ORIGINAL ARTICLE

Intermittent subcutaneous morphine regimen for postoperative pain management following abdominal hysterectomy regarding morphine- and beta-endorphin systemic concentrations

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Abstract

OBJECTIVES: Systemic β-endorphin, an endogenous opioid and stress hormone, has been demonstrated to correlate with the postoperative pain intensity, however its putative role as a postoperative pain biomarker has not been cleared.
METHODS: Thirty patients scheduled for elective hysterectomy were included into the study. Postoperative pain was assessed by a numeric rating scale from 0 to 10. Plasma morphine concentrations were determined using high performance liquid chromatography with UV detection. Plasma β-endorphin concentrations were measured by a radioimmunoassay.
RESULTS: Administration of morphine in intravenous infusion turned out to be a markedly better method of morphine administration up to 4th hour postoperatively regarding both drug concentration and pain rating. A significant correlation between systemic β-endorphin concentration and pain rating at the 4th postoperative hour was found. No association between morphine and β-endorphin concentrations was detected.
CONCLUSION: Systemic β-endorphin is not an appropriate pain marker in postoperative gynaecologic patients.

INTRODUCTION

Parenteral morphine belongs to the mainstay of pain control after abdominal hysterectomy, however, no evidence-based clinical practice guidelines on the way of administration have been formulated. The superiority of intravenous patient controlled analgesia (PCA) which may be associated with greater opioid use, more pruritus (Bell 2007) and potential human errors (Bertram 2009), over continous intravenous, or scheduled intermittent subcutaneous administration regarding strong opioids in gynecological surgery setting failed to be defined.

Subcutaneous mode of postoperative analgesia generally not advocated in some opinions should be more convenient than the intravenous route of administration and equally effective, even in such a demanding setting like cardiac surgery (Hopkins 1998, Vijayan 1997, Gregg 1999, Munro 1998).

Systemic β-endorphin, an endogenous opioid and stress hormone, has been demonstrated to correlate with the postoperative pain intensity (Matejec 2006), however its putative role as a postoperative pain biomarker has not been sufficiently cleared. Specifically in gynecologic setting relationship between circulatory β-endorphin and postoperative pain is controversial (Krug 1990, Jellinek 1990).

Aims of the study were: 1. Assessing the feasibility and defining basic pharmacokinetic and pharmacodynamic aspects of morphine nurse-administered subcutaneously as compared with the intravenous infusion in patients subjected to abdominal hysterectomy in the postoperative pain control; 2. Finding a putative association between systemic β-endorphin and analgesia in women who became subcutaneous morphine.

MATERIALS AND METHODS

After local ethics committee approval and written, informed consent, thirty patients scheduled for elective abdominal hysterectomy, aged 36–56 years and having an American Society of Anesthesiologists (ASA) physical status I or II were entered into the study.

Exclusion criteria were: history of liver and kidney diseases, chronic pain, preoperative opioid consumption and morphine allergy or intolerance.

Anaesthetic management was standardized in all patients. Patients received 7.5 mg of oral midazolam one hour before surgery, and then for induction to general anaesthesia propofol 2 mg kg^{-1} and fentanyl 3 μg kg^{-1}. Tracheal intubation was facilitated by rocuronium 0.6 mg kg^{-1}. During anesthesia the patients were ventilated with an oxygen/nitrous oxide mixture and fentanyl and rocuronium were repeated according to the attending anaesthetist. Body temperature was kept within normal ranges.

Postoperative pain was assessed by a numeric rating scale (NRS) from 0 (no pain) to 10 (the worst imaginable pain).

After surgery, on arrival to the postanesthesia care unit (PACU) all patients received 100 mg of ketoprofen intravenously.

Then, patients were randomized in a 1:1 ratio to receive morphine either subcutaneously or intravenously according to the following protocols:

1. Subcutaneous group (SC; n=15) – morphine was given subcutaneously (s.c.) at a dose of 10 mg every three or four hours via a butterfly cannula inserted in the subclavicular area (Gregg 1999).

2. Intravenous group (IV; n=15) – intravenous bolus (i.v.) of morphine with dose titration to achieve the effective dose (ED; 2 mg of morphine given i.v. every three minutes) (Aubrun 2007), then constant infusion (rate was calculated based on $T_{0.5}$ = 3 hours and the following formula: rate [mg h^{-1}] = ED/(2×3h).

In both groups breakthrough pain was treated with administration of an additional bolus doses of 2 mg i.v.

Total morphine consumption over the first 12 postoperative hours was calculated.

Postoperative monitoring included ECG, non-invasive arterial blood pressure, respiratory rate, peripheral oxygen saturation (Space Labs Medical Inc., 90309, USA) and urine outputput. Consciousness was assessed by an Aldrete scoring. All cases of undesirable effects were recorded.

Venous blood samples (5 mL, lithium heparin) were drawn postoperatively before morphine administration (sample 0) and at 1, 2, 4, 8 and 12 hours thereafter and centrifuged. Plasma was stored at –70 °C for later analysis.

Plasma morphine concentrations were determined using high performance liquid chromatography with UV detection (HPLC-UV) method (Scheider 1998) adopted and validated in accordance with the published guidelines (Chandran 2007; ICH Harmonised 2005).

Plasma β-endorphin concentrations were measured by a radioimmunoassay (Euria-β-Endorphin kit**,** Euro-Diagnostica) according to manufacturer recommendations (sensitivity 3 pM L^{-1}, intra assay variation 7.1%, inter assay variation 7.2%).

Data presented as median (interquartile range, IQR) were analyzed using Mann-Whitney (M-W) and Friedman (F) tests or chi-square contingency tables. Correlations were assessed by Spearman Rank test. The *p*-value less than 0.05 was considered statistically significant. Analyses were performed by Graph Pad Instat™ V2.05a.

RESULTS

A total of 30 patients were evaluated and no patient was excluded. Patients in the SC group were younger: median (IQR) age: 48 (43–51) vs. 55 (51–56) years in the IV group; M-W, p=0.003. No differences in weight and ASA physical status were detected.

Nausea and vomiting occurred in 4 vs. 2 cases in the SC and the IV group respectively (NS). No cases of puritus or respiratory depression (respiratory rate <8 min.) were noted.

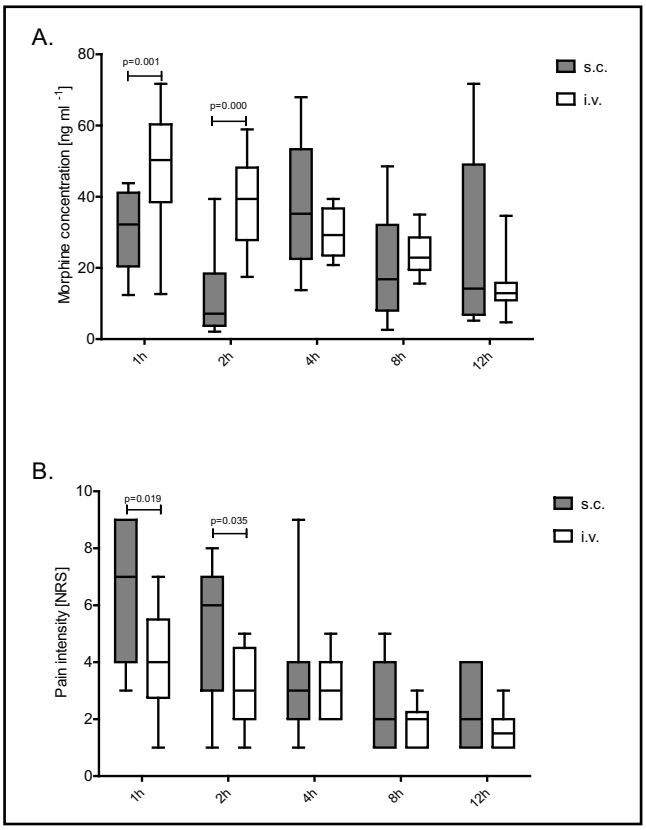
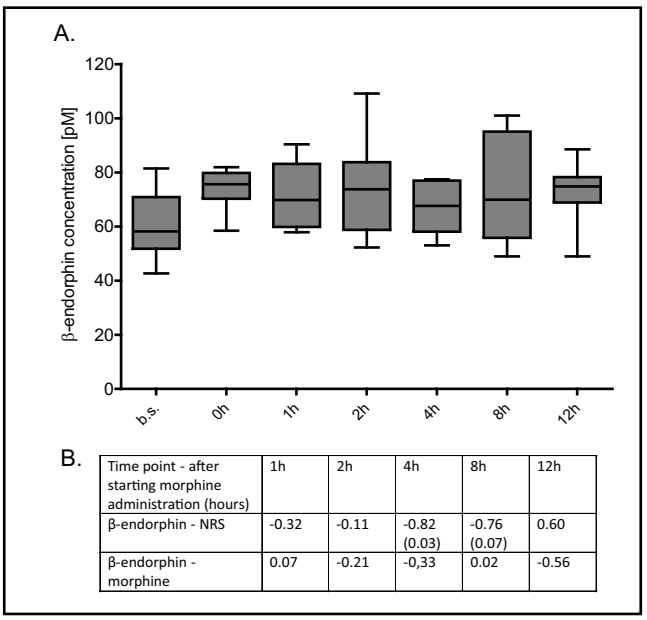


Fig. 1. Morphine concentrations (**A**) and pain intensity (**B**) over 12 hours after hysterectomy in the subcutaneous (s.c.) and the intravenous group (i.v.).
Median; boxes - IQR. At the 1st and the 2nd hours significant differences between the groups (M-W).



B.

Time point - after starting morphine administration (hours)	1h	2h	4h	8h	12h
β-endorphin - NRS	-0.32	-0.11	-0.82 (0.03)	-0.76 (0.07)	0.60
β-endorphin - morphine	0.07	-0.21	-0,33	0.02	-0.56

Fig. 2. A. β-endorphin concentrations before surgery (b.s.) and over the first 12 postoperative hours in the SC group.
Median (IQR). No significant differences were noted (F, p=0.088).
B. Correlations between systemic β-endorphin concentrations, pain intensity (NRS scores), and systemic morphine concentrations in the SC group.
(n=13, Spearman r, p if significant).

Morphine consumption was higher in the SC group: median (IQR): 40 (40–42) vs. 33 (23–42) mg in the IV group; M-W, p=0.018.

Administration of morphine in intravenous infusion turned out to be a markedly better method of morphine administration up to 4th hour postoperatively regarding both drug concentrations and pain ratings (Figure 1).

In the SC group plasma β-endorphin concentrations were initially slightly higher as compared to preoperative control values and then remained stable (Figure 2).

A significant negative correlation between systemic β-endorphin concentrations and pain ratings at the 4th postoperative hour was found. No association between morphine and β-endorphin concentrations was detected (Figure 2).

DISCUSSION

In patients subjected to abdominal hysterectomy in a multimodal postoperative analgesia model combining systemic morphine with ketoprofen we have shown that subcutaneous intermittent morphine administration in the immediate postoperative period is less effective than a continous intravenous infusion, as demonstrated by higher pain ratings and concomitant lower systemic morphine concentrations (Figure 1). Interestingly, since the 4th postoperative hour both subcutaneous and intravenous ways of morphine administration proved to be equally effective with comparable systemic drug concentrations.

In postoperative gynecologic patients subcutaneous morphine administration has been suggested to be of real advantage, i.e. due to improvements in sleep pattern, less interference with activities of living and greater staff involvement (Dawson 1999; Munro 1998), factors important for the optimization of postoperative recovery. It proved satisfactory also in major abdominal and cardiac surgery (Munro 1998). Our data indicate that the time window of the first four postoperative hours may be critical. Interestingly, it has been shown, that after 4 hours following hysterectomy IL-6 and cortisol levels, postoperative stress indicators, are the highest (Eriksson-Mjoberg 1997).

Observed by us lower and fluctuating morphine concentrations in the SC group as compared to control may reflect complex absorption dynamics from the subcutaneous tissue, but also variability of distribution and clearance. It has been shown that it takes about 17 minutes to achieve peak blood concentration after subcutaneous administration of the drug (Semple 1997). At the 2nd hour mean plasma morphine concentrations in these patients failed to reach analgetically effective critical level of 20 ng mL^{-1} (Graves 1985; Leonard 1993); this may partly explain poor pain relief (Figure 1). Later on a cumulative effect of morphine might have played a role. Consistant with earlier reports (Waldman 1984) from the 4th postoperative hour on no

difference between drug concentrations in both groups were found (Figure 1).

Unsatisfactory analgesia in the immediate postoperative period might have exposed these patients to a danger of the stress response complications and a development of chronic pain syndrome and prompted us to discontinue the study.

Our findings suggesting that the intermittent subutaneous morphine administration may not sufficiently alleviate pain in the immediate postoperative period after abdominal hysterectomy does not exclude potential feasibility of other subcutaneous techniques, like continuous infusion (Gaudi 1985). Intravenous morphine titration before subcutaneous drug injection may be of importance, however, it may be connected with undesirable sedation effect. The same problem may arise with the intraoperative morphine loading, which appeared to increase the probability of adverse events while not reducing the time to achieve pain relief in the PACU and only slightly improving analgesia (Aubrun 2007).

It is possible that covering the first four hours with a modified analgesic regime and continuing subcutaneous intermittent morphine further on could be an acceptable option.

In the SC group morphine consumption appeared also to be higher, however, these patients were younger than controls, which could influence drug requirement (Macintyre 1996). Other authors could not detect any differences in morphine consumption in subcutaneous as compared to intravenous regimen of drug administration (Hopkins 1998; Vijayan 1997), but a trend towards higher consumption was also reported (Munro 1998). On the other hand, opioid consumption may not be fully adequate as a method of pain assessment, possibly influenced by the patients' fear of dependency (Bamigboye 2009).

In women administered morphine subcutaneously we have shown, partly in line with previous findings (Leonard 1993), that β-endorphin systemic levels slightly (insignificantly) raise after surgery but than remain stable up to the 12th hour postoperatively, irrespectively of pain intensity and systemic morphine concentrations (Figure 2). Pain ratings negatively correlated with circulatory β-endorphin, but only at the 4th postoperative hour, when analgesia begun to stabilize (Figure 2).

Association between postoperative pain intensity and systemic β-endorphin is in fact a controversial issue and published data are inconsistent, reporting positive (Matejec 2006), negative (Leonard 1993; Krug 1990) or no association at all (Jellinek 1990).

In patients subjected to hysterectomy postoperative systemic β-endorphin levels were either no related to (Jellinek 1990) or adversely associated with pain intensity (higher in women who received epidural analgesia and were painfree as compared to patients in whom neuroleptanalgesia was administered; Krug 1990). Our data support these findings.

β-endorphin reactivity to pain seems to be gender specific and may also depend on the modality of pain. There are also significant gender differences regarding β-endorphin effects in pain perception – women appeared to be resistant to β-endorphin modulation of pain (Sadigh 2007). Positive correlation between β-endorphin and pain intensity was found in orthopedic patients both sexes; it is possible that the response may differ between men and women and orthopedic surgery setting, where somatic pain predominates, may not be comparable to gynecologic patients exposed predominantly to visceral pain (Matejec 2006). Another important factor may be anxiety contribution, important in gynecological patients, not estimated by us in this study.

It may not be excluded, that in our patients, partly at least, systemic β-endorphin levels might have been modulated by morphine (Farrington1993; Rassmussen 2003; Farrington 2003). However, no direct association between systemic morphine concentrations and β-endorphin levels could be detected (Figure 2). The phenomeneon needs to be confirmed on a bigger sample.

In conclusion, we suggest that subcutaneous way of morphine administration in intermittent doses combined with intravenous ketoprofen may be not suitable for effective analgesia after abdominal hysterectomy, at least up to the first four hours postoperatively.

Systemic β-endorphin is not an appropriate pain marker in postoperative gynecologic patients.

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