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Effect of antibiotic therapy in the postoperative period of third molar surgeries: a split-mouth, randomized and controlled study

Efeito da terapia antibiótica no período pós-operatório de cirurgias de terceiros molares: um estudo de boca dividida, randomizado e controlado

Efecto de la terapia antibiótica en el período postoperatorio de las cirugías de terceros molares: un estudio aleatorio y controlado de boca dividida

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Abstract
Purpose: The objective of this randomized clinical trial was to evaluate the postoperative period of 32 third molars, semi-included or included, in a split mouth, of patients from the São Paulo State University. Material and Methods: The teeth were divided into two groups, in the test group drug treatment with Amoxicillin 500 mg, Dexamethasone 4 mg and Dipyrone 500 mg and in the control group patients received treatment with Dexamethasone 4 mg and Dipyrone 500 mg. The parameters used were edema, trismus and pain, measured before and after the operation, where the benefits of antibiotic therapy were evaluated. To compare the data, an analog pain scale was used, the method of Ustün, and the millimeter ruler, being submitted to Student's T test. Results: Both test and control groups had similar values, with no statistically significant difference in the incidence of postoperative complications, as well as in the presence of edema, pain and more pronounced trismus between the groups analyzed in the study. Conclusions: In view of the statistical results obtained, it was not possible to state that the use of antibiotic therapy was beneficial when related to edema, trismus and pain.
Keywords: Molar third; Surgery oral; Edema; Trismus.

Resumo
Objetivo: O objetivo deste ensaio clínico randomizado foi avaliar o período pós-operatório de 32 terceiros molares, semi-inclusos ou inclusos, em uma boca dividida, de pacientes da Universidade Estadual Paulista. Material e Métodos: Os dentes foram divididos em dois grupos, no grupo teste tratamento medicamentoso com Amoxicilina 500 mg, Dexametasona 4 mg e Dipirona 500 mg e no grupo controle pacientes receberam tratamento com Dexametasona 4 mg e Dipirona 500 mg. Os parâmetros utilizados foram edema, trismo e dor, medidos antes e depois da operação, onde os benefícios da antibioticoterapia foram avaliados. Para comparar os dados, foi utilizada uma escala analógica de dor, o método de Ustün, e régua milimetrada, sendo submetida ao teste T de Student. Resultados: Tanto os grupos teste como controle apresentaram valores semelhantes, sem diferença estatisticamente significativa na incidência de complicações

pós-operatórias, assim como na presença de edema, dor e trismo mais pronunciado entre os grupos analisados no estudo. Conclusões: Em vista dos resultados estatísticos obtidos, não foi possível afirmar que o uso de antibioticoterapia foi benéfico quando relacionado a edema, trismo e dor.
Palavras-chave: Dente serotino; Cirurgia bucal; Edema; Trismo.

Resumen
Propósito: El objetivo de este ensayo clínico aleatorio fue evaluar el postoperatorio de 32 terceros molares, semi-inclusos o inclusos, en boca dividida, de pacientes de la Universidad del Estado de São Paulo. Material y Métodos: Los dientes fueron divididos en dos grupos, en el grupo de prueba el tratamiento farmacológico con Amoxicilina 500 mg, Dexametasona 4 mg y Dipirona 500 mg y en el grupo control los pacientes recibieron tratamiento con Dexametasona 4 mg y Dipirona 500 mg. Los parámetros utilizados fueron el edema, el trismo y el dolor, medidos antes y después de la operación, donde se evaluaron los beneficios de la terapia antibiótica. Para comparar los datos se utilizó una escala analógica de dolor, el método de Ustün, y regla milimetrada, siendo sometidos a la prueba T de Student. Resultados: Tanto el grupo de prueba como el de control presentaron valores similares, no existiendo diferencias estadísticamente significativas en la incidencia de complicaciones postoperatorias, así como en la presencia de edema, dolor y trismo más pronunciado entre los grupos analizados en el estudio. Conclusiones: A la vista de los resultados estadísticos obtenidos, no fue posible afirmar que el uso de la terapia antibiótica fuera beneficioso en relación con el edema, el trismus y el dolor.
Palabras clave: Tercer molar; Cirugía bucal; Edema; Trismo.

1. Introduction

Extraction of the lower third molars is one of the most common procedures in Maxillofacial Surgery and this can be accompanied by several postoperative complications, including pain, trismus and nerve damage. To prevent postoperative complications, several surgeons tend to prescribe antibiotics, which are around 90% for this reason (Lee et al., 2014).

Third molar extraction surgery is usually considered a clean-contaminated surgery, so the routine use of antibiotic prophylaxis is a controversial topic. Several studies of complications after third molar surgery show the incidence of 1% to 5.8% of minor postoperative infections. Another study on infections in deep spaces shows only a very low incidence of severe infections resulting from surgery on third molars, all occurring in cases with preoperative pericoronaritis. Therefore, the routine administration of antibiotic prophylaxis remains questionable (Poeschl et al., 2004).

Amoxicillin is a broad-spectrum, low-toxicity bactericidal antibiotic, with favorable pharmacological properties and minimal adverse effects. Amoxicillin diffuses readily into most tissues and body fluids and when administered orally in doses of 500 mg every 8 hours, it reaches maximum blood levels within 1 to 2 hours after its administration. Its usefulness in the treatment of oral infections has already been demonstrated (López-Cedrún et al., 2011).

Although there are many conflicting reports about the removal of the third molar, few studies investigating the impact of prophylactic or therapeutic administration of antibiotics on the control of postoperative infection have been published. The logic behind the administration of antibiotics is clearly important in frequently performed procedures, such as third molar surgery, and protocols for prescribing antimicrobials must be established (Bezerra et al., 2011).

Thus, this controlled, randomized, divided-mouth clinical trial aimed to evaluate the effects of antibiotic therapy on pain, edema and trismus in the postoperative period of extraction of third and third included molars in a divided mouth protocol.

2. Methodology

This study was a randomized, controlled and blinded clinical trial, follows the CONSORT-STATEMENT 2010 rules (Moher et al., 2012), methodologically described and supported in the book “Metodologia científica: ciência, ensino e pesquisa” (Estrela, C., 2018), and registered on the Brazilian Registry of Clinical Trials website, RBR-4yq8n9 and with approval by the Research Ethics Committee (3,073,095) of the Universidade Estadual Paulista "Júlio de Mesquita Filho" - Institute of Science and Technology - ICT / UNESP. Pre-operative, detailed anamnesis and panoramic radiography were performed. Thus, the patients who comply with the inclusion criteria were selected.

2.1 Eligibility criteria

The inclusion criteria were: ASA I patients; Patients in need of extraction of third molars, without distinction of genre; Patients with teeth in opposite hemiarches obeying the classifications of Class III and C position Pell and Gregory (Pell, G.J., & Gregory, B.T., 1933) and vertical, mesoangulated and Winter horizontal (Winter, G.B., 1926). Patients aged between 15 and 40 years; patients who did not present pathologies associated with the included and / or semi-included elements; Patients with agreement to voluntarily participate in the research, being aware of the risks and benefits and before signing the Informed Consent Term (ICT).

The exclusion criteria were: ASA II, III, IV or V patients; Patients who used anti-inflammatory drugs in the last 15 days; Patients with lower third molars in a different position and inclusion classification on both sides; Patients with erupted lower third molars; patients who presented pathologies associated with the included and / or semi-included elements; Patients allergic to the medication used.

2.2 Sample

The sample consisted of 16 patients who required extraction of the lower third molars, semi-included or included and was within the pre-established criteria. The sample size was calculated on the website Sealed Envelope™, with a minimum of 32 teeth for 80% detection and 5% significance level.

2.3 Randomization and composition of groups

After undergoing clinical evaluation, patients who met the inclusion criteria were divided into two groups, by the randomization method involving numbers and envelopes. The first group, namely Test group, consisted of 16 teeth from patients who submitted to postoperative medication of 1 Amoxicillin capsule 500mg every 8 hours for 05 days, 2 tablets of Dexamethasone 4 mg in the immediate postoperative period (1h after surgery) and Dipyrone 500mg every 6 hours for 02 days. The second group, control group, also consisted of 16 teeth from patients who submitted to postoperative medication of 2 tablets of Dexamethasone 4 mg in the immediate postoperative period (1h after surgery) and Dipyrone 500mg every 6 hours for 02 days. The first surgery for all patients was on the right side, element 48. Randomization was conducted by a researcher not involved (AG) in recruiting and treating patients, being allocated to the test and control groups. The surgeon (IJMO) and assistant (SSB) were blinded in relation to the groups.

2.4 Surgical procedure

The surgeries had an interval of twenty days between them and were performed by a single surgeon (IJMO) and assistant (SSB) at the Clinic of the Discipline of Oral and Maxillofacial Surgery and Traumatology of the Universidade Estadual Paulista "Júlio de Mesquita Filho" - Institute of Science and Technology (Unesp). Recommending all necessary biosafety and antisepsis standards. Antibiotic therapy was applied to patients in the test group, according to previous randomization and following the protocol.

2.5 Clinical evaluation of pain, edema, trismus and statistical analysis

During the postoperative period, the patients who underwent the procedure received forms and themselves noted, throughout the postoperative period, until the third day, on the pain analogue scale (VAS) the painful experience that may be contained between the parameters: zero, for “no pain”, and ten, for “worst possible pain” (Maxwell, 1978). Facial edema was measured using the technique which is based on the distance between the lateral corner of the eye and the gonion, the distance from the tragus to the labial commissure and the distance from the tragus to the soft tissue of the pogonion. (Ustün et al., 2003).

The measurements were made with a flexible ruler in the pre-operative, and in the initial period, of three and seven days. Trismus was measured in the preoperative period and later on the third and seventh days with the patients were seated, erect and also with a millimeter ruler, positioned between the incisal edges of the upper and lower central incisors. The data were submitted to statistical analysis using SPSS software version 11 (IBM Corp., Somers, NY, USA), using the Student t test with significance of 5% ($\alpha = 0.05$) for the comparison between the means.

3. Results

3.1 Recruitment and demographic data

The screenings were performed over a period of two months, with 37 patients were initially screened. After detailed anamnesis and evaluation of panoramic radiography, 17 patients exclusion criteria, thus, 20 eligible for research. However, in the course of the research, we had 4 patients excluded, one due to incompatible schedules on the part of the patient, and three patients excluded because they had complications in the postoperative period, with the final number of the sample, 16 patients, that is, 32 teeth. The patients had an average age of 20 years, of both genders, 12 of whom were female, that is, 75% and 4 were male, that is, 25%. All patients were simultaneously part of the two groups: test group (use of antibiotics in the postoperative period) and control group (without the use of antibiotics in the postoperative period), and these patients had the right (tooth 48) and left (tooth 38) sides allocated to different groups.

3.2 Values analyzed to pain, edema and trismus.

The comparison of the pain index, in the immediate postoperative period (0, 2, 4, 6 and 8 hours) and late (24, 48 and 72 hours), between the two groups was statistical insignificance, despite there was less report of pain in the post-operative period of 2, 6, 24 and 48 hours with the use of antibiotics and less pain reported in the periods of 4, 8 and 72 hours in the postoperative period of the group without the use of antibiotics. Regarding the edema, variations were presented at the different moments analyzed and there were no statistically significant differences between the two sample groups, between the moments themselves and between the anatomical points analyzed. Considering the variation presented for the parameter trismus between the groups, also no statistically significant differences were found, as can been see in Table 1.

3.3 Analysis of moments for pain, edema and trismus.

For the analysis of the moments for the pain variable, the data were separated by the time of the analysis, and after statistical analysis of ANOVA, no statistical differences were found between the hours, both for the test group and for the control group. The same analysis of the moments was performed for the edema variable, the data being subjected to ANOVA analysis, with no statistical differences being found between all moments, both in the test group and in the control group. For the trismus variable, moment analysis was performed using the ANOVA test, with statistical differences between moments, both in the test group and in the control group. However, when submitted to the Tukey test, for comparison between the means, we did not observe a statistically significant difference. (Table 2).

Table 1 - Evaluation of postoperative pain, edema and trismus.

	Period		Test	Control
Pain	**0h**		4,87±2,92	5,00±3,61
	2h		5,00 ±2,73	5,31±2,87
	4h		5,13±2,28	5,00±2,16
	6h		4,38±2,25	5,13±2,16
	8h		4,13±2,03	3,94±2,29
	24h		4,69±2,36	4,81±2,76
	48h		4,88±2,78	4,94±2,93
	72h		3,94±2,46	3,50±3,01
Edema	**Initial**	**Gô – Ct**	10,58±1,73	9,97±0,70
		Tr – Cm	11,03±0,84	10,88±0,61
		Tr – Pgô	14,05±1,63	14,50±0,79
	Day 3	**Gô – Ct**	10,73±1,92	10,46±0,94
		Tr – Cm	11,34±0,78	11,43±0,84
		Tr – Pgô	14,53±1,36	14,84±0,69
	Day 7	**Gô - Ct**	10,61±1,81	9,99±0,96
		Tr - Cm	18,08±28,52	11,28±1,66
		Tr - Pgô	14,33±1,27	14,57±0,80
Trismus	**Initial**		4,53±0,81	4,44±0,76
	Day 3		3,09±1,17	2,91±1,19
	Day 7		4,06±0,96	4,08±1,10

Average values evaluation throughout the postoperative period between test and control groups. Subtitle: a: Gonio; b: Side corner of eye; c: Tragus; d: Lip commissure; e: Pogonion. Source: Draw up by the authors.

Table 2 - Values obtained in the analysis of the moments in the variables pain, edema and trismus.

	Groups	Anatomic distances	Period	Average	Median	Standard deviation	CV	Min	Max	p-value
Pain	**Test**	-	**0h**	4,88	5	2,92	59,86%	0	10	0,847
		-	**2h**	5	5	2,73	54,65%	0	10	
		-	**4h**	5,13	6	2,28	44,42%	0	8	
		-	**6h**	4,38	5	2,25	51,37%	0	7	
		-	**8h**	4,13	5	2,03	49,19%	0	7	
		-	**24h**	4,69	5	2,36	50,31%	0	9	
		-	**48h**	4,88	5	2,78	56,98%	0	9	
		-	**72h**	3,94	4	2,46	62,53%	0	9	
	Control	-	**0h**	5	5	3,61	72,30%	0	10	0,552
		-	**2h**	5,31	5	2,87	54,00%	0	10	
		-	**4h**	5	5	2,16	43,20%	1	10	
		-	**6h**	5,13	5	2,16	42,08%	1	10	
		-	**8h**	3,94	4	2,29	58,26%	0	7	
		-	**24h**	4,81	5	2,76	57,39%	0	10	
		-	**48h**	4,94	5	2,93	59,38%	0	10	
		-	**72h**	3,5	4	3,01	86,03%	0	8	
Edema	**Test**	**Go[a] – Ce[b]**	**Initial**	10,58	10	1,73	16,31%	11	17	0,97
			Day 3	10,73	10	1,92	17,92%	10	17	
			Day 7	10,61	10	1,81	17,06%	10	17	
		Tr[c] – Lc[d]	**Initial**	11,03	11	0,84	7,66%	11	12	0,502
			Day 3	11,34	11	0,78	6,85%	11	13	
			Day 7	11,05	11	0,91	8,27%	10	13	
		Tr – Pgo[e]	**Initial**	14,05	14	1,63	11,63%	12	16	0,603
			Day 3	14,53	15	1,36	9,37%	12	16	
			Day 7	14,33	15	1,27	8,88%	12	17	
	Control	**Go - Ce**	**Initial**	9,97	10	0,7	6,77%	8	11	0,204
			Day 3	10,46	11	0,94	8,90%	9	13	
			Day 7	9,99	10	0,96	9,43%	7	11	
		Tr - Lc	**Initial**	10,88	11	0,61	5,51%	10	12	0,307
			Day 3	11,43	11	0,84	7,43%	10	13	
			Day 7	11,28	11	1,66	15,31%	9	17	
		Tr - Pgo	**Initial**	14,5	15	0,79	5,41%	13	16	0,404
			Day 3	14,84	15	0,69	4,68%	14	17	
			Day 7	14,57	14	0,8	5,57%	13	16	
Trismus	**Test**	-	**Initial**	4,53	5	0,81	17,15%	3	6	<0,001
		-	**Day 3**	3,09	3	1,17	41,72%	3	5	
		-	**Day 7**	4,06	4	0,96	23,23%	3	6	
	Control	-	**Initial**	4,44	5	0,76	16,55%	3	6	<0,001
		-	**Day 3**	2,91	3	1,19	41,93%	1	5	
		-	**Day 7**	4,08	4	1,1	26,78%	2	6	

Analysis of values obtained in each moment throughout the postoperative period between test and control groups and their statistical significance. Source: Draw up by the authors.

4. Discussion

Considering that the removal of an impacted third molar is a surgical procedure, it carries inherent risks and complications that occur in the postoperative period, such as pain, trismus, and edema formation. The amount of edema is directly proportional to the extent of tissue injury. Pain, on the other hand, is a subjective experience and influenced by factors such as age, gender, anxiety levels and also by the difficulty of the surgical procedure(George & Kavyashree, 2017).

The prescription of antibiotics in the post-operative period for extraction of third molars causes considerable controversy among professionals in the field, which favored the development of this study. Many believe that the contamination rate is high, using the medicine preventively, but it is observed in the literature that the use of postoperative antibiotics does not significantly change the incidence of infections in the removal of third molars (Reiland et al., 2017). Corroborating with our study, where the postoperative complications presented were present in both groups.

However, there are reports in the literature that show the opposite (Yoshida et al., 2020), reports a significant reduction in the rate of infection at the surgical site after the removal of third molars with the use of antibiotic therapy. The author also notes that the infection rate was even higher in patients who received 3rd generation cephalosporin administered orally when compared to patients who received penicillin. In our study, such complications are unrelated to the use of antibiotic therapy in the postoperative period.

Routine administration of antibiotics to healthy patients without risk factors is not justified (Izuzquiza et al., 2017), since the prevalence of postoperative infection is minimal and there is no significant benefit in the prescription of amoxicillin in the post -operative to prevent infections after extraction of third molars (Menon et al., 2019). This factor, observed in this study, when the antibiotic did not favor the improvement of the factors inherent to the surgical procedure.

In the present study we standardized the technique, the surgical team and selected patients with bilateral similarity, thus reducing differences due to individual variations and enabling a reliable comparison of the parameters evaluated, as well as Colombini et al., 2006; Karm et al., 2017 and McCarthy et al., 2018 studies.

Once the parameters were evaluated, it was possible to observe that the values analyzed for the formation of edema, using anatomical points for measurement and with analyzes in the test and control groups, did not reproduce significant changes in the measurements performed. As well as the data obtained in the face of trismus, in both test and control groups, they presented compatible and similar mouth opening measures. The analysis of the pain questionnaire also did not reveal any statistically significant difference between the groups observed, so the use of antibiotic therapy did not influence the parameters analyzed, as can be seen in the study by Arora et al., 2014, where there was no statistically significant difference in the incidence of postoperative complications as well as the presence of edema, pain and a more pronounced picture of trismus between the groups analyzed in the study, with one group undergoing antibiotic therapy and another group undergoing the use of placebo.

Analyzes were performed for each of the moments, evaluating them among themselves, and there were also no statistically significant differences in the postoperative period of removal of the third molars in both groups analyzed.

Despite the development of two infectious conditions in patients who participated in the clinical trial, they belonged to different groups, so the presence of the infectious condition cannot be associated with the absence of the use of antibiotic therapy in the postoperative period. Such patients were removed from the sample group so as not to influence the analyzed values of edema, trismus and pain complaints.

The use of antibiotics may involve some systemic adverse effects on patients and their use is not justified by the literature. It must be considered that the third molar is often extracted for orthodontic reasons and it does not present inflammation and this factor can strongly influence the need for antibiotic therapy (Cervino et al., 2019).

Furthermore, the scientific literature reports that patients have been exposed to higher doses of amoxicillin than necessary and with antibiotic surplus exceeding the minimum inhibitory concentration necessary to combat pathogens that cause

oral infection, leading to a selective enrichment of mutant pathogens and contributing to changes in the susceptibility of bacteria to the antibiotic (Aravena et al., 2019).

Postoperative antibiotic therapy is indicated only in cases of immunosuppression (for example, decompensated diabetes, lupus, etc.), infection in the surgical site due to poor sterilization of the instruments, or low adherence to postoperative care by the patient (Milani et al., 2015).

5. Conclusion

It was not possible to state that the use of antibiotic therapy in the postoperative period of extraction of third molars, may benefit the reduction of edema, trismus and pain.

Regarding the controversies about the use of antibiotics in third molar extraction, this study showed that its benefit is still questionable. Therefore, further studies are needed that address these frequent doubts, in order to reduce the indiscriminate use of antibiotics by professionals and patients.

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