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A double-blinded randomized evaluation of alfentanil and morphine *vs* fentanyl: analgesia and sleep trial (DREAMFAST)

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Editor's key points

- Disturbed sleep after surgery is well recognized and may impair recovery.
- This study evaluated sleep quality and pain control after two different patient-controlled analgesia combinations.
- Combining alfentanil with morphine was no better than fentanyl alone for postoperative sleep quality.
- The effects of combinations of strong opioids require further study.

Background. Patients using fentanyl patient-controlled analgesia (PCA), the standard first-line choice in our hospitals, commonly complain of postoperative sleep disruption due to pain. The aim of this study was to determine whether the PCA combination of alfentanil and morphine, which provides longer analgesia without compromising onset speed, would improve postoperative pain-related sleep interference.

Methods. Two hundred and twelve adults undergoing major surgery where PCA was the planned principal postoperative analgesic modality were randomized to either the combination of alfentanil and morphine (Group AM) or fentanyl (Group F). The primary outcome was pain-related awakenings during the second postoperative night as measured by the study questionnaire, based on the St Mary's Hospital Sleep Questionnaire. Analgesic efficacy, other sleep measures, and opioid-related side-effects were also assessed.

Results. There was no difference in pain-related sleep disturbance between the groups, with 41% of Group AM and 53% of Group F waking due to pain ($P=0.10$). Group AM had better rest and dynamic analgesia in the first 24 h with fewer requiring rescue ketamine infusion during the 2 day study period (2 *vs* 14%, $P=0.001$). Those in Group AM experienced less nausea and vomiting in the second 24 h (18 *vs* 35%, $P=0.028$) but more pruritus (40 *vs* 23%, $P=0.013$).

Conclusions. Despite better early postoperative analgesia, pain-related sleep interference was not improved by the PCA combination of alfentanil and morphine.

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I.V. patient-controlled analgesia (PCA) is widely used for postoperative pain control.[1] Our clinical observation was that many patients using PCA fentanyl, our first-line choice, complained of difficulty sleeping for sufficient periods during the night as a result of waking with pain and the need to self-administer boluses. Postoperative sleep disturbance is both common[2 3] and important, as it has been associated with worse functional recovery[4] and implicated in the pathogenesis of postoperative cognitive dysfunction.[5]

The aetiology of postoperative sleep disruption is multifactorial; however, pain is identified as a key factor.[3 6] Short-acting opioids may be particularly likely to lead to both pain-related sleep arousal and waking in pain, as the opioid concentration at the effect site declines during sleep. Adding a night-time background infusion does not improve sleep[7] and is associated with greater likelihood of adverse events.[8] Available opioids have either rapid onset with shorter duration (e.g. fentanyl, alfentanil) or slower onset with longer duration of effect (e.g. morphine, hydromorphone), but not both.

In the postoperative anaesthesia care unit, a combination of alfentanil and morphine has more rapid onset and a similar duration of effect, along with a comparable side-effect profile, than does morphine alone.[9] In the first 24 h after Caesarean section, women reported that the opioid combination in PCA, compared with morphine alone, resulted in more rapid onset and greater efficacy after each bolus, with no difference in analgesia duration or overall patient satisfaction.[10]

Combining opioids may produce both rapid onset analgesia with timely control of incident pain allowing return to sleep, and longer duration of effect, leading to consolidated periods of sleep with fewer pain-related awakenings. The primary aim of this study was to determine whether the combination of alfentanil and morphine resulted in fewer pain-related awakenings than did fentanyl, when administered by

PCA. Secondary aims were to investigate the quality of postoperative sleep, and also the efficacy and safety of the PCA alfentanil/morphine (A/M) combination.

Methods

This double-blind randomized controlled trial was conducted at two metropolitan tertiary referral hospitals. The Human Research Ethics Committees at Sir Charles Gairdner Hospital (Ref: 2007-117) and the South Metropolitan Area Health Service (Ref: S/09/9) granted approval. The study was registered with the Australian New Zealand Clinical Trials Registry (Ref: ACTRN12608000118303). All subjects provided written informed consent before participation.

Adult patients undergoing major surgery where PCA was considered appropriate for postoperative analgesia, and likely to be required for two nights, were asked to participate in the study. Inclusion criteria were age over 18 yr, the ability to provide informed consent, capacity to understand and physically activate the PCA device, and ASA physical status I, II, or III. Exclusion criteria were ASA IV or V, inability to use a PCA device, planned use of postoperative continuous regional analgesia, preoperative renal or hepatic impairment, treated obstructive sleep apnoea, previous adverse reactions to alfentanil, morphine, or fentanyl, a history of opioid abuse, chronic opioid administration, and inability to complete a written questionnaire in English.

On the day of surgery, patients were randomly assigned in a double-blinded manner (using a computer-generated randomization table) to one of the two PCA treatment groups. These were a bolus of either alfentanil 75 μg with morphine 1 mg (Group AM) or fentanyl 20 μg (Group F), both with a 5 min lockout interval. Dosing in Group AM was based on a previous study which used pharmacokinetic modelling to determine the optimal ratio of alfentanil to morphine for analgesia and then tested this model in the post-anaesthesia care unit (PACU).[9] Dosing in Group F was consistent with routine practice and standard protocols at both hospitals.

Treatment syringes, labelled only with patient identification, study number, and trial title, were prepared and dispensed by a pharmacist not otherwise involved in the study. The patient, anaesthetist, ward nursing and medical staff, acute pain service staff, and those collecting postoperative data were all blinded to the patient's treatment group.

Anaesthetic technique was at the discretion of the anaesthetist providing intraoperative care and could include a single-dose nerve block. Upon arrival in the PACU, i.v. fentanyl (20 μg every 5 min, as required) was titrated to patient comfort. Once this was achieved, the study drug was commenced. Patients also received i.v. or oral paracetamol 6 hourly for the duration of the study.

Each institution's Acute Pain Service reviewed patients daily, according to routine practice, until the PCA device had been ceased. Rescue analgesia was provided by first increasing the PCA bolus dose by 50%. If this was insufficient, an i.v. ketamine infusion (0.1 mg kg^{-1} h^{-1}) was commenced. Patients were withdrawn from the trial if analgesia remained inadequate despite these measures, side-effects did not respond to treatment, a surgical complication necessitating a return to theatre occurred, or upon patient request. The study protocol excluded the co-administration of sedatives.

Verbal rating scores (VRS) of pain at rest and with movement, nausea and vomiting scores (Sir Charles Gairdner Hospital: 0, 'none'; 1, 'mild'; 2, 'severe'; 3, 'dry retching'; 4, 'vomiting'; Fremantle Hospital: 0, 'none'; 1, 'mild'; 2 'vomiting'), sedation scores (Sir Charles Gairdner Hospital: 1, 'wide awake'; 2, 'eyes open, drowsy'; 3, 'eyes closed, rousable to verbal stimulation'; 4, 'eyes closed, rousable to physical stimulation'; 5, 'unrousable'; Fremantle Hospital: 0, 'awake and alert'; 1, 'mild, occasionally drowsy, easy to rouse'; 2, 'moderate, constantly drowsy, easy to rouse'; 3, 'severe, somnolent, difficult to rouse'; S, 'normally asleep'), and presence of pruritus ('none', 'mild', 'moderate', 'severe') were assessed. The categorical data collected for nausea and sedation were collapsed to accommodate the least detailed data collected, thus a three-point nausea scale and four-point sedation scale were used in analysis.

After two postoperative nights, patients completed a questionnaire based on the St Mary's Hospital Sleep Questionnaire which is a self-report instrument designed to measure the previous night's sleep in hospitalized patients. It includes questions about the prior night's overall sleep quality, frequency of awakenings, and satisfaction. Items were added to examine the most common reason for waking, the number of awakenings due to pain, and questions adopted from a previous PCA study assessing the speed of analgesia onset after a bolus and ability to sleep subsequently.

The primary outcome measure was defined as a reduction in the number of pain-related awakenings with a 50% decrease judged to be clinically important. A previous pilot study generated a skewed distribution with a median number of pain-related awakenings of two (range 0–6, $_{SD}$=2.21). With an α-value of 0.05 and a β-value of 0.2, it was calculated, using non-parametric tests, that 88 patients would be needed in each group.

Non-continuous data are presented as medians and ranges. The Student *t*-test was used except if data were skewed, when the Wilcoxon rank-sum test was used. Fisher's exact test was used for categorical data. Analysis was undertaken using SAS (SAS®, SAS Institute Inc., NC, USA) and was according to intention to treat.

Results

Between April 2008 and September 2010, 212 patients were recruited to the study (Fig. 1), with six subsequently excluded, three for meeting exclusion criteria and three who did not commence PCA. One hundred and two patients were randomized to Group AM and 104 to Group F. There were two protocol violations; one patient received a benzodiazepine inadvertently and another was unblinded due to