazil (number 2.969.045). Study volunteers signed an informed consent form to authorize their participation.

2.1 Study design and sample size

This was a prospective, randomized, double blind clinical trial with split-mouth design. The sample size consisted of 23 healthy volunteers with indication for bilateral impacted or semi-impacted mandibular third molar extraction, who presented to the ESFA dental clinics between September 2018 and April 2019.

The inclusion criteria consisted of healthy patients (ASA I, according to physical risk), aged between 18 and 30 years, with indication for extraction of bilateral impacted or semi-impacted mandibular third molars. The following exclusion criteria were considered: pregnant or lactating women, patients on antibiotic use in the previous two weeks, history of hypersensitivity to the study drugs, patients at high risk for infective endocarditis according to the American Heart Association guidelines (AHA) (Wilson, et al., 2007), and patients with a history of pericoronitis.
2.2 Study variables

The study variable consisted of antibiotic prophylaxis prior to the surgical procedure. Each volunteer attended two sessions. In the first visit, the volunteer was administered two capsules of amoxicillin 500 mg (Amoxil® GlaxoSmithKline, Brazil) one hour before the procedure (ATB group), while in the second visit, they were given a placebo (PCB group).

The antibiotics or placebo were coded into protocol numbers #1 and #2 by an independent assistant, who did not participate in the assessment of postoperative parameters. This was a double-blind study in which neither the volunteers nor the head examiner were aware of the study protocols. The order of drug or placebo administration and the sequence of the mouth side submitted to tooth extraction were randomized prior to the start of the study in Microsoft Office Excel® 2016. The study outcomes consisted of clinical signs and symptoms and postoperative pain, the latter being assessed by a visual analogue scale and an 11-point box numerical scale.

2.3 Data collection

One hour before the surgical procedure, volunteers were blindly administered ATB or PCB, and all of them received 4 mg dexamethasone (Decadron®, Aché, Brazil) to prevent hyperalgesia. Each volunteer attended two treatment sessions, with a minimum 21-day interval in between them. The oral surgeons were ESFA dental students who were attending the Dental Clinic II training. All procedures were performed aseptically, which included L-shaped flap, dental dissection and / or osteotomy and simple 5-0 nylon suture. The duration of each procedure was recorded in minutes.

After surgery, all volunteers received analgesic drugs (nimesulide and acetaminophen) and were instructed to return after seven days for evaluation of clinical parameters and suture removal. The postoperative assessment of volunteers consisted of visual observation for the presence of clinical signs of infection, such as pus, increased local and facial volume, ecchymosis, bleeding and flushing. A manual caliper was used to measure the maximum mouth opening, and when measurements were lower than 23 mm, then the presence of trismus was considered.

Postoperative pain was self-assessed by the volunteer using a visual analogue scale and an 11-point box numerical scale at selected time intervals of 4 h, 12 h and 24 h. When filling in the visual analogue scale, the study volunteer should draw a vertical line perpendicular to a 10-cm main horizontal line, in order to describe their painful sensation over time, with the left extremity indicating absence of pain and the right extremity indicating the worst pain possible. The 11-point box scale consists of numbers from 0 (no pain) to 10 (maximum pain), and the volunteer was instructed on how to assign a score based on their pain level.

2.4 Statistical analysis

Demographic information and data regarding the presence or absence of clinical signs of infection were analyzed by the Chi-square test. The data regarding postoperative pain (visual analogue scale), duration of the procedure and mouth opening were compared by paired Student's $t$ test (normal distribution) or Wilcoxon test (non-normal distribution). A similar analysis was carried out with the 11-point box scale data.

3. Results

Twenty-three healthy volunteers attended two sessions for third molar surgery within an interval of 21 days, totaling 46 surgical procedures, and were administered ATB or PCB. A total of 87% of the sample were females and 13% were males, with a mean age of 20.9 (± 4.1) years.
Figure 1 shows the duration of the surgical procedures in both groups. There were no statistically significant differences regarding the duration of the procedures between the two protocols ($P = 0.8850$). The median length of the procedures was 60 minutes for both protocols.

**Figure 1.** Duration of the surgical procedures with preoperative administration of amoxicillin (ATB) or placebo (PCB). Central bar = median; boxes = 1st and 3rd quartiles; swiss = maximum and minimum values (paired Wilcoxon test, $P = 0.8850$).

The data regarding third molar positioning according to Pell and Gregory’s and Winter’s classifications are shown in Table 1. There were no statistically significant differences regarding the positioning of impacted or semi-impacted third molars between the ATB and PCB groups.

**Table 1.** Classification of impacted and semi-impacted third molars, according to different authors (Pell & Gregory and Winter), by treatment group.

| Classification                                      | ATB                | PCB                | Chi-square test $P$-value |
|-----------------------------------------------------|--------------------|--------------------|--------------------------|
| Position relative to the 2nd molar long axis (Winter) |                    |                    |                          |
| Mesioangulated                                      | 8 (35%)            | 8 (35%)            | 1.0000                   |
| Distoangulated                                      | 0 (0%)             | 0 (0%)             |                          |
| Horizontal                                          | 4 (17%)            | 4 (17%)            |                          |
| Vertical                                            | 11 (48%)           | 11 (48%)           |                          |
| Position relative to the occlusal plane (Pell & Gregory) |        |                    |                          |
| A                                                   | 8 (35%)            | 7 (30%)            | 0.9481                   |
| B                                                   | 12 (52%)           | 13 (57%)           |                          |
| C                                                   | 3 (13%)            | 3 (13%)            |                          |
| Position relative to the mandibular ramus (Pell & Gregory) |        |                    |                          |
| Class I                                             | 8 (35%)            | 8 (35%)            | 0.5962                   |
| Class II                                            | 14 (61%)           | 15 (65%)           |                          |
| Class III                                           | 1 (4%)             | 0 (0%)             |                          |

Note: ATB – antibiotic prophylaxis; PCB – placebo.
Source: Authors.
On the seventh postoperative day, volunteers were examined for clinical signs of infection. The collected data are summarized in Table 2. There were no statistically significant differences regarding postoperative parameters indicative of infection. Only one volunteer, who received preoperative placebo (4.3%), had intraoral edema, while another volunteer, who received preoperative antibiotic (4.3%), presented trismus (mouth opening ≤ 23 mm).

Table 2. Postoperative clinical parameters of infection analyzed seven days after impacted or semi-impacted third molar surgery.

| Clinical parameter     | Group | Chi-square test |
|------------------------|-------|-----------------|
|                        | ATB  | PCB             | P-value |
|                        | (n = 23) | (n = 23) |                 |
| Intraoral edema        | Present | 0 (0%)  | 1 (4.3%) | > 0.9999 |
|                        | Absent  | 23 (100%) | 22 (95.7%) |     |
| Alveolitis             | Present | 0 (0%)  | 0 (0%)   | 1.0000  |
|                        | Absent  | 23 (100%) | 23 (100%) |     |
| Trismus                | Present | 1 (4.3%) | 0 (0%)   | > 0.9999 |
|                        | Absent  | 22 (95.7%) | 23 (100%) |     |
| Purulent secretion     | Present | 0 (0%)  | 0 (0%)   | 1.0000  |
|                        | Absent  | 23 (100%) | 23 (100%) |     |
| Ecchymosis             | Present | 0 (0%)  | 0 (0%)   | 1.0000  |
|                        | Absent  | 23 (100%) | 23 (100%) |     |
| Bleeding               | Present | 0 (0%)  | 0 (0%)   | 1.0000  |
|                        | Absent  | 23 (100%) | 23 (100%) |     |
| Change of temperature  | Present | 0 (0%)  | 0 (0%)   | 1.0000  |
|                        | Absent  | 23 (100%) | 23 (100%) |     |

Note: ATB – antibiotic prophylaxis; PCB – placebo.
Source: Authors.

The volunteers also had their maximum mouth opening evaluated using a manual caliper on the seventh postoperative day. As shown in Figure 2, no statistically significant differences in maximum mouth opening were found between the ATB and PCB groups (Paired Student’s t test, P = 0.8495). The mean maximum mouth opening measurement found for the ATB protocol was 43.8 mm (± 7.7 mm) as compared to 43.5 mm (± 7.8 mm) for the PCB protocol.
Figure 2. Mean (± standard deviation) maximum mouth opening measured seven days after third molar surgery in patients administered preoperative antibiotic (ATB) or placebo (PCB).

Postoperative pain was evaluated at 4 h, 6 h and 24 h after the end of the surgical procedure using the visual analogue scale (VAS) (Table 3) and the 11-point box pain scale (Figure 3).

Table 3. Median (interquartile deviation) of VAS pain levels by treatment and timepoint.

| Postoperative Timepoint | ATB     | PCB     | Wilcoxon test P-value |
|-------------------------|---------|---------|-----------------------|
| 4 h                     | 1.2 (3.3) | 1.9 (2.4) | 0.8697                |
| 6 h                     | 1.4 (1.8) | 1.9 (3.1) | 0.7146                |
| 24 h                    | 0.3 (1.8) | 2.4 (3.1) | 0.7990                |

Note: VAS, Visual Analogue Scale; ATB, antibiotic prophylaxis; PCB, placebo.

Source: Authors.

Figure 3. Pain levels based on the 11-point box numerical scale by treatment group and timepoint. Each dot indicates one event, and the vertical line corresponds to the median.

Source: Authors.
The findings revealed no statistically significant differences in pain levels between the ATB and PCB groups at any timepoint (paired Wilcoxon test).

As seen in Figure 3, the ATB group obtained median scores in the 11-point box scale of 2 after four postoperative hours and 1 after 6 h and 24 h, whereas the PCB group showed a median score of 3 after 4 h and 6 h and of 1 after 24 h. Paired Wilcoxon test indicated no statistically significant differences in postoperative pain levels between the ATB and PCB groups after 4 h ($P = 0.3723$), 6 h ($P = 0.2396$) and 24 h ($P = 0.8669$).

Eight cases of pain (34.8\% of the sample) were reported in the ATB group after the fourth postoperative day, upon cessation of pain prevention and control medication. Fifteen cases (56.5\% of the sample) of postoperative complications were found in the PCB group, which included pain after the fourth day, paresthesia (three cases) and nausea/vomiting (one case). There were no significant differences in the prevalence of postoperative complications between the two treatment groups (Chi-square test, $P = 0.1389$).

4. Discussion

The major outcome of the present study was the low incidence of clinical signs of infection after third molar surgery, regardless of the prophylactic drug protocol used (antibiotic or placebo). This confirms the authors’ null hypothesis that there would be no significant differences between the two drug protocols tested.

In our study, 87\% of the sample was composed of females, which was also observed in the studies by Siddiqi, et al. (2010) (62\% females) and Bortoluzzi, et al. (2013) (74\% females). Previously, Santos and Quesada (2008) and Trento, et al. (2009) evaluated the prevalence of third molars and their respective positions according to the classifications proposed by Winter and Pell and Gregory. In both reports, there was a predominance of vertically positioned third molars, followed by mesioangulated (the easiest for extraction), horizontal and, lastly, distoangulated. These findings are in line with those reported herein, in which the vertical position of third molars was the most prevalent one, followed by mesioangulated, horizontal and distoangulated.

As for the classification of the anterior edge of the mandible, there was a higher prevalence in our study of Class II position, followed by Class I, which is consistent with previous literature reports (Dos Santos, et al., 2008; Trento, et al., 2009). In addition, the study by Santos and Quesada (2008) indicated that third molars were mostly in occlusal plane position A, followed by position B, while the study by Trento et al. (2009) found a higher prevalence of occlusal position A, followed by C. Our data are conflicting with these previous reports, as in our sample there was a higher prevalence of occlusal plane position B, followed by A and C, respectively. These classifications are important to predict the degree of difficulty of the third molar surgery. Hence, it is ideal that both treatment groups pose a similar degree of difficulty to avoid selection bias. Consistent with this premise, there was no significant difference in the classifications of third molar position between the ATB and PCB groups in our study sample.

The duration of the surgical procedure is also directly related to the frequency of postoperative complications, including infection. In the present study, no significant differences were found regarding the median duration of the surgical procedures between both groups, which is in line with previous studies (Monaco, et al., 2009; Bezerra, et al., 2011).

Postoperative clinical parameters were also analyzed on the seventh day after surgery. The results showed only one case of trismus (4.3\% of the sample) in the ATB group and one case of intraoral edema (4.3\% of the sample) in the PCB group. No cases of alveolitis, purulent secretion, ecchymosis, bleeding or temperature change were found. As expected, there were no significant differences between the two treatment groups regarding the prevalence of signs of infection. These findings agree with those reported by Milani, et al. (2015), Bortoluzzi, et al. (2013) and Siddiqi, et al. (2010), whom found no inter-group differences regarding the incidence of edema, infection, fever, presence of purulent secretion and alveolitis. Although Bezerra,
et al. (2011) found a 50% prevalence of inflammation/infection signs on the third postoperative day, a lower frequency was observed on the seventh day, probably due to the host’s inflammatory response. Monaco, et al. (2009) reported that antibiotic prophylaxis resulted in significantly fewer postoperative infections.

Here, the drug protocol did not influence the maximum mouth opening, which was 43.8 mm and 43.5 mm in patients administered ATB and PCB, respectively. Bortoluzzi, et al. (2013) reported that 26% of their study sample of 50 volunteers showed restricted mouth opening. Intriguingly, there was a higher number of trismus cases (n = 5) in the placebo group, which could be explained by the fact that the clinical parameter was the patient's own perception of their mouth opening. In the study by Siddiqi, et al. (2010) there were 12 cases of trismus (37.57%), seven of which within the antibiotic group and five within the placebo group, with significant differences between the groups, as also observed in our study. In the study by Bezerra, et al. (2011), the mean maximum mouth opening on the seventh postoperative day was 46.88 mm in the ATB group and 43 mm in the PCB group, which is consistent with our findings. Similarly, Milani, et al. (2015) found a mean maximum mouth opening of 43.3 and 42.3 mm on the seventh postoperative day for the groups undergoing antibiotic prophylaxis and of 38.95 mm for the placebo group.

Postoperative pain was assessed by the Visual Analogue Scale (VAS) and 11-point box scale, which have been previously validated and widely used in the international literature (Jensen, et al., 1986). At the postoperative timepoints of 4 h, 6 h and 24 h, the VAS measurements were 2.2 cm, 1.9 cm and 1.2 cm for the ATB group and 2.1 cm, 2.1 cm and 1.6 cm for the PCB group, respectively. According to Collins, et al. (1997), all these measurements translate into mild pain. In addition, no significant differences between treatments were observed at any timepoint. These results corroborate those of Milani, et al. (2015), which were measured 4 h after the procedure and on the seventh postoperative day; Siddiqi, et al. (2010), who measured on the third, seventh and fourteenth postoperative day; and Bortoluzzi, et al. (2013), whose measurements were obtained from the fifth postoperative hour until the sixth day. In contrast, these results differ from those shown by Monaco, et al. (2009) and Bezerra, et al. (2011), whom found lower pain levels among patients undergoing antibiotic prophylaxis than among those receiving a placebo. The conflicting outcomes may be due to the fact that postoperative pain was measured after seven days, which may not be necessarily related to the surgical procedure itself.

The volunteer’s pain levels were also measured using the 11-point box scale and compared to the VAS results. There was similarity between both methods, which confirms the usefulness of the 11-point box scale as a possible alternative to the traditional VAS - which can be considered more difficult for the volunteer to interpret. There were eight cases of postoperative pain after the fourth day, with 34.8% in the ATB group and 56.5% in the PCB group. These rates are slightly higher than those reported by Monaco, et al. (2009), who found a 10.2% prevalence of pain after the fourth postoperative day and observed pain after one week in 3.4% of the volunteers. In the present study, there were three cases of temporary paresthesia in the PCB group, which accounted for 6.52% of the sample. Similarly, Siddiqi, et al. (2010) found two cases of temporary paresthesia, one in each group of volunteers, which corresponded to 2% of the sample.

Taken altogether, the results found in our study are consistent with the literature. The low rates of infection do not justify the need for antibiotic use in systemically healthy patients, which remains a common occurrence in dental care. The adverse effects of antibiotics and the selection of resistant strains outweigh the benefits of antibiotic prophylaxis in healthy (ASA I) patients. A standardized surgical technique and an effective drug protocol for the control of pain and inflammation are enough to prevent postoperative complications, as the host’s defense mechanisms can potentially abolish the infectious process.

Lastly, this study used a multi-operator approach to simulate the daily routine experienced by dental professionals. According to Kato, et al. (2010), the involvement of undergraduate dental students as operators does not increase the risk of
infection, concluding that it is not necessary to prophylactically prescribe antibiotics prior to clinical procedures performed by dental students.

5. Conclusion

To conclude, the use of amoxicillin as a prophylactic regimen had no advantage for systematically healthy patients undergoing extraction of impacted and semi-impacted third molars as compared to a placebo. The antibiotic drug protocol should not be performed routinely as it is not beneficial to the patient and may instead select for antibiotic-resistant strains.

Funding information

This study was supported by the Espírito Santo State Research and Innovation Foundation (Fapes) for acquisition of the pharmaceutical drugs.

References

Bezerra, T. P., Studart-Soares, E. C., Scaparo, H. C., Pita-Neto, I. C., Batista, S. H. B., & Fonteles, C. S. R. (2011). Prophylaxis versus placebo treatment for infective and inflammatory complications of surgical third molar removal: A split-mouth, double-blind, controlled, clinical trial with amoxicillin (500 mg). J Oral Maxillofac Surg. 69(11), e333–9.

Blatt, S., & Al-Nawas, B. (2019). A systematic review of latest evidence for antibiotic prophylaxis and therapy in oral and maxillofacial surgery. Infection. Springer Berlin Heidelberg. 47, 519–555.

Bortoluzzi, M. C., Capella, D. L., Barbieri, T., Pagliarini, M., Cavalieri, T., & Manfro, R. (2013). A Single Dose of Amoxicillin and Dexamethasone for Prevention of Postoperative Complications in Third Molar Surgery: A Randomized, Double-Blind, Placebo Controlled Clinical Trial. J Clin Med Res. 5(1). 26–33.

Brigantini, L. C., Marques, G. J., & Gimenes, M. (2016). Antibióticos em odontologia. Uningá. 49(S3). 121–7.

Collins, S. L., Moore, A. R., & McQuay, H. J. (1997). The visual analogue pain intensity scale: what is moderate pain in millimeters. Pain. 72:95–7.

Conrado, B. Á., Souza, S. A. de, Mallet, A. C. T., Souza, E. B. de, Neves, A. dos S., & Saron, M. L. G. (2018). Disbiose Intestinal em idosos e aplicabilidade dos probióticos e prebióticos. Cad UnIFOA. 36. 71–8.

Cubas-Jaeger, J. L., & Asmat-Abanto, A. S. (2016). Amoxicilina para prevenir la infección postexodoncia de terceros molares incluidos: ensayo clínico aleatorizado. Rev Esp Cir Oral y Maxilofac. 38(4), 188–92.

Dos Santos, D. R., & Quesada, G. A. T. (2008). Prevalência de terceiros molares e suas respectivas posições segundo as classificações de Winter e de Pell e Gregory. Rev Cir e Traumatol Bucal-Maxilo-Facial. 5458(1), 83–92.

Gill, A. S., Morrissey, H., & Rahman, A. (2018). A systematic review and meta-analysis evaluating antibiotic prophylaxis in dental implants and extraction procedures. Med. 54(6), 1–27.

Jensen, M. P., Karoly, P., & Braver, S. (1986). The measurement of clinical pain intensity: a comparison of six methods. Pain. 27(1). 117–26.

Kato, R. B., Bueno, R. de B. L., Neto, P. J. de O., Ribeiro, M. C., & Azenha, M. R. (2010). Acidentes e Complicações Associadas à Cirurgia dos Terceiros Molares Realizada por Alunos de Odontologia. Rev Cir e Traumatol Bucal-massilo-facial. 10(4). 45–54.

Milani, B. A., Bauer, H. C., Sampaio-Filho H., Horlana., A. C. R. T., Perez, F. E. G., Tortamano, I. P., et al. (2015). Antibiotic therapy in fully impacted lower third molar surgery: randomized three-arm, double-blind, controlled trial. Oral Maxillofac Surg. 19(4). 341–6.

Monaco, G., Tavernese, L., Agostini, R., & Marchetti, C. (2009). Evaluation of Antibiotic Prophylaxis in Reducing Postoperative Infection After Mandibular Third Molar Extraction in Young Patients. J Oral Maxillofac Surg. 67(7). 1467–72.

Normando, D. (2015). Third molars: to extract or not to extract? Dental Press J Orthod. 20(4). 17–8.

Roy, I., Baliga, S. D., Louis, A., & Rao, S. (2015). Importance of Clinical and Radiological Parameters in Assessment of Surgical Difficulty in Removal of Impacted Mandibular 3rd Molars: A New Index. J Maxillofac Oral Surg. 14(3). 745–9.

Santosh, P. (2015). Impacted mandibular third molars: Review of literature and a proposal of a combined clinical and radiological classification. Ann Med Health Sci Res. 5(4). 229.

Sarica, I., Derindag, G., Kurtuldu, E., Naralan, M., & Caglayan, F. (2019). A retrospective study: Do all impacted teeth cause pathology? Niger J Clin Pract. 22(4). 527–33.

Seguro, D., & Oliveira, R. V. (2014). Complicações Pós-Cirúrgicas Na Remoção De Terceiros Molares Inclusos. Rev UNINGÁ. 20(1). 30–4.
Siddiqi, A., Morkel, J. A., & Zafar, S. (2010). Antibiotic prophylaxis in third molar surgery: A randomized double-blind placebo-controlled clinical trial using split-mouth technique. *Int J Oral Maxillofac Surg*. 39(2). 107–14.

Trento, C. L., Zini, M. M., Moreschi, E., Zamponi, M., Gottardo, D. V., Cariani, J. P. (2009). Localização e classificação de terceiros molares: análise radiográfica. *Interbio*. 3(2). 18–26.

Wilson, W., Taubert, K. A., Gewitz, M., Lockhart, P. B., Baddour, L. M., Levison, M., et al. (2007). Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation*. 116(15). 1736–54.