Reports of Original Investigations

Chronobiological characteristics of postoperative pain: diurnal variation of both static and dynamic pain and effects of analgesic therapy

[Caractéristiques chronobiologiques de la douleur postopératoire : variation diurne des douleurs statique et dynamique, et effets de la thérapie antalgique]

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Background: Previous postoperative investigations report morning peaks in analgesic administration. However, few studies have examined diurnal variation of both pain and analgesic consumption and little is known about dynamic pain in this context.

Methods: The diurnal pattern of postoperative pain is described using pain intensity and analgesic consumption data from a recently published hysterectomy trial.

Results: In the presence of patient-controlled analgesia with morphine, pain at 8 a.m. was significantly higher ($P < 0.05$) than at noon, 4 p.m. or 8 p.m. on postoperative day one (for rest pain and pain evoked by sitting, forced expiration and cough) and on postoperative day two (for pain evoked by forced expiration and cough only). This temporal pattern was observed both with and without the co-administration of non-opioid analgesics (gabapentin and/or rofecoxib). Morphine use during the four hours preceding 8 a.m. on either postoperative day was not significantly lower than any of the other corresponding time intervals.

Conclusions: Based on data from our post-hysterectomy analgesic clinical trial, static and dynamic pain in the morning appears to be more intense than pain later in the day. This pattern was observed in the presence of substantial nocturnal morphine use. Based on these and other previous observations, specifically designed investigations are needed to better characterize the clinical, neurohormonal and neurophysiological features of postoperative circadian pain variation – including pain during sleeping hours. If the above observations are replicated, future study of nocturnal sustained-release opioids as well as time-shifting the administration of non-opioid co-analgesic drugs to the very early morning may be warranted.

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Contexte *: Des recherches postopératoires précédentes ont rapporté des pics matinaux dans l'administration d'antalgiques. Toutefois, peu d'études ont examiné les variations diurnes de la douleur et de la consommation d'antalgiques, et nous ne disposons que de très peu d'éléments concernant la douleur dynamique dans ce contexte.*

Méthode *: L'évolution diurne de la douleur postopératoire est décrite en se basant sur des données concernant l'intensité de la douleur et la consommation d'antalgiques tirées d'une étude sur l'hystérectomie publiée récemment.*

Résultats *: Lors d'une analgésie contrôlée par le patient avec de la morphine, la douleur à 8 h était significativement plus élevée ($P < 0,05$) qu'à midi, 16 h et 20 h le premier jour postopératoire (pour la douleur au repos et la douleur provoquée par la position assise, l'expiration forcée et la toux) et le deuxième jour postopératoire (pour la douleur provoquée par l'expiration forcée et la toux uniquement). Cette évolution temporelle a été observée avec et sans co-administration d'antalgiques non opioïdes (gabapentine et/ou rofecoxib). L'utilisation de morphine durant les quatre heures*

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précédant 8h le premier et le second jour postopératoire n'a pas été significativement plus basse qu'à aucun autre intervalle de temps correspondant.

***Conclusion** : Sur la base de données tirées de notre étude clinique antalgique post-hystérectomie, les douleurs statique et dynamique semblent être plus intenses le matin que plus tard dans la journée. Cette évolution a été observée malgré une utilisation nocturne importante de morphine. En se basant sur ces observations ainsi que sur d'autres qui les ont précédées, des recherches spécifiquement conçues sont nécessaires pour mieux caractériser les aspects cliniques, neuro-hormonaux et neurophysiologiques de la variation circadienne des douleurs postopératoires, y compris la douleur pendant le sommeil. Si les observations ci-dessus sont réitérées, une future étude d'opioïdes à libération nocturne soutenue ainsi que le décalage de l'administration d'agents co-antalgiques non opioïdes au petit matin pourraient être recommandés.*

FOR several clinical pain states, variations in pain intensity have been shown to follow circadian patterns. Describing these temporal variations may advance our understanding of the biological mechanisms of these conditions and guide more effective treatment strategies. For example, pain due to rheumatoid arthritis is most intense in the morning and least intense in mid-afternoon,[1] labour pain appears to be least severe in the morning,[2] pain due to biliary colic appears to peak in the late evening,[3,4] peak migraine frequency occurs between 08:00 and 10:00 hours[5] and neuropathic pain is lowest in the morning and progressively increases towards its highest in the evening.[6]

Several reports suggest that postoperative pain, an inflammatory condition sharing some similarities with rheumatoid arthritis, also fluctuates according to a circadian rhythm. However, most investigations reported to date have relied upon analgesic use as a surrogate of pain intensity. For example, analgesic consumption has been seen to peak between 04:00 and 12:00 hours following gynecological cancer surgery,[7,8] abdominal surgery[9,10] and oral surgery.[11] However, circadian variations in analgesic consumption may occur not only because of pain variation but also due to circadian pharmacokinetics.[12–14] Furthermore, variations in analgesic use may not accurately reflect circadian variations in underlying pain intensity *per se* since analgesic drugs obviously affect pain intensity. For example, a post-gastric bypass surgery study reporting peak opioid administration at 09:00 hours but constant pain ratings throughout the day,[15] might lead to the possibly incorrect conclusion that no diurnal pain variation exists and ultimately leaves the circadian pattern of postoperative pain undescribed. Therefore, we sought to further investigate this question by concurrently evaluating the temporal pattern of pain intensity and analgesic consumption using data from a recently published hysterectomy trial.[16]

Materials and methods

This study was conducted using pain and other secondary outcome measures from a recently published postoperative randomized-controlled analgesic trial.[16]

Postoperative pain clinical trial design

The clinical trial from which the data were gathered was approved by the Queen's University Research Ethics Board and involved ASA I–II women undergoing abdominal hysterectomy. This was a single centre, parallel randomized trial with four treatment groups (n = 25 to 30 per group): a) gabapentin 1800 mg·day^{-1} (dosed tid, at 8 a.m.–2 p.m.–8 p.m.); b) rofecoxib 50 mg·day^{-1} (dosed once daily at 8 a.m.); c) a combination of gabapentin 1800 mg·day^{-1} and rofecoxib 50 mg·day^{-1} (combination); or d) placebo.

Intraoperatively, patients received a balanced anesthetic at the discretion of the attending anesthesiologist who was blinded to treatment. Fentanyl 3–5 μg·kg^{-1} *iv*, was administered within the first 30 min of surgery. Morphine 0.1–0.2 mg·kg^{-1} *iv* was administered over 30 min, starting 30 min before anticipated completion of surgery. No local or regional anesthesia or any other analgesic drugs were used perioperatively. All patients received ondansetron 4 mg *iv*, 30 min before anticipated completion of surgery. Following surgery, all patients received patient-controlled analgesia (PCA) with intravenous morphine as the only non-study drug analgesic and were followed on a daily basis by a study nurse and the staff of the acute pain service (APS). In the postanesthetic care unit, nurse-delivered morphine boluses were administered until patients were sufficiently alert to use a PCA pump. Patient-controlled analgesia was set to deliver a 1 mg dose with a lockout of six minutes, and no continuous infusion. If necessary at any time during the study, the dose could be increased up to 2 mg and the lockout time reduced to five minutes. Patient-controlled analgesia was discontinued at the discretion of the APS upon diminishing frequency of use and patients could subsequently receive oral morphine 5–10 mg every three hours as needed as the only non-study analgesic. Ondansetron 4 mg *iv* was continued every eight hours for the first 36 hr postoperatively and dimenhydrinate 25–50 mg *iv* every four hours was allowed, as needed. Headache unresponsive to study medications or PCA morphine could be treated with acetaminophen (for

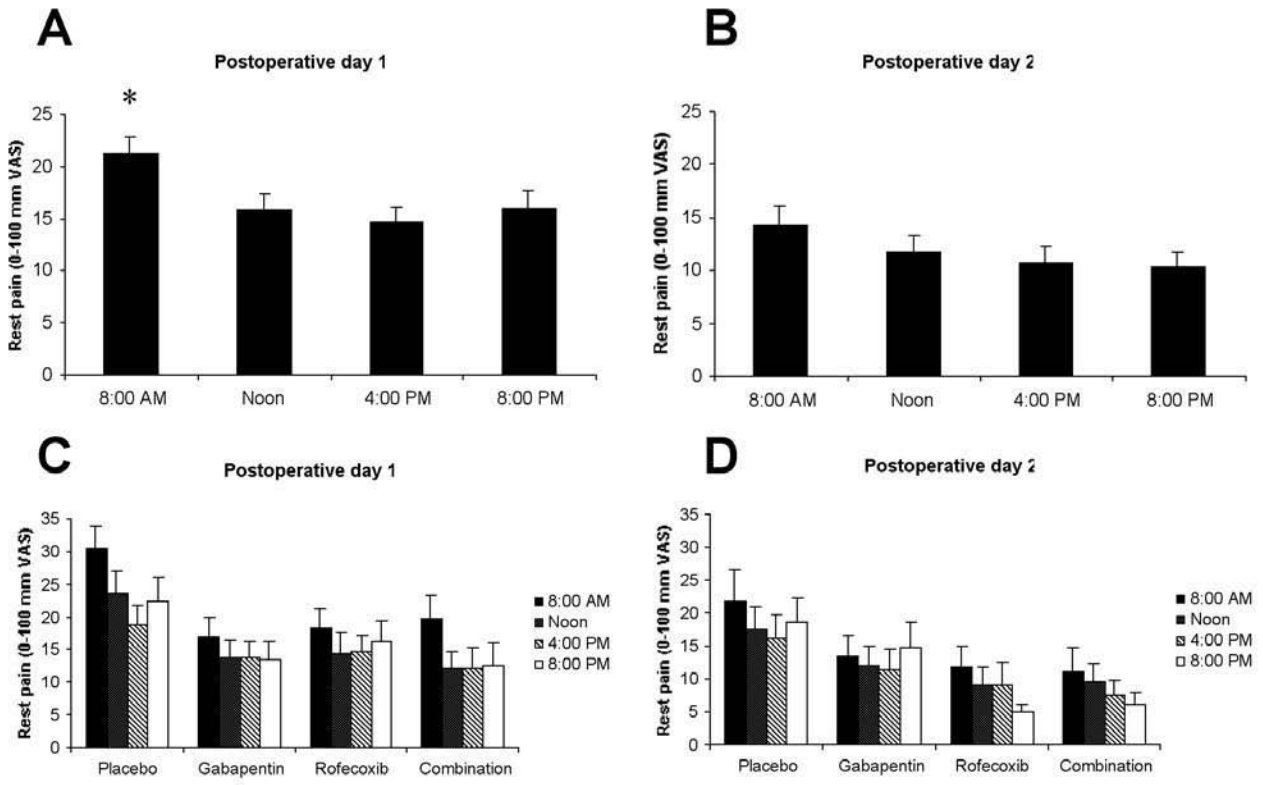

FIGURE 1 Rest pain - Temporal profile of mean pain scores at 8 a.m. noon, 4 p.m. and 8 p.m. across all treatments on postoperative days one (panel A) and two (panel B). Temporal pain profile corresponding to each treatment group on post-operative days one (panel C) and two (panel D). *Pain at 8 a.m. significantly greater ($P < 0.05$) than at noon, 4 p.m. and 8 p.m. Numbers of patients included for analysis are: placebo – 24, gabapentin – 23, rofecoxib – 29, combination – 27.

headache only) 650 mg every four hours as needed.

The primary outcome was pain intensity, at rest and with movement (i.e., sitting, forced expiration and cough), during the first and second postoperative days. Secondary outcomes included morphine consumption and several other measures. Pain and morphine consumption were recorded starting at 8 a.m. and then every four hours until 8 p.m. for the first two postoperative days.

Statistical analysis

Mean pain scores (for pain at rest and pain evoked by sitting, forced expiration and coughing) for each treatment group (i.e., placebo, gabapentin, rofecoxib and gabapentin-rofecoxib combination) at 8 a.m., noon, 4 p.m. and 8 p.m. as well as respective mean morphine consumption for the preceding four-hour periods corresponding to each of these time points were compared using two-way treatment by time repeated measures analyses of variance (ANOVA). Any significant main effect of time was further explored using Fisher's protected least significant difference *post hoc* comparisons. A P value < 0.05 was considered statistically significant.

Results

Pain

Treatment by time repeated measures ANOVA revealed a significant main effect of time ($P < 0.05$) on postoperative day one for all pain measures (i.e., rest pain and pain evoked by sitting, forced expiration and cough). A significant main effect of time ($P < 0.05$) on postoperative day two was observed only for pain evoked by forced expiration and cough. On postoperative day one, pain at 8 a.m. was significantly higher ($P < 0.05$) than at noon, 4 p.m. and 8 p.m. for pain at rest (Figure 1A) and pain evoked by forced expiration (Figure 3A) and significantly higher ($P <$

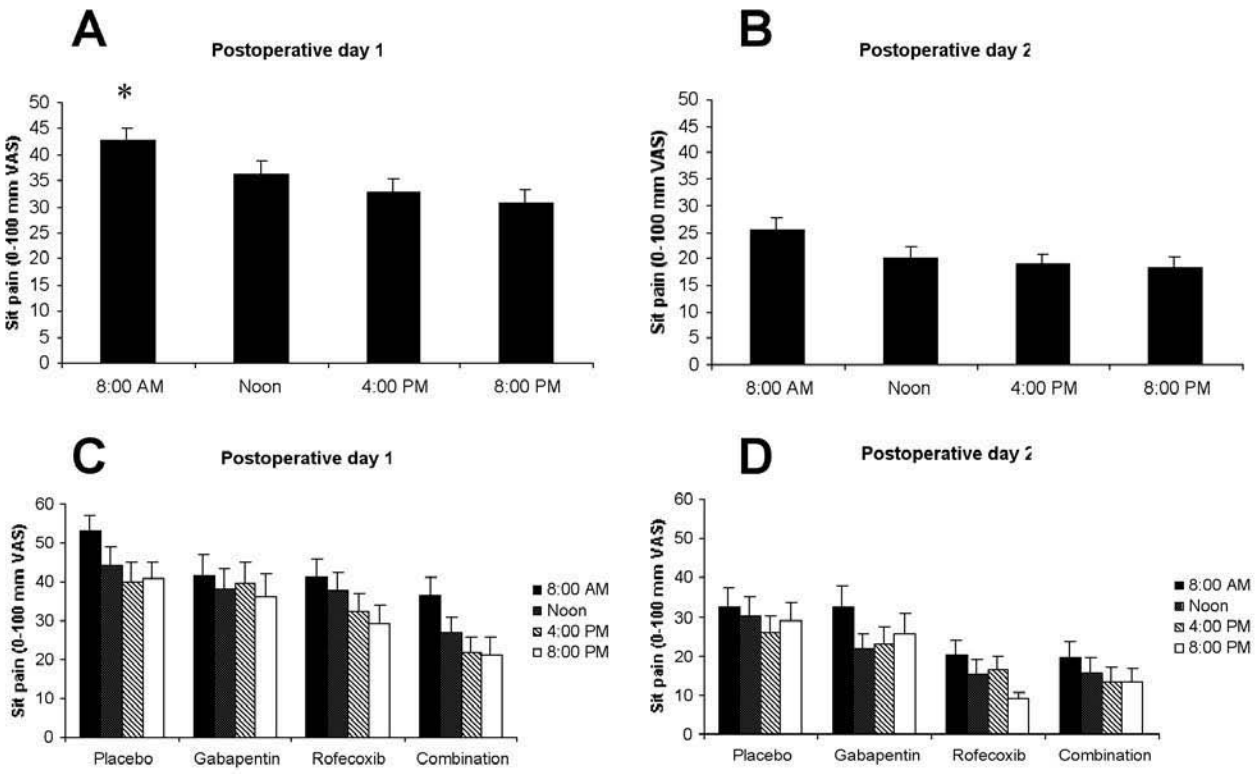

FIGURE 2 Pain evoked by sitting - Temporal profile of mean pain scores at 8 a.m., noon, 4 p.m. and 8 p.m. across all treatments on postoperative days one (panel A) and two (panel B). Temporal pain profile corresponding to each treatment group on postoperative days one (panel C) and two (panel D). *Pain at 8 a.m. significantly greater ($P < 0.05$) than at 4 p.m. and 8 p.m.. Numbers of patients included for analysis are: placebo – 24, gabapentin – 23, rofecoxib – 29, combination – 27.

0.05) than at 4 p.m. and 8 p.m. only for pain evoked by sitting (Figure 2A) and cough (Figure 4A). On postoperative day two, pain at 8 a.m. was significantly higher ($P < 0.05$) than at noon, 4 p.m. and 8 p.m. for pain evoked by forced expiration (Figure 3B) and pain evoked by cough (Figure 4B). These temporal patterns were observed in all treatment groups (Figures 1C and1D, 2C and 2D, 3D and 4D) except for the gabapentin group on postoperative day one (for pain evoked by forced expiration – Figure 3C and by cough – Figure 4C)

Morphine consumption

Treatment by time repeated measures ANOVA revealed a significant main effect of time ($P < 0.05$) on postoperative day two (but not for postoperative day one) for morphine consumption during the four hours preceding 8 a.m., noon, 4 p.m. and 8 p.m. On either postoperative day one or two, morphine consumption during the four hours preceding 8 a.m. was not significantly lower than any other time point. On postoperative day two, morphine consumption at 8 a.m. or at noon was significantly higher ($P < 0.05$) than at 4 p.m. or 8 p.m. (Figure 5B).

Discussion

This study is one of a few which examine temporal variations in postoperative dynamic pain and which examine temporal pain variation concurrently with analgesic consumption. Our results suggest that pain following abdominal hysterectomy shows temporal variations such that patients experience worse pain in the morning than later in the day. This pattern was observed despite substantial nocturnal morphine use. Our observation of higher morning pain is of clinical significance since morning pain is approximately 20 to 30% higher. This pattern holds true for pain at rest as well as pain evoked by sitting, coughing and forced

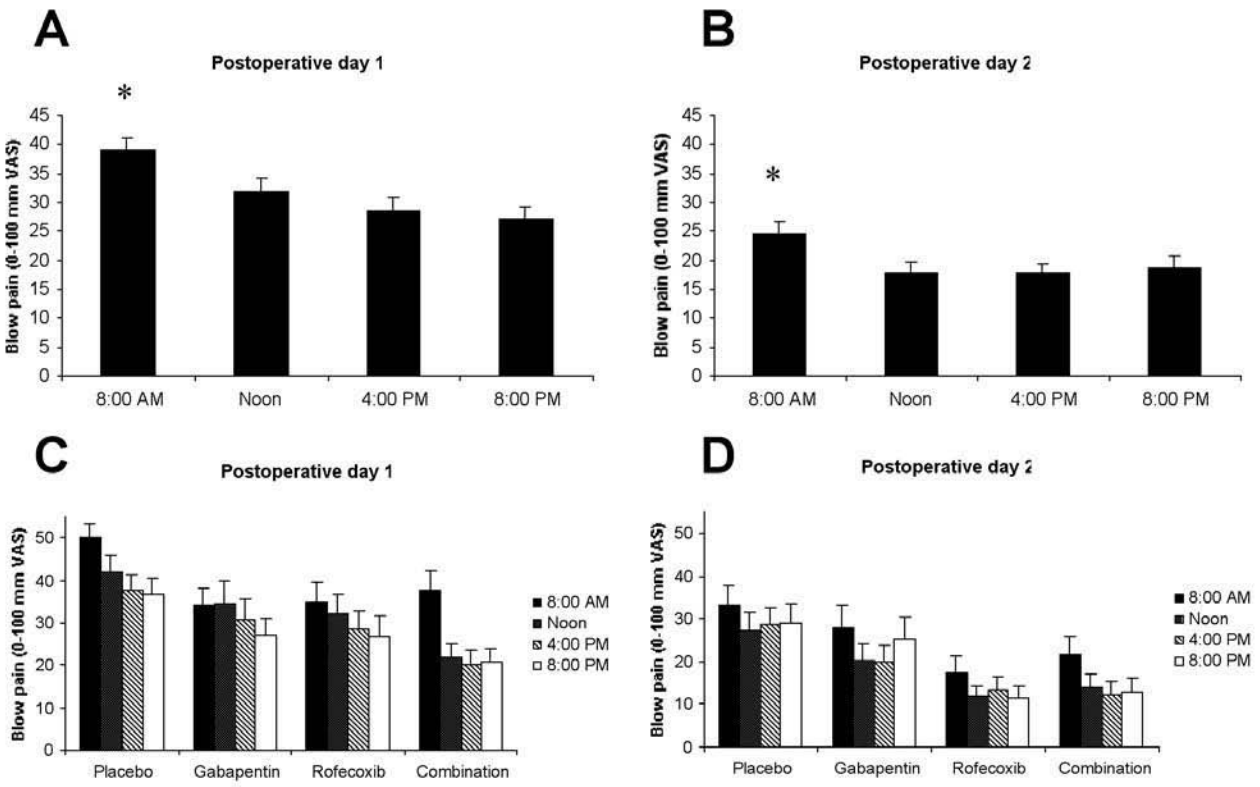

FIGURE 3 Pain evoked by forced expiration - Temporal profile of mean pain scores at 8 a.m., noon, 4 p.m. and 8 p.m. across all treatments on postoperative days one (panel A) and two (panel B). Temporal pain profile corresponding to each treatment group on postoperative days one (panel C) and two (panel D). *Pain at 8 a.m. significantly greater ($P < 0.05$) than at noon, 4 p.m. and 8 p.m. Numbers of patients included for analysis are: placebo – 24, gabapentin – 23, rofecoxib – 29, combination – 27.

expiration on postoperative day one. Furthermore, this pattern is generally preserved with or without other non-opioid treatments including rofecoxib, gabapentin or their combination. Of course, it should be noted that these results come from women following hysterectomy and further studies would be needed to determine whether this pattern is seen in other surgical procedures or patients.

The gradual improvement of postoperative pain over time (e.g., days to weeks) could be one reason for this temporal pattern. However, certain observations suggest that this alone does not satisfactorily explain our results. Firstly, pain scores were observed to plateau, or at least appear more stable across the time points of noon, 4 p.m. and 8 p.m. such that pain did not steadily diminish throughout the day. Furthermore, the differences in pain intensity between 8 a.m. to 8 p.m. on postoperative day one were far greater than those from 8 p.m. on postoperative day one and 8 a.m. on postoperative day two. Thus, while pain does generally decrease over time, it does not do so at a steady rate and morning pain indeed appears most intense.

Opioid administration via PCA has the potential to complicate the interpretation of any temporal pain variations. For example, if patients' PCA morphine consumption were to decrease during sleeping hours, this could contribute to higher morning pain. However, we observed that morphine consumption during the four hours preceding 8 a.m. was not significantly lower than subsequent time points on either postoperative day. In fact, on postoperative day two, PCA morphine consumption during the four hours preceding 8 a.m. was significantly *higher* than that corresponding to noon and 4 p.m. Therefore, it is reasonable to infer from these observations that higher morning pain intensity is in fact *not* due to decreased morphine administration.

Another potential explanation for this diurnal

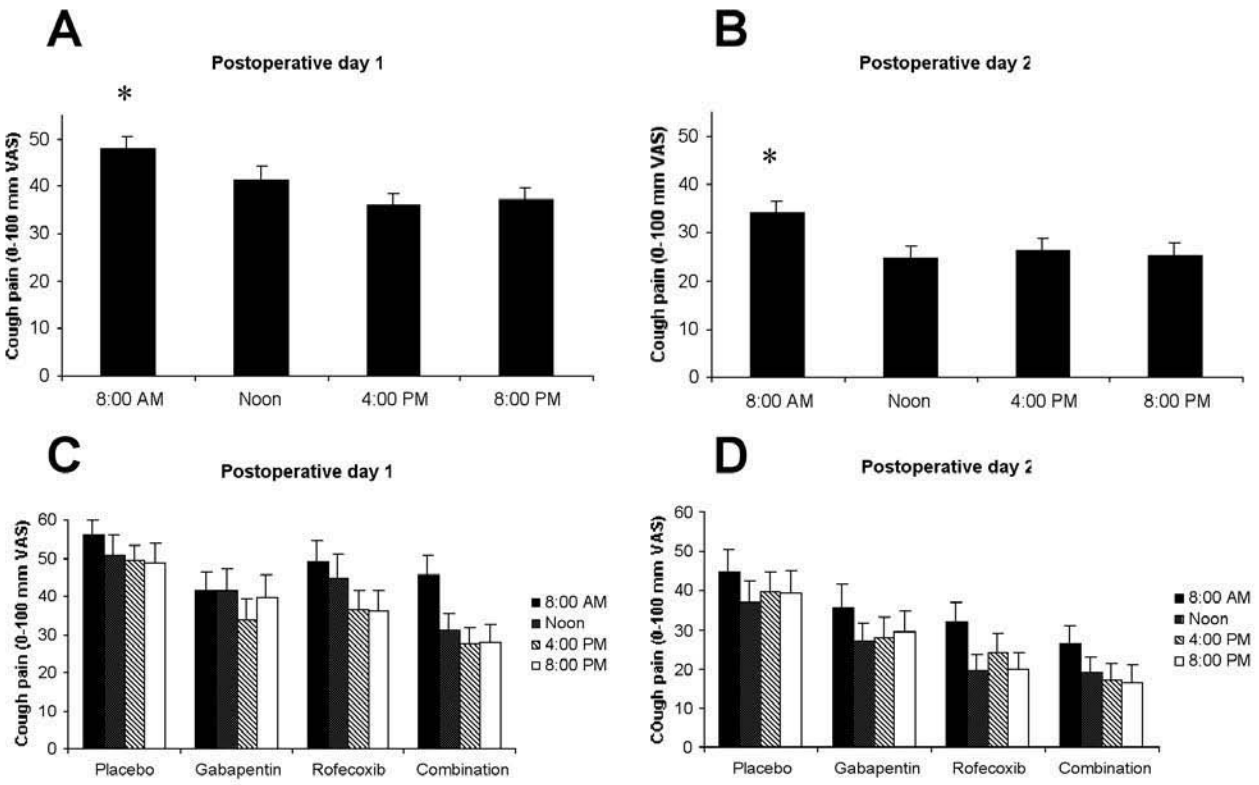

FIGURE 4 Cough-evoked pain - Temporal profile of mean pain scores at 8 a.m., noon, 4 p.m. and 8 p.m. across all treatments on postoperative days one (panel A) and two (panel B). Temporal pain profile corresponding to each treatment group on postoperative days one (panel C) and two (panel D). *Pain at 8 a.m. significantly greater ($P < 0.05$) than at 4 p.m. and 8 p.m. Numbers of patients included for analysis are: placebo – 24, gabapentin – 23, rofecoxib – 29, combination – 27.

variation might relate to the timing of non-opioid co-analgesic drugs (i.e., rofecoxib and/or gabapentin). Since neither of these medications was administered between 8 p.m. and 8 a.m., lower morning plasma levels might explain higher morning pain. However, higher morning pain was also observed in patients receiving PCA morphine only (i.e., placebo group) which argues against this possibility.

In contrast to some neuropathic pain syndromes which are associated with increasing pain intensity throughout the day,[6] it is interesting to observe an inverse pattern with inflammatory conditions such as rheumatoid arthritis[1] and, in the case of this study, postoperative pain. Given the role of corticosteroids in postoperative pain processing,[17,18] our observation that postoperative pain is higher in the morning is particularly puzzling since endogenous secretion of the anti-inflammatory glucocorticoid, cortisol, tends to peak at around 08:00 hours.[19] However, surgery has been shown to cause a phase shift in the circadian cortisol cycle such that peak cortisol levels are observed later in the day instead of early in the morning[20] which might partially explain our results. Since all study patients were receiving intravenous PCA morphine, another possible contributor to these temporal differences could be diurnal variability in morphine pharmacokinetics. For example, Gourlay *et al.*[14] reported that the peak concentration (Cmax) of morphine was higher when the drug was administered at 18:00 than at 10:00. However, this study involved oral morphine administration and it is unknown whether similar differences would have been seen with intravenous morphine administration.

These preliminary observations from secondary analyses of an analgesic trial are consistent with previous reports of increased morning analgesic use but nevertheless require further confirmation. Clearly, ongoing research efforts are needed in order to better characterize the underlying biology of circadian pain variation fol-

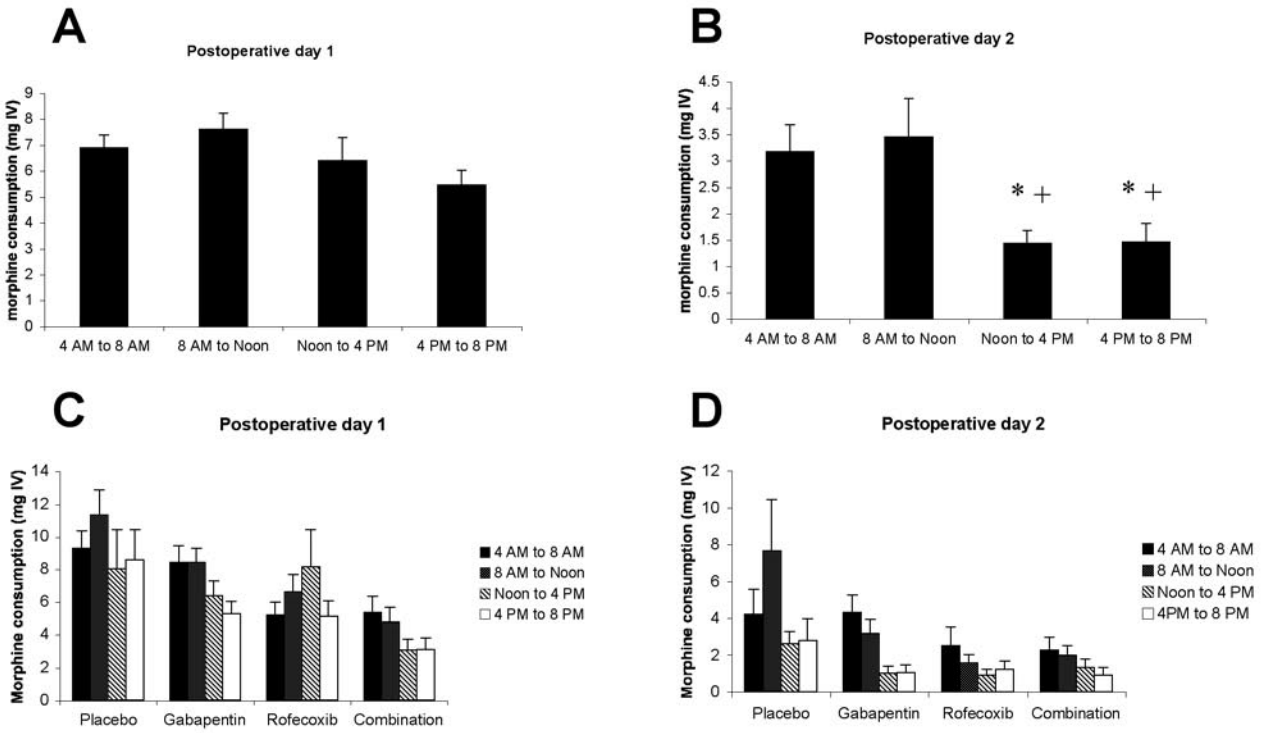

FIGURE 5 Temporal profile of intravenous patient-controlled analgesia morphine consumption during the four hours preceding 8 a.m. noon, 4 p.m. and 8 p.m. across all treatments on postoperative days one (panel A) and two (panel B). Temporal pain profile corresponding to each treatment group on postoperative days one (panel C) and two (panel D). *Morphine consumption significantly lower ($P < 0.05$) than 4 a.m. to 8 a.m. +morphine consumption significantly lower ($P < 0.05$) than 8 a.m. to noon. Numbers of patients included for analysis are: placebo – 24, gabapentin – 23, rofecoxib – 29, combination – 27.

lowing surgery. However, current recognition of diurnal postoperative pain patterns may allow us to develop more effective pain treatment strategies. For example, timing of analgesic administration could be adjusted such that peak analgesic effect overlaps with peak morning pain levels (e.g., administering parenteral non-steroidal anti-inflammatory drugs in the very early morning hours while patients are still asleep). Also, given that patients need to stay awake to use their PCA device for nocturnal pain treatment, administration of appropriate evening doses[21] of oral sustained-release opioids might be a safer, more effective strategy for minimizing sleep disturbance than continuous intravenous opioid infusions.[22,23] For example, Reuben *et al.*[24] reported less sleep interference with sustained-release oxycodone compared to short-acting oxycodone in an outpatient knee surgery trial and it would be important to learn if similar benefits could be realized in the setting of PCA.

Further measuring pain intensity at time points between 8 p.m. and 8 a.m. may be important since Closs *et al.*[9] observed a second peak of postoperative analgesic administration between 20:00 and 24:00 hours. The time points for our static and dynamic pain intensity measurements were deliberately chosen so as to minimally interfere with patients' ability to sleep. Clearly, measurement of nocturnal pain after surgery is required in order to better describe and understand the circadian variation of postoperative pain. Innovative methods to study this would be useful. For example, to avoid waking patients for pain intensity measurement during sleeping hours, one approach might involve patients self-rating their pain whenever awake at night. This would obviously scatter pain measurement time points across patients, however, calculating hourly population means could provide some temporal information.

In conclusion, these data suggest that, following hysterectomy, static and dynamic pain intensity in

the morning is significantly higher (approximately 20–30%) than later in the day. This temporal pattern appears to be unaffected by non-opioid treatment with gabapentin and/or rofecoxib. Based on these and other previous observations, specifically designed investigations are needed to better understand the clinical, neurohormonal and neurophysiological features of postoperative circadian pain variation – including pain during sleeping hours. If the above observations are replicated, future study of nocturnal sustained-release opioids as well as time-shifting the administration of non-opioid co-analgesic drugs to the very early morning may be warranted.

References

1 *Bellamy N, Sothern RB, Campbell J, Buchanan WW.* Circadian rhythm in pain, stiffness, and manual dexterity in rheumatoid arthritis: relation between discomfort and disability. Ann Rheum Dis 1991; 50: 243–8.

2 *Aya AG, Vialles N, Mangin R, et al.* Chronobiology of labour pain perception: an observational study. Br J Anaesth 2004; 93: 451–3.

3 *Rigas B, Torosis J, McDougall CJ, Vener KJ, Spiro HM.* The circadian rhythm of biliary colic. J Clin Gastroenterol 1990; 12: 409–14.

4 *Minoli G, Imperiale G, Spinzi GC, Terruzzi V, Rigas B.* Circadian periodicity and other clinical features of biliary pain. J Clin Gastroenterol 1991; 13: 546–8.

5 *Solomon GD.* Circadian rhythms and migraine. Cleve Clin J Med 1992; 59: 326–9.

6 *Odrcich M, Bailey JM, Cahill CM, Gilron I.* Chronobiological characteristics of painful diabetic neuropathy and postherpetic neuralgia: diurnal pain variation and effects of analgesic therapy. Pain 2006; 120: 207–12.

7 *Auvil-Novak SE, Novak RD, Smolensky MH, Kavanagh JJ, Kwan JW, Wharton JT.* Twenty-four hour variation in self-administration of morphine sulfate (MS) and hydromorphone (H) by post-surgical gynecologic cancer patients. Ann Rev Chronopharmacol 1988; 5: 343–6.

8 *Auvil-Novak SE, Novak RD, Smolensky MH, Morris MM, Kwan JW.* Temporal variation in self-administration of morphine sulfate via patient-controlled analgesia in postoperative gynecologic cancer patients. Ann Rev Chronopharmacol 1990; 7: 253–6.

9 *Closs SJ.* Patients' night-time pain, analgesic provision and sleep after surgery. Int J Nurs Stud 1992; 29: 381–92.

10 *Burns JW, Hodsman NB, McLintock TT, Gillies GW, Kenny GN, McArdle CS.* The influence of patient characteristics on the requirements for postoperative analgesia. A reassessment using patient-controlled analgesia. Anaesthesia 1989; 44: 2–6.

11 *Pollmann L, Harris PH.* Rhythmic changes in pain sensitivity in teeth. Int J Chronobiol 1978; 5: 459–64.

12 *Chassard D, Bruguerolle B.* Chronobiology and anesthesia. Anesthesiology 2004; 100: 413–27.

13 *Ollagnier M, Decousus H, Cherrah Y, et al.* Circadian changes in the pharmacokinetics of oral ketoprofen. Clin Pharmacokinet 1987; 12: 367–78.

14 *Gourlay GK, Plummer JL, Cherry DA.* Chronopharmacokinetic variability in plasma morphine concentrations following oral doses of morphine solution. Pain 1995; 61: 375–81.

15 *Graves DA, Batenhorst RL, Bennett RL, et al.* Morphine requirements using patient-controlled analgesia: influence of diurnal variation and morbid obesity. Clin Pharm 1983; 2: 49–53.

16 *Gilron I, Orr E, Tu D, O'Neill JP, Zamora JE, Bell AC.* A placebo-controlled randomized clinical trial of perioperative administration of gabapentin, rofecoxib and their combination for spontaneous and movement-evoked pain after abdominal hysterectomy. Pain 2005; 113: 191–200.

17 *Salerno A, Hermann R.* Efficacy and safety of steroid use for postoperative pain relief. Update and review of the medical literature. J Bone Joint Surg Am 2006; 88: 1361–72.

18 *Bisgaard T, Klarskov B, Kehlet H, Rosenberg J.* Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy: a randomized double-blind placebo-controlled trial. Ann Surg 2003; 238: 651–60.

19 *Schimmer BP, Parker KL.* Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; Inhibitors of the synthesis and actions of adrenocortical hormones. *In*: Hardman JG, Limbird LE, Molinof PB, Goodman Gilman A (Eds). Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th ed. NY: McGraw-Hill; 1996: 1459–81.

20 *Derenzo J, Macknight B, DiVittore NA, Bonafide CP, Cronin AJ.* Postoperative elevated cortisol excretion is not associated with suppression of 6-sulfatoxymelatonin excretion. Acta Anaesthesiol Scand 2005; 49: 52–7.

21 *Ginsberg B, Sinatra RS, Adler LJ, et al.* Conversion to oral controlled-release oxycodone from intravenous opioid analgesic in the postoperative setting. Pain Med 2003; 4: 31–8.

22 *Parker RK, Holtmann B, White PF.* Patient-controlled analgesia. Does a concurrent opioid infusion improve pain management after surgery? JAMA 1991; 266: 1947–52.

23 *Fleming BM, Coombs DW.* A survey of complications documented in a quality-control analysis of patient-controlled analgesia in the postoperative patient. J Pain

Symptom Manage 1992; 7: 463–9.

24 *Reuben SS, Connelly NR, Maciolek H.* Postoperative analgesia with controlled-release oxycodone for outpatient anterior cruciate ligament surgery. Anesth Analg 1999; 88: 1286–91.

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