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CASE REPORT

Effectiveness Of Low-Dose Intermittent Epidural Bolus of 1 mg Morphine as Postoperative Analgesia

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ABSTRACT

Background: Patients who have undergone major surgery typically experience postoperative pain that persists for seven days following surgery. The challenge for the anesthesiologist is to provide adequate postoperative pain control which is not always achievable. In contrast to systemic administration, epidural administration of opioids places the medications close to the site of action, allowing for relatively small doses to be effective with a low incidence of side effects. Morphine is a long-established analgesia drug that characteristically slows diffusion and long duration in epidural analgesia, making it widely used in postoperative pain management. However, giving morphine is not without any complications.

Case Illustration: Nine patients who underwent major surgeries either under combined epidural-general anesthesia or epidural anesthesia received a low-dose intermittent epidural bolus of 1 mg morphine in 10 mL normal saline every 12 hours after surgery. Postoperative pain scores were recorded at the 1st,12th,24th, 36th, and 48th hours after surgery, data of additional rescue analgesia, and the incidence of nausea, vomiting, pruritus, sedation, and respiratory depression were also collected. Only one patient needed rescue analgesia with 30 mg Ketorolac IV, and one patient needed anti-emetic with 4 mg ondansetron IV an hour after the completion of surgery. The rest of the patients have mild pain (NRS≤3/10) within 48 hours after surgery. Furthermore, there is no other adverse effects of morphine were found

Conclusion: low dose intermittent epidural bolus of 1 mg morphine can be used as effective postoperative analgesia and has fewer adverse effects.

Keywords: Epidural morphine; Major surgeries; Postoperative pain analgesia.

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INTRODUCTION

As a result of the fact that many patients continue to suffer from severe discomfort pain during the postoperative period, the effective management of postoperative pain continues to be one of the most crucial and urgent issues. The study revealed that more than 80% of patients who have undergone significant surgery typically experience acute postoperative pain that persists for several days following surgery. Approximately 75% of those have reported the severity as moderate, severe, or excruciating pain intensity. The challenge for the anesthesiologist is to ensure that adequate postoperative pain control can be achieved. Although there are guidelines for postoperative pain management, research reveals that this condition is still not receiving the best care, which affects clinical outcomes and quality of life, functional recovery, the risk of postoperative complications, and persistent postoperative pain. This is a challenge for the anesthesiologist.[1,2] Epidural analgesia refers to local anesthetics and adjuvants injected into the epidural space. It plays a significant role in the alleviation of postoperative pain. In the past few decades, it has evolved as one of the major elements of the multimodal approach in accomplishing the goal of adequate and effective control of postoperative pain besides offering superior results in comparison with systemic opioids. It also reduces the unfavorable physiology experienced during the surgery. The presence of opioid receptors in the spinal cord allows the use of morphine epidurally for managing pain.[3]

Morphine is a long-established analgesia drug that characteristically slows diffusion and long duration, making it widely used as a potent analgesic drug in epidural technique with or without the addition of a local anesthetic agent. It provides better analgesia than parenteral opioids with proven postoperative pain management in patients undergoing major abdominal, pelvic, radical nephrectomy, and lower extremity surgery. However, the optimal dose of morphine as an epidural agent that provides effective postoperative analgesia with minimal side effects is still controversial.

CASE ILLUSTRATION

This case includes a preliminary study covering the serial case, hence during its preparation, applying for an ethics license is impossible. However, the researcher has provided informed consent for patients and families regarding publication of related data. The cases involves nine adult patients of ASA classes I and II, who underwent major elective surgery namely laparotomy exploration, hip arthroplasty, radical nephrectomy, total abdominal hysterectomy bilateral salpingo-oophorectomy, adenomyosis resection, and ORIF plate and screws of femoral bone in Hasan Sadikin Hospital Bandung in early May 2022. Six patients were in epidural-general anesthesia and three patients were on epidural anesthesia have received a bolus of 1 mg morphine in 10 mL 0.9% normal saline at the end of surgery through the indwelling epidural catheter 12 hourly for about 48 hours after surgery. After surgery, the severity of pain was evaluated at the 1st, 12th, 24th, 36th, and 48th hours with numerical rating scales (NRS, an 11-points scale where 0= no pain and 10 = the worst pain). The occurrence of side effects (nausea, vomiting, pruritus, and sedation using the Ramsay Sedation Scale) and the uses and dosages of the other analgesic agents within 48 hours were also recorded. In the case of insufficient analgesia response to intermittent epidural bolus morphine (to reach an NRS ≥4/10), rescue analgesia with 30 mg of Ketorolac IV was given. For patients who developed nausea and vomiting, 4 mg of Ondansetron IV was allowed as needed. The baseline demographic and type of surgery among nine patients were listed in table 1.

All patients were reviewed one day earlier for pre-operative assessment. Before induction, standard monitoring devices such as non-invasive blood pressure (BP), pulse oximetry, and electrocardiography were attached. Six patients have undergone surgeries under combined epidural-general anesthesia, and three have received epidural anesthesia with all the injection levels at the lumbar level of L3/L4 or L4/L5. They received epidural anesthesia after the insertion of an epidural catheter using the loss of resistance technique, with a Touhy needle (18G, Portex® epidural set; Smiths Medicals, Czech Republic). Initially, a test dose of 3 mL of 2% Lidocaine + Adrenaline (1:200,000) was injected via catheter to

confirm placement and to exclude inadvertent intravascular or intrathecal placement.

Table 1. Demographic and perioperative data

Baseline Descriptions		
Gender	Male= 4 patients (44.4%)	Female= 5 patients (55.5%)
Age (year)	Minimum age = 28 years old	Maximum age = 63 years old
	Mean age = 48 years old	
BMI (kg BW/m^2)	18,7 – 28,1 (Mean BMI 22,5 kg/m^2)	
ASA PS	ASA I = 4 patients (44.4%)	ASA II = 5 patients (55.5%)
Type of anesthesia	Combined epidural-general anesthesia = 6 patients (66.6%)	Epidural anesthesia = 3 patients (33.4%)
Mean time of surgeries (h)	± 3,6 hours (minimum time of surgery is 2 hours and maximum time of surgery is 6 hours)	

A total of 12-14 mL of 0,5% plain bupivacaine was given as the initial dose over 15 minutes before induction of anesthesia for patients who received combined epidural-general anesthesia. The level of analgesia was assessed and acceptable at least up to T6 dermatomes before starting general anesthesia. Intra-operatively, analgesia was continued with an epidural infusion of 0,5% Bupivacaine 3-3,5 mL/hour. Among patients who received epidural anesthesia, the procedure was similar without induction by general anesthesia. The epidural bolus of 1 mg morphine in u to 10 mL normal saline was administered immediately after completion of the surgical procedure and before the patients were subsequently transferred to the recovery room for 2 hours of PACU observation using non-invasive blood pressure and pulse oximetry

Table 2. Type of surgeries

Description of surgeries	
Digestive surgery	**1 case** (Laparotomy exploration)
Obstetric-gynecology surgery	**2 cases** (Total abdominal hysterectomy and bilateral salpingo-oophorectomy, Adenomyosis Resection)
Orthopedic surgery	**3 cases** (Hip Arthroplasty, Correction deformity of Hallux Valgus, and ORIF Plate and screw + Biopsy excision)
Urologic surgery	**2 cases** (Radical Nephrectomy, Percutaneous Nephrolithotomy)
Vascular surgery	**1 case** (Thrombectomy + Fasciotomy)

All patients received an intermittent epidural bolus of 1 mg morphine in 10 mL normal saline every 12 hours. The severity of pain was evaluated at 1, 12, 24, 36, and 48 hours after surgery with numerical rating scales (NRS, an 11-point scale where 0= no pain and 10 = the worst pain). Additional data on rescue analgesia and incidence of opioid-related side effects such as nausea, vomiting, pruritus, sedation, and respiratory depression were also evaluated.

Table 3. Incidence of morphine adverse effects

PONV	Yes, one patient received a bolus of 4 mg Ondansetron IV an hour after surgery
Pruritus	None
Sedation effect	None
Respiratory depression	None
Rescue analgesia	One patient who underwent thrombectomy and fasciotomy of lower extremities have NRS 4/10 shorty after the epidural morphine is given, thus she received rescue analgetic with 30 mg Ketorolac IV.

One patient developed insufficient pain control with NRS ≥4/10 within an hour after surgery, thus receiving rescue analgesia with 30 mg of Ketorolac intravenously. NRS intensity has decreased following further assessment by a range of 1/10-2/10. The pain scoring was listed in figure 1.

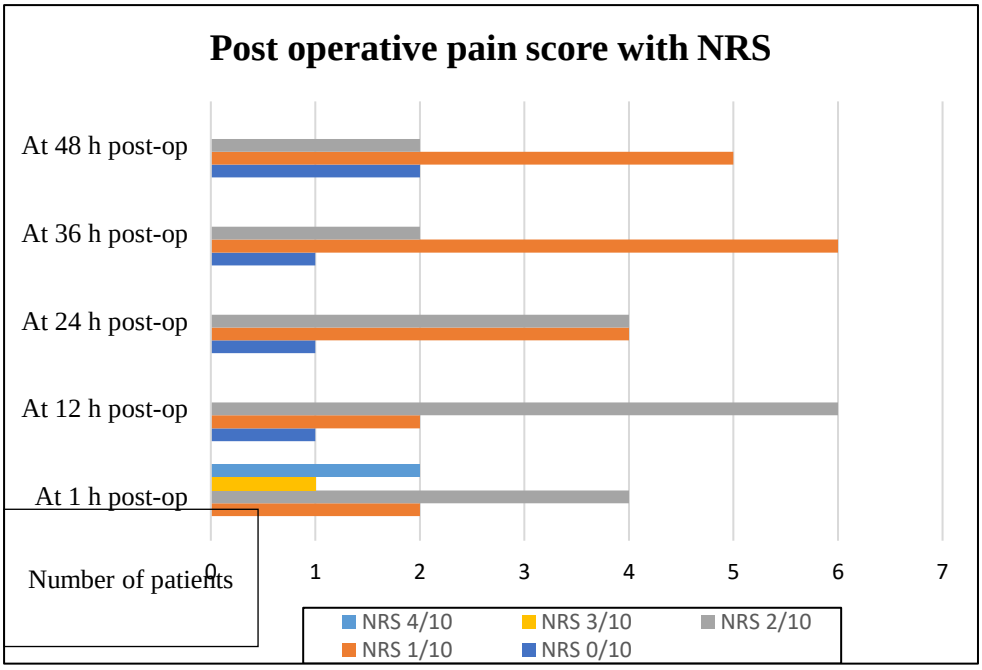

Figure 1. Post Operative pain score with NRS

Based on figure 1, it can be seen that during the first hour after surgery completion, two patients have experienced a 1/10 pain scale, four patients have experienced a 2/10 pain scale, one patient has experienced 3/10, and two patients have experienced a 4/10 of the pain scale. Meanwhile, after 24 hours, the pain scale significantly subsided with four patients having only experienced 1/10 and 2/10 of the pain scale consecutively. The pain scale was getting lower at 36 hours after surgery which six patients have experienced 1/10 and 2 patients have experienced a 2/10 pain scale. After a 48-hour surgery, five patients have experienced a 1/10 pain scale, two patients have experienced a 2/10 pain scale and the rest of them still have a 4/10 pain scale. It can be concluded that pain intensity has reduced as the surgery went by with the mildest scale was about 36 hour after surgery completed.

DISCUSSION

Postoperative pain is a major concern after surgery and appropriate management remains one of the most important and pressing issues of society in general, and health care professionals in particular. Despite advances in the knowledge, skill, and sophisticated technology that characterize most aspects of modern surgical treatment, many patients continue to experience considerable discomfort and pain during the postoperative period. Meanwhile, satisfying post-operative analgesia improves the patient's quality of life, results in fast recovery, and reduces medical costs.[7]

Epidural analgesia is an appropriate first-line route for moderate-to-severe acute postoperative pain expected to last for at least 24 hours. An abundance of research over the past two decades has demonstrated superior pain relief and improved functional outcomes after major surgery in patients who receive epidural analgesia, compared with patients receiving traditional postoperative pain management, such as IV PCA.[8] Its dosage needs to be selected according to the history of sleep apnea, coexisting diseases or conditions (e.g. diabetes, obesity), current medications (including pre-operative opioids), and adverse effects after opioid administration.[4,5] One randomized clinical study revealed that epidural morphine 11,2 $\mu g.kg^{-1}$ administered by caudal or lumbar block immediately upon completion of the surgical procedure produces adequate

pain relief for more than 12 hours in patients undergoing hip orthopedic surgery. In another study, three methods of perioperative pain management were compared in 114 patients undergoing gastric bypass surgery under general anesthesia who were randomized to receive incisional local anesthetic infiltration and postoperative IV PCA; epidural anesthesia and postoperative epidural analgesia; or postoperative IV PCA. Lower pain scores and less analgesic use were noted in those who received epidural analgesia on
PACU and 36 hours later, respectively, and the highest pain intensity scores were reported by patients who received IV PCA only.[6]

The mainstay for the treatment of acute postoperative pain is opioid drug therapy. The most commonly used opioid is morphine and administration by intermittent doses of an epidural is probably the most simple and widely used technique. Nowadays, local anesthetics and combination with adjuvant opioids are the drugs most widely used in epidural analgesia as they prolong the duration of action, give a better success rate, and increase patient satisfaction. In our institution, the regimen is a combination of 0,125% Bupivacaine and Fentanyl as the mainstay agent of continuing epidural infusion for postoperative pain analgesia. However, this method can not be frequently applied due to the limitations of the syringe pump device in the general ward, moreover, it is a less cost-effective method. Hence, this case series attempts to search for another alternative regimen of epidural bolus after surgery by using low-dose morphine with sufficient analgesia with minimal side effects as postoperative pain management.

The optimal dose of morphine administered epidurally is still controversial. Depending on the surgery being performed, the dose of epidural morphine after major abdominal surgery may vary from 30 to 90 μg/kg body weight.[9] A wide dose range (1–5 mg) of epidural morphine has also been employed, and it has shown effectiveness in diverse population subgroups. The ideal "single shot" epidural morphine dose in the USA is 2.5-3.75mg. However, the ideal dose is not an “Asian optimal dose”, due to their sensitivity to opioids. The ethnic differences in the μ-opioid receptor gene (OPRM1) break the balance between the conflicting demands of

providing optimal analgesia while minimizing dose-related adverse effects. Therefore, the epidural analgesia dose of morphine should be decreased and better, to begin with, 1-2 mg[10, 11,12]. In our case report, nine patients received 1 mg of morphine in up to 10 mL of normal saline every 12 hours with an initial dose administered immediately after the completion of the surgical procedure. However, one patient who underwent thrombectomy and fasciotomy of lower extremities reported a clinically significant moderate pain score with NRS 4/10, thirty minutes after the bolus epidural was given, thus she received rescue analgetic with 30 mg Ketorolac IV. She only has one time of rescue analgesia and for the rest of the 48 hours, she continues to receive bolus 1 mg of epidural morphine as the severity of pain began to decrease, and no significant pain issue arises afterward. It is classified as breakthrough pain which refers to a temporary increase in pain to greater than moderate intensity, which typically peaks its severity within 3-5 minutes after onset and lasts for about 30 minutes. As we know, morphine is a hydrophilic opioid with slow diffusion and long-duration characteristics as an analgesia regimen. Because of its delayed onset of analgesia, this patient might experience breakthrough pain within less than 30 minutes due to receiving her first epidural bolus of 1 mg morphine just before being transferred to PACU.[13]

Recent studies would indicate that it is possible to achieve better analgesia with lower doses of morphine epidurally.

However, giving morphine is not without any complications, there are some adverse effects, such as PONV, pruritus, sedation, and in severe cases may induce early and late respiratory depression. From large retrospective and prospective database analyses, the incidence of respiratory depression is 0–2.8% for epidural morphine with dose ranges of 2–5 mg, and that adverse effect is not greater compared to systemic administration.

Nausea and vomiting are common side effects experienced after abdominal and/or pelvic surgery. However, the incidence of these side effects is increased in patients treated with epidural opioids. The incidence requiring treatment has been reported to be approximately 25%, ranging from 22% to 29%. It has been suggested that postoperative nausea and vomiting may

be due to stimulation of the chemoreceptor trigger zone either by the vestibular apparatus or by high concentrations of opioids in plasma or cerebrospinal fluid. Several alternative therapies, such as Droperidol (0.625-1.25 mg) and Metoclopramide (10 mg) given as prophylaxis or every 4-6 hours, be effective. Intractable nausea and vomiting can be treated with an intravenous bolus of naloxone, followed by a continuous infusion of 0.5 to 1.0 μg/kg/hr. Ondansetron has become popular due to its limited side effect profile. A 2-4 mg dose intravenously quickly reduces the severity of the symptoms that the patient may be experiencing.[14] In our case series, only one patient reported nausea and vomiting an hour after the first dosage of 1 mg epidural morphine was given, which immediately reduced after 4 mg of Ondansetron was given intravenously.

Pruritus is dose-dependent in several studies and best treated with antagonists such as naloxone and naltrexone, although partial μ-receptor antagonists may also be effective in treating prophylaxis pruritus. It is theorized that naloxone's antipruritic action arises mainly from the blockade of central enkephalinergic transmission. In our case series, no one of our nine patients developed pruritus.

Sedation scale was assessed by the Ramsay sedation scale (1: alert and awake, 2: arousable to verbal command, 3: arousable with gentle tactile stimulation, 4: arousable with vigorous shaking, and 5: unarousable) and no one of the patients has a score of more than 2 points.[14,15] The incidence of respiratory depression is classified as biphasic, with early (< 2 hours) and delayed (>2 hours) presentation. Delayed respiratory depression is a phenomenon associated with hydrophilic morphine rather than lipophilic neuraxial opioids, which usually occurs 6-12 hours following epidural administration and may persist for up to 24 hours. Delayed respiratory depression is caused by the rostral spread in the cerebrospinal fluid and slow penetration into the brainstem. Studies in rats suggested that respiratory depression results from a dual effect involving μ- and δ- receptors. More recently, the preBötzinger complex located in the medulla has been identified as the site responsible for the decrease in respiratory rate following systemic administration of opioids.

Neurons in the preBötzinger complex expressing neurokinin-1 receptors are selectively inhibited by opioids, and therefore are the mediators of opioid-induced respiratory depression. The incidence of respiratory depression included decreasing respiratory rate, hypercarbia, low arterial oxygen saturation (SaO2), decreased level of consciousness, increased level of sedation, treatment with naloxone, and decreased ventilator response to hypoxia or hypercarbia. Opioid antagonists such as naloxone are available clinically to treat opioid-induced respiratory depression. A continuous naloxone infusion of 3-4 μg/kg/hour for up to 10 hours has been recommended by some to avoid several adverse effects secondary to the reversal of analgesia and release of catecholamine by a central mechanism such as pain, psychological stimulation, and sympathomimetic response including pulmonary edema in severe circumstances. In our case series, no one of our nine patients developed early or delayed respiratory. However, this case series also has limitations in that the characteristics of the samples were not homogenous, so there is the possibility of bias in terms of pain assessment for each patient.

CONCLUSION

The epidural analgesia with an intermittent bolus of 1 mg morphine is an appropriate first-line route for moderate-to-severe acute postoperative pain expected to last for at least 24 hours, especially after major surgeries. It exhibits optimal doses as an epidural agent that provides effective ostoperative analgesia and produces adequate pain relief for more than 12 hours after surgery with minimal side effects of nausea and vomiting that can be immediately reduced by an antiemetic 4 mg of Ondansetron and NSAIDs intravenously.

CONFLICT OF INTEREST

The Authors declare that they have no conflict of interest.

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