EMBJ.ORG FOR YOUNG DOCTORS

EUROMEDITERRANEAN BIOMEDICAL JOURNAL
2023,18 (17) 79-83
(*FORMERLY: CAPSULA EBURNEA*)

Original article

FENTANYL VS MORPHINE AS ADJUVANT TO SPINAL ANESTHESIA FOR CAESAREAN SECTION: AN OBSERVATIONAL STUDY

Luigi La Via [1], Carmelo Minardi [1], Serena Brancati [2], Sara Valenti [3,4], Simone Messina [5], Eugenio Garofalo [5], Andrea Bruni [5], Paolo Murabito [1], Renato Bernardini [2,6], Filippo Sanfilippo [1]

1. Anesthesia and Intensive Care Unit, Department of Surgery and Medical-Surgical Specialties, AOU "Policlinico – San Marco"
2. Department of Pharmacology, University of Catania
3. School of Specialization in General Surgery, University of Catania,
4. Department of General Surgery, General Surgery and Oncologic Section, School of Medicine, University of Catania
5. Anesthesia and Intensive Care Unit, Department of Medical and Surgical Sciences, "Magna Graecia" University Catanzaro
Section of Pharmacology, Department of Biomedical and Biotechnological Sciences, University of Catania

ARTICLE INFO

Article history:
Received 28 Apr 2023
Accepted 19 Jun 2023
Published 24 Jul 2023

Keywords:
Satisfaction, pain relief, spinal anesthesia, analgesia, pain management, patient reported outcome questionnaire.

ABSTRACT

In patients undergoing caesarean section (CS) with spinal anesthesia, the superiority of one intrathecal opioid over another one is not fully established. In order to investigate this, we joined the PAIN OUT Project (NCT02083835) for a two-year period. We surveyed patients undergoing elective CS with intrathecal anesthesia. Patients were asked to complete an anonymous questionnaire. Primary outcomes were: worst pain experienced, time spent in severe pain, relief received by treatment, satisfaction about pain management, wish for more pain treatment. We included 144 patients. The two main pain management combinations used were: bupivacaine-morphine (B-M, n=100) and bupivacaine-fentanyl (B-F, n=32). There were no differences in any of the primary outcomes between the groups. The B-F population received more intravenous/intramuscular opioids during the intraoperative ($p<0.01$) and the postoperative ($p<0.001$) period. The choice of morphine or fentanyl as adjunct to local anesthetic in spinal anesthesia for CS does not affect the patient's experience with regards to pain management.

1. Introduction

The implementation of regional anesthesia for elective caesarean section (CS) has contributed to a decrease in the CS-associated mortality rate and central nerve blockade (spinal or epidural) is the gold-standard anesthesiology technique for the perioperative management of caesarean section (CS)(1). In order to improve the quality of the nerve block, while decreasing side effects of local anesthetics (LA), and with the aim of prolonging patient's pain relief in the postoperative period, a variety of drugs, mainly opioids and clonidine, has been used in intrathecal combination with the LA(2-9). The choice of one opioid over another one is still controversial, and the combination of two opioids in the same mixture has also been tested (10).

Regional, national and continental surveys have already documented that hospitalized patients receive suboptimal pain treatment, and a United States national survey found 50–70% of patients suffered from moderate to severe postoperative pain (11-13).

Despite advances in pain management, many patients still suffer from moderate to severe postoperative pain(14). Patient-Centered Outcomes Research is a growing approach and aims at extending the concept of patient-centeredness from daily health-care delivery to health-care research(15, 16). Importantly, most studies do not include the patient's perspective as a relevant clinical outcome, and in the context of CS the impact of using different intrathecal opioids as adjuncts to the LA in spinal anesthesia has not been investigated from the patient's viewpoint.

Our center participated to a worldwide study on the management of post-operative pain, and we aimed at studying the effects of the different intraoperative anesthetic technique and drugs on the patients' perspectives regarding their postoperative pain management after CS.

2. Methods

We analyzed data prospectively collected over a 2-year period in a center participating in the worldwide study on the management of post-operative

* Corresponding author: Luigi La Via, *luigilavia7@gmail.com*
DOI: 10.3269/1970-5492.2023.18.17
 ISSN: 2279-7165 - Available on-line at www.embj.org

pain - PAIN-OUT Project, http://www.pain-out.eu (ClinicalTrials.gov Identifier: NCT02083835) – aiming at highlighting the importance of the patient's perspective on postoperative pain management. PAIN OUT Project is a prospective observational study and a pilot was conducted in the summer 2008(17). The study progressively involved a growing number of sites worldwide, and by January 2014 there were 60 collecting centers in 17 countries. We also joined a further development of the PAIN OUT international perioperative pain registry in the period 2017-2019 (10 participating countries), where data obtained from over 10.000 patients confirmed that many patients still reported poor pain-related PROs on the first postoperative day.(18)

For the purpose of the PAIN OUT study, data collection entailed the compilation of two separate charts. The first one is filled in by the investigator and contains different sections: screening criteria, patient's demographics and medical history, the surgical procedure (classified according to the ICD-9-CM classification - http://www.cdc.gov/nchs/icd/icd9.htm), information about the pre-medication, the anesthesia technique, the intra- and post-operative pain treatment. The second chart is the anonymous questionnaire voluntarily completed by the patient on postoperative day one (at least six hours after return to the ward). The questionnaire designed on the revised APS's (American Pain Society's) POQ-R (Patient Outcomes Questionnaire-Revised) (19) has been recently validated (20). The questionnaire aimed at exploring the impact of postoperative pain from different perspectives: patients were asked to answer either scoring from 0 to 10 (most of the questions) or responding "YES" or "NO". After approval of the local Ethic Committee and after several meetings and hands-on training sessions with the trainees of the School of Anesthesia, our center joined the study on the 1st April 2010. We had planned to collect data for two years and subsequently we performed the analyses on different surgical populations according to pre-established primary and secondary endpoints (Table 1).

PRIMARY ENDPOINTS	Scale
Worst Pain	0-10
Time spent in Severe Pain	%
Relief received by treatment	%
Satisfaction about pain management	0-10
Wish for more pain treatment? (Y/N)	%
SECONDARY ENDPOINTS	**Scale**
Drowsiness	0-10
Itching	0-10
Nausea	0-10
Dizziness	0-10
Did Pain wake you up? (Y/N)	%

Table 1. Primary and secondary endpoints considered in the analysis performed in Catania's centre.

In the present study, we report the analysis of a group of patients undergoing CS (ICD-9 operation code 74.0) under spinal anesthesia. The data were downloaded directly from the central database of the project. The PAIN OUT Publication Board was informed of our analysis design and formally agreed.

All the cases for the present study were collected in a highly specialized Hospital for obstetrics and gynecology.

We divided the study population into groups according to the combinations of drugs used for spinal anesthesia. For each sub-group we examined the intra- and the post-operative enteral and parenteral administration of drugs for pain relief, such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids.

The first and the second chart were collected in a variable timeframe after CS (between the 12th and the 36th postoperative hour); however, as this parameter was not recorded, we could not consider the cumulative dose of medications administered in the post-operative period. We decided in advance to exclude those patients responding to less than two primary endpoints of the questionnaire , and those patients for which there was no entry in the database regarding the intra- and the post-operative drugs given from analysis.

Statistical analysis

The data screening and reorganization, and the subsequent statistical analysis, were performed through SPSS Statistics 19.0® and PRISMA® software. The distribution of quantitative variables was tested through Kolmogorov-Smirnov test.

Continuous variables are presented as mean ± standard deviation and with median and 95% confidence interval (CI). The differences between groups were assessed by parametric tests (T-student) for variables with normal distribution, while non-parametric tests (Mann-Whitney for two samples) were used for not normally distributed cases. Categorical variables are expressed as numbers and percentages (%), and were analyzed through the Chi-square test with Yates' correction for the verification of null hypothesis. All tests were two tailed and a $p<0.05$ was considered statistically significant for all analysis.

3. Results

Over a two-year period, we collected data relating to 144 CS performed under spinal anesthesia, and no intervention required conversion to general anesthesia. All the patients enrolled filled in the entire questionnaire. The different intraoperative pharmacological combinations used for spinal anesthesia are shown in Table 2.

DRUG USED FOR SPINAL ANAESTHESIA	N
Bupivacaine only	1
Bupivacaine + Morphine	100
Bupivacaine + Fentanyl	32
Levo-Bupivacaine + Fentanyl	6
Unclear	5
Total	144

Table 2. Combination of drugs used in spinal anaesthesia for Caesarean Section.

In the two largest groups, bupivacaine was used in combination with morphine (B-M; n=100) or fentanyl (B-F; n=32). In five cases, the LA used was not recorded; however, four out of these five patients received intrathecal opioid administration (morphine n=3; fentanyl n=1).

The two groups were comparable for age (B-M: mean 31.6 ± 5.7, median 32, 95% CI 30.4 – 32.7; vs B-F: mean 32.8 ± 6.4, median 33.0, 95% CI 30.6 - 35.0; p=0.32) and for weight (B-M: mean 79.7 ± 11.9, median 80.0, 95% CI 77.3 - 82.1; vs B-F: mean 79.9 ± 13.6; median 80, 95% CI 75.0 - 84.8; p=0.97).The comparison of the Patient Reported Outcomes (PROs) between the two larger groups - B-M and B-F - did not show any difference as shown in Table 3.

PRIMARY ENDPOINTS	Bupivacaine + Morphine (N=100)	Bupivacaine + Fentanyl (N=32)	p value
Worst Pain	3.9 ± 1.9 4 (3.5 - 4.2)	4.2 ± 2.0 5 (3.4 - 4.9)	0.34
Time spent in Severe Pain (%)	18.7 ± 14.7 20 (15.7 - 21.6)	22.2 ± 13.6 20 (17.3 - 27.1)	0.13
Relief received by treatment (%)	67.9 ± 23.3 70 (63.2 - 72.5)	63.7 ± 21.8 70 (55.9 - 71.6)	0.22
Satisfaction about pain management	7.7 ± 1.6 8 (7.3 - 8.0)	7.5 ± 1.6 7 (6.9 - 8.0)	0.46
Wish for more pain treatment (%)	9.0	12.5	0.57
SECONDARY ENDPOINTS			
Drowsiness	0.4 ± 1.1 0 (0.2 – 0.6)	0.4 ± 0.8 0 (0.1 – 0.7)	0.83
Itching	1.7 ± 2.3 0 (1.3 – 2.2)	1.4 ± 1.7 1 (0.8 – 2.0)	0.91
Nausea	1.4 ± 1.8 1 (1.0 – 1.8)	1.8 ± 1.9 1 (1.1 – 2.5)	0.27
Dizziness	0.4 ± 1.0 0 (0.2 - 0.6)	0.6 ± 1.3 0 (0.1 - 1)	0.43
Did the pain wake you up? (%)	7.7	9.4	0.67

Table 3. Primary and secondary endpoints within two groups of Caesarean Sections. Continuous variables are reported as mean ± Standard deviation on the top of each box, and as median and 95% Confidence Interval at the bottom of each box. Categorical variables are expressed as percentages. Mann-Whitney or Chi-square (with Yates correction) tests and p values are shown in the last column.

The analysis of the administration of analgesic drugs during the intraoperative period in the two groups (B-M and B-F) is shown in Table 4. The number of patients receiving no intraoperative administration of drugs for pain relief was similar in the two groups (B-M, n=19, 19%; B-F, n=7, 22%; p=0.92). A combination of two drugs for analgesia was used in 11 and 4 patients in the B-M and in the B-F group respectively (11% vs 12%; p=0.93).

INTRAOPERATIVE DRUG ADMINISTRATION	Bupivacaine + Morphine (N=100)	Bupivacaine + Fentanyl (N=32)	p value
Opioid (N=8)	2	6	<0.005
Morphine (N=0)	0	0	-
Tramadol (N=8)	2	6	<0.005
NSAIDs (N=102)	80	22	=0.28
Diclofenac (N=74)	67	7	<0.001
Paracetamol (N=36)	20	16	<0.005
Ketorolac (N=3)	3	0	=0.75

Table 4. Intraoperative drug administration for pain relief in two groups of Caesarean Sections, according to the combination of drugs used for spinal anaesthesia. Chi-square test (with Yates correction) is shown in the last column. NSAIDs: Non-steroidal anti-inflammatory drugs.

With regards to the postoperative period, the analysis of the drugs used for pain relief in the two groups (B-M and B-F) is shown in Table 5.
All the patients received at least one drug for pain relief during this period.
A combination of two drugs for postoperative analgesia was used in 77 and 30 patients in the B-M and B-F groups respectively (77% and 94%; p=0.06).
Local cooling was the only non-pharmacological tool for pain relief reported by the patients in the questionnaire and it was not significantly different between the groups (B-M n=23/100; B-F 8/32; p=0.99).
When extending the analysis to all the patients receiving intrathecal morphine or fentanyl (regardless which LA had been used), and therefore adding further 10 patients (3 to the morphine group and 7 to the fentanyl group), we did not find significant changes in the above listed results.

POSTOPERATIVE DRUG ADMINISTRATION	Bupivacaine + Morphine (N=100)	Bupivacaine + Fentanyl (N=32)	p value
Opioid (N=31)	6	25	p<0.001
Morphine (N=1)	1	0	p=0.57
Tramadol (N=30)	5	25	p<0.001
NSAIDs (N=130)	99	31	p=0.98
Diclofenac (N=95)	87	8	p<0.001
Paracetamol (N=108)	78	30	p=0.08
Ketorolac (N=5)	4	1	p=0.76

Table 5. Postoperative drug administration for pain relief in the two groups of caesarean sections, according to the combination of drugs used for spinal anaesthesia. Chi-square test (with Yates correction) is shown in the last column. NSAIDs: Non-steroidal anti-inflammatory drugs.

4. Discussion

The main finding of our study is that the choice of intrathecal opioid (morphine or fentanyl) as adjunct to LA for spinal anesthesia in patients undergoing elective CS did not affect the patient's experience with regards to the pain management.
A peculiarity of our study and of the entire PAIN OUT Project design is the shift of the endpoints from clinician's assessment to PROs. Our study differs from others published so far in the fact that the target is not a set of clinical parameters assessing pain (i.e. time before first analgesic requirement or total postoperative analgesic consumption) Furthermore, intraoperative and postoperative safety issues typically investigated by other trials(21) (i.e., hypotension and vasopressors requirements, or postoperative nausea and vomiting) are not part of the main database. Conversely, our focus was the patient's point of view regarding the pain treatment received. Our study seems to be more sophisticated in its approach and uses a comprehensive, exhaustive and validated questionnaire that allows us to reflect the reality of care, where patients and care providers operate in a natural environment, as opposed to the artificial one of randomized controlled trials (20). Few studies in patients undergoing CS considered PROs. A study by Acar et al took into account postoperative patient's satisfaction in 60 patients undergoing CS, and found higher satisfaction in those treated with morphine as adjunct to LA as compared to fentanyl(22).
Our highly specialized gynecological center followed the "gold-standard" practice to combine LA and opioids for the spinal anesthesia of patients undergoing CS. For instance, a randomized controlled study on CS population showed that intrathecal LA alone provides analgesia of shorter duration in the postoperative period and increases the need for intraoperative antiemetic medication (3).

A recent meta-analysis (23) of three different regimens of intrathecal bupivacaine (high-dose, low-dose and low-dose plus opioids) for CS included over 600 patients and found that intrathecal low-dose bupivacaine plus opioids reduced the episodes of intra-operative hypotension, maintaining a reliable level of analgesia if compared with bupivacaine alone, either used in high- or low-dose. Similar findings have been highlighted by Unlugenc et al.(24), where adding intrathecal morphine to the LA in patients undergoing CS prolonged the duration of analgesia, provided a more rapid onset and a longer time to first analgesic administration compared to placebo.

In our study population, morphine was used three times more frequently than fentanyl. An interesting randomized study examined the effects of intrathecal fentanyl and morphine, alone and in combination, as adjuncts to bupivacaine in patients undergoing CS(10). The quality of postoperative analgesia with morphine, when used alone, was superior to that with fentanyl, while the combination of the two opioids offered no advantages over morphine alone. Our results do not support a better outcome with morphine as we found no difference between the two groups for PROs. However, we saw a larger intra- and postoperative administration of opioids (tramadol) and also a trend towards more frequent postoperative combination of drugs for pain relief in the fentanyl group. This finding and the better mean values in all primary PROs in the morphine group (Table 3), associated with all the limitations of the present study, leave the doors open to larger investigations. The concentration of the LA may also play a role when combining intrathecal opioids. A study by Saracoglu et al.(25) showed that intrathecal morphine provides longer duration of postoperative analgesia when combined with plain instead of heavy bupivacaine, but unfortunately our database does not support the recognition of different concentrations of LA used.

We found low scores for secondary PROs - side effects - in both groups. Evaluation of nausea in a population of CS is challenging, as despite appearing more frequently in the postoperative period (26), it is also common during the intraoperative period. Itching is a relatively minor, but common, side effect of intrathecal opioid administration with an incidence of 50–90%(27).

In the PROs we found that drowsiness and dizziness had an average value below 1 out of 10, while mean values for nausea and itching were 1.5 and 1.6 respectively. These low scores question the importance of these side effects from patient's perspectives after CS. However, it is possible that the administration in spinal anesthesia reduced the side effects of opioids, including postoperative ileus which represents an issue in the postoperative period after surgery(28).

The participation in the PAIN OUT Project allowed us to reflect on our practice on pain management, avoiding the assumption that "all is well". From this study we found that that even in a highly specialized center there is room for improvement in postoperative pain management and the patients' postoperative experience.

However, in a large PAIN OUT Project database investigation, Schwenkglenks et al.(29) analyzed the questionnaire results of almost 17.000 patients undergoing a wide range of surgical procedures. The authors found that *patient satisfaction* (median was 9/10) regarding pain management was mainly correlated with higher *pain relief received* and *no wish to have received more pain treatment*.

In our small study satisfaction was lower than in the above-mentioned study. We observed a suboptimal *pain relief received* (66%), and also patients spent 20% of the initial postoperative time in severe pain.

Implementing a quicker response to pain and/or optimizing the strategy of re-assessing pain after treatment could be two ways to ameliorate patient's experience after CS.

On the other hand, the *wish to receive additional pain treatment* (other variable correlated with patients' satisfaction in the above-mentioned study) and the worst pain experienced were both low (below 10% and 4/10, respectively).

Among its aims, PAIN OUT Project aims at increasing awareness about the necessary cultural shift in designing studies dealing with postoperative pain. Patients' perspectives cannot be ignored or just superficially investigated. We suggest that investigating the superiority of one analgesic technique/approach over another one (i.e. the choice of one intrathecal opioid over another one), the studies' design needs to combine clinical assessment with a deeper investigation of PROs, in order to answer the question also from patient's perspective (i.e. "*does the choice of opioid in spinal anesthesia for CS matter to the patient?"* in the present study).

This study has several limitations. First, this is a single center observational study and because of its design it did not evaluate the clinical parameters investigated by most of the studies (both intraoperatively, such as perfusion(30) or episodes of hypotension(31), and postoperatively, i.e. time to first analgesic requirement), and therefore there is no space for comparing our findings with most of the studies in patients undergoing CS. Secondly, due to database organization the analysis on the amount of drugs administered postoperatively for pain relief was not feasible as pharmacological data were collected at different time-points. Third, we did not have a follow-up evaluation to check the differences in the development of chronic pain; however, this may represent an issue with the administration of systemic opiods but not for intrathecal administration. Finally, the relatively small sample size and the imbalance between the groups (which simply reflects the preferred practice at our center) did not warrant deeper investigations between different doses of intrathecal LA and/or opioids as this would have been statistically meaningless.

5. Conclusions

In summary, in patients undergoing CS the PROs about postoperative pain management did not show differences regardless which opioid – morphine or fentanyl – was used in combination with bupivacaine for spinal anesthesia. Further studies addressing the optimal analgesic treatment for a surgical procedure should consider combining the analysis of clinical variables with a more comprehensive assessment of patient perspectives on their postoperative experience through a validated outcome questionnaire.

References

1. Cooper GM, McClure JH. Maternal deaths from anaesthesia. An extract from Why Mothers Die 2000-2002, the Confidential Enquiries into Maternal Deaths in the United Kingdom: Chapter 9: Anaesthesia. British journal of anaesthesia. 2005;94(4):417-23.
2. Dahl JB, Jeppesen IS, Jorgensen H, Wetterslev J, Moiniche S. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials. Anesthesiology. 1999;91(6):1919-27.

3. Dahlgren G, Hultstrand C, Jakobsson J, Norman M, Eriksson EW, Martin H. Intrathecal sufentanil, fentanyl, or placebo added to bupivacaine for cesarean section. Anesthesia and analgesia. 1997;85(6):1288-93.
4. Liu SS, McDonald SB. Current issues in spinal anesthesia. Anesthesiology. 2001;94(5):888-906.
5. Karaman S, Kocabas S, Uyar M, Hayzaran S, Firat V. The effects of sufentanil or morphine added to hyperbaric bupivacaine in spinal anaesthesia for caesarean section. European journal of anaesthesiology. 2006;23(4):285-91.
6. Choi DH, Ahn HJ, Kim MH. Bupivacaine-sparing effect of fentanyl in spinal anesthesia for cesarean delivery. Reg Anesth Pain Med. 2000;25(3):240-5.
7. Belzarena SD. Clinical effects of intrathecally administered fentanyl in patients undergoing cesarean section. Anesthesia and analgesia. 1992;74(5):653-7.
8. Yu SC, Ngan Kee WD, Kwan AS. Addition of meperidine to bupivacaine for spinal anaesthesia for Caesarean section. British journal of anaesthesia. 2002;88(3):379-83.
9. La Via L, Santonocito C, Bartolotta N, Lanzafame B, Morgana A, Continella C, et al. α-2 agonists vs. fentanyl as adjuvants for spinal anesthesia in elective cesarean section: a meta-analysis. Minerva anestesiologica. 2023;89(5):445-54.
10. Karaman S, Gunusen I, Uyar M, Biricik E, Firat V. The effects of morphine and fentanyl alone or in combination added to intrathecal bupivacaine in spinal anesthesia for cesarean section. Agri. 2011;23(2):57-63.
11. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesthesia and analgesia. 2003;97(2):534-40, table of contents.
12. Benhamou D, Berti M, Brodner G, De Andres J, Draisci G, Moreno-Azcoita M, et al. Postoperative Analgesic THerapy Observational Survey (PATHOS): a practice pattern study in 7 central/southern European countries. Pain. 2008;136(1-2):134-41.
13. Hartog CS, Rothaug J, Goettermann A, Zimmer A, Meissner W. Room for improvement: nurses' and physicians' views of a post-operative pain management program. Acta anaesthesiologica Scandinavica. 2010;54(3):277-83.
14. Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management: I. Evidence from published data. British journal of anaesthesia. 2002;89(3):409-23.
15. Methodological standards and patient-centeredness in comparative effectiveness research: the PCORI perspective. Jama. 2012;307(15):1636-40.
16. Leanza V, Zanghi G, Leanza G, Leanza A, Passanisi A, Giaimo F. A specific application of two psychological measures on pelvic organ prolapse patients. Giornale Italiano di Ostetricia e Ginecologia. 2015;37(2):82-6.
17. Zaslansky R, Chapman CR, Rothaug J, Backstrom R, Brill S, Davidson E, et al. Feasibility of international data collection and feedback on post-operative pain data: proof of concept. Eur J Pain. 2012;16(3):430-8.
18. Zaslansky R. Status quo of pain-related patient-reported outcomes and perioperative pain management in 10,415 patients from 10 countries: Analysis of registry data. Eur J Pain. 2022;26(10):2120-40.
19. Gordon DB, Polomano RC, Pellino TA, Turk DC, McCracken LM, Sherwood G, et al. Revised American Pain Society Patient Outcome Questionnaire (APS-POQ-R) for quality improvement of pain management in hospitalized adults: preliminary psychometric evaluation. J Pain. 2010;11(11):1172-86.
20. Rothaug J, Zaslansky R, Schwenkglenks M, Komann M, Allvin R, Backstrom R, et al. Patients' perception of postoperative pain management: validation of the International Pain Outcomes (IPO) questionnaire. J Pain. 2013;14(11):1361-70.
21. Setti T, Sanfilippo F, Leykin Y. Transdermal buprenorphine for postoperative pain control in gynecological surgery: a prospective randomized study. Current medical research and opinion. 2012;28(10):1597-608.
22. Acar P, Ozyuvaci E, Vatansever S, Toprak N, Akyol O. [Assessment of the effect of intrathecal levobupivacaine combined with fentanyl or morphine on postoperative analgesia in patients undergoing cesarean section]. Agri. 2010;22(4):151-8.
23. Qiu MT, Lin FQ, Fu SK, Zhang HB, Li HH, Zhang LM, et al. Combination of low-dose bupivacaine and opioids provides satisfactory analgesia with less intraoperative hypotension for spinal anesthesia in cesarean section. CNS neuroscience & therapeutics. 2012;18(5):426-32.
24. Unlugenc H, Gunduz M, Guzel B, Isik G. A comparative study on the effects of intrathecal morphine added to levobupivacaine for spinal anesthesia. J Opioid Manag. 2012;8(2):105-13.
25. Saracoglu A, Saracoglu KT, Eti Z. Comparative study of fentanyl and morphine in addition to hyperbaric or isobaric bupivacaine in combined spinal anaesthesia for caesarean section. Arch Med Sci. 2011;7(4):694-9.
26. Weber EW, Slappendel R, Gielen MJ, Dirksen R. Intrathecal addition of morphine to bupivacaine is not the cause of postoperative nausea and vomiting. Reg Anesth Pain Med. 1998;23(1):81-6.
27. Alhashemi JA, Crosby ET, Grodecki W, Duffy PJ, Hull KA, Gallant C. Treatment of intrathecal morphine-induced pruritus following caesarean section. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 1997;44(10):1060-5.
28. Sanfilippo F, Spoletini G. Perspectives on the importance of postoperative ileus. Current medical research and opinion. 2015;31(4):675-6.
29. Schwenkglenks M, Gerbershagen HJ, Taylor RS, Pogatzki-Zahn E, Komann M, Rothaug J, et al. Correlates of satisfaction with pain treatment in the acute postoperative period: Results from the international PAIN OUT registry. Pain. 2014.
30. La Via L, Sanfilippo F, Continella C, Triolo T, Messina A, Robba C, et al. Agreement between Capillary Refill Time measured at Finger and Earlobe sites in different positions: a pilot prospective study on healthy volunteers. Journal of clinical medicine. 2023;23(1):30.
31. Murabito P, Astuto M, Sanfilippo F, La Via L, Vasile F, Basile F, et al. Proactive Management of Intraoperative Hypotension Reduces Biomarkers of Organ Injury and Oxidative Stress during Elective Non-Cardiac Surgery: A Pilot Randomized Controlled Trial. 2022;11(2).