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Comparative evaluation of intrathecal morphine on postoperative course in patients undergone cardiac surgery

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ABSTRACT

BACKGROUND: The use of intrathecal morphine in cardiac surgery has the potential to enhance postoperative course. Previous studies on the use of intrathecal morphine for optimizing postoperative analgesia and reducing the duration of mechanical ventilation (MV) have shown conflicting results, indicating the need for further clarification.

AIM: To compare the effects of intrathecal morphine at a dose of 200 μg on postoperative course in patients undergoing elective cardiac surgery with cardiopulmonary bypass (CPB).

METHODS: This prospective single-center study enrolled 42 patients aged >18 years. Patients were divided into two groups: group 1 received anesthesia with sevoflurane and fentanyl; group 2 received intrathecal morphine (200 μg) 60 min prior to induction of general anesthesia. All patients underwent elective cardiac surgery with CPB. Postoperative parameters included acid–base status, blood gas changes, glycemia, extubation time, pain scores, complication rates, and mortality.

RESULTS: Intrathecal morphine administration resulted in a statistically significant reduction in the duration of MV from 300 (247; 435) to 200 (150; 360) min (p=0.017), a decrease in pain intensity by 2.1 points at 6 h postoperatively and by 1.7 points at 18–24 h postoperatively, as well as a reduced need for intravenous morphine administration during the first 24 h after surgery. The number needed to treat was 1.67.

CONCLUSION: The combination of general multicomponent anesthesia with intrathecal morphine contributes to a reduction in MV time, improves the quality of postoperative analgesia, and decreases the need for intravenous opioid administration in cardiac surgery patients.

Keywords: combined anesthesia; intrathecal morphine; postoperative pain management; extubation time; cardiac surgery.

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Сравнительная оценка влияния интратекального применения морфина на течение послеоперационного периода у кардиохирургических пациентов

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АННОТАЦИЯ

Обоснование. Интратекальное применение морфина при проведении оперативных вмешательств на сердце может улучшить течение послеоперационного периода у пациентов. Ранее исследования по использованию интратекальной формы морфина для оптимизации послеоперационного обезболивания и снижения длительности искусственной вентиляции лёгких (ИВЛ) продемонстрировали противоречивые результаты, в связи с чем данный вопрос требует дальнейшего уточнения.

Цель. Произвести сравнительную оценку влияния интратекального введения морфина в дозе 200 мкг на течение послеоперационного периода у пациентов, подвергшихся плановым кардиохирургическим вмешательствам в условиях искусственного кровообращения (ИК).

Материалы и методы. Проведено проспективное одноцентровое исследование, в которое были включены 42 пациента старше 18 лет. Пациентов разделили на две группы: в 1-й группе использовали анестезию на основе севофлурана и фентанила, 2-ю группу составили пациенты, которым за 60 минут до начала общей анестезии интратекально вводили морфин в дозе 200 мкг. Всем пациентам были выполнены плановые кардиохирургические операции в условиях ИК. В послеоперационном периоде оценивали динамику изменения кислотно-основного состояния и газов крови, глюкозы, время до экстубации пациента, интенсивность боли, количество осложнений и летальность.

Результаты. Интратекальное применение морфина у пациентов приводит к статистически значимому (p=0,017) снижению длительности ИВЛ после операций с 300 (247; 435) до 200 (150; 360) мин, снижению интенсивности болевого синдрома на 2,1 балла через 6 часов после операции и на 1,7 балла через 18–24 часа после операции, уменьшению частоты внутривенного применения морфина в первые сутки после оперативного вмешательства, показатель NNT (число пациентов, которых нужно лечить) составил 1,67.

Заключение. Сочетание общей многокомпонентной анестезии с интратекальным введением морфина способствует сокращению времени проведения ИВЛ, улучшает качество послеоперационного обезболивания и снижает необходимость во внутривенном применении наркотических анальгетиков у кардиохирургических пациентов.

Ключевые слова: сочетанная анестезия; интратекальный морфин; послеоперационное обезболивание; время экстубации; кардиохирургия.

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BACKGROUND

Modern anesthesiology is based on the multimodal approach, which involves the combination of general anesthesia with regional analgesia techniques [1, 2]. Currently, there is no evidence to support any particular method of regional anesthesia in cardiac surgery [3, 4].

On the first postoperative day, the severity of pain syndrome tends to reach its peak, and inadequate analgesia can be a contributing factor to chronic postoperative pain [5]. Conventional systemic opioid analgesics have been associated with numerous adverse effects, including prolonged mechanical ventilation, pulmonary complications, and postoperative nausea and vomiting [5, 6].

One of the most promising methods of postoperative pain management in cardiac surgery is intrathecal morphine [3]. This method is technically simple, does not require specialized skills from an anesthesiologist, and has been shown to produce a prolonged analgesic effect ranging from 20 to 48 hours after morphine administration [3, 6]. Intrathecal morphine is widely used as an anesthetic agent in a variety of surgical procedures, including thoracic, abdominal, spinal, urological, and orthopedic interventions [6].

However, scientific studies focusing on the use of this method for postoperative pain management in cardiac surgery have demonstrated conflicting results. Among the researchers, there is no consensus on the efficacy of postoperative pain reduction or the impact on the duration of mechanical ventilation [7, 8]. This issue has become the driving force behind this study.

The **study aimed** to compare the effects of intrathecal morphine at 200 μg on postoperative period in patients undergoing elective cardiac surgery with cardiopulmonary bypass (CPB).

METHODS

Study design

This was a prospective, comparative, cross-sectional, single-center study.

Study setting and duration

The study was conducted from June 1, 2023, to December 31, 2023, at the Gomel Regional Clinical Cardiological Center (Republic of Belarus).

Eligibility criteria

Inclusion criteria:

- Age 18 years and older;
- Elective coronary artery and/or heart valve surgery with CPB;
- Consent to participate in the study and to publish the study materials.

Non-inclusion criteria:

- Indication for emergency surgery or urgent surgery;
- History of hypersensitivity to the drugs used in the study;
- Use of acetylsalicylic acid and/or clopidogrel within five days before surgery;
- High risk of obstructive sleep apnea (STOP-BANG ⩾3);
- Kidney disease with glomerular filtration rate <60 mL/min;
- Left ventricular ejection fraction <35%;
- Use of glucocorticosteroids within 6 months before surgery.

Allocation of patients to study groups

The study comprised 42 patients who were randomly assigned to two groups:

- Group 1 (n = 22), sevoflurane- and fentanyl-based multimodal general endotracheal anesthesia (MGEA) protocol for the maintenance of anesthesia;
- Group 2 (n = 20), spinal block in L_3–L_4 subarachnoid space 60 min before MGEA, 200 μg intrathecal morphine.

Study endpoints

The primary endpoints for evaluating the adequacy and efficacy of anesthetic care included intraoperative hemodynamics (heart rate [HR]; systolic and diastolic blood pressure; and mean arterial pressure [MAP]), bispectral index (BIS), blood glucose, frequency of intravenous insulin infusions, blood acid–base balance, arterial blood gas analysis, and postoperative pain severity.

The length of stay in the intensive care unit (ICU) and hospital, the frequency of post-extubation respiratory distress, types and doses of analgesics administered, the incidence of intra- and postoperative complications, and mortality were documented.

The respiratory distress was defined as a respiratory rate of <8/min (normal values, 12–20/min), oxygen saturation <93% (reference values, 94%–100%), carbon dioxide >50 mmHg (normal arterial blood level, 35–45 mmHg), naloxone used to maintain adequate ventilation, and repeated mechanical ventilation (invasive and/or non-invasive).

Methods for endpoint measurement

The monitoring parameters were recorded at the following stages of the study:

- Stage 1, patient assessment at 24 hours before surgery;
- Stage 2, on admission to the operating room;
- Stage 3, at 10 min of anesthesia induction;
- Stage 4, at 5 min after the skin incision;

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- Stage 5, at 5 min after the sternotomy;
- Stage 6, at 15 min before CPB;
- Stage 7, at 15 min after CPB;
- Stage 8, after suturing;
- Stage 9, on ICU admission;
- Stage 10, at 6 hours post-surgery;
- Stage 11, at 18–24 hours post-surgery.

Perioperatively, GE Healthcare Carestation 650 Anesthesia Delivery Systems with Philips IntelliVue MP70 Patient Monitors, and Mindray SynoVent E3 Ventilators with Philips IntelliVue MP40 Patient Monitors were used.

The blood acid–base balance and gases were analyzed at Stages 2, 6, 8, 9, 10, and 11; arterial blood lactate was measured at Stages 2, 6, and 8. These measurements were obtained using Radiometer ABL 800 FLEX Analyzer (Radiometer Medical, Denmark).

The postoperative pain scores were evaluated at Stages 10 and 11 using a 10-point visual analog scale (VAS).

Intervention

All patients received premedication with 0.5 mg atropine sulfate, 20 mg promedol, and 10 mg diazepam via intramuscular injections 30 min prior to the surgical procedure.

Patients were admitted to the operating room between 8:30 and 9:30 in the morning. After the patient was positioned on the operating table, routine anesthetic monitoring was initiated, along with assessments of the bispectral index and neuromuscular transmission.

The induction of anesthesia was achieved by the intravenous infusion of midazolam, fentanyl, and propofol. The muscle relaxation for tracheal intubation was facilitated by the intravenous infusion of atracurium or suxamethonium iodide (Dithylin) (if the Simplified Airway Risk Index scored ⩾1). Anesthesia was maintained with sevoflurane (the minimum alveolar concentration [MAC] of 0.5–1 atm) before and after CPB, and with propofol titration during CPB. The continuous infusion of fentanyl was used to achieve analgesia. Atracurium or pipecuronium boluses were administered to induce muscle relaxation. Table 1 demonstrates doses of the anesthetic agents.

The surgical procedure involved conventional coronary artery bypass grafting and/or heart valve replacement/repair via a full longitudinal sternotomy.

The procedure was supported by normothermic (36.0 °C) CPB with non-pulsatile perfusion. The myocardial protection was ensured by antegrade and retrograde cold blood cardioplegia (7–9°C). CPB

Table 1. Number of drugs for induction and maintenance of anesthesia, Me (Q1; Q3)

Drug	Group 1, *n* = 22	Group 2, *n* = 20	*p*
Induction of anesthesia			
Fentanyl, μg/kg	1.6 (1.3; 1.9)	1.6 (1.4; 2.0)	0.129
Propofol, mg/kg	0.8 (0.7; 1.0)	0.9 (0.8; 1.0)	0.405
Midazolam, mg/kg	0.05 (0.04; 0.06)	0.05 (0.04; 0.06)	0.548
Suxamethonium iodide (Dithylin), mg/kg	*n* = 13	*n* = 10	0.559
	2.1 (1.9; 2.6)	2.2 (2.0; 2.6)	0.981
Atracurium, mg/kg	*n* = 9	*n* = 10	0.559
	0.46 (0.37; 0.49)	0.48 (0.36; 0.50)	0.114
Maintenance of anesthesia			
Fentanyl, μg/kg/h	2.5 (2.0; 2.9)	2.3 (2.0; 2.7)	0.770
Sevoflurane, MAC	0.7 (0.5; 0.9)	0.7 (0.6; 0.8)	0.456
Propofol at the stage of cardiopulmonary bypass, mg/kg/h	3.1 (2.9; 3.2)	3.0 (2.8; 3.1)	0.186
Atracurium, mg/kg/h	*n* = 16	*n* = 17	0.339
	0.35 (0.24; 0.36)	0.33 (0.25; 0.37)	0.649
Pipecuronium, mg/kg/h	*n* = 6	*n* = 3	0.339
	0.02 (0.01; 0.03)	0.02 (0.01; 0.03)	0.949

Note: MAC, minimum alveolar concentration.

circuits were primed with 1400 mL solution containing 1 g prednisolone. Prednisolone was administered to 13 patients in group 1 and 11 patients in group 2, with no significant differences observed in the frequency of use (p = 0.792; χ^2-test).

Anticoagulation for CPB was achieved with unfractionated heparin (UFH) at 450 U/kg. The activated clotting time (ACT) was maintained at >480 seconds. After the completion of CPB, UFH was neutralized with protamine (1:0.8) with ACT monitoring (±10% of baseline values).

Postoperatively, patients were transferred to the ICU, where they remained on mechanical ventilation until they regained full consciousness, initiated unassisted breathing, and demonstrated normal neuromuscular transmission. The post-anesthesia care included thromboprophylaxis, infusion therapy, 24-hour antibacterial therapy, and stress ulcer prophylaxis.

The postoperative pain management protocol involved 1000 mg intravenous paracetamol initiated on ICU admission and repeated every 8 hours; 50 mg intravenous dexketoprofen initiated at 2 hours post-surgery and repeated every 8 hours (for patients with no history of bleeding). Pain severity was assessed after extubation. Patients with VAS ⩾4 received intravenous morphine at an initial dose of 0.001 mg/kg/hour, with dose adjustments based on pain scores.

Ethics approval

The study was approved by the Local Ethics Committee of the Gomel Regional Clinical Cardiological Center (Protocol No. 4 dated December 16, 2021). The study was duly registered in the National Registry (No. 20230254 dated January 03, 2023). All patients provided a written consent to receive anesthetic support, including laboratory monitoring throughout the study, and spinal anesthesia.

Statistical analysis

Sample size calculation

As the previous study [9] demonstrated a 30% reduction in postoperative pain (mean VAS scores: 4.0 and 2.5 out of 10; standard deviation, 1.2), the required sample size was calculated using the paired Student's t-test. To assess postoperative pain scores, a sample size of 14 patients/group was required to have a 90% probability of significant difference at 5% alpha. Therefore, a sample size of 20 patients/group was sufficient to identify significant differences in this study.

Statistical analysis

The statistical analysis was performed using BioStat 7 (Analyst Soft Inc., USA). The normality of distribution was assessed using the Shapiro–Wilk test.

The normally distributed data were presented as the mean (M) and standard deviation (SD). The Student's t-test was used to assess the significance of differences between two independent groups.

For non-normal distribution, the median (Me), first quartile (Q1), and third quartile (Q3) were calculated, using the Mann–Whitney U test to assess the significance of differences between two independent groups.

Proportions were evaluated using the ÷^{2}-test with the Yates continuity correction. The number needed to treat (NNT) was calculated to evaluate the efficacy of the anesthesia technique. The differences were considered significant at $p < 0.05$.

RESULTS

Characteristics of study sample

There were no significant differences between the two groups in primary body measurements, characteristics of surgery and anesthesia, or concomitant diseases (Table 2).

Preoperative laboratory values were comparable between the two groups (Table 3).

Baseline ACT was 97.0 (89.0; 105.0) s in group 1 and 99.0 (92.0; 115.0) s in group 2. After the anticoagulant was administered, ACT increased to 600.0 (600.0; 770.0) s in group 1 and to 629.0 (600.0; 692.0) s in group 2. Protamine neutralization reduced ACT to 101.0 (94.0; 110.0) s in group 1 and to 108.0 (96.0; 115.0) s in group 2. No significant differences in ACT values were observed between the two groups at any of the study stages.

Moreover, there were no statistically significant differences between the two groups in the number of analgesics, anesthetics, and muscle relaxants used for the induction and maintenance of anesthesia (Table 1).

The depth of anesthesia, as measured by BIS, was found to be comparable between Groups 1 and 2, with no statistically significant differences observed (Table 4).

At the end of the surgical procedure, pleural drainage was placed in 10 patients from group 1 and 7 patients from group 2 with no significant difference in the procedure frequency between the two groups (p = 0,491; χ^2-test).

Primary results

An analysis of the mean arterial pressure across patient groups identified the following patterns. Group 1 demonstrated higher MAP compared to group 2 at Stage 4 (91.5 [85.5; 94.8] mmHg and 78.0 [71.0; 87.0] mmHg, respectively; p = 0.004; Mann–Whitney U test) and Stage 9 (92.0 [85.0; 97.3] mmHg and 79.7 [70.0; 84.0] mmHg, respectively; p = 0.026; Mann–Whitney U test). At the other stages, there were no

Table 2. General characteristics of study groups, M ± SD

Parameter	Group 1. *n* = 22	Group 2. *n* = 20	*p*
Age, years	57.7 ± 8.2	60.0 ± 6.5	0.330
Body weight, kg	86.1 ± 16.2	86.1 ± 11.9	0.178
Height, cm	168.8 ± 7.6	170.9 ± 5.8	0.139
Body mass index	30.2 ± 5.3	29.9 ± 6.4	0.243
Sex (male/female), *n* (%)	16 (73) / 6 (27)	18 (90) / 2 (10)	0.155
ASA class I–II / III–IV, *n* (%)	4 (18) / 18 (82)	4 (20) / 16 (80)	0.881
Stage I / II / III hypertension, *n* (%)	5 (23) / 11 (50) / 3 (14)	3 (15) / 10 (50) / 2 (10)	0.766
Diabetes mellitus, n (%)	3 (14)	2 (10)	0.716
Type of surgery (myocardial revascularization / heart valve replacement / combined), *n* (%)	15 (68) / 3 (14) / 4 (18)	16 (80) /2 (10) / 2 (10)	0.857
Duration of anesthesia, min	320 (260; 335)	315 (263; 335)	0.765
Duration of surgery, min	250 (210; 280)	245 (205; 285)	0.967
Duration of cardiopulmonary bypass, min	97 (80; 125)	92 (76; 123)	0.223
Volume of intraoperative blood loss, mL	825.7 (453.8; 946.4)	867.7 (635.2; 1094.2)	0.171

Note. ASA, American Society of Anesthesiologists Classification System.

Table 3. Laboratory values in study groups, Stage 1, Me (Q1; Q3)

Parameter	Group 1, *n* = 22	Group 2, *n* = 20	*p*
Hemoglobin, g/L	136,0 (127,0; 144,0)	145,0 (135,0; 148,0)	0,105
Hematocrit, %	40,0 (35,6; 41,9)	41,9 (39,2; 44,6)	0,115
Red blood cells, 10^{12}/L	4,4 (4,3; 4,9)	4,6 (4,2; 4,9)	0,944
Platelets, 10^{9}/L	220,0 (188,0; 241,0)	229,0 (161,0; 240,0)	0,955
White blood cells, 10^{9}/L	6,8 (6,1; 8,6)	7,1 (5,9; 8,5)	0,779
aPTT, s, c	28,2 (26,7; 30,3)	28,7 (27,0; 31,9)	0,500
INR	1,05 (1,01; 1,09)	1,06 (1,03; 1,13)	0,344
Fibrinogen, g/L	3,8 (2,9; 4,5)	4,1 (3,7; 5,4)	0,089
Creatinine, mmol/L	86 (77,1; 95,0)	89,8 (71,4; 96,1)	0,949
GFR, mL/min	95,8 (69,6; 105,4)	90,3 (68,5; 103,3)	0,906

Note: aPTT, activated partial thromboplastin time; INR, international normalized ratio; GFR, glomerular filtration rate.

significant hemodynamic differences between the patient groups.

Group 1 showed higher HR than group 2 at Stage 11, with median values of 80.0 (74.0; 89.0) beats per minute (bpm) and 69.0 (61.0; 72.0) bpm, respectively (p = 0.012; Mann–Whitney U test). At the other stages, no significant differences in HR were observed between the two groups.

A comparison of blood glucose and lactate levels revealed no significant differences between Groups 1 and 2.

Intravenous insulin titration was used to avoid intraoperative elevations of blood glucose levels above 10 mmol/L. Insulin was administered to 10 patients from group 1 and 3 patients from group 2. This difference was found to be statistically significant (p = 0.035; χ^2-test).

The median duration of postoperative mechanical ventilation was 300 (247; 435) min in group 1 and 200 (150; 360) min in group 2. This difference was found to be statistically significant (p = 0.017; Mann–Whitney U test).

Table 4. Bispectral index in Groups 1 and 2, M ± SD

Group	Stage						
	2-й	3-й	4-й	5-й	6-й	7-й	8-й
1-я	96 ± 2	48 ± 10	40 ± 9	40 ± 7	41 ± 7	42 ± 6	44 ± 8
2-я	95 ± 4	50 ± 12	42 ± 10	41 ± 7	42 ± 6	43 ± 6	46 ± 7
p	0.674	0.490	0.133	0.206	0.119	0.108	0.189

The postoperative pain VAS scores are presented in Table 5.

Intrathecal morphine in group 2 was associated with a 2.1 (Stage 10) and 1.7 (Stage 11) decrease in postoperative pain scores compared to group 1.

Additionally, group 2 demonstrated a 3-fold reduction in the frequency of morphine use on the first postoperative day compared with group 1, with the number-needed-to treat (NNT) calculated to be 1.67.

There were no significant differences in the frequency and doses of non-opioid analgesics used (Table 6).

In group 1, complications were documented in one patient, who experienced a non-fatal acute cerebrovascular accident that resolved without serious sequelae (disability).

In group 2, complications were reported in three patients: one case of paroxysmal atrial fibrillation occurred during ICU stay, one case of postoperative nausea and vomiting (resolved with ondansetron), and one case of moderate skin itching (resolved with intravenous antihistamine). Opioid receptor antagonists (naloxone) were not given to patients during the study.

Table 5. Pain severity by visual analogue scale in study groups, Me (Q1; Q3)

Stage	Group 1, *n* = 22	Group 2, *n* = 20	*p*
10-й	3.4 (3.0; 4.0)	1.3 (1.0; 2.5)	0.001
11-й	3.7 (3.0; 4.0)	2.0 (2.0; 3.5)	0.035

The vital signs were monitored for at least 24 hours after the intrathecal administration of morphine, and no episodes of respiratory distress were observed. Arterial blood gas levels in the study groups are presented in Table 7.

At Stage 10, group 2 demonstrated a significant increase in CO_2 levels compared to group 1 (p = 0.011; Mann–Whitney U test), yet these values remained within the physiological range.

The median length of ICU stay was 2 days (min: 1 day; max: 5 days) for both groups, whereas the median length of hospital stay was 15 days (min: 14 days; max: 21 days) for group 1 and 16 days (min: 14 days; max: 18 days) for group 2. There were no significant differences between the two groups (p = 0.324 and 0.345, respectively; Mann–Whitney U test).

DISCUSSION

Summary of primary results

The data analysis demonstrated that intrathecal morphine in group 2 resulted in a significant decrease (p = 0.017) in the duration of postoperative mechanical ventilation compared with group 1 (300 [247; 435] min and 200 [150; 360] min, respectively). Group 2 showed a 2.1 (Stage 10) and 1.7 (Stage 11) decrease in postoperative pain scores compared to group 1. The improved pain relief observed in group 2 was associated with a reduction in the frequency of intravenous morphine infusion on the first postoperative day, with the NNT calculated to be 1.67.

Table 6. Analgesics used on the first postoperative day in study groups, Me (Q1; Q3)

Drug	Group 1, *n* = 22	Group 2, *n* = 20	*p*
Morphine, mg/kg/hour	*n* = 21	*n* = 7	0.001
	0.013 (0.011;0.016)	0.010 (0.008; 0.015)	0.100
Paracetamol, mg/kg	*n* = 22	*n* = 20	–
	20.8 (15.4; 26.0)	21.5 (14.8; 29.0)	0.224
Dexketoprofen, mg/kg	*n* = 4	*n* = 4	–
	0.9 (0.7; 1.1)	0.9 (0.6; 1.2)	0.333

Table 7. Arterial blood gas levels at study stages, Me (Q1; Q3)

Parameter	Stage					
	2		10		11	
	Group 1, *n* = 22	Group 2, *n* = 20	Group 1, *n* = 22	Group 2, *n* = 20	Group 1, *n* = 22	Group 2, *n* = 20
pH	7.40 (7.39; 7.41)	7.39 (7.37; 7.42)	7.37 (7.34; 7.40)	7.34 (7.32; 7.39)	7.38 (7.36; 7.41)	7.40 (7.34; 7.41)
pCO_2, mmHg	39.5 (37.5; 40.7)	39.5 (38.0; 40.5)	36.7 (33.3; 38.2)*	44.1 (36.6; 48.0)*	38.9 (36.9; 40.9)	39.6 (37.0; 44.3)
pO_2, mmHg	109.0 (90.0; 157.0)	111.0 (73.4; 151.0)	125.0 (102.0; 152.0)	117.0 (99.6; 127.0)	93.1 (64.2; 136.0)	102.0 (84.8; 132.0)
FiO_2, %	39.0 (32.5; 40.0)	33.0 (31.0; 38.0)	40.0 (35.5; 48.0)	42.0 (33.0; 49.2)	38.0 (35.5; 42.0)	35.0 (33.0; 39.0)
SpO_2, %	98.5 (97.2; 99.7)	98.5 (97.1; 99.7)	98.7 (98.0; 99.1)	98.1 (97.0; 98.6)	98.2 (94.1; 99.0)	98.3 (96.9; 98.9)
ABE, mmol/L	0.1 (-1.4; 0.7)	-0.1 (-1.4; 0.8)	-3.4 (-5.3; -1.5)	-2.7 (-4.9; -2.0)	-0.15 (-1.5; 0.2)	-1.4 (-2.4; -0.3)
HCO_3, mmol/L	23.8 (23.3; 24.5)	23.7 (23.2; 24.8)	20.4 (19.0; 22.2)	21.6 (20.6; 23.6)	23.9 (22.3; 24.5)	23.3 (22.5; 25.0)

Note. * Differences between the groups are statistically significant ($p = 0.011$; Mann–Whitney *U* test).

Summary of primary results

In this study, 200 µg intrathecal morphine provided enhanced postoperative analgesia. group 2 demonstrated a significant decrease in pain scores at Stage 10 (1.3 [1.0; 2.5]) and Stage 11 (2.0 [2.0; 3.5]) as compared to group 1 (3.4 [3.0; 4.0] and 3.7 [3.0; 4.0], respectively). A significant decrease ($p = 0.001$) in the frequency of intravenous morphine use on the first postoperative day was observed in group 2 (7 cases) compared to group 1 (21 cases).

A similar finding was reported by Alhashemi et al., who noted a significant decrease in intravenous morphine doses among patients receiving intrathecal morphine at 250 µg and 500 µg, as compared to the control group (13.6 ± 7.8 mg, 11.7 ± 7.4 mg, and 21.3 ± 6.2 mg, respectively) [8]. Yapici et al. demonstrated a 50% decrease in pain severity along with a reduced pethidine dose from 150 mg to 50 mg within the initial 24 hours post-surgery [10]. Furthermore, a meta-analysis by Chen et al. provided evidence of a decrease in pain severity within 48 hours and the reduced duration of postoperative mechanical ventilation in patients who underwent cardiac surgery and received intrathecal morphine [11].

The findings presented in this scientific article demonstrate a significant decrease in the duration of mechanical ventilation from 300 (247; 435) min in group 1 to 200 (150; 360) min in group 2. Consistent findings were reported by Yapici et al., who observed a decrease in the duration of mechanical ventilation from (4.86 ± 1.38) hours in the control group to (3.58 ± 1.57) hours in the group that received 7 µg/kg intrathecal morphine [10]. In their study, Mehta et al. described a decrease in the duration of postoperative ventilation from 11.25 ± 3.94 hours to 9.47 ± 3.83 hours with 8 µg/kg intrathecal morphine [12]. However, Alhashemi et al. did not find a significant decrease ($p = 0.27$) in the duration of postoperative ventilation with 250 µg or 500 µg of morphine compared with the control group (441 ± 207 min, 325 ± 188 min, and 409 ± 245 min, respectively [8]. Chaney et al. reported a substantial delay in the time to tracheal extubation in patients receiving 10 µg/kg intrathecal morphine in combination with systemic fentanyl (20 µg/kg) [7].

It can be theorized that the observed discrepancies between the two studies are attributable to significant differences in the administered doses of morphine, the study design, and the clinical pain management protocols.

However, there is a consensus among authors that the most significant adverse effect associated with intrathecal morphine is delayed respiratory distress. The symptoms emerge within 2–24 hours post-injection, demonstrating significant variation in severity, which is largely determined by the administered dose. The frequency of respiratory distress in response to <1 mg intrathecal morphine varies between 0.5% and 3.0%

across studies [13–15]. To illustrate, the study by Gwirtz et al. included 5969 subjects who received 200–800 μg intrathecal morphine, and the incidence of respiratory distress (defined as a respiratory rate of <10/min or pCO_2 >50 mmHg) was 3.0% [16]. Koning et al. demonstrated that life-threatening respiratory distress only occurred with a dose >900 μg morphine or when potentiating drugs were used [14].

As evidenced by research findings, pruritus emerges as another adverse reaction with a substantial increase in incidence (up to 37%) after intrathecal morphine. The available publications offer no evidence of an increased incidence of postoperative nausea and vomiting with this particular method of administration [11, 13].

In this study, there was no significant increase in the incidence of respiratory distress after intrathecal injection of 200 μg morphine, which may be attributable to the low dose and the non-inclusion of patients with obstructive sleep apnea. Two patients experienced postoperative nausea and vomiting, and pruritus, but the number is too low to draw definitive statistical implications.

Study limitations

The study is limited by a small sample size, which necessitates further investigation in larger patient populations.

CONCLUSION

The findings from this study can contribute to enhancing the efficacy of anesthetic care for adult patients undergoing cardiac surgery with cardiopulmonary bypass. The combination of MGEA and intrathecal morphine has been shown to reduce the duration of mechanical ventilation, enhance postoperative analgesia, and decrease the frequency of intravenous use of opioid analgesics. It appears that further research is necessary to determine the optimal dose of morphine and the effect of the proposed anesthesia technique on the long-term outcomes.

ADDITIONAL INFORMATION

Author contributions: D.V. Osipenko: study design, data collection, analysis and interpretation, statistical analysis, writing—original draft, writing—review & editing; A.A. Silanov: study design, data collection, analysis and interpretation; A.V. Marochkov: study design, data analysis and interpretation, writing—original draft, writing—review & editing; V.V. Rimashevsky: writing—riginal draft, writing—review & editing. All the authors approved the final version before publication and agreed to be accountable for all aspects of the paper, ensuring that questions related to the accuracy or integrity of any part of the study are appropriately investigated and resolved.

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