Cost-effectiveness of preemptive pharmacological management of undesired effects in third molar extraction

Custo-efetividade do manejo farmacológico preemptivo de efeitos indesejados na exodontia de terceiros molares

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ABSTRACT

BACKGROUND AND OBJECTIVES: The extraction of third molars can lead to undesired effects such as pain, trismus, and edema, necessitating preemptive therapy to alleviate these effects. For this purpose, an economic evaluation was conducted to analyze the cost-effectiveness of preemptive drugs used in the extraction of third molars.

METHODS: Costs were obtained from a market survey. Effectiveness measures were limitation of interincisal distance and postoperative pain, obtained from randomized clinical trials in the literature. For both models, a Monte Carlo simulation generated a hypothetical cohort of a thousand individuals, considering a 5% variation in estimates. The evaluated therapies were dexamethasone 8 mg (DX8); methylprednisolone 40 mg (MP); diclofenac 50 mg associated with tramadol 50 mg (DCTR); and dexamethasone 4mg associated with tramadol 50 mg (DXTR).

RESULTS: MP and DCTR therapies were dominated in all scenarios. For the reduction of postoperative pain, DXTR treatment showed the best cost-benefit, with a net monetary benefit (NMB) gain of 31.10% compared to the lowest-cost treatment (DX, R$ 1.76). Considering the reduction in limitation of interincisal distance, DXTR medication presented higher cost-benefit compared to DX8 (NMB gain = 18.25%), being a preferred option alongside DX8**.**

CONCLUSION: In the extraction of third molars, preemptive administration of dexamethasone 4mg associated with tramadol 50mg is the preferred cost-effective option to reduce postoperative pain and limitation of interincisal distance after 48 hours.

Keywords: Cost-effectiveness analysis, Patient comfort, Surgery oral.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A exodontia de terceiros molares pode acarretar efeitos indesejados, como dor, trismo e edema, sendo necessário ofertar uma terapia preemptiva para amenizá-los. Para tal, realizou-se uma avaliação econômica para analisar o custo-efetividade de fármacos preemptivos utilizados na exodontia de terceiros molares.

MÉTODOS: Os custos foram obtidos a partir de uma pesquisa de mercado. As medidas de efetividade foram: limitação da distância interincisal e dor pós-operatória, sendo obtidas em ensaios clínicos randomizados da literatura. Para os dois modelos, uma simulação de Monte Carlo gerou uma coorte hipotética de mil indivíduos, considerando uma variação de 5% das estimativas. As terapias avaliadas foram: dexametasona 8 mg (DX8); metilprednisolona 40 mg (MP); diclofenaco 50 mg associado a tramadol 50 mg (DCTR); e dexametasona 4 mg associada a tramadol 50 mg (DXTR).

RESULTADOS: As terapias com MP e DCTR foram dominadas em todos os cenários. Para redução da dor pós-operatória, o tratamento com DXTR apresentou o melhor custo-benefício, com ganho de benefício monetário líquido (NMB) de 31,10% comparado ao tratamento de menor custo (DX, R$ 1,76). Considerando a redução da limitação da distância interincisal, o

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HIGHLIGHTS

- This study points to a new vision in pharmacological practices in third molar exodontia, but also reinforces the economic importance of choosing the right strategies. The work offers valuable insights into optimizing costs on dental procedures, contributing to efficient management of oral health resources.
- By comparing different preemptive drugs, the study not only quantifies costs, but also promotes innovation in treatment. This promotes a paradigm shift by encouraging the adoption of more efficient and personalized pharmacological strategies.
- In addition to the economic aspects, the study focuses on improving post-surgical quality of life for patients undergoing third molar extraction. The analysis is not limited to monetary costs, but highlights the impact of different treatments in the post-surgical period.

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fármaco DXTR apresentou maior custo-benefício em relação à DX8 (ganho de NMB = 18,25%), sendo uma opção de escolha junto a DX8.
CONCLUSÃO: Na exodontia de terceiros molares, a administração preemptiva de dexametasona 4 mg associada com tramadol 50 mg é a opção de escolha, do ponto de vista de custo-efetividade, para reduzir a dor pós-operatória e limitação da distância interincisal após 48 horas.
Descritores: Análise de custo-efetividade, Cirurgia bucal, Conforto do paciente.

INTRODUCTION

The third molar extraction procedure is a common practice in dental care and is indicated for a variety of clinical reasons, including extensive carious lesions, recurrent pericoronaritis, malocclusion, presence of cysts or tumors, problems related to eruption and a higher risk of periodontal disease or carious lesions in adjacent teeth[1-3].
However, this surgical procedure can have undesirable effects, such as pain, trismus (limited interincisal distance) and edema[2,3]. The location at the end of the alveolar ridge, the proximity to important chewing muscles, the presence of significant nerve branches and blood vessels all contribute to these body biological responses[4]. Lesions to the buccal, lingual and inferior alveolar nerves are possible complications[3,5].
The challenging positioning of third molars makes surgical maneuvers difficult, especially due to the varying location and shape of the roots, often requiring osteotomy, which can result in a more intense inflammatory response[6-8]. Factors such as professional experience, surgical time and techniques used can also influence the inflammatory reaction, due to more intense tissue damage[9].
Currently, steroidal anti-inflammatory drugs (SAIDs), such as dexamethasone and methylprednisolone, have shown greater efficacy in controlling post-operative symptoms compared to older molecules[9,10]. Among the mechanisms of action of SAIDs are inhibition of the enzyme phospholipase A2 and control of diapedesis, reducing inflammatory pain and edema[10]. Their single-dose preemptive use has shown no adverse effects[9].
Non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac, are also commonly indicated, acting by inhibiting cyclooxygenase (COX) to provide an anti-inflammatory and analgesic effect[11]. Centrally acting opioids, such as tramadol, act directly on the nervous system to control pain. However, adverse effects such as nausea and dizziness can be observed[12].
Despite these therapeutic options, unwanted post-operative effects still occur, impacting on the patient's quality of life in the first few days after surgery[13,14]. Preemptive administration of SAIDs has been shown to be an effective strategy for reducing these effects, surpassing post-operative approaches[2,15].
Considering the need to improve clinical results and minimize unwanted effects, it is pertinent to analyze the cost-effectiveness of preemptive drugs in third molar extraction. The present study's objective was to carry out an economic analysis to evaluate the cost-effectiveness of these preemptive drugs, with a view to improving pain control and reducing the limitation of the interincisal distance after surgery.

METHODS

A complete economic cost-effectiveness type evaluation was carried out, based on mathematical modeling and outlined according to the Economic Evaluation Guidelines of the Brazilian Network for Health Technology Assessment (REBRATS)[16]. The focus of the analysis was to determine the best preemptive drug to reduce unwanted effects in third molar extractions. The variability of the model was addressed using a Monte Carlo microsimulation.
The study adopted a private perspective, considering the prices of active pharmacological ingredients available to the public in pharmacies and online. The study population consisted of a hypothetical cohort of 1000 adult patients, reflecting the average biannual attendance of patients with an indication for lower third molar extraction in a private clinic. Extractions of other dental elements were not considered in the present study.
Given that the perspective was that of the dental surgeon purchasing the substances, the prices of the drug doses were included for each patient. If the perspective adopted had been for the patient to purchase the drugs, the analysis parameters would have been adjusted. In this case, the costs would consider the purchase prices of the boxes of drugs per patient, not just the single dose of the therapeutic regimens evaluated, resulting in a higher final cost per patient.

The following interventions were compared:

Methylprednisolone (MP)
1. Pharmacological class: SAID
2. Concentration: 40 mg/mL
3. Route of administration: Injectable
4. Quantity administered: 1 mL

Diclofenac + Tramadol (DCTR)
1. Pharmacological class: diclofenac: NSAID + tramadol: Opioid
2. Concentration: diclofenac 50 mg and tramadol 50 mg
3. Route of administration: Oral
4. Quantity Administered: 1 diclofenac tablet + 1 tramadol capsule

Dexamethasone + Tramadol (DXTR)
1. Pharmacological class: dexamethasone: SAID + tramadol: opioid
2. Concentration: dexamethasone 4mg and tramadol 50mg
3. Route of administration: Oral
4. Quantity administered: 1 dexamethasone tablet + 1 tramadol capsule

Dexamethasone (DX8)
1. Pharmacological class: SAID
2. Concentration: 8 mg
3. Route of administration: Oral
4. Quantity administered: 2 dexamethasone 4mg tablets.

TIME HORIZON AND DISCOUNT RATE

The time horizon adopted was 48 hours after the surgical procedure. Given the shortness of this period, cost and effectiveness discount rates were not applied, in accordance with the guidelines of the REBRATS Methodological Guidelines[16].

MODEL STRUCTURE

Two decision trees were developed for this study (Figure 1), representing the interventions and possible outcomes to cover the economic situations related to the choice of drugs and their clinical consequences. The decision trees included the outcomes of whether or not to reduce postoperative pain and whether or not to reduce interincisal distance limitation. The model was analyzed using a Monte Carlo microsimulation.

MODEL INPUT PARAMETERS

Cost measures

The costs were expressed in Brazilian *Reais*, considering the buying perspective of the dental surgeon. A market survey was carried out, obtaining three price sources for each pharmacological active ingredient chosen. The data was tabulated using the Microsoft Excel 2019 software, calculating the mean and standard deviation of the prices of each drug evaluated. The cost values are shown in table 1.

MEASURES OF EFFECTIVENESS

Effectiveness measures were based on data from relevant clinical studies. These clinical trials were selected because they presented similar parameters, including routes of pharmacological administration, time of administration prior to surgery and methods of assessing clinical outcomes, when compared to other studies. Postoperative pain was assessed using the Visual Analog Scale (VAS), with values ranging from 0 to 100. The metric method was used to measure the limitation of the interincisal distance, i.e. measuring the maximum distance between the incisal margins of the upper and lower incisors in mm. The effectiveness data for pain and interincisal distance limitation are also presented in table 1.

COST-EFFECTIVENESS ANALYSIS

The analyses were carried out using the TreeAge Pro software version 2019 R1.1, coding the models using a Monte Carlo microsimulation, generating dynamic tests and acceptability curves. Gamma-type distributions were obtained for the cost and effectiveness parameters, considering a 5% variation. The cost-effectiveness of the interventions was compared using the net monetary benefit (NMB) and willingness to pay (WTP) parameters. The NMB was calculated using the formula: NMB = (Effectiveness * WTP) - cost, where WTP was represented by the value of the lowest cost pharmacological treatment. The percentage gain in net monetary benefit (%NMB) was calculated by dividing

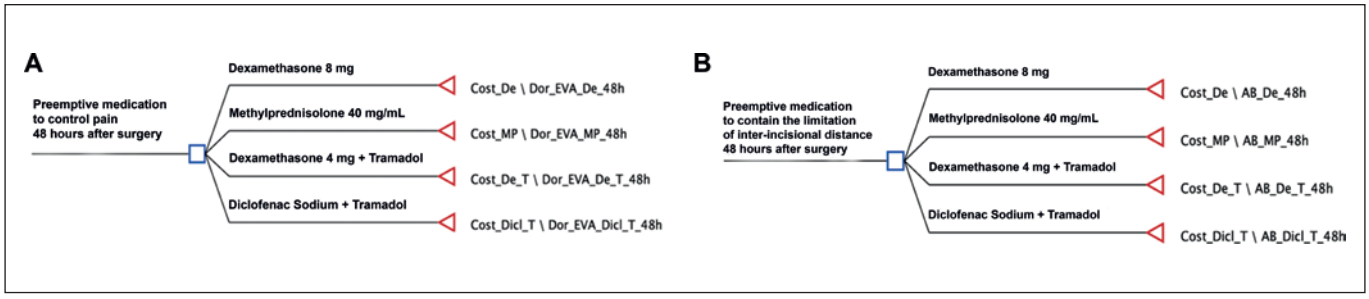

Figure 1. **A.** Decision tree about postoperative pain reduction, 48 hours after the surgical procedure. Blue square = study problem; red triangle = end state. **B.** Decision tree about the reduction in postoperative interincisal distance, 48 hours after the surgical procedure. Blue square = Study problem; Red triangle = Terminal state.

Table 1. Costs of the drugs and pharmacological treatments administered, collected from market research on pharmacy websites, means and standard deviation of clinical effectiveness parameters for reducing postoperative pain (VAS score) and reducing interincisal distance limitation (difference in pre- and postoperative interincisal distance in mm) 48 h after the surgical procedure[17,18]

Drugs	Average price (R$)	Quantity of drugs in the price lists	Cost of each tablet/mL of drug (R$)	Average price of administered treatments	Average pain (SD)	Average interincisal distance limitation (SD)
Dexamethasone 4 mg	8.80	10 tablets	0.88	DX8: 1.76	20 (1)	14.4 (9.82)
Diclofenac 50 mg	11.07	20 tablets	0.55	DCTR: 2.71	18.97 (0.95)	17.3 (4.0)
Tramadol 50 mg	21.57	10 capsules	2.15	DXTR: 3.04	13.57 (0.68)	11.6 (3.1)
Methylprednisolone 40 mg/mL	23.87	2 mL – 40 mg/mL	11.93	MP: 11.93	40 (2)	19.97 (7.88)

SD = standard deviation.

the difference between the NMB value of the alternative technology and the NMB value of the lower-cost technology by the value of the lower-cost technology and multiplying this result by 100. The %NMB helped determine which technology was not dominated in the analysis and therefore presented the best cost-benefit.

RESULTS

In the cost-effectiveness analyses carried out, both for reducing pain after 48 hours (Table 2) and for reducing the interincisal distance after the same period (Table 3), the most cost-effective pharmacological therapy was DXTR, with a Net Monetary Benefit (NMB) gain compared to DX8 of 31.10% for reducing postoperative pain and 18.25% for reducing the postoperative interincisal distance. Next, DX8, despite being the lowest cost and being used as a reference in the analyses, was surpassed in effectiveness by the DXTR drug combination.

Regarding the Net Monetary Benefit (NMB), which is the score that indicates the overall benefit, taking into account clinical efficacy, willingness to pay and costs, there was a quantitative percentage increase in the NMB for pain reduction and limitation of postoperative interincisal distance when opting for the DXTR association over the DX8 pharmacological regimen, as shown in tables 2 and 3.

The Incremental Cost-Effectiveness Ratio (ICER), a proportional measure that expresses the variation in monetary value and effectiveness between the therapies evaluated, without considering willingness to pay, was also calculated.

As a result of the hypothetical cohorts, the distribution of cost and effectiveness data was obtained in terms of probability. These distributions are shown in figure 2, both for pain reduction and for reduction of the interincisal distance, where the most cost-effective therapeutic regimens are at the bottom and right of the figures.

The cost-effectiveness analyses for pain reduction after 48 hours and for interincisal distance reduction after the same period,

Table 2. Cost-effectiveness analysis for postoperative pain reduction, 48 hours after the surgical procedure

Dominance	Strategy	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER	NMB	% NMB gain
Not dominated	DX8	1.75		-19.98			-201.55	0.00
Dominated	DCTR	2.72	0.96	-18.95	1.03	0.94	-192.23	4.62
Not dominated	DXTR	3.04	1.28	-13.58	6.40	0.20	-138.88	31.10
Dominated	MP	11.91	8.88	-39.95	-26.36	-0.34	-411.40	-104.11

Table 3. Cost-effectiveness analysis for the reduction and limitation of the postoperative interincisal distance, 48 hours after the surgical procedure

Dominance	Strategy	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER	NMB	% NMB gain
Not dominated	DX8	1.76		-14.61			-147.83	0.00
Dominated	DCTR	2.71	0.95	-17.35	-2.74	-0.35	-176.21	-19.20
Not dominated	DXTR	3.03	1.27	-11.78	2.83	0.45	-120.84	18.25
Dominated	MP	11.94	8.91	-20.03	-8.25	-1.08	-212.27	-43.60

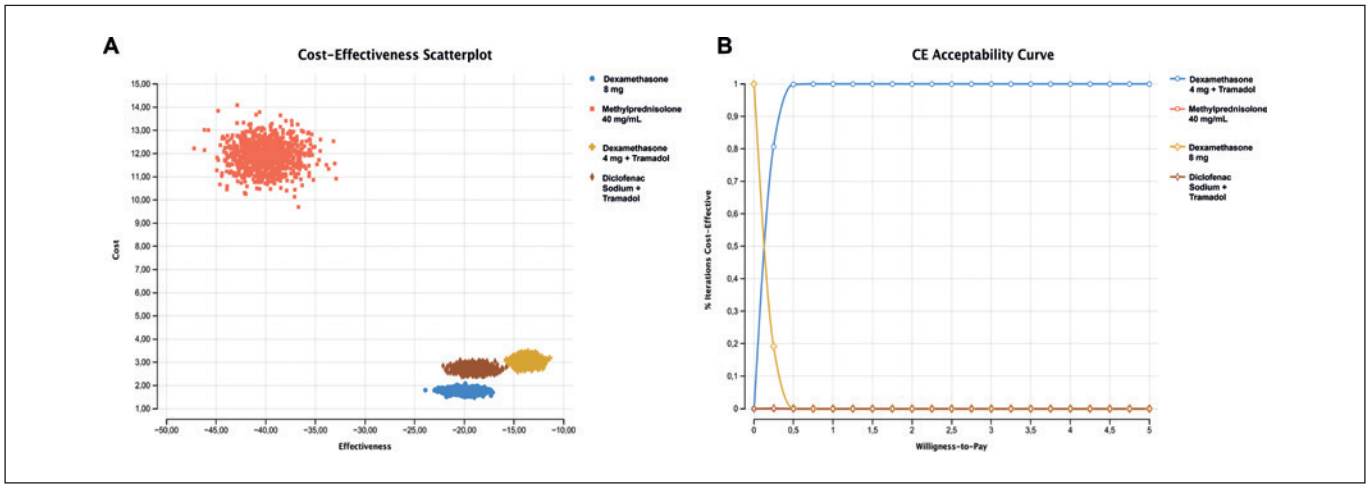

Figure 2. Cost-effectiveness analysis and acceptability curve for reducing post-operative pain 48 hours after surgery. Distribution of costs (in Brazilian Reais) and effectiveness of the drugs under research. The preemptive drug MP is shown in red, DX8 is shown in blue, DCTR is shown in brown, and DXTR is shown in dark beige.

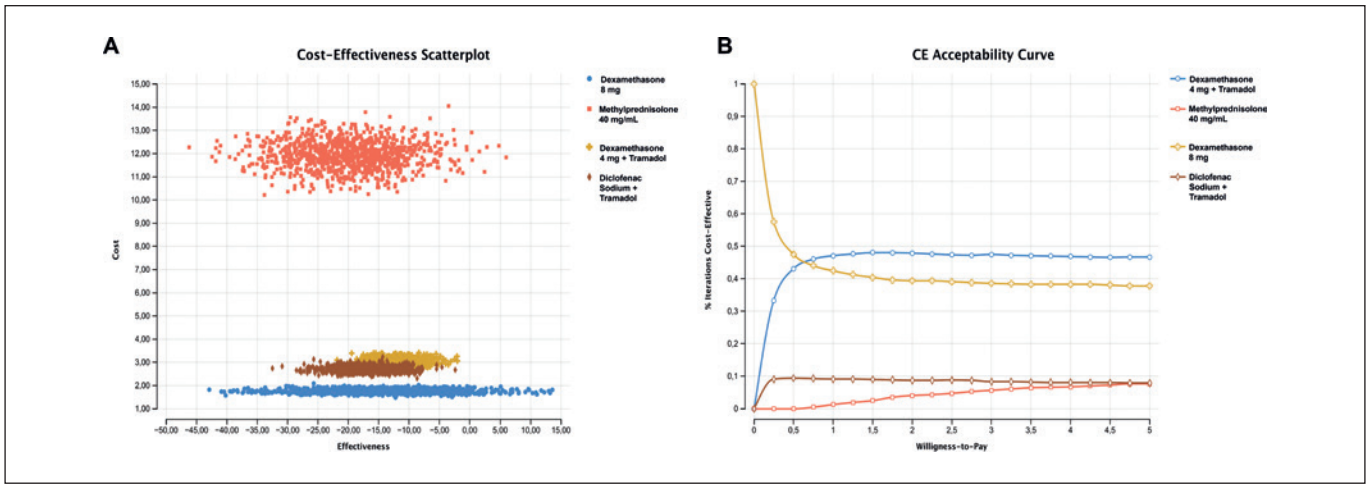

Figure 3. Cost-effectiveness analysis and acceptability curve for decision-making on each of the drugs to be adopted, considering the interincisal distance according to willingness to pay. The most cost-effective technologies occupy the top of the figure according to willingness to pay. The preemptive drug MP is represented in red, DX8 is represented in dark beige, DCTR is represented in brown, and DXTR is represented in blue.

illustrated in figure 3, indicated the dominance of the DXTR and DX8 treatment conducts over MP and DCTR. This suggests that the dominated conducts are less effective at a higher cost. Figure 3 also illustrates the acceptability curve of treatments in relation to willingness to pay, in which acceptability varies according to willingness to pay on the part of the dental surgeon and, consequently, the patient, with the best benefit being obtained when there is greater willingness to pay.

DISCUSSION

Based on the data collected and the cost-effectiveness analyses carried out, it is important to highlight these evaluations in guiding clinical decisions in dentistry. The diversity of pharmacological treatments available requires careful evaluation, taking into account not only clinical efficacy, but also the associated costs.

As shown in the present study, methylprednisolone (MP) therapy is more expensive and has shown reduced clinical efficacy compared to dexamethasone (DX8)[9,10]. Therefore, its use is not recommended. DCTR treatment, on the other hand, despite combining NSAIDs with opioids, has been shown to be less cost-effective due to inferior clinical results.

Moreover, the importance of cost considerations on the part of the professionals responsible for administering the drugs should be noted. The choice of the most appropriate treatment can vary according to the budget available, which highlights the importance of a detailed financial analysis. Another aspect to be considered is the patient's health conditions which may contraindicate the use of certain drugs, as well as possible pharmacological interactions with other drugs in continuous use.

From a long-term perspective, taking into account the economic impact of decisions in a private clinic, the choice between different drugs can have significant implications. The analysis suggests that DXTR, despite having a higher cost compared to DX8, is more cost-effective in terms of NMB.

In the context of a public health unit, where patients receive the drug on prescription from the dental surgeon, the choice of the substance is more closely linked to its clinical efficacy. However, even in this scenario, an economic analysis can help to make more efficient and economical decisions, with potential benefits for public health.

As for the study limitations, it is important to mention the difference between the oral and injectable forms of methylprednisolone, which can influence the results due to variable costs. In addition, the economic analysis is specific to the Brazilian context, using prices in Brazilian *Reais* currency, and does not include the materials needed to administer the drugs.

CONCLUSION

The study's cost-effectiveness analyses suggest preemptive pharmacological therapy with the combination of dexamethasone 4 mg + tramadol 50 mg was the most cost-effective option among those analyzed for reducing postoperative pain and limiting postoperative interincisal distance, both 48 hours after the surgical procedure of third molar extraction. This conclusion provides practical guidance for the choice of drugs in surgical procedures that are frequently performed within dentistry scenarios.

AUTHORS' CONTRIBUTIONS

Leonardo de Freitas Ferreira
Data Collection, Conceptualization, Research, Writing - Preparation of the original
Rênnis Oliveira da Silva
Writing - Review and Editing, Validation, Visualization
Edson Hilan Gomes de Lucena
Validation, Visualization
Yuri Wanderley Cavalcanti
Statistical analysis, Methodology, Writing - Review and Editing, Software, Supervision, Validation

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