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Morphine at "sub-analgesic" background infusion rate plus low-dose PCA bolus control pain better and is as safe as twice a bolus-only PCA regimen: A randomized, double blind study

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ABSTRACT

Morphine for postoperative pain control is commonly titrated via intravenous patient-controlled analgesia (IV-PCA). An IV morphine background infusion is rarely used. We investigated whether analgesia is effectively attained and morphine consumption is reduced if PCA titration is coadjuvated by a continuous infusion protocol. Following colorectal cancer surgery, consenting patients were randomized to receive a minimal ("sub-analgesic") dose of morphine 0.01 mg/kg/h background infusion plus a 0.01 mg/kg bolus (BI), or a 1.5 mg bolus-only morphine (B0) (bolus ratio ~1:2). Bolus lockout time was 7 min in either case. All patients received 0.1 mg/kg morphine before protocol initiation, and diclofenac 75 mg intramuscularly b.i.d. during the study period, lasting 48 h. Eighty-six patients (51 males, age 26–95 years) participated in the study. The total mean morphine consumption during the 48 h was 25% lower in the BI than in the B0 group ($P < 0.05$). Although the former applied the PCA device for boluses 19% less than the latter ($P < 0.05$), their pain score was lower ($P < 0.05$) most of the time, and they reported greater satisfaction ($P < 0.05$) on a 10-scale numerical rating score. Pre- and postoperative vital signs were similar for both groups. No patient depicted hypoxemia or lapsed into deep sedation. Four BI and three B0 patients required treatment for postoperative nausea and vomiting. One BI patient had transient pruritus and one B0 69-year individual became disoriented 24 h into treatment; either event subsided soon after stopping their respective regimen without the need for treatment. The main conclusions of the results are that very-low-dose background morphine infusion combined with small-dose PCA boluses may provide better pain relief, lower morphine consumption, and minimal complication rate as a 1.5 mg PCA bolus-only protocol.

1. Introduction

Postoperative pain management is still a challenge to clinicians of various medical fields. Morphine is the most widely used postoperative analgesic. Nevertheless, concerns still exist regarding side effects, although these and its efficacy are only moderate compared to other perioperatively used opioids [1]. Its reputation probably lies in the fact that it is less potent and therefore risky than synthetic opioids, such as fentanyl or alfentanyl, mainly for naïve or elderly individuals, and where close monitoring of vital signs (e.g., blood pressure, respiratory rate, and oxygenation) are seldom available as on the ward.

Patient-controlled analgesia (PCA) is the most common mode of intravenous (IV) titration of opioids for controlling moderate-to-severe postoperative pain. Although the administration of small IV boluses (~1.0–2.5 mg) allows for rapid and safe titration of the dose needed for adequate pain relief, adverse effects have still been reported, among them sedation, respiratory depression and hypoxia. Lockout time is implemented to prevent these untoward sequelae, and its duration is fixed between 3 and 10 min, depending on the patient's characteristics, the type of opioid and its pharmacology, and the amount of each bolus.

The IV-PCA bolus dose of morphine (and other opioids) depends on many factors, such as pain intensity, previous use of opioids, and co-morbidities. In patients under close observation, as in the

Abbreviations: ASA, American Society of Anesthesiologists; B0, bolus only; Ce_{max}, the maximum concentration in the effect compartment; ICU, intensive care unit; IM, intramuscularly; IV, intravenous; MAC, minimal alveolar concentration; NRS, numerical rating scale; OIH, opioid-induced hyperalgesia; PACU, post-anesthesia care unit; PCA, patient-controlled analgesia; PONV, postoperative nausea and vomiting; SpO_2, pulse-derived oxygen saturation; VAS, visual analog scale.

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setting of a post-anesthesia care unit (PACU) or intensive care unit (ICU), a continuous infusion of the opioid has been advocated mainly in children [1–3], under the presumption that it would provide constant anti-nociception, while minimizing adverse events by curtailing fluctuations in blood concentration [4]. It has been reported that a standard dose of morphine infusion may accumulate in hypovolemic or elderly patients, as well as in individuals suffering from kidney or liver dysfunction if administration is prolonged [5]. Another disadvantage is that infusion is less readily re-adjustable in cases where pain fluctuates during the postoperative course. One example is large bowel surgery, after which considerable pain can be expected for several days during early recovery. We have shown that a combination of an infusion topped-up with boluses could profit the latter cases, by providing rapid, adequate and safe pharmacological response to intervallic needs for postoperative pain [6]. Sucato et al. have reported the combination of a basal infusion of morphine in their PCA protocol in spine-operated patients, which was kept constant at 0.015 mg/kg/h [7].

Due to the inconsistency of opinions regarding the above protocols, the acknowledgement of the utility of background plus PCA regimen, while no large randomized studies have been undertaken to compare such protocols, we performed a prospective, double-blind, randomized study aiming to evaluate the antinociceptive added value and the occurrence of side effects of minimal continuous background infusion of morphine when combined with self-administered IV-PCA titrated low-dose boluses of morphine, versus twice the bolus dose in a bolus-only titration mode, in patients who underwent colorectal surgery.

2. Patients and methods

After obtaining the local institutional review board (IRB) permission to conduct this study, 100 patients were invited to participate, of whom 90 agreed and signed the IRB-approved informed consent form. There was no age limit, given that the elderly are an especially suitable target population of this study for their pathology, and both complications and optimal pain control. During the preoperative interview, all the patients were taught how to discern what defined an unacceptable level of pain, and instructed to request initiation of the PCA setup if and when their pain reached that level [8]. Each patient was shown how to use a standard 10-cm numerical rating scale (NRS) to enable postoperative pain and satisfaction assessments.

All the patients underwent the same surgical procedure under standardized general anesthesia, and by the same teams. Exclusion criteria included American Society of Anesthesiologists (ASA) physical class >3, non-colorectal abdominal surgery, planned prolonged mechanical ventilation or an extended stay in an ICU for any reason, history of drug abuse or chronic pain, patients scheduled for minimally invasive surgery (e.g., laparoscopic surgery) or needing urgent intervention, or those known to have hypersensitivity to any drug administered during the 48-h study period. Patients with severe liver, cardiac, renal or pulmonary disease, recent (<6 mo) cerebrovascular accident or cardiac event, or mental incapacity, were also excluded. Subjects were dropped if they required >4 h of unplanned postoperative assisted ventilation, underwent re-operation during the study period, had ad-hoc need for ICU transfer, were incoherent or lacked adequate comprehension of their surroundings after surgery, and those for whom there were intra-operatively decided changes in surgical plan. Other cause for a later disqualification were core temperature <35.0 °C upon arrival to the PACU, pain not relieved by the applied regimen, and the presence of continuing (>15 min) blood de-saturation (<92% on 40% oxygen mask). The data of all those subjects were not included in the final analyses.

All patients were given IV midazolam up to 0.05 mg/kg, fentanyl 1.5 μg/kg, propofol 1–1.5 mg/kg and 0.7 mg/kg of rocuronium for the induction of anesthesia. Maintenance consisted of isoflurane-enriched nitrous oxide-in-oxygen 66/33%, aiming at end-tidal minimal alveolar concentration (MAC) of 0.8–1.2. A muscle relaxant was added as deemed necessary, and the fentanyl dosage was further adjusted to hemodynamic drifts and signs of pain. At the end of surgery, relaxation was reversed and the patients were transferred to the PACU.

2.1. Randomization

The quality of the study was assessed using the following Jadad criteria: random allocation of treatments with a clear description of the randomization procedure, blinding of the patient for the assigned treatment, blinding of the outcome assessor, and description of dropouts and missing values [9]. Following the surgical procedure, the PCA device was connected to the patient and started by the attending anesthesiologist. The syringe and the device were prepared and programmed based on the randomization list in the institutional pharmacy and by an individual uninvolved in the study, respectively. In case of complication, only one researcher (A. A. W.) had access to the computerized list of study group assignment. In addition, the data of patients who were withdrawn or who dropped out were incorporated in the 'intention-to-treat' analyses of the baseline data, and their outcomes were omitted from further assessment. Any patient could quit the study for any reason, and his/her data were not used for analyses.

2.2. Drug protocols and study goals

The first series of vital sign measurements and confirmation of the patient's coherence were obtained upon arrival to the PACU from the operating room. Following our standard protocol for postoperative care, patients in both study groups received a titrated loading dose of IV morphine 0.1 mg/kg during a 15-min period. This allowed all patients to start PCA use while under a similar nociception–antinociceptive equilibrium. The IV-PCA device was connected to the IV line of the patient as soon as he/she reported of pain that requested analgesia. The device was programmed to deliver either a 1.5 mg/bolus morphine as deemed necessary to the patient, to be comfortable with pain at deep breath, with a lockout time of 7 min (the B0 group), or a 0.01 mg/kg bolus at the same criteria, in combination with a continuous background infusion of 0.01 mg/kg/h of morphine (the BI group) [1]. The B0 protocol represents our institution's long-standing protocol, which is based on pharmacological application of a mean of 0.02 mg/kg morphine in individuals weighing about 70–75 kg [1,3,10–14]. The infusion hourly dose was based on earlier reports of infusion of morphine in the immediate postoperative period [1,15]. In order to evaluate the added value of the infusion, the BI protocol applied only 50% the B0 bolus dose, so that antinociceptive pharmacological effect was evident, and infusion-dependent safety could be maintained, while effective titration was available for sporadic pain intensifications.

Diclofenac 75 mg IM was the rescue drug available to each patient, and it was given at fixed times twice daily, starting at 1 h after starting the PCA regimen. This enabled the evaluation of the analgesic effect of morphine in either group, specifically the contribution of the background infusion.

All the patients were transferred to the surgical ward 3 h after starting the regimen, assuring for enough time to reach levels of pain high enough to be eligible to start using the PCA device, and to allow close monitoring of its safe implementation