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ORIGINAL ARTICLE

Tapentadol versus oxycodone analgesia and side effects after laparoscopic hysterectomy

A randomised controlled trial

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BACKGROUND Tapentadol is an opioid, which acts as a μ-opioid receptor agonist and inhibits noradrenaline reuptake in the central nervous system. This dual mechanism of action results in synergistic analgesic effects and potentially less side effects. This has been shown in treatment of chronic pain but postoperative studies are sparse.

OBJECTIVES The main aim was to compare the analgesic effect of tapentadol with oxycodone after laparoscopic hysterectomy. Opioid side effects were recorded as secondary outcomes.

DESIGN Randomised, blinded trial.

SETTING Single-centre, Oslo University Hospital, Norway, December 2017 to February 2019.

PATIENTS Eighty-six opioid-naïve American Society of Anesthesiologists physical status 1 to 3 women undergoing laparoscopic hysterectomy for nonmalignant conditions.

INTERVENTION The patients received either oral tapentadol (group T) or oxycodone (group O) as part of multimodal pain treatment. Extended-release study medicine was administered 1 h preoperatively and after 12 h. Immediate-release study medicine was used as rescue analgesia.

MAIN OUTCOME MEASURES Pain scores, opioid consumption and opioid-induced side effects were evaluated during the first 24 h after surgery.

RESULTS The groups scored similarly for pain at rest using a numerical rating scale (NRS) 1 h postoperatively (group T 4.4, 95% CI, 3.8 to 5.0, group O 4.6, 95% CI, 3.8 to 5.3). No statistically significant differences were found between the groups for NRS at rest or while coughing during the 24-h follow-up period ($P = 0.857$ and $P = 0.973$). Mean dose of oral rescue medicine was similar for the groups ($P = 0.914$). Group T had significantly lower odds for nausea at 2 and 3 h postoperatively ($P = 0.040$, $P = 0.020$) and less need for antiemetics than group O. No differences were found for respiratory depression, vomiting, dizziness, pruritus, headache or sedation.

CONCLUSION We found tapentadol to be similar in analgesic efficacy to oxycodone during the first 24 h after hysterectomy, but with significantly less nausea.

TRIAL REGISTRATION ClinicalTrials.gov, NCT03314792.

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Introduction

Opioids remain first-line drugs as part of multimodal postoperative pain treatment but the use of opioids is limited by well known side effects. Most feared in the postoperative setting is respiratory depression but nausea, vomiting, constipation, pruritus, sedation, dizziness and headache may also cause patient discomfort or complications.[1,2] Given these limitations from pure opioid agonists, the search for strong analgesics with a better side effect profile in postoperative pain treatment is highly relevant.[3]

Tapentadol is a new mixed ligand opioid, which acts as a μ-opioid receptor (MOR) agonist and also inhibits noradrenaline reuptake in the central nervous system.[4] This dual mechanism of action is believed to result in synergistic analgesic effects.[5,6] As opioid side effects are

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strongly related to MOR stimulation, tapentadol is expected to have less side effects than the pure opioid agonists.[6,7]

Tapentadol has been shown to be effective for acute and chronic nociceptive, neuropathic or cancer-related pain,[7,8] but there is a lack of broad-based evidence for tapentadol in the postsurgical setting.[9] To our knowledge, the published studies on analgesic effects from tapentadol are mainly industry-funded studies on orthopaedic and dental patients,[10–12] and few are related to procedures with major components of visceral pain, such as laparoscopy.[13,14] A review of tapentadol studies in the postoperative setting indicated less nausea, vomiting, constipation and pruritus compared with oxycodone but no difference in somnolence, headache or dizziness.[10] Studies on respiratory depression from tapentadol in any setting are sparse.[9,12]

The aim of this study was to compare the analgesic effect of tapentadol with oxycodone during the initial 24-h period after laparoscopic hysterectomy. The primary outcome was pain at rest 1 h postoperatively but pain at rest and while coughing were also recorded at several time points during the first 24 h postoperatively. Further secondary outcomes were nausea, vomiting, respiratory depression, sedation, pruritus, dizziness, headache, need for rescue medication and overall satisfaction with pain treatment.

Methods

The protocol of this randomised, parallel group, blinded, single-centre study on women undergoing elective laparoscopic supracervical or total hysterectomy for nonmalignant conditions was approved by the Regional Committee for Medical and Health Research Ethics in Eastern Norway (Chairperson Prof B-I Nesheim; 31 May 2017; protocol number 2017–001285-23) and the Norwegian Medicines Agency. The study was registered at clinicaltrials.gov (NCT03314792) and EudraCT (2017-001285-23). The study was independently monitored by the Clinical Trial Unit at Oslo University Hospital, and data analysis was performed after the final monitor report was done to ensure that requirements for Good Clinical Practice and the Declaration of Helsinki were met.

Women aged between 18 and 65 years and classified as American Society of Anesthesiologists physical status 1 to 3 were included after written informed consent was obtained. Patients with weight less than 55 kg or more than 85 kg, or body mass index greater than 31 kg m^{-2}, were excluded. Other exclusion criteria were chronic pain syndromes in organ systems other than the female reproductive system, severe heart, lung, liver or kidney failure, severe psychiatric disorders, malignancy in the previous 5 years, chronic medication with opioids, steroids, benzodiazepines, gabapentinoids, tramadol, clonidine or serotonin-noradrenaline reuptake inhibitors, alcohol or drug abuse and allergy or intolerance to any medication in the study.

The patients' demographic data and preoperative risk factors for postoperative pain, such as pain from any organ system, analgesics used during the last 4 weeks, disposition for catastrophising and episodes of anxiety or depression were recorded. Previous postoperative nausea and vomiting (PONV), disposition for motion sickness and smoking status were registered and used to calculate the Apfel score for prediction of PONV.[15] The patients were instructed in the use of the numerical rating scale (NRS) to rate pain verbally on a scale from 0 to 10 (0 = no pain, 10 = worst pain imaginable).

Dosing was based on previous studies on surgical patients, showing approximately 1 : 5 equipotency in analgesic effect between oral oxycodone and tapentadol.[9,16] Oral tapentadol depot 50 mg (Grünenthal GmbH, Aachen, Germany) was chosen as the equivalent extended-release medicine to oral oxycodone depot 10 mg (Mundipharma Pharmaceuticals, Cambridge, UK), and immediate-release oral tapentadol 50 mg as the equivalent to oxycodone 10 mg for rescue medicine.

According to a computer-generated code, using block randomisation by blocks of 10, patients were allocated to receive either tapentadol (group T) or oxycodone (group O) during the study period. Patients in group T received oral extended-release tapentadol 50 mg and group O received oral extended-release oxycodone 10 mg as part of premedication. After 12 h, all patients received an additional dose of extended-release study medication. Immediate-release tapentadol 50 mg or oxycodone 10 mg were available as rescue medications. Study medication was distributed in opaque, identical looking dosing boxes prepacked by a physician not participating in the treatment or evaluation of the patients. A dummy dosing box was demonstrated to the patients at the time of inclusion in order to prepare them for self-administration of rescue medicine. The researchers involved in inclusion, treatment and evaluation of the patients were blinded to which study medication the patients received.

All patients also received paracetamol (1.5 g for <60 kg, 2.0 g for ≥60 kg) and etoricoxib (90 mg for <60 kg, 120 mg for ≥60 kg) as oral premedication. Metronidazole 1.5 g and cefuroxime 1.5 g were administered intravenously as prophylactic antibiotics. The patients underwent surgery under general anaesthesia with propofol and remifentanil. Rocuronium 0.6 mg kg^{-1} was administered only when required for surgical access. All patients received intravenous dexamethasone 8 mg and ondansetron 4 mg, and 20 ml of bupivacaine 0.25% was infiltrated at the incision sites. Fentanyl 2 μg kg^{-1} was given intravenously 10 min before the end of surgery. Monitoring constituted ECG, pulse oximetry, noninvasive blood pressure and end-tidal carbon dioxide ($ETCO_2$).

Immediate-release study medication was available for breakthrough pain both in the postanaesthesia care unit (PACU) and in the gynaecological ward. In the PACU, intravenous fentanyl 1 $\mu g\,kg^{-1}$ was allowed as rescue medicine for initial urgent pain relief. Rescue analgesic medication was titrated according to effect in patients who rated pain as 4 or more on the NRS and requested additional analgesia. The patients also received oral paracetamol every 6 h during the study period. Intravenous metoclopramide 10 mg was the drug of choice for PONV, followed secondly by ondansetron 4 mg and thirdly droperidol 0.625 mg.

The primary outcome, pain at rest 1 h postoperatively, was evaluated with the NRS. Pain at rest and while coughing was recorded at 15 and 30 min, 1, 2, 3 and 24 h postoperatively as secondary outcomes. Furthermore, nausea, vomiting, pruritus, dizziness, headache, sedation, respiratory rate and use of rescue medication were recorded at 30 min, 1, 2, 3 and 24 h postoperatively. Nausea, vomiting, pruritus, dizziness and headache were yes/no questions, whereas sedation was scored using the Pasero opioid-induced sedation scale (S = sleep; 1 = awake; 2 = slightly drowsy; 3 = frequently drowsy; 4 = somnolent).[17] The cumulative doses of rescue analgesics were recorded in micrograms for fentanyl and number of immediate-release study medications taken. Time to first requirement of intravenous or oral rescue medicine was registered. Oxygen saturation (SpO_2) and nasal $ETCO_2$ were monitored continuously [Smart CapnoLine Plus O_2 (Oridion Medical 1987 Ltd., Jerusalem, Israel), IntelliVue MX500 and X2 (Philips Healthcare, Böblingen, Germany)] and data collected at 30 min, 1, 2, 3 and 24 h (SpO_2 only) postoperatively. At the end of the study, overall patient satisfaction with pain treatment, taking into consideration both analgesic effect and side effects, was evaluated using a five-point scale (0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent).

Statistical analysis

In a previous study on oxycodone after hysterectomy, we found that patients at rest had a mean NRS pain score of 4 with a standard deviation (SD) of 1.5 at 1 h postoperatively.[18] Using these data, the statistical power of 80% and a significance level alpha of 5%, we would need 36 patients in each group to reveal a clinically relevant difference of 1 unit on the NRS.

Continuous data are presented as mean ± SD, and categorical data as counts and percentages. Confidence intervals (CI) for the means were constructed using bootstrapping. Data were analysed using the independent samples *t*-test for parametric data, the Mann–Whitney *U*-test for nonparametric data and the χ^2-test for categorical data. Some of the secondary outcomes were also analysed using generalised mixed models for repeated measures with identity link for continuous data or logit link for categorical data whenever appropriate. These results are expressed as odds ratios (OR) with 95% CI and the baseline defined as 30 min postoperatively. All models were fitted with type of treatment, time and an interaction term time × type of treatment to assess if the development over time differed between the two treatments.

The significance level was set at 0.05. As the study was considered exploratory for the secondary outcomes, no correction for multiple testing was performed for these measures. All tests were two-sided and statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, New York, USA) and Stata version 16 (StataCorp LP, College Station, Texas, USA).

Results

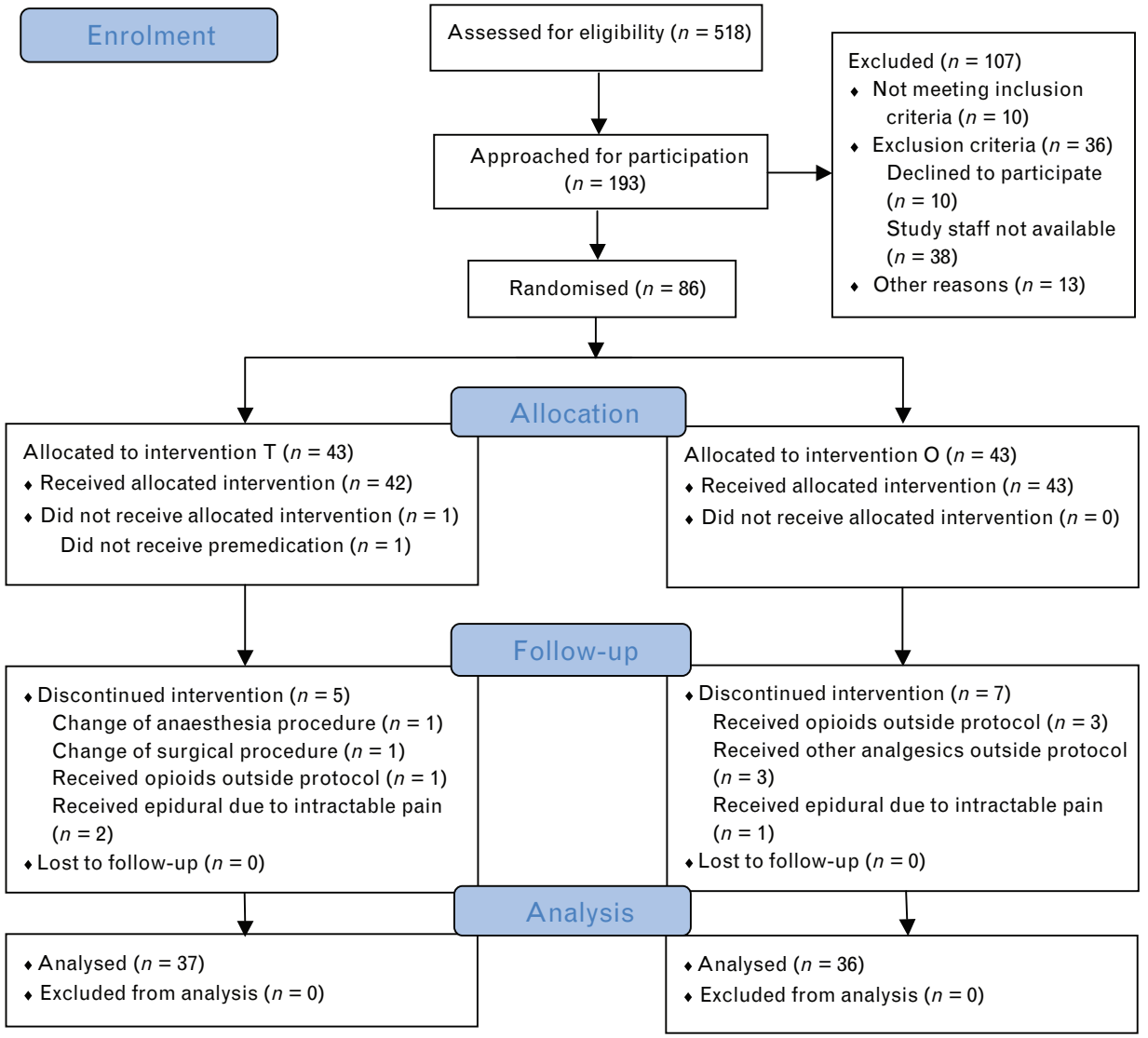
Recruitment was from 16 December 2017 to 28 February 2019 at Oslo University Hospital. Of 518 potentially eligible patients, 193 patients were approached for participation and 86 were enrolled and entered into the study (Fig. 1). The final evaluation included 37 patients allocated to the tapentadol group and 36 patients to the oxycodone group. Demographic and baseline subject characteristics, including preoperative risk factors for postoperative pain and nausea, as well as intra-operative variables, were similar between the two groups (Table 1).

The mean level of pain was similar in both groups when assessed with the NRS at rest 1 h postoperatively (group T 4.4, 95% CI, 3.8 to 5.0 vs. group O 4.6, 95% CI, 3.8 to 5.3) (Fig. 2).

The groups were also similar in respect of pain while coughing at 1 h postoperatively; the mean NRS was 5.1 (95% CI, 4.4 to 5.8) in group T and 5.3 (95% CI, 4.6 to 6.0) in group O (Fig. 3). There were no statistically significant differences between the groups for NRS at rest or NRS while coughing over time when considering the whole 24 h follow-up period ($P = 0.857$ and $P = 0.973$; Figs. 2 and 3). Mean ± SD dose of intravenous rescue fentanyl was 279 ± 175 μg in group T and 238 ± 138 μg in group O, whereas mean numbers for oral rescue medicine were 3.8 ± 1.7 and 3.0 ± 1.6 in group T and group O, respectively. Furthermore, no statistically significant differences were found between the groups for rescue medication doses of fentanyl or oral immediate-release study medication over time ($P = 0.619$ and $P = 0.914$). The groups were also similar in respect of time to first dose of intravenous rescue medicine (group T 15 ± 15 vs. group O 19 ± 15 min) and oral rescue medication (group T 28 ± 26 vs. group O 27 ± 20 min).

At 24 h, 44% of patients in group O reported nausea vs. 22% in group T ($P = 0.038$, Table 2). Both groups had significantly increased odds for nausea over time compared with baseline (OR 3.3, 95% CI, 1.2 to 9.5; $P = 0.026$). When estimating the interaction between groups and time, we found that group T had significantly lower odds for nausea than group O at 2 and 3 h postoperatively compared with

Fig. 1 CONSORT study flow chart



O, oxycodone; T, tapentadol.

baseline ($P = 0.040$ and $P = 0.020$), with a trend towards significance at 24 h ($P = 0.060$). There was also a significantly higher need for antiemetics and repeated administrations of antiemetics in group O as shown in Table 2. Relatively few patients vomited during the observation period (Table 2), and while the odds for vomiting were numerically higher for group O, the odds ratio was not significant (OR 1.7, 95% CI, 0.6 to 4.9; $P = 0.371$).

There were no significant differences in mean values for respiratory variables between the groups (Table 3). When analysing $ETCO_2$, SpO_2 and respiratory rate over time compared with baseline, no significant differences between odds ratios were observed ($P = 0.771$, $P = 0.441$ and $P = 0.220$, respectively). Furthermore, we did not find any significant differences between the groups when examining the incidences of dizziness, pruritus, headache or sedation (Table 3) or when estimating the odds for these outcomes (data not shown). The proportions of patients who scored their satisfaction with pain treatment as high (scores good, very good and excellent satisfaction pooled) were similar (group T 89% and group O 97%; $P = 0.364$). No relevant serious adverse events were reported during the study.

Discussion

We have shown that tapentadol was not significantly different from oxycodone for treatment of acute postoperative pain after hysterectomy. The pain intensity at rest

Table 1 Patient characteristics and intra-operative variables

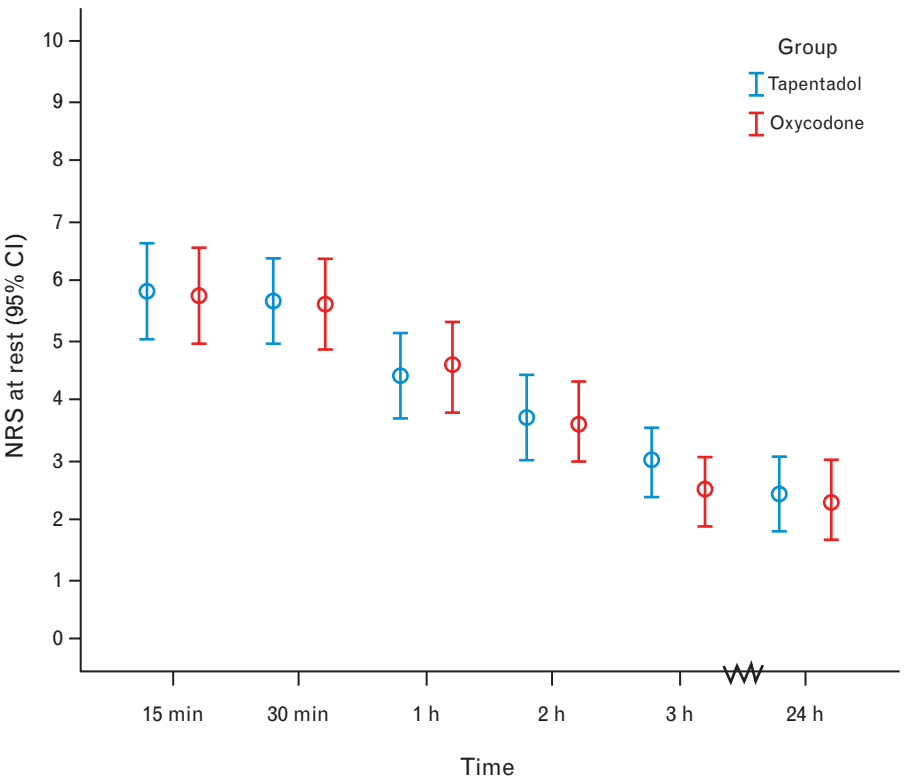
	Tapentadol ($n=37$)	Oxycodone ($n=36$)
Age (years)	43.1 ± 5.9	44.6 ± 7.4
ASA physical status 1/2/3	27/10/0	26/10/0
Height (cm)	168 ± 5	167 ± 5
Weight (kg)	68 ± 9	67 ± 9
BMI (kg m^{-2})	24.0 ± 3.3	24.1 ± 2.6
Apfel score	2.6 ± 0.6	2.7 ± 0.5
Pain related to surgical area last week before surgery (NRS)	2.8 ± 2.8	2.9 ± 3.2
Pain in other organ systems last week before surgery (NRS)	1.9 ± 2.3	1.1 ± 2.1
Any type of analgesic last 4 weeks before surgery	24 (65)	23 (63)
Anxiety	6 (17)	6 (21)
Depression	11 (31)	9 (24)
Catastrophisers	4 (11)	2 (6)
SpO_2 before surgery	99.3 ± 0.9	99.6 ± 0.8
Anaesthesia duration (min)	130 ± 28	133 ± 33
Surgery duration (min)	83 ± 30	86 ± 31
Type of surgery (LH/LSH)	84/16	81/19
Total propofol (mg)	1046 ± 238	1078 ± 286
Total remifentanil (μg)	1636 ± 538	1739 ± 635
Intra-operative fentanyl dose (μg)	136 ± 18	133 ± 17
Intra-operative muscle relaxant	3 (8)	2 (6)

Values are mean ± SD, number of patients or number (%). BMI, body mass index; LH, laparoscopic hysterectomy; LSH, laparoscopic supracervical hysterectomy; SpO_2, peripheral capillary oxygen saturation.

was similar not only at 1 h postoperatively, which was the primary outcome, but throughout the 24-h study period for both pain at rest and while coughing. Tapentadol was favourable in terms of less nausea and need for antiemetics, but there were no differences between the groups for respiratory depression, vomiting, dizziness, sedation, pruritus or headache.

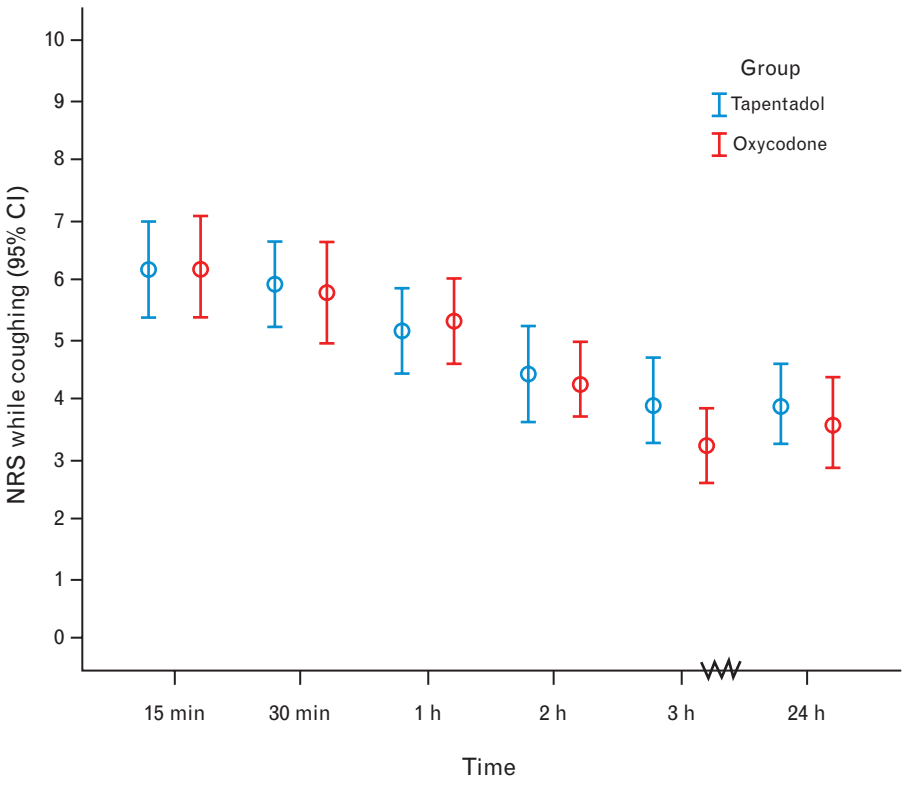
Our results are in agreement with previous findings on tapentadol after dental or orthopaedic surgery, indicating

Fig. 2 Pain measured with numerical rating scale at rest



Values are plotted as mean with 95% confidence interval.

Fig. 3 Pain measured with numerical rating scale while coughing



Values are plotted as mean with 95% confidence interval.

comparable analgesic effects with oxycodone, but less nausea.[9,10,19–21] Two systematic reviews on tapentadol versus oxycodone, morphine, tramadol or placebo included both postoperative and musculoskeletal pain.[11,12] The reviews concluded with similar analgesic effects from tapentadol compared with other opioids but less gastrointestinal side effects and dizziness from tapentadol. Although our findings are partially in accordance with these systematic reviews, the patient data are not fully comparable. Most of the studies in the reviews were on orthopaedic patients, and the results from a sole hysterectomy study have not been published in a peer-review journal to date. Also, the inclusion of patients with musculoskeletal pain in the reviews may result in findings that are not relevant to postoperative pain. All studies in the reviews were on immediate-release tapentadol but we have found one study comparing extended-release tapentadol with oxycodone.[13] The study was on parturients 24 to 48 h after caesarean section and failed to prove superiority of tapentadol over oxycodone. They found no differences in side effects, but there was uneven administration of antiemetics between the groups as this was not standardised in the protocol, which could have affected reported gastrointestinal side effects. As PONV affects recovery, complications, discharge and overall satisfaction after surgery,[22,23] tapentadol may be a favourable drug in the postoperative setting. Moreover, the resulting need for less antiemetics with potential side effects would be beneficial.

Table 2 **Comparison of secondary outcomes related to nausea and vomiting**

	Tapentadol ($n=37$)	Oxycodone ($n=36$)	*P*
Nausea 30 min, baseline	13.5	11.1	1.000
Nausea 1 h	16.2	8.3	0.479
Nausea 2 h	10.8	8.3	1.000
Nausea 3 h	8.1	19.4	0.190
Nausea 24 h	21.6	44.4	0.038[a]
Vomiting 30 min, baseline	2.7	0	1.000
Vomiting 1 h	2.7	0	1.000
Vomiting 2 h	0	5.6	0.240
Vomiting 3 h	0	5.6	0.240
Vomiting 24 h	18.9	27.8	0.417
Any antiemetic	48.6	72.2	0.040
Antiemetic several administrations	21.6	44.4	0.038

Values are percentage of patients. [a]No correction for multiple testing.

The most feared opioid side effect is respiratory depression because of its potentially fatal outcome.[2,24] An experimental study found a significantly larger respiratory depressant effect from oxycodone 20 mg than tapentadol 100 mg when measuring the ventilatory response to hypercapnia and ventilation at an extrapolated $ETCO_2$ of 7.3 kPa.[25] We have only found one clinical study

Table 3 Comparison of secondary outcomes related to respiration, dizziness, pruritus, headache, sedation and overall satisfaction with pain treatment

	Tapentadol ($n=37$)	Oxycodone ($n=36$)	*P*
Incidents of $ETCO_2$ >7 kPa first 3 h	0	0	
Incidents of respiratory rate <10 min^{-1} first 3 h	6 (16.2)	8 (22.2)	0.512
Respiratory rate 30 min (breath min^{-1})	12.8 ± 2.7	13.8 ± 2.9	0.070
Respiratory rate 1 h (breath min^{-1})	13.7 ± 2.9	13.2 ± 2.8	0.472
Respiratory rate 2 h (breath min^{-1})	14.5 ± 2.9	13.5 ± 2.8	0.150
Respiratory rate 3 h (breath min^{-1})	14.7 ± 2.8	13.8 ± 2.7	0.159
Respiratory rate 24 h (breath min^{-1})	16.0 ± 2.4	15.0 ± 2.2	0.155
$ETCO_2$ 30 min (kPa)	4.8 ± 0.6	4.8 ± 0.6	0.853
$ETCO_2$ 1 h (kPa)	4.8 ± 0.6	4.8 ± 0.6	0.834
$ETCO_2$ 2 h (kPa)	4.9 ± 0.5	4.8 ± 0.4	0.320
$ETCO_2$ 3 h (kPa)	4.8 ± 0.5	4.9 ± 0.4	0.868
SpO_2 30 min (%)	98.2 ± 2.2	98.4 ± 1.8	0.949
SpO_2 1 h (%)	98.5 ± 1.9	99.1 ± 1.1	0.293
SpO_2 2 h (%)	97.7 ± 1.9	97.8 ± 2.1	0.827
SpO_2 3 h (%)	97.1 ± 1.7	97.5 ± 1.6	0.214
SpO_2 24 h (%)	97.3 ± 1.3	97.6 ± 1.4	0.300
Dizziness 30 min	9 (24.3)	7 (19.4)	0.659
Dizziness 1 h	12 (32.4)	7 (19.4)	0.206
Dizziness 2 h	11 (29.7)	6 (16.7)	0.187
Dizziness 3 h	9 (24.3)	8 (22.2)	0.832
Dizziness 24 h	12 (32.4)	19 (52.7)	0.079
Pruritus 30 min	0	1 (2.7)	0.486
Pruritus 1 h	2 (5.4)	5 (13.8)	0.261
Pruritus 2 h	7 (18.9)	5 (13.8)	0.562
Pruritus 3 h	6 (16.2)	8 (22.2)	0.515
Pruritus 24 h	6 (16.2)	9 (25)	0.321
Headache 30 min	2 (5.4)	0	0.493
Headache 1 h	0	0	
Headache 2 h	0	0	
Headache 3 h	1 (2.7)	0	1.000
Headache 24 h	8 (21.6)	3 (8)	0.113
Sedation 30 min (Pasero scale S/1/2/3/4)	3/19/12/3/0	3/10/20/3/0	0.167
Sedation 1 h (Pasero scale S/1/2/3/4)	6/20/9/2/0	6/17/12/1/0	0.803
Sedation 2 h (Pasero scale S/1/2/3/4)	7/23/7/0/0	6/17/13/0/0	0.319
Sedation 3 h (Pasero scale S/1/2/3/4)	6/25/6/0/0	9/23/3/1/0	0.460
Sedation 24 h (Pasero scale S/1/2/3/4)	2/35/0/0/0	4/32/0/0/0	0.334
Overall satisfaction 24 h (0/1/2/3/4)	0/4/6/13/14	0/1/8/17/10	0.364

Values are mean ± SD, number of patients or number (%). $ETCO_2$, end-tidal carbon dioxide partial pressure; SpO_2, peripheral capillary oxygen saturation.

evaluating respiratory depression from tapentadol as part of safety assessments.[19] The authors claim that all incidents of low SpO_2 in the study could have been because of technical failure of the pulse oximetry device and conclude that there was no evidence that tapentadol caused respiratory depression. However, opioid-induced respiratory depression is difficult to measure and has no clear definition in the literature, with arbitrary thresholds for desaturation, bradypnoea and hypercapnia.[2] In our study, we chose to monitor respiratory rate, $ETCO_2$ and SpO_2 based on previous studies,[24,26] and we found no differences between the groups in any of these respiratory parameters. Continuous measurement of $ETCO_2$ has been shown to be a more sensitive measure than SpO_2 for respiratory depression.[27] Even though $ETCO_2$ was recorded only at set time points for study purposes in our study, there were no reports of $ETCO_2$ out of range during continuous monitoring in the PACU. Although there were some incidents of respiratory rate less than 10 breath min^{-1} in both groups, they were resolved by verbal stimulation of the patient, leaving no clinical impact on oxygenation.

Reduction of opioid side effects is important in postoperative pain treatment to reduce complications and shorten hospital stay.[23] In terms of patient comfort, a previous study has shown that patients will accept some level of pain if opioid side effects are reduced.[28] The side effects from tapentadol in surgical patients need further exploration in clinical studies.

Our study has some limitations. Due to the matrix construction of depot tablets and capsule format of immediate-release oxycodone, it was not possible to re-encapsulate the study medication into identical units for optimal blinding of the groups. Another limitation is our choice of intravenous opioid for urgent pain relief during the initial period in the PACU. Tapentadol is not licensed for intravenous use in Europe, so intravenous fentanyl was chosen as rescue medication. Fentanyl predominantly affects MORs but the fentanyl doses were low and similar between the groups, so we cautiously contend that our findings are associated with tapentadol. Opioid-induced hyperalgesia may be a problem with our study design of preoperative opioids in combination with a peri-operative remifentanil infusion. However, any potential hyperalgesia induced by opioids could have been limited by the Cox-II inhibitor etoricoxib, total intravenous anaesthesia with propofol and low-dose remifentanil administered to all patients in the study.[29–31] As the remifentanil dose was identical in both study groups it should not have interfered with the interpretation of the main study results. As tapentadol has been studied in the postoperative setting very rarely, the design of combined preoperative and postoperative study medication was chosen in order to tease out potential differences between the study medications in the immediate postoperative period, not necessarily reflecting an ideal setup in clinical practice. It may also be a limitation that data from three patients who received epidural analgesia because of severe pain were not included. These patients received an epidural early in the study period, and further analgesic effects of the study drugs were overruled by the effective epidural analgesia. The study was limited to healthy, adult women, so we cannot extrapolate our findings to men as there may be differences in opioid analgesic potency and side effects between the sexes.[32] Finally, the study is limited to patients without preoperative chronic pain syndromes or chronic opioid therapy, which can be important confounders for postoperative pain.

The patients were studied for only 24 h after surgery as a previous study on the same patient population by our research group had shown no need for extended-release opioids at regular intervals beyond 24 h when treated with immediate-release opioids prn., paracetamol and

nonsteroidal anti-inflammatory drugs.[18] A strength of our study is the consideration of predisposing factors for increased postoperative pain: anxiety, depression, catastrophising, pain and use of analgesics before surgery. As these factors were equally distributed between the groups, they are not expected to be confounders to the pain results of the study. We also believe that this study is one of the first independently funded studies to explore the effects of extended-release and immediate-release tapentadol versus oxycodone on visceral pain, as the majority of previous studies have been industry-sponsored studies on tapentadol immediate-release after orthopaedic or dental surgery.[11] The overall evaluation of pain treatment was positive in more than 93% of the patients, indicating that both tapentadol and oxycodone work well as part of a multimodal treatment with paracetamol, nonsteroidal anti-inflammatory drugs and steroids for postoperative pain.

In conclusion, we found tapentadol to be similar in analgesic efficacy to oxycodone in the first 24 h after hysterectomy. Tapentadol resulted in less nausea than oxycodone but no differences were found for respiratory depression, vomiting, dizziness, pruritus, headache, sedation or patient satisfaction.

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Conflicts of interest: none.

Presentation: none.

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