



# Postoperative Opioid Analgesia: Time for a Reconsideration?

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*Postoperative pain relief has improved in recent years with the development of new analgesics, additional routes of administration and the appearance of the hypothesis of preemptive as well as balanced analgesia (Kehlet H: Postoperative pain relief—what is the issue? Br J Anaesth 1994;72:375–8). Many initial improvements simply involved the administration of opioid analgesics in new ways, such as continuous or on demand intravenous (IV) or epidural infusion. These methods allow lower total opioid dosages, provide a more stable concentration of opioid at the receptor and correspondingly better analgesic effects, and also fewer unwanted side effects.*

*Although opioids have played a prominent role in postoperative analgesia for centuries and are still often administered as a matter of routine, their frequent minor side effects and the increasing availability of suitable alternatives may limit their future use in some situations. Thus, the recent emphasis on ambulatory surgery and accelerated surgical stay programs, both with a focus on early recovery of organ function and provision of functional analgesia [ie, pain relief that allows normal function (Kehlet H: Postoperative pain relief—what is the issue? Br J Anaesth 1994;72:375–8)] provide an opportunity for a reappraisal of opioid use in these settings. For this debate, controlled clinical studies on the opioid-sparing effect of different analgesic techniques are mentioned, and preferably studies with multiple dosing of analgesics and/or a reasonably large patient sample size. These data do not allow a proper meta-analysis to be performed because of the large variability in surgical procedures, dosing regimens, assessment criteria, among others.*

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## The Pros and Cons of Postoperative Opioid Treatment

### Central Nervous System Effects

*Analgesia* Opioids have well-documented analgesic effects. However, opioid analgesia is most effective during rest, rather than function (eg, cough, mobilization).<sup>1–3</sup> Therefore, opioids alone cannot provide functional pain relief. This may be achieved by a balanced analgesia regimen,<sup>4</sup> including small doses of opioids, or replacing opioids with more effective analgesics (local anesthetics in the wound, peripheral and central blocks, etc.). Based on experimental studies, opioids have been effective in the preemptive analgesia technique, but clinical

studies have been largely negative, with unimproved pain scores during rest and function.<sup>5</sup> A modest postoperative opioid-sparing effect has been observed in some studies, but without other documented clinical advantages.<sup>1-3</sup> Opioid analgesia per se is therefore satisfactory in relatively minor procedures and in major procedures to provide pain relief at rest, but is not optimal in accelerated postoperative stay programs or in major procedures with a high pain intensity.

**Sedation** The sedative effect of opioids may be desirable in some perioperative situations, but must be considered a negative side effect in outpatient and accelerated surgical stay programs. The well-documented opioid-sparing effect of perioperative nonsteroidal antiinflammatory drug (NSAID) administration<sup>6</sup> may reduce sedation, although this was only significant in four<sup>7-10</sup> of 15 controlled studies comparing NSAIDs with placebo or opioids.<sup>7-21</sup> Reduction of sedation may be important since sedation may contribute to alveolar hypoventilation, obstructive apneas, and aggravate postoperative hypoxemia (see below).

**Sleep** Although sedative, opioid analgesia may also contribute to pronounced postoperative sleep disturbances with initial disappearance of rapid eye movement (REM) sleep followed by a rebound on the second to fourth postoperative night,<sup>22</sup> because reduction of REM sleep and slow-wave sleep has been demonstrated in volunteers given morphine.\* The clinical implications of postoperative REM rebound include severe episodic hypoxemia, hemodynamic instability, and ECG abnormalities.<sup>22</sup> Inhibition of REM sleep seems to be a specific mu receptor-mediated effect.<sup>23</sup> The effect of opioid-free analgesia or opioid reduction by NSAIDs on postoperative sleep has not been evaluated, although it was noted in one<sup>21</sup> of 15 NSAID studies<sup>7-21</sup> that sleep was improved.

### Respiratory Effects

The effect of opioids on respiratory function may be of potential advantage regarding suppression of unwanted coughing or improvement in respiratory mechanics when impaired by postoperative pain. However, no analgesic technique can completely prevent postoperative impairment in pulmonary function. Nevertheless, effective analgesia may improve pulmonary function, but systemic or epidural opioid analgesia may be less effective than epidural local anesthetics.<sup>24</sup> Negative effects of opioids on respiratory function are well known and include depression of the cough reflex, a reduced sensitivity to hypoxemia and hypercapnia, and reduced chest wall compliance, respiratory rate, tidal volume, and expiratory force. Characteristically, opioids may especially reduce respiratory function during sleep.<sup>25</sup> Several studies have shown an increased incidence and severity of both episodic and con-

stant hypoxemia with opioid analgesia compared with regional anesthesia with local anesthetics.<sup>26,27</sup> Also, equivalent analgesia with less need for opioids and less hypoxemia has been achieved by adding clonidine to opioid regimens.<sup>28,29</sup> The opioid-sparing effect of NSAID treatment may improve respiratory function, although this was only demonstrated in two<sup>9,14</sup> of 15 controlled studies.<sup>7,11,12,17,21</sup>

### Gastrointestinal Effects

**Emesis** In some patients, opioid analgesia may have positive effects on pain induced nausea and vomiting,<sup>30</sup> although opioids otherwise are well known to stimulate the vomiting center to induce nausea and vomiting, especially during ambulation.<sup>31</sup> Even a single opioid dose may lead to prolonged vomiting after outpatient surgery.<sup>32</sup> Postoperative nausea is reduced when epidural bupivacaine is used instead of epidural morphine.<sup>33</sup> The use of NSAIDs instead of opioid improves gastric emptying in both volunteers<sup>34</sup> and postoperative patients.<sup>35</sup> Opioid-sparing by NSAID treatment has resulted in reduction of nausea or use of antiemetics in five<sup>7,11,12,17,21</sup> and increased nausea in one<sup>13</sup> of 15 controlled studies.<sup>7-21</sup> In addition, several of these studies showed a nonsignificant reduction of nausea and vomiting.

Since early oral nutrition is essential for early recovery, these results call for opioid-free regimens in outpatient and accelerated stay programs provided that sufficient analgesia can be achieved by such techniques.

**Gastrointestinal paralysis** Gastrointestinal (GI) paralysis is an important factor to delay discharge after surgery. From studies in volunteers, systemic and epidural opioids are well known to have negative effects on GI motility.<sup>34,36,37</sup> In the postoperative state, GI paralysis is more pronounced during analgesia with opioids used as patient-controlled analgesia (PCA), conventional, or epidural treatment than with epidural local anesthetic regimens.<sup>38,39</sup> Combinations of low doses of local anesthetics and opioids may improve functional pain relief and probably preserve the positive effects on intestinal motility achieved with local anesthetics alone.<sup>38-41</sup> The use of NSAIDs to reduce or replace opioids may also improve GI motility since ileus was reduced in four<sup>7-21</sup> of 15 controlled studies.<sup>7,8,11,21</sup> Perioperative opioid usage should therefore be reduced whenever possible in procedures where early recovery of bowel function is important.

### Urinary Effects

Both systemic and epidural opioids have negative effects on urinary bladder function, which may result in urinary retention.<sup>42,43</sup> This could be important in accelerated surgical stay programs where early removal or avoidance of bladder catheterization is necessary, although dose-response studies are not available to quantitate a potential advantage of opioid-free analgesic regimens. However, in 15 controlled studies,<sup>7-21</sup> the opioid-sparing effect of perioperative NSAID treatment significantly reduced uri-

\*Moote CA, Knill RL, Skinner MI, Rose EA: Morphine disrupts nocturnal sleep in a dose-dependent fashion [Abstract]. *Anesth Analg* 1989;68:S200.

nary retention only in one study<sup>8</sup> and bladder spasm in another.<sup>11</sup>

### Stress Response

Opioids may reduce surgical stress and they have been demonstrated to have a significant positive effect on classical stress hormones when used in very high doses intraoperatively and in the early postoperative period.<sup>38</sup> However, such an approach is only feasible in certain high-risk patients and cardiac procedures and not in outpatient or accelerated stay programs. The effect of PCA with opioids on the stress response is small or absent, while epidural opioids may have a moderate inhibitory effect, although not comparable to epidural local anesthetics.<sup>38</sup>

### Cardiovascular Effects

The well-known cardiovascular side effects, including hypotension with the use of higher doses, are probably not relevant for postoperative epidural or PCA opioids. Opioids may have some myocardial protective effects due to the reduced catecholamine-induced increase in myocardial work when patients are in pain. Thus, under well-defined investigational circumstances opioid analgesia resulted in fewer early postoperative cardiac ischemic episodes.<sup>44</sup> However, similar or more pronounced advantageous effects may be expected with effective epidural or other nonopioid regimens, although they have yet to be demonstrated.

### Immunofunction

It is well established that anesthesia and surgery lead to immunosuppression,<sup>45</sup> which may lower resistance to infection as well as enhance postoperative tumor growth. The effect of opioid versus opioid-free analgesic regimens on postoperative immunosuppression has not been clearly established in clinical studies, although epidural local anesthetics may be more effective in improving postoperative immunosuppression than opioid regimens.<sup>38,45</sup> However, some, but not all, experimental studies suggest a negative effect of morphine administration on surgery-induced immunosuppression and enhancement of tumor growth.<sup>46-49</sup> One clinical study in volunteers showed morphine in conventional analgesic doses to inhibit spontaneous and cytokine-enhanced natural killer cell cytotoxicity.<sup>50</sup> Further studies are needed to clarify the potentially advantageous effects of different analgesic techniques on postoperative immunofunction, and no conclusions can be drawn as to whether an opioid or opioid-free regimen is preferred.

### Discussion

The current efforts to improve postoperative pain relief and to use such pain relief in accelerated postoperative

stay programmes<sup>51,52</sup> may warrant a reconsideration of the use of opioids for postoperative pain relief.

It appears that the analgesic effects of low dosages of opioids are only modest, and insufficient to allow early ambulation. In addition, a number of well-known and potential side effects may limit early recovery when opioids are used in postoperative pain relief. Although none of these side effects is potentially life-threatening or represents a risk for serious morbidity in healthy patients, they should receive increased attention in high-risk patients and in the ambulatory and semi-ambulatory setting. The available data, however, are not conclusive because they have included a limited number of patients from a variety of surgical procedures. In addition, the primary aim of these studies has often been to investigate analgesia and opioid-sparing effects of various analgesics and not opioid-induced side effects per se. These data should therefore merely serve as a stimulus for further development of multi-modal analgesic regimens with limited or no use of opioids in order to evaluate a potentially faster recovery by elimination of opioid-induced side effects and weighed against potential side effects of other analgesics. In this context, it is thought-provoking that an opioid-free regimen combined with stress reduction by laparoscopic-assisted surgery with epidural and incisional local anesthesia eliminated nausea, vomiting, and ileus, and reduced hospital stay to two days after colonic resection in high-risk patients.<sup>53</sup> Future multimodal analgesic regimens with limited or no use of opioids may include combinations of local anesthetics, NSAIDs,  $\alpha_2$ -adrenergic antagonists, and *N*-methyl-D-aspartate receptor antagonists (eg, ketamine). Also, the recent clinically available bradykinin and substance-P antagonists, leukotriene synthesis blockers, and glucocorticoids may find a place in such balanced analgesia programs. Finally, attention should be paid to a peripheral treatment of the surgical wound and the local inflammatory response to minimise postoperative pain. In this context, opioids also have been demonstrated to have a peripherally mediated analgesic effect.<sup>54</sup> Therefore, local application of opioids at the site of injury and with opioids that do not penetrate the blood-brain barrier may provide analgesia, but with a reduced incidence of side effects.

In summary, opioids have been available and have been used for centuries in the treatment of postoperative pain with good results, and it is only because of developments in other areas of analgesic research that the question of opioid-free analgesia may be appropriate. Hopefully, the next few years will answer the question whether we should change our traditional use of opioids in acute pain treatment.

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