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Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia

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Background. Perioperative use of dexmedetomidine is associated with reduction in postoperative analgesic requirements. This study examined whether dexmedetomidine added to i.v. patient-controlled analgesia (PCA) morphine could improve analgesia while reducing opioid-related side-effects.

Methods. In this double-blinded, randomized, controlled study, 100 women undergoing abdominal total hysterectomy were allocated to receive either morphine 1 mg ml^{-1} alone (Group M) or morphine 1 mg ml^{-1} plus dexmedetomidine 5 μg ml^{-1} (Group D) for postoperative i.v. PCA, which was programmed to deliver 1 ml per demand with a 5 min lockout interval and no background infusion. Cumulative PCA requirements, pain intensities, cardiovascular and respiratory variables, and PCA-related adverse events were recorded for 24 h after operation.

Results. Compared with Group M, patients in Group D required 29% less morphine during the 0–24 h postoperative period and reported significantly lower pain levels from the second postoperative hour onwards and throughout the study. Whereas levels of sedation were similar between the groups at each observational time point, decreases in heart rate and mean blood pressure from presurgery baseline at 1, 2, and 4 h after operation were significantly greater in Group D (by a range of 5–7 beats min^{-1} and 10–13%, respectively). The 4–24 h incidence of nausea was significantly lower in Group D (34% *vs* 56.3%, $P<0.05$). There was no bradycardia, hypotension, oversedation, or respiratory depression.

Conclusions. The addition of dexmedetomidine to i.v. PCA morphine resulted in superior analgesia, significant morphine sparing, less morphine-induced nausea, and was devoid of additional sedation and untoward haemodynamic changes.

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Maximizing pain relief and minimizing analgesic-related side-effects are vital to patient recovery after surgery. A multimodal approach, using different classes of analgesics, is the currently recommended method to obtain this goal.[1] Of the multimodal protocols, combining an adjunct drug with an opioid in i.v. patient-controlled analgesia (PCA) as a convenient regimen for pain management is gaining worldwide popularity in current clinical practice. Various adjunct drugs, including antiemetic,[2] non-steroidal anti-inflammatory drugs,[3] pure opioid-antagonist,[4] opioid agonist–antagonist,[5] and ketamine,[6] have been used in such a multimodal effort. However, dexmedetomidine, a potent and highly selective α_2-adrenoreceptor agonist possessing multifaceted attributes of analgesia, anxiolysis, sedation, sympatholysis, and no respiratory depression,[7–10] coadministered with morphine by way of PCA has not yet been investigated.

The aim of this study was to evaluate whether dexmedetomidine added to PCA morphine could enhance analgesia while reducing side-effects related to PCA morphine administration. Side-effects related to the dexmedetomidine–morphine mixture were also investigated.

Methods

After institutional review board approval of this randomized double-blinded controlled study, informed consent was obtained from 100 female patients aged between 18 and 65 yr, ASA I or II, undergoing total abdominal hysterectomy with general anaesthesia. Patients were excluded if there was a history of hypertension, ischaemic heart disease, or conduction disturbance, if they were taking antidepressants or β-adrenoreceptor blockers, if they had underlying gastrointestinal diseases, a history of previous postoperative nausea and vomiting, motion sickness, or a known sensitivity to any of the medications used.

Our hospital pharmacy was in charge of the study medication preparation and group assignment. A computer-generated randomization table was used to allocate patients into two groups (n=50 per group). The 100 ml solution in the PCA reservoir bag contained 100 mg of morphine in normal saline (1 mg ml^{-1}) in Group M or 100 mg morphine plus 500 μg of dexmedetomidine in normal saline (morphine 1 mg ml^{-1}; dexmedetomidine 5 μg ml^{-1}) in Group D. The PCA dose of dexmedetomidine (Precedex®; Hospira, Inc., Lake Forest, IL, USA) was based on the 0.5 μg kg^{-1} h^{-1} infusion divided by six. This average number of PCA doses in the first hour after surgery was based on a prior study in a similar population.[2] Both patients and observers were blinded with respect to the group allocation. Double-blinding was achieved by labelling the PCA reservoir bags with a particular identification number only. The blinding code retained by the pharmacy was opened after completion of study. For reasons of patient safety, a sealed opaque envelope containing the treatment assignment was kept with the patient in the post-anaesthesia care unit (PACU) and general ward. Unblinding would be carried out when an unexpected serious adverse event (circulatory failure, conscious disturbance, and respiratory depression) occurred and this knowledge was required for emergency treatment.

Routine presurgery baseline heart rate (HR) and mean blood pressure (MBP) were documented after ward admission. Before the surgery, all patients were instructed on the operational use of PCA system (Lifecare 5500 PCA; Abbott Laboratories) and a 0–10 verbal rating scale (VRS), where 0 represented no pain and 10 the worst pain imaginable. The goal of PCA analgesia was to maintain the VRS at rest ≤4 between 4 and 24 h after operation. A standard general anaesthetic was given, comprising thiopental 3–5 mg kg^{-1}, fentanyl 1.5–3 μg kg^{-1}, and cisatracurium 0.5–0.8 mg kg^{-1}. Anaesthesia was maintained with isoflurane 0.8–1.5% in nitrous oxide 60% and oxygen 40%. Edrophonium 0.5–1 mg kg^{-1} and atropine 0.015 mg kg^{-1} were given to reverse residual neuromuscular block at the end of surgery. The patients were attached to a PCA machine upon arrival in the PACU. As soon as the patients were awake, their pain was assessed using the VRS. If the patient reported a VRS at rest of 5 or higher, an anaesthetist not involved in the study titrated PCA solution i.v. 2 ml at 5 min intervals until the VRS was 4 or less. Then, the patients were encouraged to self-administer their own PCA medications. The setting for PCA was 1 ml bolus with a 5 min lockout. There was no background continuous infusion throughout the postoperative period. Patients were monitored and received nasal O_2 supplementation. The HR, Sp_{O_2}, and MBP were recorded at specific time points (0, 15, 30, 45, and 60 min after arrival to the PACU) during the 1 h PACU stay.

Patients were assessed at 1, 2, 4, and 24 h after operation. The cumulative PCA requirements were recorded in PCA machines, and the data were transferred to a computer for interpretation. Pain intensity was evaluated with VRS at rest (VRSR) and upon movement (VRSM). Patients were asked to score their worst VRSR and VRSM since the previous assessment. VRSR was assessed with the patient lying supine and VRSM assessed during change from supine to lateral position. Nausea, vomiting, and pruritus were investigated by incidence and severity. The severity of an adverse event was defined as mild (discomfort noticed, but no disruption of anticipated normal activity), moderate (discomfort sufficient to reduce or affect anticipated normal activity), or severe (inability to perform anticipated normal daily activity).[11] Patients were made aware that rescue antiemetic (prochlorperazine 10 mg i.v.) and rescue antipruritic (diphenhydramine 30 mg i.v.) would be available on request. Level of sedation was assessed with a five-point scoring scale (0, fully awake; 1, drowsy, closed eyes; 2, asleep, easily aroused with light tactile stimulation or a simple verbal command; 3, asleep, arousable only by strong physical stimulation; and 4, unarousable).[12] Each patient was asked to grade satisfaction (yes/no) with pain relief at the end of PCA use.

PCA treatment was considered a failure if the VRSR remained >4 during 4–24 h after operation or if patients required more than three administrations of rescue medications for nausea, vomiting, or pruritus.[4] Adjunctive analgesic with i.v. meperidine 50 mg or ketorolac 30 mg would be administered for insufficient analgesia. Persistent nausea, vomiting, or pruritus would warrant PCA termination with the patient then being switched to an alternate analgesic modality. PCA-related bradycardia (HR <50 beats min^{-1}), hypotension (>20% decrease in MBP from presurgery baseline), somnolence (sedation score ≥3), and respiratory depression (ventilatory frequency <8 bpm lasting for more than 10 min) were considered as severe adverse events. If severe adverse events occurred, the use of PCA was stopped immediately and the adverse effects were treated with appropriate treatment. Hypotension or bradycardia was treated with volume expansion, ephedrine, or atropine. Respiratory depression was treated with naloxone and oxygen.

The power calculation for the study was based on morphine consumption in the first 24 h after surgery, assuming