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

A. Lee1*, E. O’Loughlin3,4 and L. J. Roberts1,2

1 Department of Anaesthesia and 2 Department of Pain Management, Sir Charles Gairdner Hospital, Hospital Ave, Nedlands, WA 6009, Australia 3 Department of Anaesthesia, Fremantle Hospital, Alma St, Fremantle, WA 6160, Australia 4 School of Medicine and Pharmacology, University of Western Australia, Western Australia, Australia

* Corresponding author. E-mail: alee@meddent.uwa.edu.au

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. Analgesia 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.

Australian New Zealand Clinical Trials Registry: Ref: ACTRN1260800118303.

Keywords: analgesia, patient-controlled; analgesics, opioid; pain, postoperative; sleep disorder, environmental

Accepted for publication: 24 July 2012

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 common3 and important, as it has been associated with worse functional recovery4 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 sleep7 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: ACTRN1260800118303) 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 postanaesthesia care unit (PACU). 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’; 5, ‘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 of 17.5 awakenings in the A/M group, a standard deviation of 18.9, and a skewness of 2.21. With an a-value of 0.05 and a b-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...
non-availability of the next trial syringe. Patients withdrawn as a result of a surgical complication, protocol violation, or patient request were excluded from data analysis. Ninety-seven patients in Group AM and 101 in Group F contributed data towards endpoints on an intention-to-treat basis, with primary endpoint data available for 91 patients in Group AM and 85 in Group F. Most missing data related to questionnaires that were not returned or were incomplete.

The two groups were similar with regard to age, gender, weight, ASA physical status, smoking history, operation type, the adjunctive use of a single-dose regional technique, and preoperative sleep quality (Table 1).

There was no significant difference in pain-related awakenings between the groups (Fig. 2). Although fewer patients in Group AM were woken by pain (41%) when compared with Group F (53%), this did not reach statistical significance ($P=0.10$).

In the first 24 h, patients in Group AM had lower median VRS for pain at rest and on movement than did Group F (Fig. 3). This difference was not maintained into the second postoperative day. Fewer patients in Group AM required a rescue PCA bolus dose increase (5% Group AM, 13% Group F, $P=0.082$) and adjunctive ketamine infusion (2% Group AM, 14% Group F, $P=0.0016$).

There was no difference in nausea and vomiting in the first 24 h (46% Group AM, 51% Group F, $P=0.15$). However, in the second 24 h, patients in Group AM had less nausea and vomiting (18% Group AM, 35% Group F, $P=0.028$) and were less likely to be administered anti-emetics (18% Group AM, 35% Group F, $P=0.020$). Pruritus was reported more frequently in Group AM (40% vs 23% Group F, $P=0.013$).

Sedation levels were not significantly different between groups, with the greatest degree of sedation (excluding sleep) for most patients either ‘wide awake’ or ‘mildly drowsy (eyes open)’ in both the first 24 h (64% Group AM, 61% Group F) and second 24 h (86% Group AM, 85% Group F). One patient in Group AM was administered naloxone for a respiratory rate of 5 bpm and one patient in Group F had a single reported respiratory rate of 4 bpm, but no treatment was administered. Neither patient had any adverse sequelae from these incidents. One patient in each group was reviewed by a Medical Emergency Team, according to fixed institutional criteria. The patient in Group AM was assessed for postural hypotension occurring during transfusion of

---

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients Contributed Data</th>
<th>Primary Endpoint Data Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group AM</td>
<td>97</td>
<td>91</td>
</tr>
<tr>
<td>Group F</td>
<td>101</td>
<td>85</td>
</tr>
</tbody>
</table>

---

**Fig 1.** Participant flow. Group AM (alfentanil morphine PCA) and Group F (fentanyl PCA).
packed red blood cells to treat anaemia (Hb 70 g dl\(^{-1}\)). The patient in Group F was reviewed for oliguria.

There were no significant differences between the groups with respect to secondary sleep outcome measures. Both groups described disturbed sleep on the second postoperative night with only 25% overall (29% Group AM, 20% Group F) reporting that they slept ‘well’ or ‘very well’ and 44% overall (41% Group AM, 47% Group F) rating their sleep as ‘poor’ or ‘very poor’. Both groups reported frequent sleep disruption from all causes with over 90% waking more than twice (91% Group AM, 92% Group F) and a majority waking five or more times per night (63% Group AM, 66% Group F).

Reported reasons for sleep disturbance on the second postoperative night were similar between the groups. Most commonly described was ‘activity in the room’ (49% Group AM, 41% Group F). Pain or needing to use the PCA was the primary reason for waking in 24% of Group AM and 27% of Group F. Others were ‘unfamiliar surroundings’ (6% Group AM, 9% Group F) and ‘other’ causes (22% Group AM, 23% Group F).

A majority of patients were ‘satisfied’ or ‘very satisfied with the previous night’s sleep (61% Group AM, 60% Group F). Many rated the speed of pain relief after a bolus as ‘fast’ or ‘very fast’ (58% Group AM, 63% Group F), and most reported being able to return to sleep after activating the PCA device (90% Group AM, 89% Group F).

### Discussion

In adults undergoing a range of surgical procedures, pain-related sleep disturbance on the second postoperative night was not improved with PCA AM when compared with PCA fentanyl. This was despite the AM combination improving analgesia as evidenced by a clinically, and statistically, significantly lower requirement for rescue ketamine infusion throughout the 2 day study period and slightly lower rest and dynamic pain scores in the first 24 h after operation. PCA AM was associated with less nausea and vomiting, although pruritus was more frequent. Postoperative sleep disruption was common and pain was reported as the primary cause by one in four patients in each treatment arm.

This is one of a small number of studies addressing the effects of analgesic technique on postoperative sleep disturbance. No prior studies examine sleep quality with fentanyl PCA. The addition of a nighttime PCA background infusion of morphine (1 mg h\(^{-1}\)) after abdominal hysterectomy results in no improvement in overnight sleep, 7 and increases the incidence of serious adverse effects. 8 Women undergoing major reconstructive or gynaecological surgery reportedly experience less sleep disturbance with subcutaneous than with i.v. PCA diamorphine. 11 However, this was a non-blinded comparison that relied on retrospective recall of pain and did not use validated sleep measurement tools.

Sleep quality is inherently subjective and can only be assessed by patient self-report. There are high levels of agreement between self-report measures and postoperative EEG sleep measurement. 12 The St Mary’s Hospital Sleep Questionnaire, a self-report measure, was developed to assess the prior night’s sleep in inpatients and has demonstrated test–retest reliability. 13 14 As it does not specifically
examine pain and sleep, this study used a modified and expanded version. The use of a formal measurement instrument is a strength of the current study and may explain differences from other studies that used imprecise tools.

The relationship between the experience of pain and sleep is complex and may involve a degree of reciprocity due to common neurobiological origins. Mechanisms of sleep disruption include disturbance of circadian rhythms, the magnitude of which relates to the extent of surgery. Pain itself, and also opioid consumption, may also be subject to circadian variation. Not only does pain disturb sleep, but sleep disturbance may impair pain perception. In volunteers, one night’s sleep deprivation increases pain intensity perception along with impaired activation of pain modulating pathways with difficulty attending to or disengaging from pain. In patients with burns, a poor night’s sleep is associated with greater pain on the following day, perhaps due to increased pain perception as a result of sleep deprivation. Some prior studies showing an association between pain and sleep disturbance reported much higher pain scores than were found in this study. It may be that there is a threshold above which pain interferes significantly with sleep.

There is very limited information about opioid analgesia and pain-related sleep disturbance. This study shows that just combining two opioids does not reduce pain-related awakenings by 50% or more. It may be that the effect size is less than that for which this study was powered. While this study was not primarily examining efficacy, the opioid combination was more effective than fentanyl alone. This is consistent with the growing evidence that, due to variability in activity of different agents at opioid receptors, opioid combinations may have greater efficacy than single agents alone.

The small but significant difference in pain scores between our groups in the first 24 h after operation indicates that a difference in pain-related awakenings may have been found if sleep assessment had occurred after the first postoperative night. The second postoperative night was chosen to avoid the confounding effect of the intense period of observation (and thus sleep disturbance) that occurs on initial return to the wards, from the PACU, after major surgery. Other factors that can affect sleep quality, such as single or shared room occupancy and perioperative anxiety, were not controlled for, although these effects were most likely minimized by reasonable patient numbers and randomization. There were some questionnaire non-responders and partial responders; this was addressed by a per-protocol analysis.

On a population basis, there is little variation in the side-effect profile of different opioids when used as sole agents for i.v. PCA, with the exception being the incidence of pruritus. A comparison of fentanyl–morphine PCA with fentanyl alone showed no difference in either pain scores or side-effects. The finding of improved efficacy and reduced nausea and vomiting with alfentanil and morphine PCA should be further investigated. It may be useful to examine the AM combination in patients where difficulties with postoperative analgesia might be expected but who were excluded from this trial, for example, those with opioid tolerance. The influence of other analgesic techniques, for example, continuous regional analgesia, on postoperative

---

**Fig 3** Pain VRS at rest and on movement on Days 1 and 2 in Group AM (alfentanil morphine PCA, n=102) and Group F (fentanyl PCA, n=104). Boxplots represent median, inter-quartile range and the whiskers represent the range. *P=0.003, †P=0.017, no significant differences on Day 2.
pain-related sleep disturbance is unknown and may be worthy of future study.

Postoperative sleep disruption arises from multiple potential causes, broadly classified as environmental, physiological, and psychological.23–27 The observation that factors other than pain disturbed postoperative sleep points to strategies apart from analgesia that may be important in addressing postoperative sleep. This is consistent with prior studies which have identified environmental factors, such as noise from other patients and staff, light, room temperature, and nursing interventions, as disruptive of patients’ sleep, particularly in surgical wards.23 26 27

In conclusion, patients wake frequently in the postoperative period, for many reasons. Pain is just one factor, and may be of less importance than others such as activity in the room. While the A/M PCA combination does not reduce pain-related sleep disruption, it may provide better analgesia.

Acknowledgements
The authors would like to thank Mr Richard Parsons, Faculty of Health Sciences, Curtin University for statistical analysis and advice, Ms Gemma Ayres for data collection and entry, and the Acute Pain Services involved in this study.

Declaration of interest
None declared.

Funding
This work was supported by a project grant from the Fremantle Hospital Medical Research Foundation.

References
9 Ludbrook GL, Macintyre PE, Douglas H, Ong L, Upton RN. A mixture of alfentanil and morphine for rapid postoperative loading with opioid: theoretical basis and initial clinical investigation. Anesthesiology 2001; 56: 739–44
11 Dawson L, Brockbank K, Carr ECJ, Barrett RF. Improving patients’ postoperative sleep: a randomized control study comparing subcutaneous with intravenous patient-controlled analgesia. J Adv Nurs 1999; 30: 875–81
12 Hedges C, Redeker NS. Comparison of sleep and mood in patients after on-pump and off-pump coronary artery bypass surgery. Am J Crit Care 2008; 17: 133–40
18 Lavigne GJ. Effect of sleep restriction on pain perception: towards greater attention! Pain 2010; 148: 6–7
26 Spence J, Murray T, Tong AS, Butler RS, Albert NM. Nighttime noise issues that interrupt sleep after cardiac surgery. J Nurs Care Qual 2011; 26: 88–95