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Randomised Clinical Trial

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Effectiveness of nicotine patch for the control of pain, oedema, and trismus following third molar surgery: a randomized clinical trial

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Abstract. The aim of this study was to evaluate the effectiveness of a nicotine patch for the control of pain, oedema, and trismus following lower third molar surgery. A prospective, randomized, triple-blind, split-mouth trial was performed involving 20 patients who underwent two surgical procedures at different times. A patch containing 14 mg nicotine was used in the experimental group, whereas a patch without nicotine (placebo) was used in the control group. The nicotine patch was effective at controlling pain after 4 hours and 8 hours ($P = 0.023$ and $P = 0.005$, respectively). The nicotine patch also had a significant effect on the control of oedema at 24 hours ($P = 0.002$), 48 hours ($P = 0.001$), and 72 hours ($P = 0.005$) following the intervention. Postoperative mouth opening was significantly greater among the patients who received the nicotine patch after 72 hours and 7 days. The number of rescue analgesics required was lower ($P = 0.026$) and the level of satisfaction was significantly higher ($P = 0.008$) when the patch was used, although higher levels of nausea were found in the nicotine group ($P = 0.031$ at 30 minutes, $P = 0.008$ at 4 hours). The nicotine patch was effective at controlling pain, oedema, and trismus following third molar surgery.

Key words: pain; nicotine; third molar.

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Third molar removal is one of the most common procedures performed by maxillofacial surgeons and is often associated with postoperative pain, oedema, and trismus, which are inflammatory signs and symptoms that can have an important impact on quality of life[1–3]. Corticosteroids and non-steroidal anti-inflammatory drugs are the main therapeutic agents used to control inflammatory processes following the surgical removal of impacted teeth. However, these drugs have undesirable side effects, such as gastrointestinal irritation, systemic haemorrhage, renal dysfunction, and an imbalance in cardiovascular homeostasis, especially when used for longer than 48 hours[2,4,5].

In the search for new therapeutic methods for the control of postoperative pain that minimize the effects associated with anti-inflammatory drugs, optimize analgesia, and reduce excessive medication intake, recent clinical research has investigated nicotine. Nicotine is an important therapeutic adjunct for regulating the pain process and controlling the intensity of the acute inflammatory process, acting through the modulation of nociceptive pathways in the central nervous system[6,7]. This agent also has the advantage of offering alternative routes of administration (transcutaneous or nasal route) that do not interfere or come into direct contact with the operated site. Moreover, nicotine is readily bioavailable, does not cause dependence in isolated doses, and can either suppress or significantly minimize the number of analgesics and/or anti-inflammatory drugs used postoperatively[8–10].

Despite evidence of the control of pain and inflammation following soft tissue surgeries on the genitourinary tract, studies measuring the effectiveness of nicotine for the control of pain and the inflammatory process following hard tissue surgery are lacking. A search of the literature revealed no studies that have measured pain, oedema, and trismus following third molar surgery with regard to this pharmacokinetic modality (Supplementary Material, Table S1). Therefore, the aim of this study was to evaluate the analgesic and anti-inflammatory effectiveness of the cutaneous administration of nicotine (14 mg) following mandibular third molar surgery and to assess patient satisfaction.

Methods

A clinical trial was conducted based on the Consolidated Standards of Reporting Trials (CONSORT) statement guidelines, following approval from the Human Research Ethics Committee of the University of Pernambuco (certificate 85547615.5.0000.5207) (Supplementary Material, Figure S1). All participants signed a statement of consent agreeing to participate in the study.

A prospective, randomized, triple-blind clinical trial with a split-mouth design was conducted with a sample of 20 healthy non-smokers, ranging in age from 18 to 33 years, with an indication for the bilateral surgical extraction of mandibular lower third molars. The third molars needed to have symmetrical impaction topography according to the classifications proposed by Winter and by Pell and Gregory. All patients underwent treatment at the Centre for Clinical Research in Maxillofacial Surgery, University of Pernambuco, Brazil. Patients with acute symptoms or pathological lesions associated with third molars or surrounding tissues, as well as those allergic to any drugs, were excluded from the study. All procedures were performed under local anaesthesia (mepivacaine 2% and epinephrine 1:100,000; DFL, Rio de Janeiro, RJ, Brazil) and an equivalent dose of anaesthetic was used for both sides. Each surgical procedure was timed and a 21-day interval was observed between interventions.

The study was conducted by researchers who were given specific tasks and who had undergone training and calibration exercises in a pilot study. For the calibration exercise, 10 individuals were evaluated at regular 15-day intervals by each researcher in their respective assignments in the study, and intra-examiner kappa coefficients higher than 0.89 were obtained.

A surgeon and assistant who were unaware of the content of the patches used in each intervention performed the surgical procedures. Another researcher who was also unaware of the patch content was in charge of the facial measurements and baseline monitoring of vital signs (blood pressure, oxygen saturation, and heart rate). A third researcher was responsible for performing the computerized randomization (random allocation) to determine the side to be operated first and the type of patch to be used for each procedure, thereby ensuring allocation concealment.

The randomization process was performed in two steps: (1) the definition of the intervention to be performed first (nicotine or control patch), and (2) the definition of the side to be operated first. The two methods were balanced to ensure the same number of interventions with each type of adhesive on the same side (Table 1). Sequentially numbered sealed opaque envelopes containing the randomized patch to be applied were used. The patch was placed in the region of the trapezoid muscle by a fourth researcher who did not know its content. Data were compiled and annotated in a chart for subsequent comparisons at the end of the study.

The sample was distributed into a control group (skin patch without the active ingredient) and test group (skin patch containing nicotine as the active ingredient (NiQuitin 14 mg; GSK)) (Fig. 1). The placebo patches were made of the same material and were of the same colour, texture, consistency, and size as the nicotine patches. One hour prior to the procedure, the patch was placed in the region of the trapezoid muscle ipsilateral to the procedure side. The patch was coated with opaque Micropore, which does not alter drug bioavailability and ensured both blinding and protection of the patch during the period of use. All patches were kept in place for 24 hours.

The patients ingested two dexamethasone tablets (8 mg) 1 hour after the procedure and were prescribed rescue analgesics for the postoperative period (dipyrone 500 mg (Lafepe – Laboratório Farmacêutico de Pernambuco), one tablet orally every 4 hours, as needed). For patients allergic to dipyrone, the rescue analgesic was paracetamol (750 mg every 6 hours, as needed). The number of analgesics taken was recorded on a specific chart.

Variables analyzed

Pain was measured cross-sectionally on six occasions: 30 min (baseline), 2 h (after the effect of the anaesthesia had worn off), 4 h, 8 h (time of peak pain), 12 h, 24 h (removal of adhesive), and 72 h (peak inflammatory effect and period of pharmacological clearance of nicotine), and recorded by the patients using a visual analogue scale (VAS) ranging from 0 (absence of pain) to 10 (worst pain imaginable). Oedema and trismus were also evaluated at 24, 48, and 72 hours and at 7 days after the surgery.

For the evaluation of patient satisfaction, the volunteers classified their experience regarding the therapy on a five-point scale: 0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent.

Oedema was evaluated using a metric tape. Three measurements were performed using five reference points: (A) corner of the eye/angle of the mandible; (B) tragus/corner of the mouth; (C) tragus/pogonion (Fig. 2). Measurements were performed

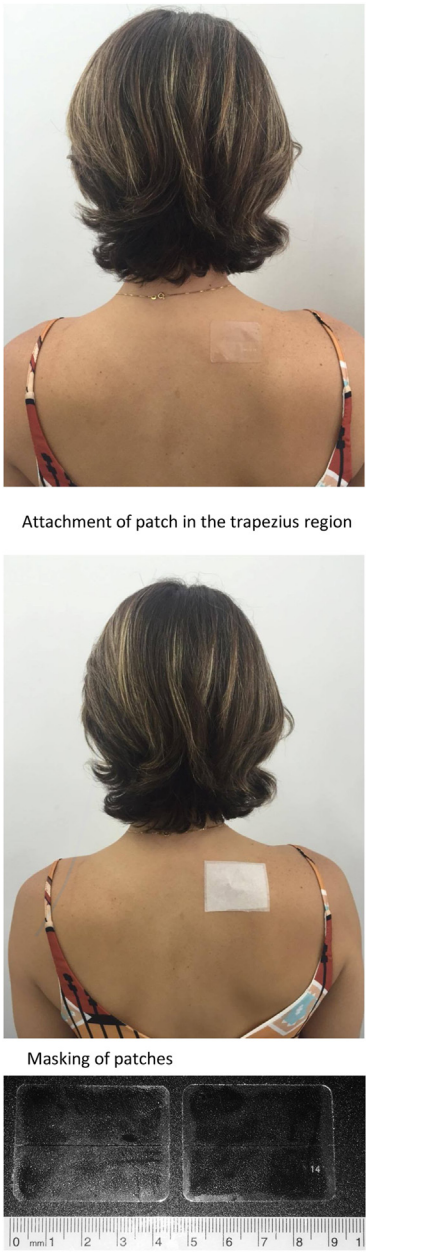

Fig. 1. Patches used in study.

during the preoperative period (baseline), as well as at 24, 48, 72 h, and 7 days after the surgical procedure. The evolution of oedema was obtained by subtracting the total value at each postoperative evaluation (mean of three measurements) from the mean at baseline (preoperative period).

Surgery time

The surgical procedure was timed beginning with the placement of the patch, and included the time to perform local anaesthesia, incision, excision, suturing, and a 2-minute period after suturing for the determination of blood pressure, heart rate, and oxygen saturation.

During the procedure, systolic blood pressure, diastolic blood pressure, mean blood pressure, heart rate, and oxygen saturation were recorded on a specific chart. Blood pressure, heart rate, and oxygen saturation were determined during the initial clinical examination (baseline or T0), prior to surgery (pre-anaesthesia or T1), 5 minutes after the administration of anaesthetic (post-anaesthesia or T2), and at the end of the procedure (post-surgery or T3).

Statistical analysis

Absolute and relative frequencies were calculated for the categorical variables. Numerical variables were expressed as the mean and standard deviation (SD) and the median, and analyzed inferentially using comparative statistical tests. The Shapiro–Wilk test was used to determine the normality of the data. McNemar's test was used for the inter-group comparisons of the categorical variables and either the paired Student *t*-test (data with a normal distribution) or paired Wilcoxon test (data with a non-normal distribution) was used for the inter-group comparisons of the numerical data. The level of significance for the decisions on the statistical tests was set at 5%, with the hypothesis of equality considered rejected when $P < 0.05$. The data were entered into an Excel spreadsheet, and IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analyses.

Results

The sample consisted of 20 patients aged 18 to 33 years (mean 23.45 years), 70% of whom were female. The sample was selected based on spontaneous demand, considering different types of lower third molar positions to enable the evaluation of the effectiveness of the patch with different tooth position topographies.

Sixty-five percent of the sample consisted of impacted teeth, 35% were partially impacted, and 5% were fully erupted teeth. The surgical intervention data are shown in Table 2.

Regarding the surgery time, this was 1.30 minutes longer in the group that used the placebo patch; however, this difference did not achieve statistical significance ($P = 0.517$). Moreover, no significant difference was found in the number of anaesthesia tubes used in the procedures ($P = 0.312$). A statistically significant difference was found in the number of analgesic tablets taken in the postoperative period, with greater consumption in the placebo group than in the nicotine patch group (mean 4.35 and 2.35, respectively) ($P = 0.026$) (Table 3).

Patient satisfaction regarding quality and postoperative comfort was measured in both groups taking into account the overall statistical analysis of the scores. A larger percentage difference occurred in the 'excellent' category when the nicotine group was compared to the placebo group (70% vs. 35%, respectively). In the 'good' and 'very good' categories, a 10% difference was found between the two groups.

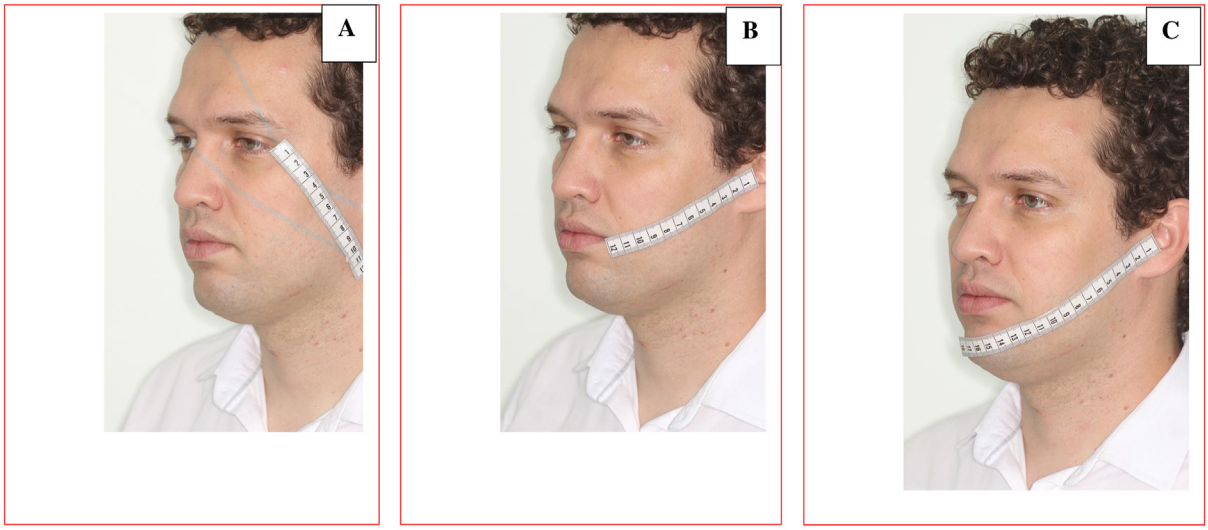

Fig. 2. Reference points and oedema measurement times.

Table 1. Randomization of the order of the procedure and side to be operated.

Patient	Patch allocated to:		Patch allocated to:	
	Intervention 1	Side	Intervention 2	Side
1	Placebo	Right	Nicotine	Left
2	Nicotine	Left	Placebo	Right
3	Nicotine	Right	Placebo	Left
4	Nicotine	Right	Placebo	Left
5	Placebo	Right	Nicotine	Left
6	Nicotine	Left	Placebo	Right
7	Placebo	Right	Nicotine	Left
8	Placebo	Left	Nicotine	Right
9	Placebo	Left	Nicotine	Right
10	Placebo	Left	Nicotine	Right
11	Nicotine	Right	Placebo	Left
12	Placebo	Right	Nicotine	Left
13	Placebo	Right	Nicotine	Left
14	Nicotine	Left	Placebo	Right
15	Placebo	Left	Nicotine	Right
16	Nicotine	Left	Placebo	Right
17	Placebo	Left	Nicotine	Right
18	Nicotine	Left	Placebo	Right
19	Nicotine	Right	Placebo	Left
20	Nicotine	Right	Placebo	Left

The results of the self-evaluations for the 'poor' and 'fair' categories were 15% for the patients in the placebo group and null for the patients in the nicotine group. Mean and median scores were correspondingly higher in the nicotine group, with a statistically significant difference between the groups ($P = 0.008$) (Table 4).

Oedema was greater at the different evaluation times when the placebo patch was used. The difference ranged from 0.07 cm at 7 days (12.09 cm vs. 12.02 cm) to 0.22 cm at 48 hours (12.35 cm vs. 12.13 cm), with significant differences between the groups at 24, 48, and 72 hours. In the nicotine group, mean oedema at the 7-day evaluation was the same as that found in the preoperative period, and the value ranged from 12.12 cm to 12.18 cm at the other evaluation times. On multiple comparison testing, mean oedema at the 24 -h evaluation differed significantly from the values found in the preoperative period and at the 7-day evaluation. In the placebo group, the mean preoperative value was 12.02 cm, which increased to 12.38 cm at 24 hours and reduced to 12.09 cm at 7 days. A significant difference was found between the day 7 measurement and the other evaluation times. Differences in oedema measurements compared to baseline were smaller in the nicotine group (0.00 to 0.16 cm) compared to the placebo group (0.08 to 0.37 cm) (Table 5). Significant inter-group differences were found at all evaluation times, except the baseline and 7-day evaluations.

Mean mouth opening was greater in the nicotine patch group than in the placebo

Table 2. Clinical and radiographic data.

Variable	Type of patch				*P*-value[a]
	Nicotine		Placebo		
	n	%	*n*	%	
Total	20	100.0	20	100.0	
Third molar impaction classification					
Horizontal – Winter	5	25.0	5	25.0	1.000
AI – Pell and Gregory	1	5.0	1	5.0	
BI	1	5.0	1	5.0	
BII	6	30.0	6	30.0	
CI	3	15.0	3	15.0	
CII	4	20.0	4	20.0	
Type of incision					
Envelope	6	30.0	6	30.0	1.000
Triangular	14	70.0	14	70.0	
Need for tooth sectioning					
Yes	17	85.0	17	85.0	1.000
No	3	15.0	3	15.0	
Type of tooth sectioning					
No need	3	15.0	3	15.0	1.000
Long axis	10	50.0	10	50.0	
Partial of crown	1	5.0	1	5.0	
Total of crown	6	30.0	6	30.0	
Need for osteotomy					
Yes	17	85.0	17	85.0	1.000
No	3	15.0	3	15.0	
Type of osteotomy					
No need	3	15.0	3	15.0	1.000
Distal	1	5.0	1	5.0	
Vestibular and distal	8	40.0	8	40.0	
Occlusal + vestibular	7	35.0	7	35.0	
Occlusal + vestibular + distal	1	5.0	1	5.0	
Use of antibiotics					
Yes	4	20.0	4	20.0	1.000
No	16	80.0	16	80.0	

[a] Using McNemar's test.

Table 3. Surgery time, number of anaesthesia tubes, and number of rescue analgesics per group.

Variable	Type of patch		*P*-value
	Nicotine Mean ± SD (median)	Placebo Mean ± SD (median)	
Surgery time (min)	20.35 ± 8.42 (18.50)	21.65 ± 7.82 (23.00)	0.517[a]
Number of tubes used	2.08 ± 0.24 (2.00)	2.18 ± 0.34 (2.00)	0.312[b]
Number of analgesics used	2.35 ± 2.46 (1.50)	4.35 ± 4.18 (4.00)	0.026[b,*]

SD, standard deviation.
[a] Paired Student *t*-test between types of patch.
[b] Paired Wilcoxon test between types of patch. *significant difference at 5.0% level.

group, with the largest differences found at 48 hours (33.95 mm vs. 30.50 mm), 72 hours (37.20 mm vs. 32.10 mm), and 7 days (41.85 mm vs. 37.00 mm); these differences were statistically significant at 72 hours and 7 days ($P = 0.001$). Mean mouth opening was greatest at the preoperative evaluation (45.40 mm in the nicotine patch group and 45.65 mm in the placebo group). At the subsequent evaluations, mean mouth opening increased from 31.65 mm at 24 hours to 41.85 mm at 7 days in the nicotine group, with significant differences between baseline and day 7 ($P = 0.001$) as well as between 24 hours and 72 hours ($P = 0.006$). In the placebo group, mean mouth opening increased from 30.05 mm at 24 h to 37.00 mm at 7 days. The differences in comparison to baseline reduced over time, but were comparatively higher in the placebo group, with significant differences at the last two evaluations (Table 5).

Regarding pain, means VAS scores were higher when the placebo patch was used at all evaluation times. These differences were significant and the paired comparisons revealed inferential differences, with lower pain intensity in the nicotine group at 4 hours ($P = 0.023$) and 8 hours ($P = 0.005$) (Table 6). Mean VAS scores for the assessment of nausea were higher in the nicotine patch group from the 30-minute to the 12 -h evaluation, with significant inter-group differences found at 30 minutes (mean 1.75 vs. 0.15) and 4 hours (mean 1.15 vs. 0.10). Significant results were also found between groups for the differences at 24 h and 72 h in comparison to the 30-minute evaluation (Table 7).

No significant differences were found between groups or evaluation times with regard to blood pressure, heart rate, or oxygen saturation (Tables 8 and 9).

Discussion

Davis et al. first described the analgesic properties of nicotine in 1932 in a feline visceral pain model[11]. More recently, the anti-nociceptive mechanism induced by nicotine has been related to the modulation of the pain process in the central nervous system through the selective agonist effect on $\alpha 4\beta 2$ nicotinic recep-

Table 4. Degree of patient satisfaction according to the type of patch used.

Satisfaction	Type of patch				*P*-value
	Nicotine		Placebo		
	n	%	*n*	%	
Poor	-	-	1	5.0	
Fair	-	-	2	10.0	
Good	1	5.0	3	15.0	
Very good	5	25.0	7	35.0	
Excellent	14	70.0	7	35.0	
Total	20	100.0	20	100.0	
Mean ± SD of scores	3.65 ± 0.59		2.85 ± 1.18		
Median of scores	4.00		3.00		0.008[a,*]
Interquartile range	1.00		2.00		

SD, standard deviation.
[a] Paired Wilcoxon test.*significant difference at 5.0% level.

tors located in the brain and spinal cord[12,13].

The pre-synaptic activation of these neuronal receptors induces the release of neurotransmitters involved in the control of pain and the modulation of the pain process, such as acetylcholine, dopamine, gamma-aminobutyric acid, and noradrenaline[14], besides minimizing the production of tumour necrosis factor and oedema after surgical procedures on soft tissues[7,15–20].

Flood and Daniel[9] demonstrated the effectiveness in blocking the pain pathways of 3 mg of nicotine applied via nasal spray in the immediate postoperative period after uterine surgery performed under general anaesthesia. Nicotine administration led to the significant control of pain in both the first hour ($P < 0.001$) and on the first day ($P < 0.01$) after the procedure and reduced the need for morphine in the postoperative period by half compared to the placebo group ($P < 0.05$). Habib et al.[8] also demonstrated the effectiveness of a nicotine patch for the control of pain in patients submitted to radical retropubic prostatectomy under general anaesthesia, reporting that the nicotine group required significantly less morphine in 24 hours than the placebo group ($P = 0.002$).

Despite the favourable results described in the literature on the use of nicotine in surgical procedures under general anaesthesia, the present study is novel in investigating the use of nicotine in procedures performed under local anaesthesia. This study makes an important counterpoint with regard to possible biases in the results obtained from individuals submitted to general anaesthesia, as some drugs compete for nicotinic receptors and may alter the expected clinical outcomes for the control of pain with the use of nicotine, especially when the general anaesthetic is isoflurane[21]. This possible interaction was reported by Martins-Filho et al.[22], who used a nicotine patch with 14 mg for the treatment of pain following laparoscopic cholecystectomy in comparison to a placebo patch and found that the highest pain scores 6 hours after the procedure were in the nicotine group. The authors attributed this undesirable effect to the interaction with the drugs used for general anaesthesia. The intervention group had significantly lower pain levels compared to the placebo group after 24 hours, suggesting that the time required for clearance of the drugs used for general anaesthesia during the operation may mask the true therapeutic effectiveness of nicotine.

The study of pain in the first hour and 24 hours after a procedure is a methodological trend in studies involving soft tissue surgery that compare pain experiences in different individuals submitted to the

Table 5. Oedema and trismus findings according to the evaluation time point and type of patch. MMO, maximum mouth opening; SD, standard deviation.

Variable/evaluation time	Type of patch		*P*-value
	Nicotine Mean ± SD (median)	Placebo Mean ± SD (median)	
Oedema (centimetres)			
Preoperative	12.02 ± 0.58 (12.08)	12.02 ± 0.55 (12.00)	1.000[a]
24 h	12.18 ± 0.57 (12.33)	12.38 ± 0.55 (12.25)	0.002[a,*]
48 h	12.13 ± 0.59 (12.25)	12.35 ± 0.53 (12.33)	0.001[a,*]
72 h	12.12 ± 0.54 (12.25)	12.30 ± 0.54 (12.33)	0.005[a,*]
7 days	12.02 ± 0.58 (12.08)	12.09 ± 0.58 (12.00)	0.078[a]
Mean of absolute difference			
24 h–preoperative	0.16 ± 0.18 (0.17)	0.37 ± 0.28 (0.33)	0.001[a],*
48 h – preoperative	0.11 ± 0.18 (0.00)	0.33 ± 0.28 (0.33)	<0.001[a,*]
72 h – preoperative	0.10 ± 0.17 (0.00)	0.28 ± 0.29 (0.00)	0.002*
7 days – preoperative	0.00 ± 0.00 (0.00)	0.08 ± 0.11 (0.00)	0.016[a,*]
Trismus (MMO) (millimetres)			
Preoperative	45.40 ± 5.40 (45.50)	45.65 ± 4.80 (46.00)	0.750[a]
24 h	31.65 ± 10.62 (29.00)	30.05 ± 9.75 (30.00)	0.426[b]
48 h	33.95 ± 9.99 (34.50)	30.50 ± 9.70 (29.50)	0.106[b]
72 h	37.20 ± 7.72 (37.00)	32.10 ± 9.60 (33.00)	0.006[b,*]
7 days	41.85 ± 5.88 (42.00)	37.00 ± 7.27 (37.50)	0.001[b,*]
Mean of absolute difference			
24 h – preoperative	−13.75 ± 10.02 (−14.50)	−15.60 ± 9.37 (−13.00)	0.355[b]
48 h – preoperative	−11.45 ± 9.20 (−10.00)	−15.15 ± 9.49 (−17.50)	0.073[b]
72 h – preoperative	−8.20 ± 6.37 (−7.50)	−13.55 ± 9.15 (−16.00)	0.002[a,*]
7 days – preoperative	−3.55 ± 3.76 (−2.50)	−8.65 ± 6.17 (−8.00)	<0.001[a,*]

[a] Paired Wilcoxon test; *significant difference at 5.0% level.
[b] Paired Student *t*-test; *significant difference at 5.0% level.

Table 6. Visual analogue scale (VAS) for pain at each evaluation time and according to the type of patch.

Variable/evaluation time	Type of patch		*P*-value
	Nicotine Mean ± SD (median)	Placebo Mean ± SD (median)	
VAS – pain			
30 min	0.60 ± 1.05 (0.00)	1.20 ± 2.26 (0.00)	0.213[a]
4 h	2.40 ± 2.19 (1.50)	3.70 ± 2.32 (4.00)	0.023[b,*]
8 h	1.75 ± 2.17 (1.00)	4.00 ± 3.09 (4.50)	0.005[b,*]
12 h	1.75 ± 2.22 (1.00)	2.50 ± 2.50 (2.00)	0.127[b]
24 h	1.35 ± 1.79 (0.50)	1.65 ± 2.35 (0.50)	0.544[a]
72 h	0.85 ± 1.23 (0.00)	1.40 ± 2.21 (1.00)	0.205[a]
Mean of absolute difference			
4 h–30 min	1.80 ± 2.31 (1.00)	2.50 ± 3.00 (3.00)	0.267[b]
8 h–30 min	1.15 ± 2.18 (0.00)	2.80 ± 3.94 (3.00)	0.076[b]
12 h–30 min	1.15 ± 1.81 (0.00)	1.30 ± 3.26 (0.50)	0.815[b]
24 h–30 min	0.75 ± 1.97 (0.00)	0.45 ± 2.95 (0.00)	0.629[b]
72 h–30 min	0.25 ± 1.21 (0.00)	0.20 ± 2.86 (0.00)	0.861[a]

SD, standard deviation.
[a] Paired Wilcoxon test.
[b] Paired Student *t*-test.*significant difference at 5.0% level.

Table 7. Visual analogue scale (VAS) for nausea at each evaluation time and according to the type of patch.

Variable/evaluation time	Type of patch		*P*-value[a]
	Nicotine Mean ± SD (median)	Placebo Mean ± SD (median)	
VAS – nausea			
30 min	1.75 ± 2.75 (0.00)	0.15 ± 0.67 (0.00)	0.031*
4 h	1.15 ± 1.81 (0.00)	0.10 ± 0.31 (0.00)	0.008*
8 h	0.40 ± 0.99 (0.00)	0.00 ± 0.00 (0.00)	0.125
12 h	0.25 ± 0.91 (0.00)	0.00 ± 0.00 (0.00)	0.500
24 h	0.05 ± 0.22 (0.00)	0.10 ± 0.45 (0.00)	1.000
72 h	0.00 ± 0.00 (0.00)	0.00 ± 0.00 (0.00)	1.000
Mean of absolute difference			
4 h– min	−0.60 ± 2.09 (0.00)	−0.05 ± 0.76 (0.00)	0.308
8 h–30 min	−1.35 ± 2.46 (0.00)	−0.15 ± 0.67 (0.00)	0.063
12 h–30 min	−1.50 ± 2.56 (0.00)	−0.15 ± 0.67 (0.00)	0.063
24 h–30 min	−1.70 ± 2.79 (0.00)	−0.05 ± 0.83 (0.00)	0.027*
72 h–30 min	−1.75 ± 2.75 (0.00)	−0.15 ± 0.67 (0.00)	0.031*

SD, standard deviation.
[a] Paired Wilcoxon test.*significant difference at 5.0% level.

same intervention. The present study involved the evaluation of clinical outcomes after a hard tissue surgery and employed a split-mouth design with randomization, blinding of the interventions, and the evaluation of variables at standardized time intervals over the course of 1 week, which is considered compatible with the regression of symptoms following oral surgery. This methodological care enabled scientific evidence to be obtained with a lower risk of bias.

Peak pain intensity of an inflammatory origin after oral surgical procedures occurs after 4–8 hours and the triggering of the inflammatory process occurs within the first 36 hours[23]. In the present study, the single application of a nicotine patch was effective at controlling peak pain and inflammation at these time intervals. Statistically significant results were found for the control of pain, number of rescue analgesics, reduction in oedema at 24, 48, and 72 hours, and the reduction in trismus at 72 hours and 7 days compared to the control group. These findings suggest the isolated effectiveness of nicotine for the reduction of pain, oedema, and trismus, since the use of local anaesthesia does not affect receptors of pain and inflammation modulation. Thus, the real effect of nicotine was demonstrated.

The administration route and dose of the drug (nicotine) may contribute directly to the control of pain and the need for rescue analgesics following oral surgery. The literature reports lower pain scores following third molar surgery when nicotine is administered through nasal instillation, although no reduction in rescue analgesics in the postoperative period was found when the nasal route was used with a dose of 3 mg[24]. In the present study, a nicotine patch with a dose of 14 mg led to a significant reduction in pain levels ($P < 0.05$) and significantly lower use of rescue analgesics following third molar surgery ($P = 0.026$), suggesting that this administration route achieves better results.

The use of a nicotine patch improves the pharmacokinetic properties and enables the gradual absorption of the active ingredient over a period of up to 24 hours, with the plasma peak achieved after 4 hours, which coincides with the period of greatest pain intensity, thereby contributing to greater patient comfort and a reduced need for supplementary analgesics in the postoperative period. The results of the present study are in agreement with those of Fishbein et al.[25] regarding the effectiveness of nicotine between 4 and 8 hours after the procedure ($P = 0.005$). When instilled nasally, the results may vary, since the plasma peak of nicotine spray occurs within 10 minutes after instillation, leading to a larger circulating dose of the drug in a shorter period of time and, consequently, an increased possibility of undesirable effects and shorter duration of action of the desired pharmacological effect[25].

Besides binding to the specific $\alpha 4\beta 2$ neuronal receptor, nicotine released from a skin patch may adhere to μ receptors, thereby enhancing and prolonging the analgesic effect, especially when combined with the administration of morphine in the postoperative period, which can confound the isolated effect of nicotine[26,27]. Nonetheless, the present study was able to demonstrate the intrinsic effects of nicotine, since it was used exclusively with local anaesthesia and only analgesics were used in the postoperative period, when needed. Moreover, the non-use of an opiate minimizes the adverse effects associated with this class of drug, such as respiratory depression and dependence, which did not occur in the present experiment. It should be pointed out, however, that the majority of third molar surgeries are performed as an outpatient procedure for which the use of morphine is not frequent. Analgesics with peripheral action make the clinical management more versatile, with lower risk and cost.

In some cases, the positive analgesic effect is seen earlier in the postoperative period. Such a result is attributed to the difference in weight between individuals submitted to the same dose of nicotine (14 mg), which may exert an influence on the pharmacokinetics. Individuals with

Table 8. Blood pressure readings at each evaluation time and according to the type of patch.

Variable/evaluation time	Type of patch		*P*-value
	Nicotine Mean ± SD (median)	Placebo Mean ± SD (median)	
Systolic blood pressure			
Preoperative	112.45 ± 8.88 (111.00)	109.10 ± 9.89 (110.50)	0.334[a]
Before surgery	111.90 ± 8.96 (111.00)	109.85 ± 10.39 (110.50)	0.510[b]
5 min after anaesthesia	114.35 ± 10.57 (112.00)	112.25 ± 8.44 (111.00)	0.429[b]
After surgery	113.35 ± 10.29 (113.00)	112.30 ± 5.71 (111.50)	0.673[b]
Mean of absolute difference			
Before surgery – preoperative	−0.55 ± 7.32 (0.00)	0.75 ± 10.96 (0.00)	
5 min after – preoperative	1.90 ± 8.90 (1.00)	3.15 ± 11.12 (1.00)	0.699[b]
After surgery – preoperative	0.90 ± 9.39 (0.00)	3.20 ± 10.35 (2.50)	0.178[a]
Diastolic blood pressure			
Preoperative	78.15 ± 8.66 (77.00)	76.05 ± 7.95 (76.50)	0.443[b]
Before surgery	75.65 ± 8.85 (78.00)	77.75 ± 9.49 (76.00)	0.323[b]
5 min after anaesthesia	77.35 ± 10.19 (77.00)	73.40 ± 9.46 (75.00)	0.170[b]
After surgery	78.10 ± 11.04 (75.00)	76.10 ± 10.49 (75.50)	0.518[b]
Mean of absolute difference			
Before surgery – preoperative	−2.50 ± 8.62 (0.00)	1.70 ± 14.06 (−1.00)	0.158[b]
5 min after – preoperative	−0.80 ± 9.32 (0.00)	−2.65 ± 11.35 (−0.50)	0.374[a]
After surgery – preoperative	−0.05 ± 10.88 (−0.50)	0.05 ± 14.07 (0.00)	0.980[b]

SD, standard deviation.
[a] Paired Wilcoxon test.
[b] Paired Student *t*-test; *significant difference at 5.0% level.

Table 9. Heart rate and oxygen saturation at each evaluation time and according to the type of patch.

Variable/evaluation time	Type of patch		*P*-value
	Nicotine Mean ± SD (median)	Placebo Mean ± SD (median)	
Heart rate			
Preoperative	76.90 ± 18.97 (79.50)	77.90 ± 15.74 (79.50)	0.798[a]
Before surgery	83.90 ± 19.43 (85.00)	83.65 ± 18.97 (80.00)	0.960[a]
5 min after anaesthesia	95.20 ± 17.71 (102.00)	93.60 ± 16.68 (93.50)	0.649[a]
After surgery	89.85 ± 18.16 (89.50)	84.70 ± 14.41 (86.00)	0.181[a]
Mean of absolute difference			
Before surgery – preoperative	7.00 ± 17.14 (5.50)	5.75 ± 20.81 (1.50)	0.850[a]
5 min after – preoperative	18.30 ± 13.02 (17.50)	15.70 ± 15.69 (16.00)	0.590[a]
After surgery – preoperative	12.95 ± 14.75 (13.50)	6.80 ± 15.19 (10.50)	0.279[a]
Oxygen saturation			
Preoperative	97.50 ± 3.97 (98.50)	97.50 ± 3.89 (99.00)	1.000[b]
Before surgery	98.50 ± 0.83 (99.00)	98.25 ± 0.97 (98.00)	0.349[a]
5 min after anaesthesia	98.75 ± 0.72 (99.00)	98.75 ± 0.72 (99.00)	1.000[b]
After surgery	98.75 ± 0.72 (99.00)	98.60 ± 0.94 (99.00)	0.614[a]
Mean of absolute difference			
Before surgery – preoperative	1.00 ± 3.70 (0.00)	0.75 ± 3.95 (0.00)	0.449[a]
5 min after – preoperative	1.25 ± 3.82 (0.00)	1.25 ± 3.80 (0.00)	1.000[a]
After surgery – preoperative	1.25 ± 4.10 (0.50)	1.10 ± 3.64 (0.00)	0.614[a]

SD, standard deviation.
[a] Paired Student *t*-test.
[b] Paired Wilcoxon test.

a smaller body mass may have the drug bioavailable in a shorter period of time, leading to an earlier effect. The literature offers no clinical parameters regarding the dose of nicotine and body mass for this therapeutic purpose, which hinders the definition of therapeutic and posological regimens that can determine the appropriate dose based on body weight. Therefore, the present study could serve as a basis for future studies involving probabilistic samples with comparison of doses that could delineate the effective therapeutic profile of nicotine per unit of weight and minimize the possible undesirable effects and overdose of the medication. Such studies should compare clinical findings with plasma levels.

Nicotine is a direct large-spectrum agonist of central nicotinic receptors that mediates sympathetic transmission in the ganglia. It can therefore increase the heart rate and blood pressure, interfere with the perfusion of oxygen in tissues, and cause nausea[20]. In the present study, a statistically significant difference in the sensation of nausea was found between patients in the nicotine patch group and those in the control group at 30 minutes ($P = 0.031$) and 4 hours ($P = 0.008$) after the procedure, with a mean of 1.75 on the VAS at 30 minutes. However, no patient required an antiemetic in the postoperative period, as the reported inten-

sity of the sensation was relatively low. Analyzing studies in which general anaesthesia was used, postoperative nausea was significantly high and the authors commented on the medication used during surgery as the probable cause of this symptom, leading to the need for an antiemetic to attenuate the effects of the general anaesthesia.

Yagoubian et al. (2011)[24] found a slight increase in heart rate, but with no clinically significant interference on the patterns of normality and no statistically significant difference in blood pressure. In the present study, surgery was performed under local anaesthesia and no significant changes in heart rate, blood pressure, or oxygen saturation were found at any of the four time intervals studied. Despite the premise of the sympathetic stimulation by nicotine, a meta-analysis involving 3752 patients who participated in a randomized clinical trial involving nicotine replacement therapy demonstrated no increase in the incidence of cardiovascular disease (myocardial infarction, stroke, tachycardia, arrhythmia, and angina), suggesting the clinical safety of topical nicotine.

The positive findings in the present study in surgeries performed under local anaesthesia are in agreement with data from systematic reviews that have reported the effectiveness of nicotine in the control of postoperative pain following surgery under general anaesthesia[28,29]. Moreover, this study establishes a new prevention and treatment modality regarding pain, oedema, and trismus in a versatile, convenient, safe, and effective form, thereby minimizing gastrointestinal and cardiovascular disorders caused by the use of anti-inflammatory drugs in third molar surgeries.

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Competing interests

None.

Ethical approval

Study approved by the institutional ethics committee of the University of Pernambuco under protocol number 85547615.5.0000.5207.

Patient consent

Consent term applied.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijom.2019.08.013.

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