

PAIN

# Oral oxycodone offers equivalent analgesia to intravenous patient-controlled analgesia after total hip replacement: a randomized, single-centre, non-blinded, non-inferiority study

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## Editor's key points

- Total hip replacement causes moderate-to-severe pain that must be adequately treated in order to facilitate recovery.
- There is no one method of postoperative analgesia that has been shown to be better, but there are potential advantages to using effective oral analgesia.
- This study demonstrates that as part of a multimodal analgesic regimen, oral oxycodone (OOXY) provides equivalent analgesia to i.v. patient-controlled analgesia (IVPCA) with morphine.
- Oral OOXY and PCA morphine have a similar side-effect profile, with a small but significant reduction in the antiemetic use from oral OOXY.

**Background.** To determine if oral oxycodone (OOXY) could provide equivalent postoperative analgesia and a similar side-effect profile to i.v. patient-controlled morphine in patients undergoing elective primary total hip replacement (THR) under spinal anaesthesia.

**Methods.** We studied 110 consecutive patients aged 60–85 yr. After operation, patients were randomly allocated to receive either oral controlled- and immediate-release OOXY or i.v. patient-controlled analgesia (IVPCA) with morphine. Both groups received regular co-analgesia and antiemetics. The primary outcome measures were: (i) postoperative pain at rest and movement and (ii) nausea score recorded 12 hourly. The secondary outcome measures were: (i) time to first mobilization, (ii) total amount of opioid consumed, (iii) number of additional antiemetic doses, and (iv) time to analgesic discontinuation.

**Results.** There were no statistically significant differences in the primary outcome measures of pain at rest and movement ( $P > 0.05$ , 95% confidence intervals  $-0.41$ ,  $+0.96$ ) or nausea score ( $P > 0.5$ ). The secondary outcome measures showed no significant difference in the total amount of opioid consumed (102 vs 63 mg;  $P > 0.05$ ) or time to mobilization (24.45 vs 26.6 h,  $P = 0.2$ ). The number of antiemetic doses required in the first 24 h was significantly lower in the OOXY group (1.1 vs 1.4,  $P < 0.05$ ). The time to analgesic discontinuation was significantly shorter in the OOXY group (50.5 vs 56.6 h,  $P < 0.05$ ). Oral analgesia with OOXY was approximately GBP 10 less expensive per patient than IVPCA.

**Conclusions.** Oral analgesia with OOXY after THR offers non-inferior analgesia to IVPCA and may offer some logistical and cost advantages.

**Keywords:** analgesia, patient-controlled; analgesics opioid, morphine, oxycodone; surgery, orthopaedic

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Anaesthesia and analgesia for total hip replacement (THR) is challenging, as patients may be elderly and have significant co-morbidities. Although a consensus is emerging that THR should be performed under neuroaxial block (spinal or epidural anaesthesia),<sup>1</sup> there are many different regimens for postoperative pain relief.<sup>2</sup> I.V. patient-controlled analgesia (IVPCA) using morphine is commonly used,<sup>3</sup> but requires trained staff and expensive equipment.<sup>4</sup> IVPCA may delay mobilization and patients may have difficulty understanding or operating the device. Consequently, oral analgesic administration appears to offer many attractions.

The pain after THR is usually moderate to severe, and simple analgesics and non-steroidal anti-inflammatory

drugs are insufficient to control it. The choice of strong oral opioid presents some difficulties: oral morphine is cheap, but has low and unpredictable bioavailability<sup>5</sup> and may be unsuitable for use in the acute pain setting where rapid titration and predictable effect are essential.<sup>6,7</sup> The absorption of oral controlled-release oxycodone (OOXY) is significantly more consistent than that of oral controlled-release morphine<sup>6</sup> and it is effective in alleviating the postoperative pain associated with several types of surgery.<sup>8–11</sup>

We compared oxycodone hydrochloride with IVPCA after THR (immediate-release Oxynorm<sup>®</sup>, controlled-release Oxycotin<sup>®</sup>; NAPP Pharmaceuticals, Cambridge, UK)<sup>12</sup> with the aim of assessing analgesic equivalence.

## Methods

The study was approved by our local ethics committee (Ref: 07/H1002/76). Written informed consent was obtained from all subjects. The study was conducted in accordance with ICH-GCP. At the time of study approval, registration in a clinical trial database was not a prerequisite for publication.

### Inclusion criteria

Patients undergoing THR, age 60–85 yr, ASA health status class I–III, and willing to undergo spinal anaesthesia.

### Exclusion criteria

Weight <45 kg, long-term strong opioid therapy before operation (regular codeine or tramadol was permitted); abnormal preoperative mental status; inability to operate the IVPCA device; or known allergy to OXY or morphine.

### Conduct of the study

Before surgery, patients were instructed in the use of the IVPCA device and on the use of the 0–10 numerical pain rating scale (NRS). A total of 114 randomly ordered sealed envelopes were prepared; half contained details of the oral OXY group and half the IVPCA group. After a successful spinal block was achieved, randomization to either of the two arms of the trial was by opening the next envelope in the series.

### Anaesthesia

No premedication was given. Spinal anaesthesia was performed at an appropriate lumbar interspace in an aseptic fashion using standard 25 G Whitacre needles (Smiths Medical, Ashford, UK). Clonidine 75 µg in 0.5% hyperbaric bupivacaine was injected with a total injectate volume of 2.2–2.7 ml. Sedation was achieved with either i.v. midazolam or a continuous propofol infusion. Patients were given 1 mg of granisetron as antiemetic.

After a successful spinal block was established, the sealed envelope was opened and the patient assigned to IVPCA or OXY. The envelope contained instructions on the drugs to give before operation, data collection sheets, and pre-printed prescription labels to be attached to the drug chart.

All patients had successful spinal anaesthesia and had no pain on arrival in recovery. The OXY group were given oral OXY slow release (Oxycontin) 20 mg and were reminded to ask for additional oral analgesia when required. IVPCA patients had a PCA infusion commenced with i.v. morphine. The IVPCA settings were 1 mg bolus, 5 min lockout time, and no loading dose. IVPCA patients were re-educated to use the PCA device and were asked to give themselves two bolus doses of 1 mg morphine to confirm they could operate the device. If pain occurred in the recovery area titration to adequate analgesia (NRS ≤ 3) was achieved with extra oral OXY on the OXY group, or i.v. morphine boluses from the pump in the IVPCA group. Any analgesia given in recovery was included in the total opioid consumption record.

All patients received oral paracetamol 1 g, oral diclofenac 50 mg, and oral prochlorperazine 10 mg in recovery.

### Postoperative care

After operation, both groups received regular paracetamol 1 g orally 6 hourly; diclofenac 50 mg orally 8 hourly for 5 days with omeprazole 20 mg once daily if required; and prochlorperazine 10 mg orally 12 hourly for 3 days.

All patients were prescribed oral or i.m. cyclizine 50 mg and ondansetron 4 mg as required for postoperative nausea and vomiting (PONV). Oral tramadol 50–100 mg 6 hourly was used as step-down analgesia after the discontinuation of the IVPCA or OXY.

IVPCA patients continued with the PCA until either they wished to discontinue it or they were using <1 mg h<sup>-1</sup>.

OXY patients were given 20 mg controlled-release OXY (Oxycontin™) 12 hourly for 3 days or until they wished to discontinue. Breakthrough analgesia was provided by 10 mg immediate-release OXY (OxyNorm™) up to every 4 h as required.

### Data handling

To minimize observer bias, we separated patient observations taken during the study period from the collection of data afterward: all patients underwent routine postoperative nursing observations, including pain and nausea scoring, by ward staff in the standard fashion. Once the 72 h study period was completed, data for the study were transcribed from the study patients' observation charts, drug charts, and the hospital notes, by a member of the study team. Data were entered into a custom database (Filemaker Pro, Filemaker UK) and analysed by a different team member. Postoperative pain scores (NRS 0–10) at rest and movement were collected 4 hourly. Data collection commenced when the patient was transferred from the recovery room to the ward and continued for 72 h thereafter. Nausea scores (0–4 scale: 0, no nausea; 1, mild nausea; 2, antiemetic given; 3, nausea despite antiemetic; 4, vomiting) and number of doses of antiemetic given were recorded every 12 h. The time to mobilization, duration of the use of IVPCA or OXY, and total amount of analgesia used were also recorded.

### Statistics

#### Power calculation

Assuming that the NRS pain scores were normally distributed, and with type I and II errors of 0.05 and 0.20, respectively, with a limit of equivalence of 1 (on a 10-point NRS) and a standard deviation (SD) in the population of 1, then a total of 102 patients (51 patients per group) would be required to prove equivalence. If the sample size in each group was 51, a two-group 0.05 one-sided *t*-test would have 80% power to reject the null hypothesis that the test and SD are not equivalent in favour of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0.00 and the common SD is 1.00 (nQueryAdvisor, Version 3). Like all

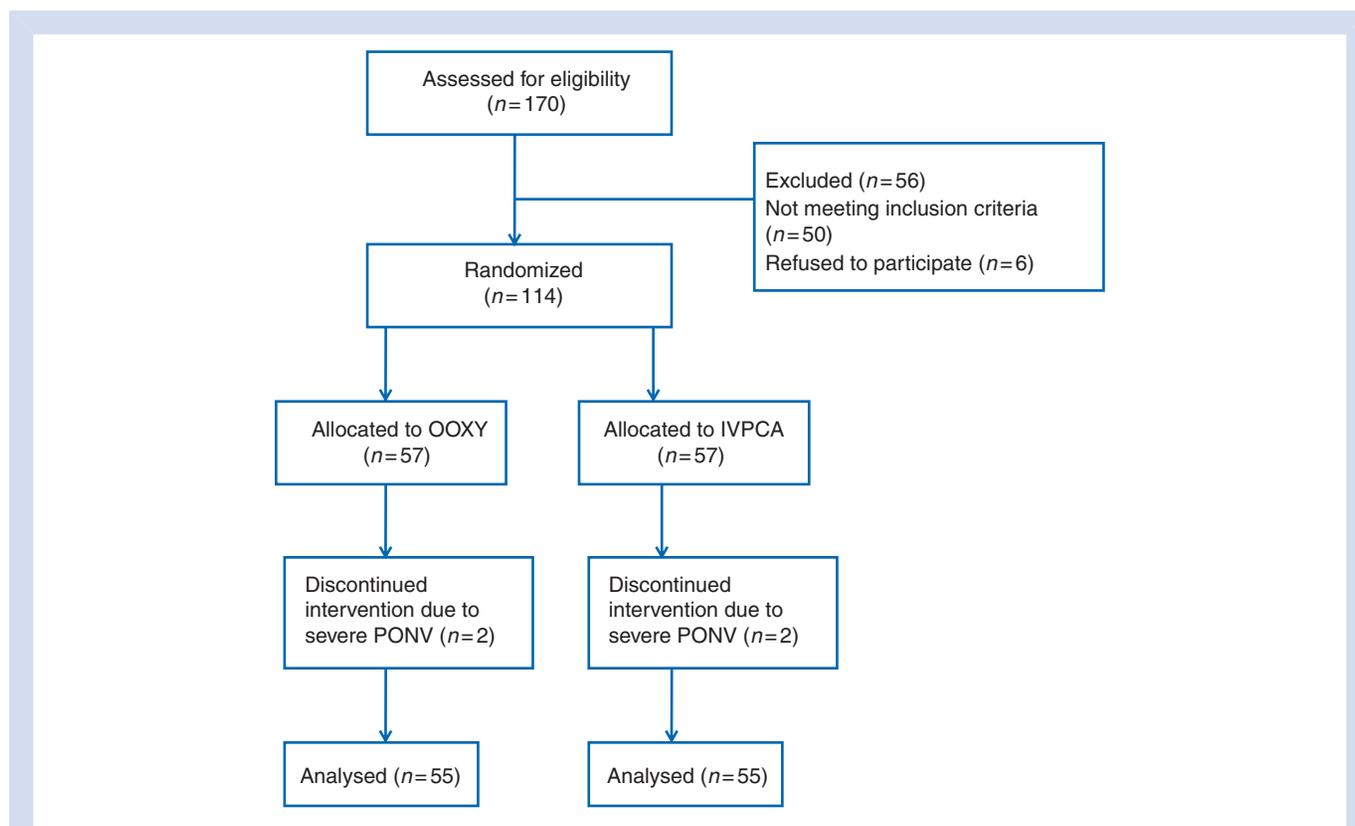


Fig 1 Flow diagram of patient distribution.

power calculations, this calculation is based on assumptions that may not strictly hold (lack of normality, etc.), but was used to guide our choice of sample size. Our subsequent analyses (reported below) confirmed that the trial was of an adequate size to demonstrate equivalence.

Stata software was used for statistical analysis (www.stat.com). A value of  $P < 0.05$  was considered significant. Pain, nausea scores, and time to mobilization were compared using an independent group's *t*-test using the Summary Stats approach for longitudinal data.<sup>13</sup> This widely used approach is much simpler and easier to report than a complex repeated-measures analysis. Data for pain scores at rest and on movement were collected every 4 h. For statistical analysis, the pain score data were pooled into 24 h periods.

For each variable, the equivalent of a standard *t*-test (regression) was performed. A total of 1000 bootstrap samples were used in order to obtain a good estimate of the confidence interval (based on percentiles) for the effect. Bootstrapping is a non-parametric procedure.<sup>14</sup>

## Results

Over 19 months, 114 patients undergoing primary THR fulfilled the inclusion criteria (Fig. 1). Two patients in each limb withdrew within 24 h of randomization due to intolerable nausea or vomiting. All were successfully converted to either tramadol 50–100 mg or required no further opioid

Table 1 Patient characteristics. Data expressed as mean (range) for age, or mean (SD) unless otherwise stated. ASA, American Society of Anesthesiologists. OOXY, mean 71 (60–79); PCA 72 (60–79)

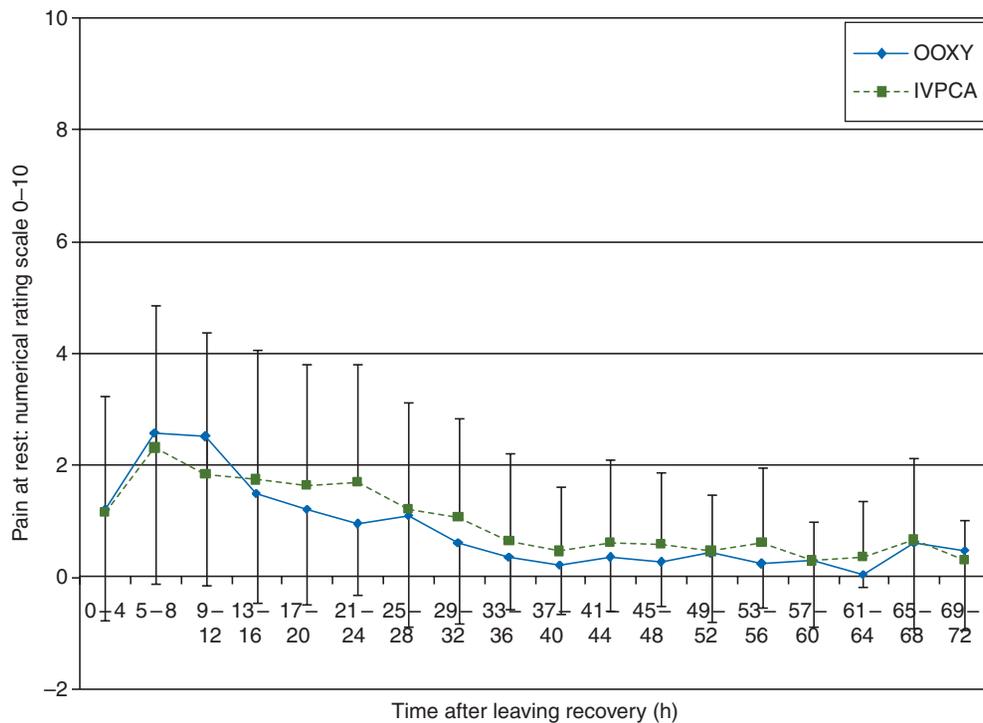
Variables	OOXY (n=55)	IVPCA (n=55)
Age (yr)	72 (60–79)	71 (60–79)
Weight	76 (14.8)	77 (12.9)
Sex, M/F	26/29	24/31
ASA status I, II, III	11, 42, 2	2, 46, 7
Duration of surgery (min)	84 (31.3)	85.6 (39.9)
Time to mobilization (h)	24.45 (8.39)	26.6 (9.23)

analgesia. Data on these patients were excluded from analysis. The rationale of all the comparisons was based on the intention-to-treat principle, while acknowledging that this was not strictly possible because of the four early withdrawals from the trial. The effect of these four withdrawals on the conclusions, however, is likely to be negligible.

Patient and clinical characteristics for each group are presented in Table 1.

### Primary outcome measures

The data set for the primary outcome measures was 91% complete (4809 out of possible 5280 observations were recorded). There were no statistically significant differences



**Fig 2** Mean (SD) pain score at rest in each 4 h period in 110 patients after THR. Fifty-five patients received oral OOXY and 55 received i.v. patient-controlled analgesia (IVPCA) with morphine. Pain scores recorded on 0–10 numerical rating scale. For clarity, only one error bar at each data point is displayed.

in pain scores at rest and on movement between the OOXY and the IVPCA groups in any time period ( $P > 0.05$ ). There was no significant difference in nausea scores between the two groups ( $P > 0.05$ ) (Figs 2 and 3, Tables 2 and 3). Patients in the OOXY group used a mean of 85 mg (range 20–140 mg) of slow-release OOXY after operation, corresponding to a mode of 4 doses of 20 mg controlled-release OOXY, or 48 h postoperative use. The mean number of breakthrough doses of immediate-release OOXY 10 mg was 1.5 (range 0–5 doses, mode 0). These results are consistent with our previous unpublished audit findings that patients required a mean of 2 days OOXY therapy.

Nausea scores recorded on a 0–4 NRS were analysed in 24 h periods and showed no significant difference between the two groups ( $P > 0.1$ ).

### Secondary outcome measures

There was no significant difference in the time to mobilization between the OOXY and the IVPCA groups (24.45 vs 26.6 h,  $P = 0.20$ ).

All patients received one regular antiemetic drug (prochlorperazine 10 mg orally 12 hourly). We recorded the number of extra doses of antiemetic required over and above this. The number of antiemetic doses given in the first 24 h was significantly lower in the OOXY group (1.11 vs 1.44,  $P = 0.03$ ).

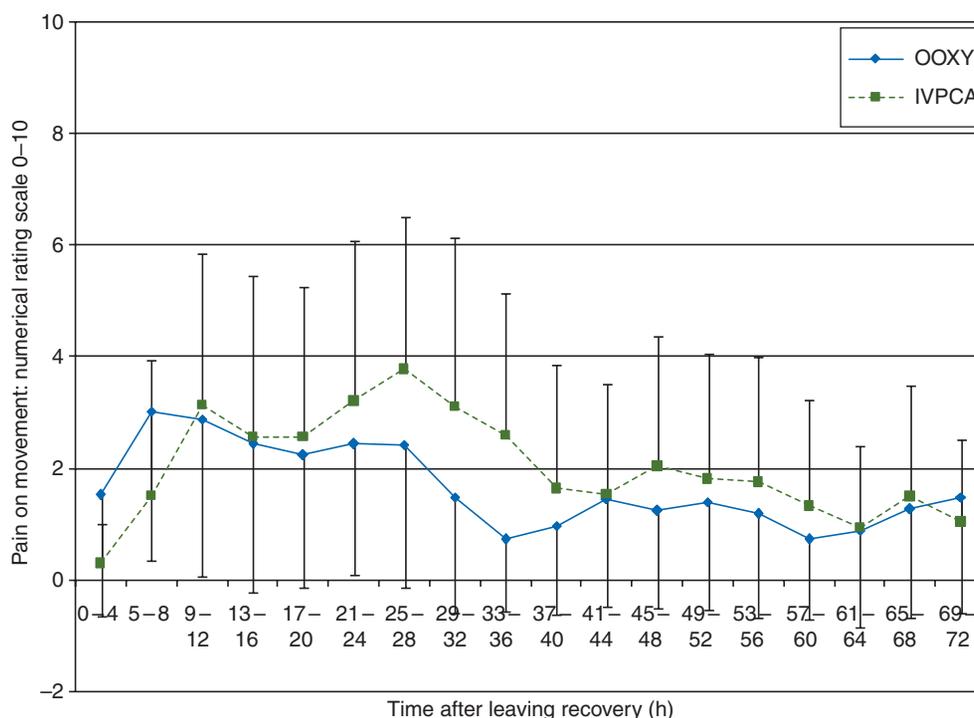
The time to analgesic discontinuation was significantly shorter in the OOXY group (50.53 vs 56.58 h,  $P = 0.04$ ). We

feel that this is probably due to the fact that the two doses of controlled OOXY were prescribed between 08:00 and 10:00 h in the morning and 16:00 and 20:00 h in the evening. The decision to stop OOXY was usually made in the morning, so most patients received their last dose between 08:00 and 10:00 h. Previous studies have shown that the decision to stop IVPCA is often quite arbitrary, with one-third wanting to restart 24 h after discontinuation.<sup>15</sup> In our study, the decision to stop IVPCA was made whenever the patient was using  $< 1 \text{ mg h}^{-1}$ , or decided they no longer wanted the pump and therefore could occur at any time, resulting in a more even spread of IVPCA discontinuation times. There were no instances of significant respiratory depression in either group.

## Discussion

### Main findings

There were no clinically or statistically significant differences in pain scores at rest or on movement between the groups in any time period and no significant difference in nausea scores. There was no significant difference in the time to mobilization. The number of antiemetic doses given in the first 24 h was significantly lower in the OOXY group and the time to analgesic discontinuation was significantly shorter in the OOXY group, but these differences are unlikely to be of any clinical importance.



**Fig 3** Mean (SD) pain score on movement in each 4 h period in 110 patients after THR. Fifty-five patients received oral OXY and 55 received i.v. patient-controlled analgesia (IVPCA) with morphine. Pain scores recorded on 0–10 numerical rating scale. For clarity, only one error bar at each data point is displayed.

**Table 2** Primary and secondary outcome measures in 110 patients undergoing elective THR under spinal anaesthesia. Fifty-five patients received oral OXY and 55 received i.v. patient-controlled analgesia (IVPCA) with morphine; \* = significant

Outcome measure	OXY (n=55)	IVPCA (n=55)	P-value
Pain at rest 0–24 h: mean (SD)	1.65 (2.21)	1.73 (2.32)	0.887
Pain at rest 25–48 h: mean (SD)	0.47 (1.26)	0.77 (1.57)	0.407
Pain at rest 49–72 h: mean (SD)	0.36 (1.18)	0.47 (1.10)	0.964
Pain on movement 0–24 h: mean (SD)	2.40 (2.54)	2.77 (2.79)	0.344
Pain on movement 25–48 h: mean (SD)	1.39 (1.99)	2.19 (2.48)	0.057
Pain on movement 49–72 h: mean (SD)	1.17 (1.76)	2.00 (2.30)	0.639
Nausea score 0–24 h: mean (SD)	0.59 (1.22)	0.70 (1.41)	0.654
Nausea score 25–48 h: mean (SD)	0.46 (1.05)	0.42 (1.08)	0.618
Nausea score 49–72 h: mean (SD)	0.34 (0.96)	0.15 (0.57)	0.136
Time to mobilization: mean (SD) (h)	24.45 (8.39)	26.6 (9.23)	0.204
Total amount of analgesic used: mean (SD) (mg)	102.55 (26.33)	62.12 (32.88)	0.053
Time to analgesic discontinuation: mean (SD) (h)	50.53 (17.27)	56.58 (13.24)	0.042*
Number of additional antiemetic doses: mean (SD) 0–24 h	1.11 (0.84)	1.44 (0.75)	0.03*
Number of additional antiemetic doses: mean (SD) 25–48 h	0.76 (0.77)	0.93 (0.91)	0.292
Number of additional antiemetic doses: mean (SD) 49–72 h	0.46 (0.66)	0.64 (0.84)	0.214

**How the results fit with previous studies**

Previous studies have demonstrated the efficacy of IVPCA after THR,<sup>1–3</sup> the efficacy of regional anaesthesia in THR,<sup>1</sup> and the efficacy of oral OXY after various surgeries.<sup>8–11</sup> Combining OXY with paracetamol and other drugs as part

of a multimodal analgesic regime has been shown to have analgesic and safety advantages.<sup>16 17</sup>

Multimodal, pre-emptive analgesia including OXY is associated with lower opioid consumption and shorter hospital stay than IVPCA alone.<sup>18</sup> Controlled-release OXY used in

**Table 3** Statistical analysis of primary outcome measures in the OOXY and IVPCA groups. There were no statistically significant differences in the primary outcome measures

Variable analysed	Statistical procedure	Coefficient	Standard error	t	P-value	95% confidence interval
Pain at rest 0–24 h	t-test	−0.04	0.30	−0.14	0.887	−0.63, +0.55
	Bootstrap	−0.04	0.29	0.83		−0.67, +0.43
Pain at rest 25–48 h	t-test	+0.21	0.25	0.83	0.407	−0.29, +0.71
	Bootstrap	+0.21	0.25			−0.29, +0.72
Pain at rest 49–72 h	t-test	+0.01	0.23	0.05	0.964	−0.45, +0.47
	Bootstrap	+0.01	0.23			−0.43, +0.45
Pain on movement 0–24 h	t-test	+0.32	0.33	0.95	0.344	−0.35, +0.98
	Bootstrap	+0.32	0.34			−0.41, +0.96
Pain on movement 25–48 h	t-test	+0.75	0.39	1.93	0.057	−0.02, +1.52
	Bootstrap	+0.75	0.39			−0.03, +0.87
Pain on movement 49–72 h	t-test	+0.17	0.36	0.47	0.639	−0.55, +0.89
	Bootstrap	+0.17	0.36			−0.53, +0.52
Nausea score 0–24 h	t-test	+0.09	0.21	0.45	0.654	−0.32, +0.50
	Bootstrap	+0.09	0.21			−0.28, +0.52
Nausea score 25–48 h	t-test	−0.09	0.19	−0.50	0.618	−0.46, +0.28
	Bootstrap	−0.09	0.18			−0.46, +0.24
Nausea score 49–72 h	t-test	−0.20	0.13	−1.50	0.136	−0.46, +0.06
	Bootstrap	−0.20	0.13			−0.47, +0.05

a group of patients undergoing both total knee replacement and THR resulted in superior analgesia and lower side-effects;<sup>8</sup> however, given the complicated dosing regimen used and the heterogeneity of the patients and the modalities of postoperative analgesia, this work was not generalizable to our study population. Other work reported similar analgesia with either IVPCA or oral OOXY, but also used mixed hip and knee replacement patients and included both general and regional anaesthesia.<sup>10</sup> Our study was designed to assess whether oral OOXY was not inferior to a 'gold standard' analgesic regime of IVPCA after a single type of surgery (THR) and a single type of anaesthetic (intrathecal).

We chose to use OOXY because of its favourable pharmacokinetics; about 60–87% of an oral dose of OOXY reaches the central compartment in comparison with a parenteral dose.<sup>12</sup> This high oral bioavailability is due to low pre-systemic first-pass metabolism,<sup>19</sup> and is superior to oral morphine (15–50% bioavailability), making OOXY better suited to the acute pain setting where rapid titration and predictable effect are essential.<sup>6, 7</sup>

### Why the results are different/the same

Unpublished audits showed 10 mg slow-release OOXY to be insufficient to control postoperative pain and that 20 mg was superior. Although the pharmacokinetics of morphine and OOXY are not necessarily different in the elderly,<sup>20</sup> our decision to exclude patients older than 85 yr and patients <45 kg from the study was based on our experience that these patients are better managed with lower doses of slow-release OOXY.

OOXY is often considered expensive when compared with other oral opioid preparations. However, oral OOXY after laparoscopic colorectal surgery has been shown to be more cost-effective than IVPCA.<sup>11</sup> In our study, the average cost per patient of OOXY in the OOXY group was GBP 4.12. The cost of providing IVPCA was GBP 14.39 per patient (100 ml IVPCA morphine GBP 6.89 plus IVPCA infusion line GBP 7.50). Given that the other drug costs were the same in both groups, OOXY would appear to be cost-effective when compared with IVPCA after THR.

Clonidine has been shown to have analgesic properties when used alone<sup>21</sup> or in combination with local anaesthetics in intrathecal and epidural injection.<sup>22, 23</sup> The optimal dose of clonidine remains unclear,<sup>22</sup> although high dose (150 µg) appears to be associated with sedation after general anaesthesia.<sup>21</sup> Doses as low as 15 µg have been shown to improve analgesic quality and duration after knee arthroscopy.<sup>23</sup> Our chosen dose of 75 µg (0.5 ml) is in line with published dose recommendations<sup>24</sup> and, when added to local anaesthetic, is a convenient volume to administer intrathecally.

Using clonidine in combination with local anaesthetic for intrathecal injection probably reduces the risk of delayed respiratory depression which can be associated with the use of intrathecal lipophobic opioids,<sup>25</sup> especially if followed by postoperative strong opioids.

The analysis included the use of 'bootstrapping', a computer-based method of assigning measures of accuracy to sample estimates.<sup>14</sup> Broadly speaking, this technique randomly extracts a new sample of results from the sampled data and replaces it with random data. By doing this many times (1000 in our study), it creates a large number of data sets. By analysing each data set, an estimate of the

distribution of the statistic is obtained. The key to the strategy is to create alternative versions of data that 'might have been seen'.<sup>26</sup> Apart from the computing power required, bootstrapping is simple and provides estimates of standard errors and confidence intervals for complex estimators of complex parameters of the distribution. It is also an appropriate way to control and check the stability of the results.

### What this study adds to knowledge

We believe that this is the first prospective, randomized study to demonstrate that an oral analgesic regimen based on oral OXY can provide equivalent analgesia to IVPCA with morphine after elective primary THR performed under spinal anaesthesia.

### Weaknesses of the study

During the design phase, we considered whether double-blinding was possible in a district general hospital (DGH) setting. Double-blinding would have involved placebo i.v. infusion and placebo OXY capsules. We concluded that the logistical, practical, and financial costs involved in this approach were not feasible for an unfunded study in a DGH. We focused on reducing observer and investigator bias: both IVPCA and OXY analgesia regimes are routinely used on our orthopaedic wards and nurses routinely collect the observations required for the study. Apart from encouraging nurses to complete all their usual observations in all THR patients, the study team had no involvement in recording scores. Data were collected from each patient once the 72 h study period was over and were entered into the database and analysed by different team members.

### Future studies

When designing this study, the mean length of stay for THR patients was 5 days and we chose not to record data on length of stay as part of the study. However, eight patients were discharged before the 72 h study period finished. We suggest any future studies include data on length of stay.

Recent work suggests that oral combinations of morphine and OXY may be more effective than single opioid regimes and could be a topic for future study.<sup>27</sup>

### Conclusions

Our study showed that oral controlled- and immediate-release OXY after THR provides equivalent analgesia to IVPCA with morphine with a similar degree of PONV. We believe that controlled- and immediate-release OXY offers an excellent alternative to IVPCA after THR, obviates many of the logistical disadvantages of IVPCA, and may be more cost-effective.

### Conflict of interest

Before 2004, M.P.R. received honoraria from Napp pharmaceuticals, Roche pharmaceuticals, and Jansen-Cilag for lectures on postoperative pain and postoperative nausea and vomiting to a number of hospitals, general practices and meetings.

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