International Journal of Obstetric Anesthesia (2013) 22, 47–51
0959-289X/$ - see front matter © 2012 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.ijoa.2012.10.007

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ORIGINAL ARTICLE

Efficacy and safety of intraoperative intravenous methadone during general anaesthesia for caesarean delivery: a retrospective case-control study

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ABSTRACT
Background: Most patients undergoing caesarean delivery with general anaesthesia require systemic opioid administration. Due to its rapid onset and long duration of action, intravenous methadone may make it suitable for analgesia after caesarean delivery. Intraoperative methadone combined with postoperative intravenous patient-controlled analgesia with fentanyl or morphine has recently been introduced in our unit.
Methods: A retrospective case-control study of 25 patients who had received methadone was performed. Fifty control patients undergoing elective or emergency caesarean delivery were matched for the use of postoperative intravenous patient-controlled analgesia, transversus abdominis plane (TAP) block and regular non-steroidal anti-inflammatory drugs. Exclusion criteria included preoperative neuraxial analgesia or pre-delivery opioid consumption greater than 10 mg of intravenous morphine equivalents.
Results: Patients in the methadone group had lower pain scores and were less likely to require intravenous opioid supplementation in the post-anaesthetic care unit ($P < 0.001$). Opioid consumption over 48 h was significantly lower in the methadone group. Delayed discharge from the post-anaesthesia care unit was due to sedation in one patient in the methadone group compared to three control patients in whom it was due to sedation and inadequate analgesia.
Conclusion: A single intraoperative bolus of intravenous methadone appeared to provide effective analgesia with an acceptable side-effect profile.

Keywords: Caesarean delivery; General anaesthesia; Methadone; Patient-controlled analgesia

Introduction

Most caesarean deliveries at our institution are performed using neuraxial techniques with intrathecal or epidural opioids given for postoperative analgesia. When general anaesthesia is required, the multimodal analgesic regimen includes intravenous opioids after delivery of the baby. Methadone is a mu-opioid receptor agonist with mixed antinociceptive activity, including non-competitive N-methyl D-aspartate antagonism, and prevention of 5-hydroxytryptamine and noradrenaline reuptake. Methadone is often used orally in opioid dependency and chronic pain, but infrequently in the perioperative setting.[1,2] The latter may be due to issues that include a stigma associated with its use for opioid dependence, misperceptions about the speed of onset, and concern about side effects, especially prolonged sedation or respiratory depression. However, potential benefits of a single dose of intravenous methadone include improved early postoperative analgesia; prolonged efficacy, which may eliminate the need for patient-controlled intravenous analgesia (PCIA); efficacy against neuropathic pain, and possible prevention of chronic wound pain; and low cost.[1] There is renewed interest in intraoperative methadone administration,[1,3–5] but publications in the obstetric literature are limited to the use of oral methadone administration in opioid dependence.[6]

The use of intraoperative, post-delivery, intravenous methadone during general anaesthesia for caesarean delivery has recently gained popularity in our institution. The primary aim of this study was to examine

Accepted October 2012
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the effect of intraoperative methadone on opioid consumption in the first 48 h. Secondary aims looked at opioid consumption in the post-anaesthesia care unit (PACU) and the first 24 h, and assessed complications and side effects. Since most patients receive general anaesthesia for emergency delivery, making a randomised-controlled trial difficult, a retrospective case-control study was used. A chart review explored the efficacy and side effects from a single intraoperative intravenous dose of methadone and these patients were compared with matched controls who received intravenous fentanyl and/or morphine.

Methods

The study received approval from the regional ethics committee. A retrospective case-control study of patients who had undergone caesarean delivery under general anaesthesia between 1st August 2010 and 15th March 2012 was performed. Patients who had received intraoperative methadone (methadone group) and those who had not (control group) were identified from the department database. Each patient who received methadone and postoperative PCIA was matched to two controls for factors that might alter postoperative analgesic requirements. The controls were the next two chronological patients in the same setting (elective or emergency surgery), who had received the same anaesthetic technique, including use of transversus abdominis plane (TAP) blocks and regular postoperative non-steroidal anti-inflammatory drugs (NSAIDs). Patients were excluded if they had received preoperative neuraxial analgesia, a pre-delivery opioid dose >10 mg of intravenous morphine equivalents, were non-English speaking, or in whom a Pfannenstiel incision had not been used. Only patients with postoperative PCIA were matched and included in the case-control study. To explore the safety profile of methadone further, data were collected on patients who received methadone and were managed without PCIA.

Patients received opioids immediately after delivery and cord clamping. Most patients received postoperative analgesia and antiemetic therapy according to departmental guidelines: regular paracetamol and/or NSAIDs (ibuprofen 400 mg 8-hourly, celecoxib 200 mg 12-hourly); as required tramadol orally or intravenous (50–100 mg 1-hourly) or oral oxycodone (5–15 mg 1–2 hourly) in addition to PCIA. Intravenous naloxone (50 μg 1-hourly) was prescribed to treat severe pruritus. The PCIA regimen used either fentanyl (20 μg) or morphine (2 mg) boluses with a 5-min lockout and no basal infusion. Standardised order sheets prescribed antiemetics in a stepwise approach using ondansetron (4 mg 6-hourly), metoclopramide (20 mg 4-hourly), droperidol (0.5 mg 6-hourly) and promethazine (25 mg 6-hourly). Patients were reviewed daily by the Acute Pain Service. Verbal numerical pain scores (VNPS) (0 = no pain, 10 = worst pain imaginable) were recorded 2-hourly by nursing staff.

Data were extracted retrospectively from the Acute Pain Service database, anaesthesia medical records, PACU and inpatient observation charts. Outcomes were examined across three time periods: the PACU stay; after PACU discharge and up to 24 h postoperatively; and 24–48 h after surgery. Analgesic outcomes included the worst VNPS (0–10) and opioid consumption. Opioid doses were converted to intravenous morphine equivalents. Intravenous morphine 10 mg was considered equivalent to either intravenous fentanyl 0.1 mg, intravenous methadone 10 mg, oral oxycodone 20 mg, intravenous tramadol 120 mg or oral tramadol 150 mg.[7,8] If administered, pre-intubation, single bolus doses of either remifentanil or alfentanil were not included. Complication outcomes were over-sedation (sedation score of 3 – difficult to rouse), respiratory depression (respiratory rate <9 breaths/min, need for reversal with naloxone or respiratory arrest), hypotension (systolic blood pressure <90 mmHg or treatment with a vasopressor drug), desaturation (<90%, or extra oxygen requirement), altered mental state (confusion and/or hallucinations) or delayed recovery (>45 min to discharge from PACU due to patient factors). Treatment of side effects such as pruritus, nausea or vomiting and the duration of extra oxygen requirement were noted.

Statistical analyses

Categorical data are presented as percentage or number and were analysed using the Fisher's exact test. Continuous data are presented as mean (SD) or median (IQR [range]) as appropriate and were analysed by Mann Whitney tests for non-parametric data and Student's t tests for parametric data. Statistical analysis was performed using Prism 5.0a (GraphPad Software, Inc., La Jolla, CA, USA). A P value of <0.05 was considered statistically significant.

Results

During the study period a total of 3151 caesarean deliveries were performed, 252 (8%) conducted under general anaesthesia. The indications for general anaesthesia were fetal compromise (46%), failed neuraxial anaesthesia (21%), patient request (20%), contraindication to neuraxial anaesthesia (5%) and other (8%). Forty-four patients received intraoperative methadone; 25 of these received PCIA, and 19 received oral opioids. Those who received PCIA were matched to 50 controls for emergency caesarean delivery (76%), intra-operative TAP blocks (24%) and NSAIDs (76%).

Demographic and obstetric characteristics were similar for age, body weight and height, body mass index,

Table 1 Demographic and obstetric characteristics

	Methadone ($n = 25$)	Controls ($n = 50$)
Age (years)	30 ± 6	31 ± 7
Weight (kg)	87 ± 24	90 ± 24
Height (cm)	164 ± 6	164 ± 9
Body mass index (kg/m^2)	32 ± 8	33 ± 8
Gestational age (weeks)	36 ± 4	35 ± 5
Parity	1 (0–2[0–6])	1 (0–2[0–5])
Primary caesarean delivery	68%	72%

Data are mean ± SD, median (IQR [range]) or percentage.

gestational age, parity and primary or repeat caesarean delivery (Table 1).

The mean dose of intravenous methadone was 14 ± 5.0 mg, equivalent to 0.17 ± 0.06 mg/kg, with a range from 7 to 20 mg (0.1–0.32 mg/kg). In addition to methadone, 20 patients (80%) received intraoperative fentanyl or tramadol (mean dose 15 ± 11 mg morphine equivalents). The use of other intraoperative and postoperative drugs was similar (Table 2) and regular postoperative paracetamol was charted for 92% and 94% of methadone and control patients respectively.

Analgesic outcomes are presented in Table 3 and Figure 1. The duration of PCIA use was 33 ± 12 vs. 39 ± 11 h for the methadone and control groups, respectively ($P = 0.045$).

There were no significant differences between groups for either complications or the need to treat side effects (Table 4). No patient in the methadone group had a clinically significant complication requiring a change of discharge planning, the need for airway manoeuvres, vasopressor drug therapy or naloxone treatment of respiratory depression. Two control patients received naloxone in the operating theatre because of respiratory depression.

The duration of PACU stay was 58 ± 30 min vs. 64 ± 35 min ($P = 0.4$) for the methadone and control groups, respectively. Prolonged stay (>45 min) was usually related to a pre-existing medical problem or a logistical delay rather than inadequate analgesia or respiratory depression. One patient who received methadone 10 mg (0.19 mg/kg) and fentanyl 200 μg had respiratory depression, was slow to rouse and required supplemental oxygen with prolonged observation for 2 h. Discharge from PACU was delayed for three patients in the control group; two due to poor analgesia and one due to excessive sedation and respiratory depression. Requirement for oxygen therapy was longer in the methadone group than in the control group: 168 ± 286 vs. 103 ± 205 min; the difference was not statistically significant.

Table 2 Intraoperative therapy

	Methadone ($n = 25$)	Controls ($n = 50$)
Total opioid dose in morphine equivalents (mg*)	29 ± 16	32 ± 13
Paracetamol	80%	80%
Parecoxib	52%	52%
Ondansetron	84%	74%
Dexamethasone	80%	76%
Other antiemetic drugs†	12%	18%

Data are mean ± SD or percentage; No significant differences between groups; *Opioid consumption in intravenous morphine equivalents; †Droperidol, metoclopramide or promethazine.

Nineteen patients received intraoperative methadone and oral analgesics postoperatively. These patients received more intraoperative methadone (mean dose 18 ± 3.4 mg, equivalent to 0.22 ± 0.05 mg/kg, $P = 0.025$), and less non-methadone opioids 4.5 ± 6.4 mg. No major complications were detected and no patient required additional review or commencement of PCIA.

Discussion

This retrospective study showed that intraoperative administration of a single bolus of intravenous methadone provided effective analgesia after caesarean delivery under general anaesthesia, and was associated with reduced subsequent opioid consumption and a similar incidence of side effects compared with control patients. The findings are consistent with a recent randomised controlled trial of patients undergoing complex spinal surgery; a 50% reduction in opioid requirement was found in the first 48 h compared with intraoperative sufentanil infusion.[3] No patient in our study had a serious complication. Delay in PACU discharge due to opioid effects was infrequent, and mainly due to sedation in the methadone group, and poor analgesia and sedation in the control group.

Most patients in the methadone group received an intraoperative dose of 15 or 20 mg (0.15–0.25 mg/kg) and similar adjunctive treatment. Despite receiving a lower intraoperative morphine equivalent, they experienced less severe pain and had lower analgesic requirements in PACU. This is likely to be due to rapid central nervous system equilibration with plasma concentrations of methadone ($t_{1/2}$ke0.4 min, compared to fentanyl 5 min, and morphine 2–4 h).[4]

For the first 48 h after surgery, patients in the methadone group used approximately 40% less PCIA morphine equivalents than those in the control group, which is consistent with previous studies.[3,5] Methadone has a prolonged duration, and sustained therapeutic blood concentrations may explain the reduced postoperative opioid consumption and shorter duration of PCIA usage.[4] The highest pain scores were not worse in the methadone group. No major complications were seen in the methadone group and side effects were similar in both groups.

Table 3 Analgesic outcomes

	Methadone ($n = 25$)	Controls ($n = 50$)	P value
PACU			
Worst pain score	0 (0–3.5 [0–6])	4.5 (0–6 [0–10])	0.0002
VNPS $\geqslant 7$	0	22%	<0.0001
Opioid analgesia required	16%	69%	0.0001
Opioid consumption in morphine equivalents (mg)	2.2 ± 6.2	8.5 ± 9.3	0.0007
Post-PACU to 24 h			
Worst pain score	3 (2–5 [0–8])	4 (3–5 [1–10])	0.06
Opioid consumption in morphine equivalents (mg)	73 ± 59	135 ± 75	0.0001
24–48 h			
Worst pain score	2 (1–4 [0–6])	2.5 (2–4 [0–8])	0.6
Opioid consumption in morphine equivalents (mg)	40 ± 42	68 ± 51	0.008
Total			
Opioid consumption in morphine equivalents (mg)	115 ± 94	213 ± 104	0.0002

Data are mean ± SD, percentage or median (IQR [range]). PACU: post-anaesthesia care unit, VNPS: verbal numerical pain scores.

Table 4 Complications and treatment of side effects in methadone vs. control group

	PACU	Post-PACU to 24 h	Second 24 h
Sedation score = 3*	0 vs. 2%	0 vs. 0	0 vs. 0
Respiratory depression	4% vs. 2%	0 vs. 0	0 vs. 0
Desaturation	0 vs. 0†	4% vs. 6%	0 vs. 0
Antiemetic therapy	8% vs. 4%	36% vs. 32%	12% vs. 14%
Hypotension	4% vs. 2%	0 vs. 0	0 vs. 0
Naloxone for pruritus	0 vs. 0	0 vs. 2%	0 vs. 2%
Altered mental state	N/A	0 vs. 0	0 vs. 0

Data are percentages in methadone and control groups; No significant differences between groups; * Difficult to rouse after 10 min in PACU; † All patients received oxygen on arrival in PACU.

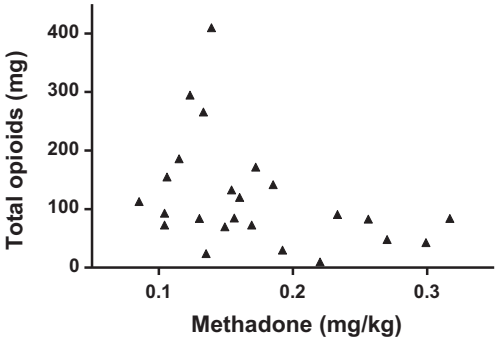

Fig. 1 Total postoperative opioid consumption in intravenous morphine equivalents (mg) by the intraoperative intravenous methadone dose.

There are no data on which to base a mean methadone dose in the obstetric population, but it was observed that some women had been either under- or over-dosed. Lower doses (5–10 mg) are redistributed rapidly, resulting in limited duration of analgesic efficacy and greater postoperative opioid requirements, whereas with larger doses (20 mg) the duration of clinical effect is also influenced by the prolonged systemic elimination of methadone.[4] Most non-obstetric clinical studies have used doses of either 20 mg or 0.2 mg/kg.[3,9,10] While acknowledging the wide variability of opioid requirements in general,[11–13] and of methadone specifically,[1] the current findings suggest that this is an appropriate initial dose in the obstetric population.

Mean PCIA usage in the methadone group was 73 mg morphine equivalents in the first 24 h (3 mg/h) and was lower in patients who received higher intraoperative methadone doses. The modest PCIA usage suggests that postoperative analgesia requirements could be managed with oral opioids rather than PCIA. Nineteen patients were managed effectively with methadone followed by oral oxycodone and tramadol but were excluded from the case-control study. These patients did not require additional reviews or escalation of analgesia. The study suggests that, after an intravenous intraoperative dose of methadone 0.2 mg/kg, postoperative multimodal oral analgesia is likely to prove simple and effective.

One potential concern of perioperative methadone administration is prolongation of the QT interval,

predisposing to torsades de pointes. Methadone-induced torsades de pointes has been reported with chronic high-dose use rather than single perioperative dose.[14] Perioperative torsades de pointes is rare, despite significant QT interval prolongation occurring in 80% of all patients during general anaesthesia. Many drugs used in anaesthesia may prolong the QT interval. The effect on the QT interval of perioperative methadone is similar to that of isoflurane and ketorolac.[15] In the current study, no dysrhythmias were seen in the 44 patients who received methadone. Our institution does not request preoperative electrocardiograms for patients who are likely to receive intraoperative methadone.

There are several limitations of this study. It was retrospective and therefore open, not randomised and subject to confounders. The knowledge of methadone administration may have influenced nurse recording of VNPS and subsequent administration of recovery analgesia. Nevertheless, patients were free to self-administer PCIA opioid but still required less pain relief than those who had received other intraoperative opioids. An attempt was made to match the methadone group with a control group likely to have similar postoperative analgesia requirements. Both groups had similar demographic and obstetric features and received standardised adjunctive analgesic and antiemetic therapy, but other pharmacogenomic and situational confounders may have been present.

In addition, a range of intraoperative methadone doses was used and there was concurrent use of other intraoperative opioids. When methadone was first introduced in our unit, lower doses of methadone (5–10 mg) in combination with other intravenous opioids were used. Current local guidelines suggest administration of 0.2 mg/kg, to a maximum of 20 mg of methadone as a sole agent immediately after cord clamping, with the option of either PCIA or oral opioids postoperatively. Our study did not assess the effects of intraoperative methadone on the infant, but previous studies report low transfer to breast milk and have concluded that methadone is compatible with breastfeeding.[16–18]

Despite limitations, this retrospective study suggests benefit from administration of a single intraoperative dose of intravenous methadone. Its continued use and further investigation are warranted.

Disclosure

Michael Paech is a recipient of a Pfizer Australia investigator-initiated research grant and on a clinical advisory panel of Schering-Plough (MSD).

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