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PREEMPTIVE ANALGESIA WITH AMITRIPTYLINE IN WOMEN UNDERGOING ABDOMINAL HYSTERECTOMY: A RANDOMIZED CLINICAL TRIAL

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ABSTRACT The concept of preemptive analgesia, albeit long-standing, has reemerged. Consequently, recent research has focused on testing a variety of drugs preoperatively to prevent the occurrence of postoperative pain, a major factor of morbidity. Amitriptyline is a tricyclic antidepressant used to treat chronic pain. Because amitriptyline acts on pain transmission pathways, it could theoretically be used as an agent for the prevention of postoperative pain. This study evaluated the effectiveness of amitriptyline in preventing pain in patients submitted to hysterectomy, the most commonly performed gynecological surgery. A randomized, double-blind clinical trial was conducted with 145 patients, 72 of these receiving amitriptyline and 73 placebo. All patients were evaluated at 6, 12, 24 and 48 hours after surgery using a visual analog scale (VAS) for pain and algometry to determine the pressure-pain threshold. Statistical analysis was conducted using the chi-square test of association, Student's t-test, and the Mann-Whitney test, with Fisher's exact test being used whenever appropriate. No statistically significant difference was found between the two groups with respect to pain at any of the time points evaluated, leading to the conclusion that at a dose of 25 mg, amitriptyline is ineffective in preventing postoperative pain in patients submitted to abdominal hysterectomy.

KEYWORDS : analgesia; amitriptyline; hysterectomy.

INTRODUCTION

Hysterectomy is the second most commonly performed surgery in women in the United States. The procedure assumes particular importance due to the fact that over 600,000 hysterectomies are performed each year in that country for benign conditions alone (Doll, Dusetzina & Robinson, 2016). Total abdominal hysterectomy - one of the modalities of the procedure - is linked with relevant postoperative pain (Azari, Santoso & Osborne, 2013), however, in a considerable percentage of cases the management of postoperative pain fails to be dealt with optimally (Kuusniemi & Pöyhiä, 2014).

Preemptive analgesia consists of the administration of analgesic medication even before surgical incision (Rosero & Joshi, 2016). The objective of this antinociceptive therapy is to attenuate - or, ideally, prevent - the postoperative increase in pain (Kelly, Ahmad & Brull, 2001). Many drugs have been tested as preemptive analgesics such as magnesium sulfate (Omar, 2018), ketorolac and meperidine (Khezri, Mosallaei, Ebtehaj & Mohammandi, 2018), gabapentin (Ajori, Nazari & Mazloomfard, 2012) (Alayed, Alghanaim, Tan & Tulandi, 2014) (Mao, Wu & Ding, 2016) (Peng, Li, Qu, Wu, 2017), pregabalin (Martinez, Pichard & Fletcher, 2017) (Sebastian, Talikoti, Nelamangala & Krishnamurthy, 2016), non-steroidal anti-inflammatory drugs (Costa *et al.*, 2015) and tramadol (Farzi *et al.*, 2016) have been tested as preemptive analgesics, but only gabapentin has been tested specifically as premedication for postoperative pain in patients undergoing hysterectomy. A 2014 systematic review concluded that it was effective for this purpose (Alayed *et al.*, 2014).

The tricyclic antidepressant amitriptyline has been used off-label for the treatment of chronic pain. Amitriptyline increases the synaptic serotonin and/or norepinephrine levels in the central nervous system by inhibiting specific uptake pumps on the presynaptic neuronal membrane (UpToDate, 2018), and has already been tested as an adjunct to opioids for the treatment of postoperative pain in patients submitted to orthopedic surgery (Kerrick, Fine, Lipman & Love, 1993).

The objective of the present study was to evaluate the effectiveness of amitriptyline for preemptive analgesia in women submitted to total abdominal hysterectomy.

METHODS

A randomized, double-blind, placebo-controlled clinical trial was conducted with two groups of women undergoing abdominal hysterectomy to compare the use of preemptive analgesia with amitriptyline 25 mg versus placebo. The study was conducted at the Pedro I Municipal Hospital of the Campina Grande Municipal Health Department between June 2015 and October 2018 following approval from the internal review board of the Paraíba School of Medical

Sciences under reference CAAE 43741515.9.0000.5178. The study was registered at ClinicalTrials.gov under identifier NCT03587025. All the patients were duly informed with respect to the study objectives and were only admitted after they had signed an informed consent form.

Sample size was calculated using OpenEpi, version 2.3.1 (Atlanta, GA, USA). Estimates were based on a previous clinical trial comparing gabapentin and placebo (Ajori *et al.*, 2012), which found a mean visual analog scale (VAS) pain score of 0.2 ± 0.8 (standard deviation [SD]) for the gabapentin group and 0.9 ± 1.3 for the placebo group. For a power of 95% and a significance level of 5%, 124 patients, distributed in two groups of 62 women each, would be required. To compensate for any losses or exclusions following randomization, this number was increased by 20%, leading to an estimate of 150 women, 75 in each group. All the women referred to this hospital for a total abdominal hysterectomy from June 2015 onwards were invited to participate in the study and were selected in a consecutive, non-probabilistic sampling procedure.

The inclusion criteria consisted of patients of 18 to 60 years of age who had been referred to the hospital for an abdominal hysterectomy due to benign conditions such as uterine fibroids or hemorrhage. Patients with abnormal Pap smears, uterine prolapse, a history of intolerance to opioids or narcotics, women for whom amitriptyline was contraindicated (due to conditions such as glaucoma, heart disease, etc.), alcoholics and drug addicts, women who had used analgesics in the 24-hour period immediately preceding hospitalization, those unable to give their informed consent and those for whom spinal anesthesia was not the proposed type of anesthesia were excluded from the study.

A list of random numbers was previously prepared by a statistician not otherwise involved in the study, using Random Allocation software, version 2.0 (Isfahan, Iran). Seventy-five patients were to be assigned to each study group, the amitriptyline and the placebo arm, respectively.

Both the amitriptyline 25 mg tablets and the placebo were similar in appearance (size, shape, weight and color). Adequate allocation concealment kept both investigators and patients blinded, with the tablets being arranged in boxes numbered from 1 to 150 for each consecutively randomized patient by a pharmacist not otherwise involved in this study. Tablets were administered orally with water, between 6 and 12 hours prior to the surgical procedure by a blinded nurse.

Previously trained assistants evaluated the patients postoperatively by applying the VAS for pain, measuring the pressure-pain threshold by algometry, and evaluating satisfaction using the Faces Pain Scale - Revised (FPS-R).

The independent variable consisted of the use of amitriptyline 25 mg by the oral route, administered 6-12 hours prior to total abdominal hysterectomy to prevent or reduce the intensity of acute postoperative pain. The dependent variables included primary and secondary endpoints. The primary endpoints were pain scores according to the VAS and pressure algometry at 6, 12, 24 and 48 hours after surgery. The secondary endpoints consisted of the degree of patient satisfaction according to the FPS-R, surgery duration, and the frequency of intraoperative and postoperative complications and adverse events.

The statistical analysis was conducted using Epi-Info, version 7.1.3 (Atlanta, GA, USA). The groups were initially identified as A or B, with the randomization list only being opened after the results had been obtained and the tables prepared. Therefore, it was only known which group had received amitriptyline and which had received placebo at the end of the analysis.

The chi-square test of association and Fisher's exact test were used to compare the categorical variables, as appropriate. Student's t-test was used to compare the means of the continuous numerical variables when distribution was normal, while the Mann Whitney test was used for the numerical variables when distribution was not normal and for the ordinal variables. Significance was set at 5% for all the stages of the analysis and all the p-values adopted were two-tailed.

RESULTS

Of 159 screened patients, 150 were randomized, with 145 remaining in the study and five being excluded due to surgery cancellation after the study medication had already been administered. The patients ranged in age from 33 to 60 years, with no significant difference between the two groups (p=0.59). The principal indication for surgery was uterine fibroids, corresponding to around 82% of all indications in both groups (p=0.97). All the other baseline characteristics were similar in both groups, as shown in Table 1.

Table 1 Baseline characteristics of the participants according to study group.

Characteristic	Amitriptyline	Placebo	p-value
Age (years)			
Range	36 - 56	33 – 60	0.59*
Median/IQR	44 (41.5-48)	43 (40-48)	
Skin color (n, %)			
White	23 (31.9)	20 (27.4)	0.55†
Brown/black	49 (68.1)	53 (72.6)	
Body mass index			
Range	17.1 - 44.6	20.2 - 46.8	0.85 ‡
Mean ± SD	29.0 ± 6.0	29.2 ± 5.7	
Parity			
Nulliparous	15 (20.8)	17 (23.9)	0.66†
Parity ≥ 1	57 (79.2)	54 (76.1)	
Median/IQR	2 (1-3)	2 (1-3)	0.76*
Schooling (years of formal education)			
Range	0-21	0-16	0.62*
Median/IQR	7 (5-9)	6 (5-10)	
Indication for hysterectomy (n, %)			
Uterine fibroids	59 (81.9)	60 (82.2)	0.97†
Adenomyosis	6 (8.3)	1 (1.4)	0.06§
Endometriosis	0	3 (4.1)	0.24§
Others	6 (8.3)	9 (12.3)	0.43†
Comorbidities (n, %)			
Arterial hypertension	30 (41.7)	35 (48.0)	0.45†
Diabetes mellitus	6 (8.3)	9 (12.3)	0.43†

IQR: interquartile range.
* Mann-Whitney's test
† Association Chi-Square
‡ Student's t Test
§ Fischer's Exact Test

Postoperative pain, measured by pressure algometry six hours following surgery, showed a mean of 11.9 ± 4.1 Newton (N) for the amitriptyline group and 12.0 ± 4.7 N for the placebo group (p=0.92). At twelve hours after surgery, the mean was 11.6 ± 3.6 N and 10.9 ± 3.6 N, respectively (p=0.33). At 24 hours following surgery, the means recorded were 10.1 ± 3.4 and 10.2 ± 2.8 N (p=0.79) and, finally, at 48 hours following hysterectomy, the values recorded were 9.2 ± 3.4 and 9.5 ± 4.4 N, respectively (p=0.69) (Table 2).

The VAS pain scale showed similar results, with a median of 0 for both groups at 6 hours after surgery (p=0.82), a median of 1 for the amitriptyline group and 2 for the placebo group at 12 hours (p=33), a median of 1 for both groups after 24 hours (p=0.92) and 1 again for both groups at 48 hours following hysterectomy (p=0.98) (Table 2).

Table 2 Evaluation of acute postoperative pain according to study group.

Time point	Amitriptyline	Placebo	p-value
6 hours			
Pain as evaluated by algometry			
Range	3.5 - 23.5	2.5 - 26.8	
Mean ± SD	11.9 ± 4.1	12.0 ± 4.7	0.92*
Pain as evaluated by the VAS pain score			
Range	0 -10	0 - 9	
Median/IQR	0 (0-3)	0 (0-2)	0.82‡
12 hours			
Pain as evaluated by algometry			
Range	5.2 - 22.6	3.7 - 19.8	0.33*
Mean ± SD	11.6 ± 3.6	10.9 ± 3.6	
Pain as evaluated by the VAS pain score			
Range	0 - 9	0 - 10	0.33‡
Median/IQR	1 (0-3)	2 (0-4)	
24 hours			
Pain as evaluated by algometry			
Range	4.5 - 23.3	4.7 - 18.3	0.79*
Mean ± SD	10.1 ± 3.4	10.2 ± 2.8	
Pain as evaluated by the VAS pain score			
Range	0 - 9	0 - 10	0.92‡
Median/IQR	1 (0-3)	1 (0-4)	
48 hours			
Pain as evaluated by algometry			
Range	3.6 - 20.2	3.1 - 23.1	0.69*
Mean ± SD	9.2 ± 3.4	9.5 ± 4.4	
Pain as evaluated by the VAS pain score			
Range	0-8	0-10	0.98‡
Median/IQR	1 (0-2)	1 (0-2)	

SD: standard deviation; IQR: interquartile range. * Student's t-test; ‡Mann-Whitney test.

Satisfaction, as analyzed using the FPS-R, was similar in both groups, with a median of 2 in both groups at all the time points evaluated. The most common adverse event reported at six hours following surgery was dry mouth, with 8 patients in the amitriptyline group (11.1%) and 11 in the placebo group (15.1%) reporting this side effect (p=0.48). At 6 hours following surgery, other types of side effect were recorded in 13 individuals in the amitriptyline group (18.1%) and 9 in the placebo group (12.3%) (p=0.33). At 12 hours following surgery, vomiting was more common in the placebo group (9 cases; 12.3%) compared to the amitriptyline group (2 cases; 2.8%) (p=0.03). There was no need for rescue analgesia in any of the cases evaluated in the present study.

DISCUSSION

Amitriptyline 25 mg proved ineffective as preemptive analgesia in women submitted to total abdominal hysterectomy, with extremely similar results in both the intervention and placebo groups for pain (as evaluated according to the VAS pain score and by algometry) and for satisfaction (evaluated using the FPS-R).

The present findings differ from another study in which gabapentin was found to be effective in preventing postoperative pain in patients submitted to hysterectomy (Alayed *et al.*, 2014). Nonetheless, these findings are similar to results described in a systematic review that evaluated the effectiveness of pregabalin for the prevention of chronic postoperative pain in various types of surgery, including thoracic, abdominal and orthopedic surgery, among others (Martinez *et al.*, 2017). Likewise, in another study that tested amitriptyline as an adjunct to opioids for the treatment of pain in patients submitted to orthopedic surgery, no difference was found between the group using amitriptyline and an opioid and the group using the opioid alone (Kerrick *et al*, 1993).

On the other hand, if the effectiveness of amitriptyline could not be confirmed, the similarity in the side effects observed in the two groups evaluated here highlights the safety of its use, which may encourage other studies to be conducted with the drug at other dose levels and/or at different intervals of administration.

The many strongpoints associated with this study include the fact that it was a randomized, double-blind, placebo-controlled clinical trial with an adequate sample size and data quality assurance. Nevertheless, some limitations include the choice of the dose of amitriptyline, which was based on the usual daily dose for the treatment of chronic pain without a pilot study having been conducted to determine the ideal dose. Also, a considerable number of the patients were significantly overweight or obese and the low dose of amitriptyline administered here may have been insufficient. In addition, since patients receive an analgesic (dipyrone), a non-steroidal anti-inflammatory drug (tenoxicam) and a weak opioid (tramadol), postoperative pain tends to be rare and limited, hampering the perception of different degrees of postoperative pain.

A search of the PubMed, Scopus and Embase databases using the key words "amitriptyline", "analgesia" and "postoperative" pain revealed few studies, with the majority being considerably old and dealing with phantom pain and neuropathies. This highlights the potential for further investigation into this drug, bearing in mind the rationale represented by its mechanism of action at the synapse.

CONCLUSIONS

Amitriptyline at a dose of 25 mg was not found to be effective for the prevention of postoperative pain in patients submitted to abdominal hysterectomy, with results being similar to those found with placebo in the population evaluated here.

The field of preemptive analgesia for abdominal surgery, particularly gynecological procedures, remains a vast territory to be explored, and new drugs, doses and routes of administration should be tested to achieve advances in the effective prevention of postoperative pain, since the problem persists and little research has been conducted on the subject in recent decades. Further randomized clinical trials will surely shed more light on this subject and will contribute to an increase in the strategies available for the treatment and prevention of postoperative pain.

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