Epidural Morphine for Geriatrics Undergoing Lower Abdominal Cancer Surgery: A Dose-Response Study

Clinical Study Protocol

By

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Background

Acute postoperative pain is a common complaint for several days after surgery (1). However, acute postoperative pain remains even more under controlled in elderly patients, especially those with cognitive impairment and malignancy (2,3). Geriatric population is reported to be at higher risk for unwanted side effects from analgesic treatments compared to younger patients due to different major risk factors such as: decline in organ function, polypharmacy, pharmacokinetics, drug sensitivity, and frailty (4). Despite of the higher risk of opioids, especially morphine, causing toxicity and adverse effect; they are still the cornerstone treatment of severe acute postoperative pain (5). Morphine in those patients is very likely to cause toxicity because of accumulation of its active metabolites compared to other opioids with fewer or no active metabolites (6). Epidural morphine is an effective route for an effective drug.(7,8) Furthermore, unwanted side effects with neuraxial opioids are minor and managed easily.(9) Regarding clinical outcomes, clinical studies showed a lot of improvements associated with postoperative opioid analgesia (10–12). Now, there is a clinical necessity to achieve the best management of acute postoperative pain in elderly patients with the least possibility of adverse side effects. We aim in this randomized, assessor blinded, clinical trial at Assuit University to determine the optimum dose of epidural morphine for the highest control of acute postoperative pain in geriatrics who are planned to have lower abdominal cancer surgery.

Aim of the research

Our primary outcome is total patient-controlled analgesia (PCA) morphine sulphate (MS) consumption within seventy-two hours after surgery. Secondary outcomes include pain-intensity, measured using visual analog scale (VAS), Ramsay sedation scale (RSS), and nausea, vomiting and pruritus scale. Each of all the previous outcomes is to be recorded at 2, 8, 16, 24, 36, 48 and 72 hours after surgery.

Research Methods and Procedures

1- Study Design: randomized, assessor blinded, clinical trial.

2- Study Setting: Assuit University Hospitals, Anaesthesia and ICU department.

3- Study subjects:

A) Inclusion criteria:

Eligible patients are men and women aged ≥ 60 years, who are planned to undergo lower abdominal cancer surgery. Surgeries via infra-umbilical abdominal incision are considered eligible such as ovary, bladder, and colorectal surgeries.

B) Exclusion criteria:

We excluded patients with contraindications to neuraxial analgesia. The absolute contraindications are lack of consent from the patient, elevated intracranial pressure (ICP), primarily due to intracranial mass and infection at the site of the procedure (risk of meningitis). While the relative contraindications are (13,14):

- Pre-existing neurological diseases (particularly those that wax and wane, e.g., multiple sclerosis).

- Severe dehydration (hypovolemia), due to the risk of hypotension. The risk factors for hypotension include hypovolemia, age greater than 40 to 50 years, emergency surgery, obesity, chronic alcohol consumption, and chronic hypertension.
- Severe mitral and aortic stenosis and left ventricular outflow obstruction as seen with hypertrophic obstructive cardiomyopathy.
- Thrombocytopenia or coagulopathy (especially with epidural anaesthesia, due to the risk of epidural hepatoma. Of note about coagulopathy, the placement of neuraxial block requires revaluation. The American Society of Regional Anaesthesia (ASRA) publishes updated guidelines that detail timing for neuraxial anaesthesia for patients on oral anticoagulants, anti-platelets, thrombolytic therapy, unfractionated, and low molecular weight heparin. Review the latest guidelines before proceeding with the procedure.

C) Groups:

Patients were randomized (by using a table of random numbers) to one of four groups to receive a single dose of epidural preservative-free morphine out of four doses: 0 mg (group D); 1.5 mg (Group A); 3mg (Group B) and 4.5 mg (Group D) at the beginning of surgery. A total volume of 10 mL was injected; 5 mL of bupivacaine hydrochloride 0.125% with the previously mentioned study doses of preservative-free morphine diluted in 5 mL preservative-free normal saline by the hospital pharmacist.

D) Sample Size Calculation:

The sample size will be calculated using G* Power software 3.1.9.2 considering a study power of 80% and a significance level of 0.05 to detect an effect size of 0.75 using one-

way ANOVA test/t-test. Assuming total IV-PCA morphine consumption is the main outcome variable, and the maximum total IV-PCA morphine consumption was 12 ± 16 mg while in healthy controls was 70 ± 35 mg according to previous studies (15-17), the estimated minimum required sample size, after assuming 33% dropouts, will be 88 patients (22 patients in each group).

Statistical Analysis Plan

Data will be analyzed using IBM SPSS statistics version 24 for Windows 10. A value of $P < 0.05$ was considered significant. The data will be tested for normality using the Shapiro–Wilk test. Normally distributed variables such as age and BMI are presented as the means ± SDs and will be compared with ANOVA. When the assumption of normality was rejected, the nonparametric Kruskal–Wallis test for independent samples will be used for comparison. Significant Kruskal–Wallis test values will be Bonferroni corrected when various time points are investigated and when multiple tests are applied. For data presented as counts and percentages, a chi-squared test will be applied.

Procedure

A standardised epidural catheter insertion protocol will be followed in all the study groups. A 20-gauge, open-tip epidural catheter will be inserted into the T9-10 interspace and advanced 5 cm into the epidural space while patients are in the setting position. A total volume of 10 mL will be injected; 5 mL of 0.125% bupivacaine hydrochloride was mixed with each of the study doses and diluted in 5 mL of preservative-free normal saline by the hospital pharmacist. We will not use

the test dose of 0.5% lidocaine or 1:200000% epinephrine and will only use Dogilotti's principle for confirmation of correct epidural catheter placement. If there are no rapid onset within 1-2 minutes of neuraxial sensory block, which will be observed only during the intrathecal delivery of the local anaesthetic, the placement of the epidural catheter will be activated. After 30 min, the sensory block around the level of T8-T10 will be tested by pinprick. The diluted preservative-free epidural morphine studied doses will be identical in appearance to be unrecognizable, so neither the patient nor the attending anaesthesiologist could identify the administered dose. General anaesthesia will be then induced using 2 mg/kg propofol and 2 mcg/kg fentanyl. Endotracheal intubation will be performed with rocuronium (0.5 mg/kg), and general anaesthesia will be maintained with sevoflurane and rocuronium (0.2 mg/kg on demand). Heart rate and mean arterial blood pressure (MAP) will be kept within 20% of the preoperative baseline values as determined by the attending anaesthesiologist. Ondansetron (4 mg) will be given as an antiemetic at skin closure. At the end of the surgery, muscle relaxation will be reversed by treatment with 0.05 mg/kg neostigmine and 0.01 mg/kg atropine. After extubation, the patients will be admitted to the post-anaesthesia care unit (PACU) until they are fully recovered from anaesthesia.

Thereafter, the patients will be transferred to the ICU, and a standardised close monitoring will be performed for 72 hours to detect early or late respiratory depression. The same doses of epidural morphine for each patient will be administered at 24 hr and 48 hr postoperatively.

Strength points and Limitations

The main strengths of this study are that it is highly reproducible and addresses the daily clinical aspects of epidural morphine in older adults. However, this study is limited by its focus on lower abdominal cancer surgeries only; additionally, it is a single centre study focused on unimodal analgesia. Therefore, the generalizability of our results is limited. All other systemic analgesics are as under-researched as epidural morphine in this age group. Therefore, further studies with larger sample on other drugs and on different types of surgeries are needed to tailor adequate multimodal pain management protocols with the least risk to the older adults. The study is also limited to clinical response and pharmacodynamics of epidural morphine in the older adults and did not investigate the pharmacokinetics, which should be examined in future studies. Due to the vulnerability of older adults, we included only ASA I and II patients to assess the balancing dose of epidural morphine versus age only. The relationship between the dose of epidural morphine and common comorbidities in this age group should also be investigated.

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