Original Article

DOI: 10.4274/haseki.galenos.2023.9090
Med Bull Haseki 2023;61:172-177

Opioid-free versus Opioid-Based General Anesthesia in Cesarean Sections: A Cross-sectional Analysis

Elif Ongel, Burcu Saglanmak, Esra Adiyeke, Nurten Bakan

University of Health Sciences Turkey, Istanbul Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Istanbul, Turkey

Abstract

Aim: Guidelines recommend opioid-free (OF) anesthesia in elective cesarean sections (CS). However, opioids are commonly administered after a baby's delivery for postoperative pain in daily practice. Our aim was to compare OF and opioid-based (OB) general anesthesia in elective surgery (CS).

Methods: The study was a cross-sectional study including patients who had undergone elective CS with OF (Group OF) and OB (Group OB) general anesthesia between June 1, 2022, and November 30, 2022. Intraoperatively administered analgesics for postoperative pain mainly included acetaminophen and non-steroidal anti-inflammatory drugs (NSAID) in Group OF and fentanyl, acetaminophen, and tramadol in Group OB. Non-steroidal anti-inflammatory drugs were administered as analgesics at the maternity ward.

Results: Of 368 patients, 278 were excluded due to regional anesthesia. In 90 patients, 45 were in Group OF and 45 were in Group OB. Group OF received less intraoperative fluid compared with Group OB. Two groups required a similar number of NSAIDs on postoperative day zero. Group OF had more NSAID consumption on postoperative days one and two.

Conclusion: Opioid-free general anesthesia did not change the required number of NSAIDs 24 hours after surgery and necessitated less intraoperative crystalloid fluid. Our study supports Enhanced recovery after surgery protocols, which recommend multimodal analgesics and sparing opioids in CS, and adds to the accumulating evidence that suggests the use of OF general anesthesia in CS.

Keywords: Obstetrics, cesarean section, general anesthesia, opioid analgesics, postoperative pain, perioperative care

Introduction

Cesarean section (CS) is one of the most common surgical procedures, with a rate of 32% of all births and 1.27 million patients annually in the United States (1). Since taking care of two lives-mother and fetus-has gained extra importance, improving patient outcomes has gained extra importance (2). Obstetric mortality reductions in CS are based on regional anesthesia increases and enhancing the safety of general anesthesia (3). Over the last few decades, general anesthesia applications for CS have declined. It was shown that general anesthesia was performed in less than 1% of CSs in a tertiary care facility (4). However, general anesthesia may still be requested by patients, preferred in emergent CS, or used when regional anesthesia is contraindicated due to hemodynamic, neurological, or spinal abnormalities. In both general and regional anesthesia, pregnant women require comprehensive perioperative care.

Enhanced recovery after surgery (ERAS) includes perioperative care to accelerate patient recovery. Enhanced recovery after surgery protocols in obstetrics recommend prescribing multimodal analgesics with a combination of drugs that have different mechanisms of action and sparing opioids (5). Furthermore, newborns are affected by opioids administered during birth. The use of neuraxial or systemic opioids is associated with unpredicted maternal and neonatal outcomes. To decrease fetal opioid exposure, opioids should be minimized or avoided before delivery. However, minimal opioid use can still lead to unwanted outcomes. The side effects of neuraxially administered opioids are significantly lower than those of systemically administered opioids (6,7). Avoiding opioids in general anesthesia will discard the risk of potential maternal and

Address for Correspondence: Elif Ongel, University of Health Sciences Turkey, Istanbul Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, Clinic of Anesthesiology and Reanimation, Istanbul, Turkey
Phone: +90 533 462 91 88 E-mail: elifongelmd@gmail.com ORCID: orcid.org/0000-0002-2206-9928
Received: 17.02.2023 **Accepted:** 09.06.2023

fetal opioid side effects. In addition, guidelines suggest encouraging breastfeeding as normal following CS and opioid-sparing anesthesia in breastfeeding women. Immediately after delivery, the intercellular gaps in the milk glands are fully open for immunoglobulin passage to the baby, and during this period, drugs are also freely able to pass into breast milk. Also, they suggest extra caution for infants less than six weeks of age. Recent guidelines recommended using multimodal analgesia with non-opioid drugs for postoperative pain after delivery, including non-steroidal anti-inflammatory drugs (NSAID) and acetaminophen (8).

Even though guidelines recommend opioid-free (OF) anesthesia in elective CS, in daily practice, opioids are commonly administered after the delivery of a baby for postoperative pain. Because of the rarity of applying OF general anesthesia in CS, it has been difficult to determine the perioperative management difference between OF and opioid-based (OB) general anesthesia in CS. In this study, we compared the perioperative management of OF and OB general anesthesia in elective CS.

Materials and Methods

Compliance with Ethical Standards

This study was approved by the Ethics Committee of University of Health Sciences Turkey, Istanbul Sancaktepe Şehit Prof. Dr. Ilhan Varank Training and Research Hospital (date: 19/12/2022, decision no: E-46059653-050.99).

Study Design

We retrospectively screened patients who had undergone elective CS with general anesthesia from June 1, 2022, to November 30, 2022. All patients with American Society of Anesthesiologists (ASA) II and III who had undergone elective CS with general anesthesia were included in our study. Patients who were ASA IV and had undergone CS with regional anesthesia were excluded. Patients were divided into two groups: 1) patients who were operated under OF general anesthesia (Group OF); and 2) patients who were operated under OB general anesthesia (Group OB).

All patients received anesthesia induction with i.v. propofol (2 mg/kg) and rocuronium (0.6 mg/kg) and were maintained with sevoflurane in a mixture of 50% oxygen and air with a 2 L/min flow rate. The patient's anesthesia depth was recorded by bispectral index (BIS) monitoring while maintaining a value between 40 and 60. Sevoflurane MAC was increased according to the patient's BIS values. Lungs were ventilated with a tidal volume of 6-8 mL/kg and a positive end-expiratory pressure of 5 cm H_2O. End-tidal carbon dioxide was maintained between 35 and 40 mmHg by adjusting the tidal volume and respiratory rate. Group OF and Group OB anesthesiologists were different physicians, and postoperative analgesia management was different in both groups. In Group OF, intraoperatively administered analgesics for postoperative pain included acetaminophen (1000 mg) and NSAID (75 mg diclofenac sodium i.m.) with magnesium (1.5 mg in crystalloid solution) and a single 10 mL 0.5% bupivacaine injection under the skin before wound closure. In Group OB, intraoperative analgesics for postoperative pain after delivery included fentanyl (50 or 100 mcg), paracetamol (1000 mg), and tramadol (100 mg) with ondansetron (4 mg).

Demographic variables were age, body mass index, weight, height, ASA score, previous CS, comorbidities (diabetes mellitus, hypertension, lung disease, thyroid disease), and smoking history. Intra-operative data included pre-operative and post-operative mean arterial pressure (MAP), pre-operative and post-operative heart rate (HR), total amount of administered fluid, surgery time, time difference between start of anesthesia and delivery of the baby, and emergence from anesthesia time (time between end of surgery and transfer to the recovery room). Postoperative data included NSAID consumption, which was administered according to the patient's demand at the maternity ward, on day zero (24 hours after surgery), day one, day two, and the patient's hospital length of stay (LOS). All the data from the two groups was compared.

Statistical Analysis

A power analysis was run to evaluate the size of the sample. To obtain a statistical power of 80 percent with an effect size of 0.6 in the study, we needed to enroll a minimum of 2×21 subjects to detect significant differences between groups. The mean, standard deviation, median, minimum, maximum value, frequency, and percentage were used for descriptive statistics. The distribution of variables was checked with the Kolmogorov-Smirnov test. The independent sample t-test and Mann-Whitney U test were used for the comparison of quantitative data. The Wilcoxon signed-rank test was used for repeated measurement analysis. The chi-square test was used for the comparison of qualitative data. SPSS 28.0 was used for statistical analyses.

Results

Two hundred and sixty-eight patients who had undergone elective CS between June 1, 2022, and November 30, 2022, were screened. One hundred and seventy-eight patients were excluded due to regional anesthesia. Ninety patients were enrolled in the study (Figure 1). Forty-five patients had OF general anesthesia (Group OF) and 45 patients had OB general anesthesia (Group OB) in elective CS surgeries. There were no

significant differences in the demographic variables of the two groups (Table 1).

In intraoperative variables, there were no significant differences between pre- and postoperative MAP or the variation of MAP between groups. There were significant differences between the pre-operative HR (p=0.025) and post-operative HR (p=0.005) of the groups. There was no significant difference in the variation of HR between

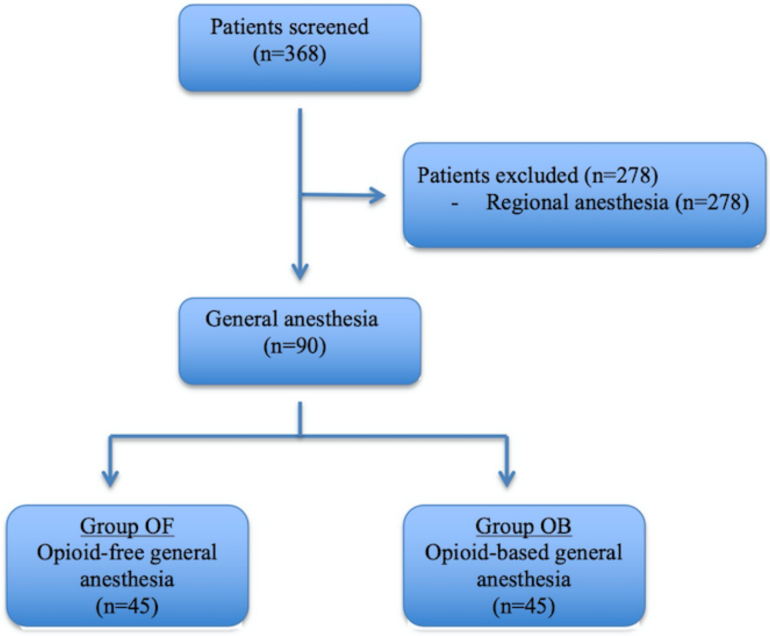

Figure 1. Flow chart
OF: Opioid-free, OB: Opioid-based

Table 1. Demographic variables of all patients

Variables	Overall (n=90)	Group OF (n=45)	Group OB (n=45)	p-value
Age (yr)	28 (25 to 33)	29 (26 to 34)	27 (25 to 32)	0.167[m]
Weight (kg) Height (cm) BMI	76 (70 to 87) 165 (160 to 168) 28 (26 to 31)	80 (69 to 85) 160 (160 to 166) 29 (26 to 31)	75 (70 to 90) 165 (160 to 170) 28 (26 to 32)	0.916[m] 0.172[m] 0.729[m]
ASA II III	 86 (96) 4 (4)	 42 (93) 3 (7)	 44 (98) 1 (2)	 0.616[x2]
Previous CS 0 1 2 3	 17 (19) 49 (54) 22 (25) 2 (2)	 6 (13) 23 (51) 14 (32) 2 (4)	 11 (24) 26 (58) 8 (18) 0 (0)	 0.178[x2]
Comorbidities HT DM Asthma Thyroid disease	 1 (1) 6 (7) 1 (1) 10 (11)	 1 (2) 4 (9) 1 (2) 5 (11)	 0 (0) 2 (4) 0 (0) 5 (11)	 0.494[x2] 0.398[x2] 1.000[x2] 1.000[x2]
Smoking Never Current Former	 78 (87) 7 (8) 5 (5)	 38 (84) 5 (11) 2 (5)	 40 (89) 2 (4) 3 (7)	 0.535[x2]

Data are presented as the median (interquartile range) or absolute number (percentage).
[m]: Mann-Whitney U test; [X2]: Chi-square test
P-values in bold represent statistically significant results (p<0.05).
BMI: Body mass index, CS: Cesarean section, HT: Hypertension, DM: Diabetes mellitus

groups. Intraoperatively administered fluids were all crystalloids and significantly different between groups (p=0.012). There was no significant difference in surgery time, time between the start of anesthesia and delivery of the baby, or emergence from anesthesia time between the groups (Table 2).

In postoperative variables, there was no significant difference in postoperative day zero NSAID consumption between the groups. The mean NSAID consumption on postoperative days one (p=0.001) and two (p=0.031) was significantly different between groups. On postoperative day one, the mean NSAID use was 1.1±0.5 in Group OF and 0.7±0.7 in Group OB. On postoperative day two, the mean NSAID use was 0.8±0.4 in Group OF and 0.6±0.5 in Group OB. Hospital LOS was not significantly different between the groups (Table 2).

Discussion

In this study, we compared OF and OB general anesthesia in elective CS. We found differences in intraoperative crystalloid fluid amount, NSAID consumption on postoperative days one and two between the two groups.

Systemic opioids are used in the general anesthesia of CS after the delivery for pain relief. However, opioids have many side effects, including hypotension, which could result in administering more intraoperative fluid than necessary. The results showed that OF general anesthesia in CS patients received less intraoperative fluid than OB general anesthesia (1075 vs. 1217 mL). Iatrogenic overload side effects have not been reported so far, but hypervolemia was associated with endothelial damage (9). Literature supports our results by finding better outcomes in abdominal surgery patients who had restrictive fluid management compared to conventional fluid management during surgery (10).

Our other result was the amount of NSAIDs consumed on postoperative day zero, which was not significantly different between Group OF and Group OB. Our data are consistent with the literature, which showed that

Table 2. Peri-operative variables of all patients

Variables	Overall (n=90)	Group OF (n=45)	Group OB (n=45)	p-value
Mean arterial pressure (mmHg)				
Preoperative	91 (86 to 97)	90 (86 to 95)	91 (86 to 98)	0.532[m]
Postoperative	85 (80 to 93)	83 (80 to 93)	87 (80 to 93)	0.585[m]
Variation	-5 (-12 to -2)	-6 (-11 to -1)	-4 (-12 to -2)	0.684[t]
Heart rate (per min)				
Preoperative	92 (84 to 104)	95 (88 to 105)	87 (81 to 98)	**0.025[m]**
Postoperative	91 (80 to 100)	100 (89 to 107)	90 (70 to 115)	**0.005[m]**
Variation	2 (-11 to -12)	1 (-10 to -15)	2 (-14 to -9)	0.876[t]
Crystalloid fluid (mL)	1146±272	1075±200	1217±315	**0.012[m]**
Times (min)				
Surgery	65 (55 to 76)	63 (52 to 78)	66 (55 to 75)	0.802[m]
Difference between anesthesia start and baby delivery	7 (5 to 9)	7 (6 to 9)	7 (5 to 8)	0.265[m]
Emergence from anesthesia	5 (5 to 10)	5 (5 to 8)	5 (5 to 10)	0.226[m]
Post-operative day zero NSAID				
Mean	1.1±0.8	1.2±0.7	1±0.8	0.305[m]
0	25 (28)	9 (20)	16 (36)	
1	34 (38)	20 (44)	14 (31)	0.218[x2]
2	31 (34)	16 (36)	15 (33)	
Post-operative day one NSAID				
Mean	0.9±0.6	1.1±0.5	0.7±0.7	**0.001[m]**
0	22 (24)	3 (7)	19 (42)	
1	58 (64)	36 (80)	22 (49)	**<0.001[x2]**
2	8 (9)	5 (11)	3 (7)	
3	2 (2)	1 (2)	1 (2)	
Post-operative day two NSAID				
Mean	0.7±0.5	0.8±0.4	0.6±0.5	**0.031[m]**
0	28 (31)	9 (20)	19 (42)	
1	60 (67)	35 (78)	25 (56)	**0.023[x2]**
2	2 (2)	1 (2)	1 (2)	
Hospital LOS (day)	3.2±1	3.3±1.4	3.1±0.6	0.266[m]

Data are presented as the mean ± SD, median (interquartile range), or absolute number (percentage).
[m]: Mann-Whitney U test, [X²]: Chi-square test
P-values in bold represent statistically significant results (p<0.05).
NSAID: Non-steroidal anti-inflammatory drug, LOS: Length of stay

NSAIDs were equally effective 24 hours after surgery compared with opioids (11,12). Toleska and Dimitrovski (13) found that patients who had OF general anesthesia in laparoscopic cholecystectomy operations needed less postoperative analgesia in 24 hours compared to the OB group. In addition, Fletcher and Martinez (14) published a meta-analysis about opioid-induced postoperative hyperalgesia. They showed that high-dose intraoperative opioid use was associated with increased opioid use in the postoperative 24 hours. Moreover, it was recommended as Grade A to use OF multimodal analgesia for postoperative analgesia in CS, including acetaminophen and NSAIDs (8).

As an adjuvant for postoperative pain management, we used i.v. magnesium in Group OF. Magnesium is an NMDA receptor antagonist and plays many important roles in nociception. Likewise, our results and the meta-analysis by De Oliveira et al. (15) showed that perioperative systemic magnesium administration minimizes postoperative pain. In addition, it was shown that intravenous maternal magnesium therapy is not expected to affect serum magnesium levels in breastfed infants (16).

Non-steroidal anti-inflammatory drugs consumption on postoperative days one and two was significantly different between groups. Ninety percent of two groups were required to take one or two NSAIDs on postoperative day one, and 98% of two groups were required to take one or two NSAIDs on postoperative day two. The maximum dose of diclofenac sodium was 150 mg, and all of our patients received less than 150 mg per day. Ostensen and Musby (17) showed no drug in patients' colostrum after receiving 150 mg of diclofenac sodium following CS in 48 h. Diclofenac sodium IM injections were found to be safe at repeated doses and a good analgesic to use alone for postoperative pain in CS (18).

Lastly, we injected 10 ml of 0.5% bupivacaine under the skin before wound closure in Group OF for postoperative pain. Supporting us, it was recommended as Grade A to use single-shot local anesthetic wound infiltration for reducing postoperative pain in CS (19). Our findings on bupivacaine injection to the wound area agree with those reported by Gurbet et al. (20), who showed lower postoperative pain scores and lower analgesic consumption in 24 h in patients who received wound infiltration with 10 mL of 0.5% bupivacaine.

Even patients who received low-dose intrathecal opioids experienced bradypnea (21) at least once and were recommended to schedule respiratory monitors every 2 hours for 12 hours (22). Opioids could be very hazardous in systematic use after CS for patients and infants.

Study Limitations

Our study had several limitations. First, it was a retrospective study with a limited number of patients in the groups due to the lower use of OF general anesthesia in CS. Second, patients did not have any records about previous CS, intraoperative diuresis, sevoflurane MAC value, or postoperative pain scales, such as NRS or VAS. Despite these limitations, including CS patients with OF general anesthesia, which is recommended but less practiced in daily use, is one of the strengths of the study.

Conclusion

Opioid-free general anesthesia did not change the required number of NSAIDs 24 hours after surgery and necessitated less intraoperative crystalloid fluid. Our study supports ERAS protocols, which recommend multimodal analgesics and sparing opioids in CS, and adds to the accumulating evidence that suggests the use of OF general anesthesia in CS. Our cohort included a limited number of patients. Therefore, larger prospective studies with longer follow-up are needed to establish the perioperative management of OF general anesthesia in CS.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Turkey, Istanbul Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital (date: 19/12/2022, decision no: E-46059653-050.99).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.O., B.S., E.A., N.B., Design: E.O., B.S., E.A., N.B., Data Collection or Processing: E.O., B.S., Analysis or Interpretation: E.O., B.S., E.A., N.B., Literature Search: E.O., B.S., E.A., N.B., Writing: E.O., B.S., E.A., N.B.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declare that this study has received no financial support.

References

1. Hamilton BE, Martin JA, Osterman MJ, Curtin SC, Matthews TJ. Births: Final Data for 2014. Natl Vital Stat Rep 2015;64:1-64.
2. Molina G, Weiser TG, Lipsitz SR, et al. Relationship between cesarean delivery rate and maternal and neonatal mortality. JAMA 2015;314:2263-70.

3. D'Angelo R. Anesthesia-related maternal mortality: a pat on the back or a call to arms? Anesthesiology 2007;106:1082-4.
4. Palanisamy A, Mitani AA, Tsen LC. General anesthesia for cesarean delivery at a tertiary care hospital from 2000 to 2005: a retrospective analysis and 10-year update. Int J Obstet Anesth 2011;20:10-6.
5. Kalogera E, Dowdy SC. Enhanced Recovery Pathway in Gynecologic Surgery: Improving Outcomes Through Evidence-Based Medicine. Obstet Gynecol Clin North Am 2016;43:551-73.
6. Carvalho B. Respiratory depression after neuraxial opioids in the obstetric setting. Anesth Analg 2008;107:956-61.
7. Pöpping DM, Elia N, Marret E, Wenk M, Tramèr MR. Opioids added to local anesthetics for single-shot intrathecal anesthesia in patients undergoing minor surgery: a meta-analysis of randomized trials. Pain 2012;153:784-93.
8. Mitchell J, Jones W, Winkley E, Kinsella SM. Guideline on anaesthesia and sedation in breastfeeding women 2020: Guideline from the Association of Anaesthetists. Anaesthesia 2020;75:1482-93.
9. Silva PL, Cruz FF, Fujisaki LC, et al. Hypervolemia induces and potentiates lung damage after recruitment maneuver in a model of sepsis-induced acute lung injury. Crit Care 2010;14:114.
10. Erdogan-Ongel E, Coskun N, Meric AH, Goksoy B, Bakan N. Post-operative outcomes of intra-operative restrictive and conventional fluid management in laparoscopic colorectal cancer surgery. J Minim Access Surg 2023;19:239-44.
11. Mahdavi A, Telkabadi Z, Aleyasin A, Agha Hosseini M, Safdarian L, Momenzadeh A. Comparison of Morphine Suppository and Diclofenac Suppository for Pain Management After Elective Caesarean Section. Acta Med Iran 2016;54:709-12.
12. Thippeswamy T, Krishnaswamy B, Bengalorkar GM, Mariyappa N. Comparison of Efficacy and Safety of Intramuscular Piroxicam and Tramadol for Post-operative Pain in Patients Undergoing Caesarean Delivery. J Clin Diagn Res 2016;10:FC01-FC04.
13. Toleska M, Dimitrovski A. Is Opioid-Free General Anesthesia More Superior for Postoperative Pain Versus Opioid General Anesthesia in Laparoscopic Cholecystectomy? Pril (Makedon Akad Nauk Umet Odd Med Nauki) 2019;40:81-7.
14. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. Br J Anaesth 2014;112:991-1004.
15. De Oliveira GS Jr, Castro-Alves LJ, Khan JH, McCarthy RJ. Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology 2013;119:178-90.
16. Magnesium Sulfate. In: Drugs and Lactation Database (LactMed®). Bethesda (MD): National Institute of Child Health and Human Development; February 15, 2021.
17. Ostensen M, Musby G. Antirheumatic drug treatment during pregnancy and lactation. Scand J Rheumatol 1985;14:1-7.
18. Al-Waili NS. Efficacy and safety of repeated postoperative administration of intramuscular diclofenac sodium in the treatment of post-cesarean section pain: a double-blind study. Arch Med Res 2001;32:148-54.
19. Roofthooft E, Joshi GP, Rawal N, et al. PROSPECT guideline for elective caesarean section: updated systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia 2021;76:665-80.
20. Gurbet A, Bekar A, Bilgin H, Ozdemir N, Kuytu T. Preemptive wound infiltration in lumbar laminectomy for postoperative pain: comparison of bupivacaine and levobupivacaine. Turk Neurosurg 2014;24:48-53.
21. Biava AM, Cipriani G, Bilotta F. Is opioid-free analgesia the first tier choice in anesthesia for cesarean delivery? J Anesth 2023;37:492-3.
22. Bauchat JR, Weiniger CF, Sultan P, et al. Society for Obstetric Anesthesia and Perinatology Consensus Statement: Monitoring Recommendations for Prevention and Detection of Respiratory Depression Associated With Administration of Neuraxial Morphine for Cesarean Delivery Analgesia 2019;129:458-74.