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PHARMACOLOGY

ANALGESIC EFFICACY AND SAFETY OF TAPENTADOL IN COMPARISON WITH OXYCODONE IN PATIENTS AFTER OPEN ABDOMINAL HYSTERECTOMY

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Abstract: Tapentadol is the newest opioid with a dual mechanism of action, that gives the potential to spare some opioid-induced adverse events. Studies involving this drug in acute pain are not numerous. The aim of this study was to compare the efficacy and tolerance of tapentadol and oxycodone in patients after abdominal hysterectomy. Patients were randomly allocated into two groups receiving: I. tapentadol (50 mg) and II. oxycodone (10 mg), every 12 h postoperatively. The Numerical Rating Scale (NRS), vital signs, main adverse events (postoperative nausea and vomiting, sedation) and other side effects would be recorded until discharge. Total opioid consumption, the patients' satisfaction, adjuvants consumption, and length of hospital stay were also assessed. Mean NRS scores for tapentadol and oxycodone after 24, 48 and 72 h were: 3.43 (± 1.29) vs 3.59 (± 1.37), 2.87 (± 1.07) vs 3.24 (± 1.21), 2.80 (± 1.05) vs 3.19 (± 1.24), respectively. In the tapentadol group, superior pain control ($p < 0.05$) in few time points during the day second was observed although demand for rescue analgesics was slightly higher ($p > 0.05$). Mucosal dryness affected over > 90% of patients in both groups. The incidence of postoperative nausea was 39.5% (tapentadol) and 27% (oxycodone) on the first day. The incidence of drowsiness was 42.1% (tapentadol) and 37.8% (oxycodone). Other adverse events' level, satisfaction with treatment, length of stay after surgery, effect on vital signs were comparable.

Keywords: tapentadol, oxycodone, abdominal hysterectomy, postoperative pain

Hysterectomy for benign gynecological diseases is one of the most frequent gynecological procedures. The multifactorial origin of pain following abdominal hysterectomy (incisional, visceral, and dynamic pain) requires a multimodal approach. The first-line treatment involves opioids but their use is limited due to common side effects. Local anesthetic techniques are gaining increasing interest in a variety of abdominal procedures. Multimodal analgesia is the optimal method for postoperative analgesia either in systemic administration, as well as a part of local anesthesia. The combination of pharmacological agents that act in multiple pharmacologic sites allows lowering opioid doses which decreases the incidence of opioid-induced side effects (1-3).

Tapentadol (TAP) is the first compound of a group called combining μ-opioid receptor (MOR) agonists and noradrenaline reuptake inhibitors (NRIs) (4, 5). Both mechanisms of action can produce analgesia in their own right and interact synergistically at the spinal and supraspinal levels. This dual mechanism makes tapentadol "a multimodal analgetic in a single molecule". Such an interaction explains why, despite a 50-fold lower affinity for the MOR, this drug is only 2- to 3-fold less potent than

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morphine (6). Conversion ratios between tapentadol and other opioids are as follows: tapentadol : oxycodone : morphine : fentanyl 10 : 2 : 3 : 0.03 (7).

Because of tapentadol's weak affinity to MOR, there might be a reduction of common side effects associated with opioid use, such as: nausea, dizziness, vomiting, somnolence, and constipation (8, 9). Currently, TAP ER is most commonly used for the treatment of chronic, especially neuropathic pain (8). There are also trials proving good efficacy in treating musculoskeletal pain (10). For the treatment of chronic cancer pain, TAP has been shown to be neither more nor less effective and well-tolerated than morphine or oxycodone (11).

In terms of acute (including postoperative) pain, documentation of TAP's advantages is limited to certain types of surgeries, especially orthopedic and dental surgery (4, 12-14). We also came across single studies after cardiac surgery (15) and the Cesarean section (16). While debate remains on the optimal dose for management of moderate to severe pain, there is a parallel need for studies assessing potential benefits in other patient populations (16).

The purpose of this study was to assess analgesic efficacy, adverse events, and second-point data (length of hospital stay, vital signs, patients' satisfaction, total opioid consumption) of TAP in comparison with standard opioid oxycodone (OXY) in women that had undergone abdominal hysterectomy.

EXPERIMENTAL

Methodology

This study took place at the gynecological ward of Pleszewskie Centrum Medyczne between March 2016 and July 2018 and involved 76 women who had undergone total (uterus + cervix ± ovaries amputation) or subtotal abdominal hysterectomy (uterus body ± ovaries amputation).

Patients with known allergies to opioids, hepatitis, renal failure and known history of drug abuse were excluded from the study. The purpose of the study anticipated side effects, numerical rating scale (NRS) calculation method were explained to the patients along with routine information about the surgical procedure, following which written consent forms were collected.

Subsequently, the patients were randomly allocated into either oxycodone (OXY) or tapentadol (TAP) group. For randomization, the GraphPad Prism® 6.01 procedure was used (GraphPad Software Inc., US). All the women received transabdominal hysterectomy through a traditional abdominal incision in the lower abdomen, and the surgical procedure was similar in all patients.

The patients were given preanesthetic midazolam 7.5 mg *p.o.* half an hour before the surgery. During the surgery, spinal anesthesia with 12.5-20 mg 0.5% bupivacaine was applied to all the patients, as well as 0.05-0.1 mg of fentanyl *i.v.*. The doses depended on the surgery duration and the patient's weight.

On day 0 following the procedure, both groups were treated with continuous *i.v.* infusion of oxycodone in normal saline, at a flow rate of 1.5-3 mg/h. There were also additional analgesics, available on the patient's request: paracetamol *i.v*. (maximum dose 1 g/24 h), metamizole *i.v.* (max. 5 g/24 h), and ketoprofen *i.v.* (max. 200 mg/24 h). Pain intensity on day 0 was assessed at 0.5 h, 2 h, 4 h, 6 h, 8 h, 12 h, 18 h after the surgery and at 6 am on the following day. The intensity of pain on further days was scored 4 times a day, with an 8-hour night gap. As of on day 1, the OXY group would be receiving 10 mg of oxycodone CR (controlled release) tablet twice a day, and TAP group 50 mg of tapentadol ER tablet twice a day. According to data, such doses of these opioids are equianalgesic (7). The study medicines would be administered for as long as the patients expressed the demand for the drug. Apart from the study drugs, similarly to day 0, there were also additional anesthetics available on request, as listed above. The number of additional analgesic requests, total opioid consumption, pain intensity, side effects, and length of hospital stay after surgery were evaluated and recorded. We registered also the use of any other drugs, especially laxatives, tranquilizers, antiemetics.

Saturation, heart rate, and blood pressure were registered at the same time points as pain intensity, starting from day 1. We also monitored the most common opioid-associated adverse events: nausea (4 times a day, 4-point scale), vomiting (4 times a day, number of episodes), sedation (once a day, 3-point scale), drowsiness, sleeping disorders/anxiety, mucosal dryness, fatigue, loss of concentration (once a day, 4-point scale). Any other adverse events not listed above but declared by the patient were noted.

Pain intensity was measured using the 11-point NRS, with 0 indicating no pain and 10 unbearable pain. For the degree of sedation, a score of 0 was given if the patient's level of consciousness was as clear as before the surgery, a score of 1 if the patient was drowsy and verbal stimulation was enough to awake her, and a score of 2 if the patient was drowsy and had to be physically stimulated to be woken up.

For the other adverse events, a score of 0 meant no adverse event, 1 – a slight adverse event, 2 – a strong adverse event, 3 – a very strong adverse event.

The patients' satisfaction was assessed prior to discharge, and the rating levels were divided into very satisfied (3), satisfied (2), neutral (1), and dissatisfied (0). For the analysis of overall analgesic efficacy, the difference between day 0 NRS and mean further days NRS was used.

Statistical analysis

Statistica® (StatSoft Inc., Tulsa, OK, USA) was used for statistical analysis. The calculated data were recorded in the form of mean or mean ± standard deviation (SD). A comparative analysis was performed using the following tests: U-Mann-Whitney (patients' characteristic; NRS scores; NRS differences; SBP (systolic blood pressure), DBP (diatomic blood pressure), SpO_2 (saturation), HR

Table 1. Details of the patients (n = 76) and surgeries (abdominal hysterectomy).

	TAP (n = 39)	OXY (n = 37)
The patients' characteristics		
Mean age	50.77 ± 8.88	51.22 ± 11.33
< 30	0	0
30-39	2	5
40-49	22	12
50-59	6	12
60-69	8	5
≥ 70	1	3
BMI	26.81 ± 4.91	25.93 ± 4.48
< 20	0	1 (2.7%)
20 - 25	16 (41.0%)	14 (37.8%)
25.1 - 30	13 (33.3%)	16 (43.2%)
30.1 - 35	8 (20.5%)	4 (10.8%)
>35	2 (5.1%)	2 (5.4%)
Non-smokers	31 (79.5%)	33 (89.2%)
Smokers, <10 cigarettes/day	4 (10.3%)	3 (8.1%)
Smokers, 10-19 cigarettes/day	4 (10.3%)	0
Smokers, ≥ 20 cigarettes/day	0	1 (2.7%)
Mean day 0 NRS	5.39 ± 1.53	4.95 ± 1.64
Surgery indication		
Uterine fibroid	24 (61.5%)	24 (64.9%)
Abnormal uterine bleeding	2 (5.1%)	2 (5.4%)
Uterine prolapse	5 (12.8%)	2 (5.4%)
BRCA 2 mutation	1 (2.6%)	0
Ovarian neoplasms	10 (25.6%)	8 (21.6%)
Endometriosis. Endometrial hyperplasia	6 (15.4%)	4 (10.8%)
Endometrial cancer	0	1 (2.7%)
Type of surgery		
Subtotal hysterectomy	10 (25.6%)	8 (21.6%)
Subtotal hysterectomy + appendectomy	6 (15.4%)	7 (18.9%)
Total hysterectomy	7 (17.9%)	4 (10.8%)
Total hysterectomy + appendectomy	16 (41.0%)	18 (48.6%)

BMI - Body Mass Index; BRCA - Breast cancer gene

(heart rate) scores; additional analgesics requests; total number of opioid doses; length of stay after surgery; mean values of adverse events), unpaired t-test (NRS difference 24 h, 48 h, and 72 h), Chi-square test of independence or Fisher exact test (total anxiolytics requests; patients requiring bisacodyl by withdrawal; adverse events values from particular time points, patients' satisfaction level). All tests were considered statistically significant at $p < 0.05$.

Ethical approval

This study was conducted upon obtaining approval from the Bioethics Committee, at the

Table 2. Results: efficacy of tapentadol vs. oxycodone and additional data in patients undergoing abdominal hysterectomy (n = 76).

Results		TAP (n = 39)	OXY (n = 37)	p-value
Analgesic efficacy				
Day 0 NRS (mean)		5.39 ± 1.53	4.95 ± 1.64	0.201
Day 1, 12 am		3.76 ± 1.57	3.78 ± 1.77	0.845
Day 1, 6 pm		3.36 ± 1.44	3.51 ± 1.39	0.533
Day 1, 10 pm		3.14 ± 1.84	3.57 ± 1.56	0.173
Day 2, 6 am		2.20 ± 1.45*	3.00 ± 1.51*	0.042
Day 2, 12 am		2.15 ± 1.75**	3.11 ± 1.31**	0.006
Day 2, 6 pm		2.26 ± 1.16	2.93 ± 1.33	0.064
Day 2, 10 pm		2.30 ± 1.22*	3.29 ± 1.52*	0.024
Day 3, 6 am		2.00 ± 1.41	2.62 ± 1.77	0.256
Day 3, 12 am		2.33	3.13	-
Day 3, 6 pm		3.00	4.50	-
Day 4, 6 am		2.50	4.00	-
Day 4, 12 am		2.00	3.00	-
Day 4, 6 pm		No patients	5.00	-
Day 4, 10 pm		No patients	3.00	-
Day 5, 6 am		No patients	3.00	-
Day 5, 12 am		No patients	3.00	-
Mean NRS day 1.		3.43 ± 1.29	3.59 ± 1.37	0.914
Mean NRS days 1 - 2		2.87 ± 1.07	3.24 ± 1.21	0.168
Mean NRS days 1 - 3		2.80 ± 1.05	3.19 ± 1.24	0.149
Day 0 NRS - mean Day 1 NRS (24 h)		1.96 ± 1.29	1.36 ± 1.76	0.092
Day 0 NRS - mean Days 1-2 NRS (48 h)		2.52 ± 1.29*	1.71 ± 1.65*	0.019
Day 0 NRS - mean Days 1-3 NRS (72 h)		2.59 ± 1.31*	1.76 ± 1.68*	0.018
Additional analgesics required / 24 h (n)		1.33 ± 0.73	1.09 ± 0.67	0.198
Additional data				
Total number (n) of opioid doses	mean	3.72 ± 1.34	4.11 ± 1.71	
	median	4	5	
Length of stay after surgery (days)	mean	3.31 ± 0.61	3.51 ± 1.26	
	median	3	3	
Total antiemetics requirement (n)		5	-	-
Total anxiolytics requests (n)		11	9	0.756
Patients requiring bisacodyl by withdrawal		30 (76.9%)	28 (75.7%)	0.788
The patients' satisfaction (0-3)		1.97 ± 0.63	2.22 ± 0.61	0.307

*$p < 0.05$ (U-Mann-Whitney test or unpaired t-test); **$p < 0.001$ (U-Mann-Whitney test); "-"statistical analysis was not performed (results not numerous enough); NRS - Numerical Rating Scale

Table 3. Adverse effects of tapentadol vs. oxycodone in patients (n = 76) undergoing abdominal hysterectomy- frequency.

	TAP (n = 39)			OXY (n = 37)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Patients (n)	38	28	6	37	28	10
Vomiting	5 (13,2%)	0	0	2 (5.4%)	0	0
Nausea	15 (39.5%)	4 (14.3%)	1 (16.7%)	10 (27.0%)	1 (3.6%)	2 (20.0%)
Sedation	10 (26.3%)	5 (17.9%)	1 (16.7%)	7 (18.9%)	6 (21.4%)	2 (20.0%)
Anxiety	1 (2.6%)	4 (14.3%)	0	2 (5.4%)	1 (3.6%)	0
Mucosal dryness	35 (92.1%)	11 (39.3%)	1 (16.7%)	35 (94.6%)	6 (21.4%)	0
Drowsiness	16 (42.1%)	3 (10.7%)	1 (16.7%)	14 (37.8%)	4 (14.3%)	1 (10.0%)
Loss of concentration	0	1 (3.6%)	1 (16.7%)	0	1 (3.6%)	0

Table 4. Adverse effects of tapentadol vs. oxycodone in patients (n=76) undergoing abdominal hysterectomy - magnitude.

Mean level (0-3)	TAP (n = 39)	OXY (n = 37)	p*
Nausea	0.1382	0.1194	0.244
Sedation	0.0862	0.1266	0.883
Anxiety	0.0897	0.0541	-
Mucosal dryness	1.4102	1.1171	0.066
Drowsiness	0.4915	0.3829	0.716

* - U-Mann-Whitney test; - - not numerous enough to conduct statistical analysis.

Poznan University of Medical Sciences (N^{o} 37/16, obtained 04.02.2016).

RESULTS

Total number of patients who completed the study was n = 76 (nTAP = 39, nOXY = 37). There were no statistically significant differences between the two groups in terms of age, BMI (body mass index), surgery indications, day 0 NRS, type of surgery (Table 1). Due to diagnostic procedures, it was not possible to collect all data in every time point assumed. These gaps, however, did not affect overall outcomes since the results are featured by mean scores.

Analgesic efficacy

Mean NRS score decreased from 5.39 (TAP) and 4.95 (OXY) on day 0 (reference day/baseline) to 3.43 and 3.59 after 24 h; 2.87 and 3.24 after 48 h; 2.8 and 3.19 after 72 h in further days of hospitalization, respectively. There was no documented statistical difference between NRS scores on day 0 (reference day) and mean NRS score during the examination, although the latter was lower in the TAP group. The difference between the baseline and NRS after 48 h (TAP 2.52 vs OXY 1.71) and 72 h (TAP 2.59 vs OXY 1.76) following the surgery was still significant: ($p < 0.05$). The difference between NRS 24h after the surgery and the baseline was not significant (TAP 1.96 vs OXY 1.36).

We documented significantly lower NRS scores for TAP at three-time points during day 2 after surgery ($p < 0.05$) which probably yielded a lower mean NRS in this group. Simultaneously, more additional analgesics in the TAP group were requested during all days of hospitalization ($p > 0.05$). Data are collected in Table 2.

Adverse drug reactions (ADRs)

In our study, the most common side effect was mouth dryness, and its both number and weight were higher in the TAP group. It affected over 90% of patients during day 1 of treatment in both groups. The second most common ADR was nausea, more common and stronger in TAP group. Drowsiness reported by the patients was higher in TAP group, while sedation reported by medical staff was stronger in the OXY group. Vomiting occurred occasionally but more frequently in the TAP group. Moreover, 4 patients in TAP group required additional antiemetic administration (5 requests alto-

gether), compared to none in the OXY group. We also documented a few cases of anxiety (inability to fall asleep) and loss of concentration in both groups. Despite the differences in ADR frequency, none of them turned out to be statistically significant. The demand for anxiolytics was also at a comparable level (Table 2). Data about ADRs are depicted in Table 3 and Table 4.

Dizziness was the most common spontaneously reported side effect and numbers of reports were equal in both groups. There were also a few cases of headache, back pain, hot flushes, fever, heart palpitations, and peristaltic problems in both groups. The patients also reported: heartburn, vertigo (OXY), unpleasant aftertaste, hallucinations, diarrhea, chapped lips, persistent hiccup (TAP). Three ADRs were not listed in the manufacturer's drug characteristic: chapped lips, unpleasant aftertaste, and hiccup. Numbers of spontaneous reports are pictured in Table 5.

Constipation was not evaluated as the mean patients' length of stay (3.2 days) was too short to

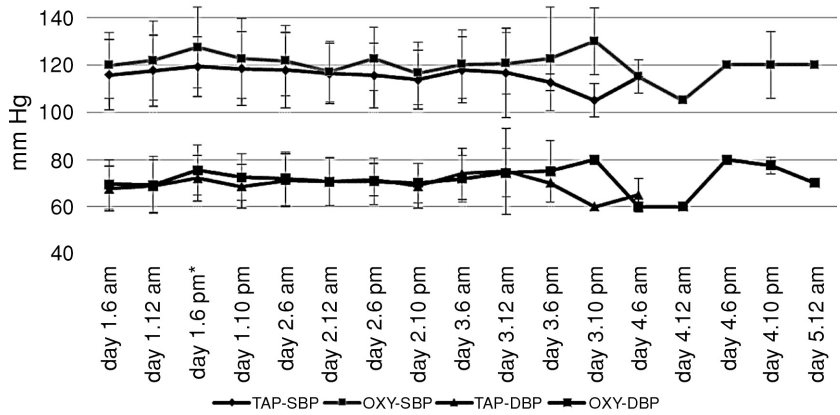

Figure 1. Systolic and diastolic blood pressure (mean ± SD) in patients after open abdominal hysterectomy (n = 76) following oral administration of tapentadol and oxycodone. TAP – tapentadol OXY – oxycodone SBP – systolic blood pressure DBP – diastolic blood pressure mmHg – millimeters of mercury * – statistically significant difference ($p < 0.05$) (U-Mann-Whitney test) in terms of SBP.

Table 5. Number of spontaneously reported adverse events in patients (n = 76) after abdominal hysterectomy, receiving tapentadol or oxycodone.

	TAP (n = 39)	OXY (n = 37)
Dizziness	9 (23.1%)	9 (24.3%)
Peristaltic problems	3 (7.7%)	1 (2.7%)
Headache	3 (7.7%)	3 (8.1%)
Hot flushes	1 (2.6%)	2 (5.4%)
Back pain	1 (2.6%)	1 (2.7%)
Persistent hiccup	2 (5.1%)	0
Heart palpitations	1 (2.6%)	1 (2.7%)
Fever	1 (2.6%)	1 (2.7%)
Diarrhea	1 (2.6%)	0
Chapped lips	1 (2.6%)	0
Unpleasant aftertaste	1 (2.6%)	0
Hallucinations	1 (2.6%)	0
Vertigo	0	1 (2.7%)
Heartburn	0	2 (5.4%)

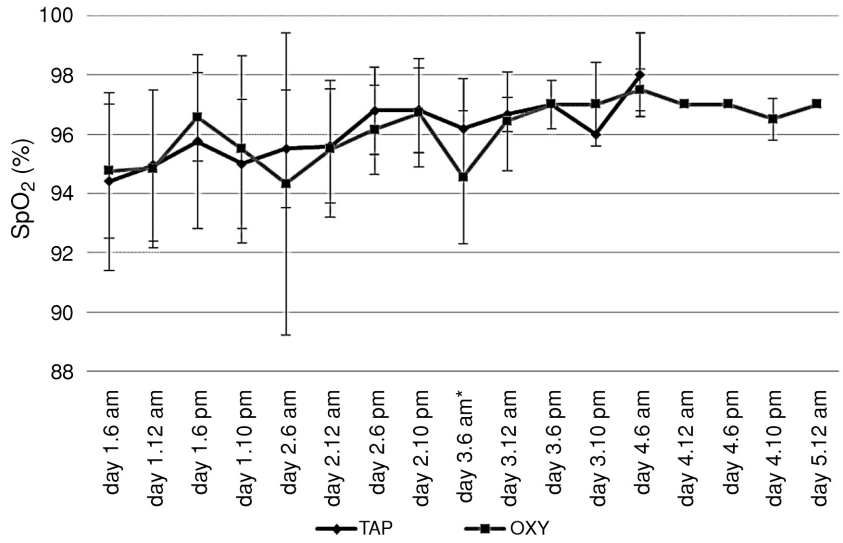

Figure 2. Oxygen saturation (mean ± SD) in patients after open abdominal hysterectomy (n = 76) following oral administration of tapentadol and oxycodone. TAP – tapentadol OXY – oxycodone SpO2 – saturation * – statistically significant difference ($p < 0.05$) (U-Mann-Whitney test).

assess this side effect. Pleszewskie Centrum Medyczne where the study was conducted has a procedure in place, however, requiring that patients after surgery report on their defecation. If the patient fails to defecate, bisacodyl 20 mg p.r. is prescribed. In this study, most of the patients required bisacodyl prescription (TAP 76.9%, OXY 75.7%), and there were no statistically significant differences.

Vital signs

Blood pressure values were comparable at nearly every single time point (Fig. 1). No discrepancies have been noticed at any time point in terms of DBP or HR. SBP was significantly lower ($p < 0.05$) for TAP group (119.31 TAP vs. 127.42 OXY) at just one single time point (day 1, 6 pm). Theoretically, a lower affinity for MOR should, however, result in higher values of blood pressure parameters for TAP, as in Biondi assay (17). The difference only in SBP and only at a single time point indicates a coincidental event that can be explained by heterogeneity of the groups.

The saturation level for both drugs was > 94% at all time points (Fig. 2). In both groups, values of saturation were comparable. Only at a single time point, after two days of treatment (day 3, 6 am) saturation percentage was higher with $p < 0.05$ for the TAP group (96.18 TAP *vs* 94.55 OXY). At the same time, it was the last time point when both groups were the most numerous. At subsequent time points, the majority of the patients would have been discharged and the number of participants was significantly lower. Therefore, to assess whether this saturation discrepancy was a trend or was coincidental, further examination is required. In terms of heart rate, both groups demonstrated no differences (Fig. 3).

Other data

The length of stay, patients' satisfaction, use of anxiolytics were comparable. In patients' satisfaction survey, positive responses (satisfied, very satisfied) amounted to 84.6% (TAP) and 78.4% (OXY), while negative responses (neutral, dissatisfied) – 15.4% (TAP) and 8.1% (OXY). In OXY group, 13.5% of responders did not return the survey. The total number of opioid doses was slightly higher in OXY group (Table 2). Patients received oral opioids for as long as they wished. Thus, such a decrease in the number of doses requested can be explained in higher ADR score in TAP group which resulted in earlier therapy discontinuation. The above ratios did not display any statistically significant differences.

DISCUSSION

Opioids remain the first-line drugs in the treatment of moderate to severe acute peri-operative pain. According to the mechanism of action, they do not present analgesic ceiling. Nevertheless, their use is limited by side effects. Multimodal analgesia remains a usable strategy of minimizing opioid-related adverse events (18-20). Tapentadol acts as a multimodal analgesic in a single molecule, thus

being a useful alternative for classic opioids. In routine clinical practice, it is important to switch or rotate between different opioids. TAP, the most recently registered opioid, gives physicians such an opportunity.

The purpose of this study was to compare the analgesic efficacy, side effects, vital signs, and the patients' satisfaction for two opioid drugs: the commonly used oxycodone and the newly introduced tapentadol. Due to the fact that tapentadol *i.v.* form is not available, our comparison was conducted starting from the next day after surgery (Day 1). As stated by the Polish Pain Society Guideline 2018, *i.v.* would be the preferred route of administration directly following the surgery. As of the following day, the patients can be administered analgesics orally (21). Both substances had been compared in many studies, but we failed to find any direct comparison of these two drugs after hysterectomy. The newly-published study by Viscusi et al. demonstrated statistically significant improvements of IR (immediate-release) TAP *vs* placebo and non-inferiority to morphine IR in women after abdominal hysterectomy and this is the first example of utilizing TAP in this particular group of patients (22).

There are studies proving that IR TAP has similar analgesic effects with fewer gastrointestinal side-effects than OXY (13, 23). In the latest study by O'Carroll (2018), however, TAP did not demonstrate either superior pain control or better tolerability compared to OXY in women post an elective Cesarean section (16).

In phase III clinical study, IR TAP and IR OXY had similar efficacy for pain after arthroscopic shoulder surgery, but a greater overall improvement would be reported by physicians for IR TAP (24). Haeseler et al. compared the ER form of TAP with oxycodone/naloxone in a study on orthopedic/trauma surgery pain, and TAP presented neither inferiority nor superiority over the reference drug (25).

In Cochrane meta-analysis by Santos et al. (2015), TAP was considered to be a better analgesic for chronic musculoskeletal pain than OXY – in terms of both safety and efficacy (10). Paris et al. developed an electronic spreadsheet-based cost calculator. In their study, they found that using IR TAP instead of traditional μ-opioid shows the potential for reduced gastrointestinal (GI) events and subsequent cost savings in the postsurgical hospital setting (26).

Nevertheless, there are also studies documenting the non-inferiority of TAP to OXY (27) and to oxycodone/naloxone, as mentioned (25, 28).

Based, among others, on the Haeseler's study (25) in our research, ER forms of both TAP and OXY were utilized. To our knowledge, this is the first study using ER forms of opioids for managing postoperative pain after hysterectomy. ER formulations are not commonly used in treating acute postoperative pain. However, the use of ER tablets of other analgesics was described in managing postoperative pain both in animal (29) and human trials (30-32). In Park study, for example, ER formula of tramadol proved to be non-inferior to IR tramadol in patients with acute pain following total knee replacement (30). Administration of ER forms of opioids may reduce their fluctuations in plasma levels which may result in better analgesia and reduction of side effects (25).

We conclude that TAP's analgesic effect is comparable with that of OXY for patients suffering from pain after abdominal hysterectomy. Both drugs are effective analgesics and can be successfully used

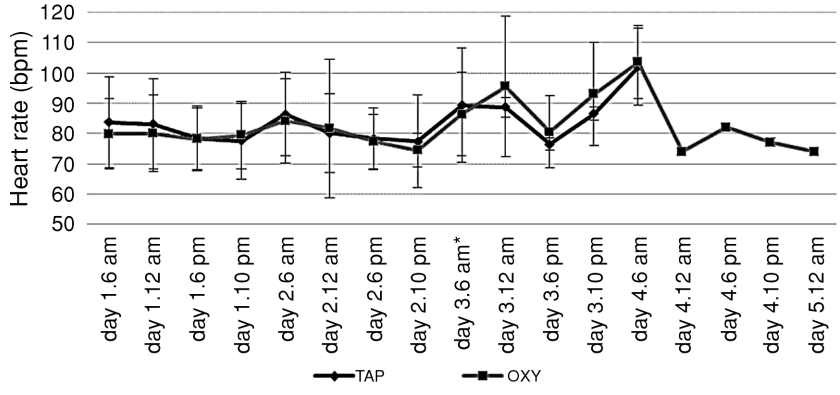

Figure 3. Heart rate (mean ± SD) in patients after open abdominal hysterectomy (n = 76) following oral administration of tapentadol and oxycodone. TAP – tapentadol OXY – oxycodone bpm – beats per minute.

interchangeably within the adopted conversion ratio (TAP : OXY 5 : 1).

This study failed to confirm the predominance of TAP in terms of adverse drug reactions (ADRs). In TAP group, most ADRs were more frequent and more intense, including post-operative nausea and vomiting (PONV). In terms of side effects, our study did not show any benefits of using tapentadol over oxycodone (Table 3, 4). GI events (nausea and vomiting) occurred even more frequently in TAP group. Other ADRs were greater in both frequency and magnitude in TAP group (Table 3 and 4). The only ADR that was lower in TAP group was sedation. The use of antiemetics was also greater in TAP group. Differences in ADRs were not statistically different.

As for the vital signs, we can confirm slightly less respiratory depression potential for TAP. This difference possibly arises from weaker MOR affinity of TAP compared to OXY.

In literature, there has been established property of lowering heart rate for escitalopram (SSRI-Selective Serotonin Reuptake Inhibitor drug) (33). Theoretical influence for serotonin circuit for TAP could also produce such effect, but we haven't noticed such a feature.

The ratios concerning additional data did not display any statistically significant differences. Therefore, we came to the conclusion that the type of opioid chosen after abdominal hysterectomy did not affect either length of stay or the patient's satisfaction with analgesia. We did not confirm the claim that TAP acting as a multimodal analgesic would reduce the length of hospital stay, similarly to the multimodal analgesia in Santoso's assay (19). This might be due to the fact that in Santoso's study multimodal analgesia consisted of many different drugs and procedures as opposed to classic opioid treatment. In our study, a single drug, albeit one presenting double mechanism, failed to be sufficiently "multimodal" to facilitate the time of discharge.

Summing up, a better analgesic efficacy came at the cost of lower tolerance, as stated by Haeseler et al. (25) in tapentadol and oxycodone/naloxone comparative study. The results of this study also suggest that the benefits of TAP over other opioids observed elsewhere may not be readily transferrable to the postoperative period in women after hysterectomy. Our results are similar to the study by O'Carroll, perhaps because of a certain resemblance to the surgery and the population (females only, lower abdomen incision).

There were some limitations to the study. The purpose of the comparison was to evaluate the efficacy and tolerance of both drugs under the conditions of daily practice at a gynecological department. As a consequence, there was heterogeneity in terms of the surgery operator and time of surgery. Different surgery hours resulted in different first postoperative movements on Day 1 that have not been included in the analgesic protocol.

The relatively small subgroup sizes limit the generalizability of the results. There was dissimilarity of the groups in terms of concomitant diseases, particularly noticeable for hypertension. Many patients had been taking antihypertensive drugs. Some of them had to be adjusted (doses changed or withdrawn) strictly after the surgery, according to clinical conditions. Such variation makes vital signs measurement less reliable. Considering this restriction, we restrained from sharp concluding about the effect of both drugs on blood pressure, even when statistical difference occurred.

The analgesic protocol on day 0 was unified and included *i.v.* administration of oxycodone. As a result, patients from TAP group could also experience reactions caused by partly eliminated oxycodone, particularly on day 1. If such a phenomenon occurs, further investigation – especially with pharmacokinetic determination – is required.

CONCLUSIONS

Tapentadol and oxycodone used are both effective analgesics used after abdominal hysterectomy. The analgesic efficacy of oral tapentadol is comparable with that of oral oxycodone. General satisfaction with treatment, length of stay after surgery, and effect on vital signs are comparable. Tapentadol presented more adverse drug reactions than oxycodone, but without any statistical difference. The conversion ratio for the two drugs is 5 : 1 (TAP : OXY). This study has limitations that are avoidable in further combined pharmacokinetic and pharmacodynamic studies.

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Conflict of interest

The authors declare no conflicts of interest.

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