

DOI: <https://doi.org/10.5554/22562087.e940>

Comparison among subarachnoid opioid mix for cesarean section – An observational study

Comparación de mezcla de opioides subaracnoideos para cesárea. Estudio observacional

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Abstract

What do we know about this topic?

- We know that the effective dose ED-90 for intrathecal hydromorphone is 75 µg.
- The limited literature available ascertains that the combination of bupivacaine, hydromorphone and fentanyl compared against bupivacaine, morphine and fentanyl shows no statistically significant differences with regards to the quality of the anesthesia, analgesia or adverse effects.
- The morphine hydrochloride available in Colombia has no indication in the safety data sheet for intrathecal use, whilst hydromorphone does.

What are contributions of the study?

The mixture of hydromorphone and bupivacaine may be a valid option to replace the traditional mixture with bupivacaine, morphine and fentanyl, for subarachnoid anesthesia in cesarean section, with the added advantage of improved postoperative pain control over the first 12 hours.

How to cite this article

Osorio-Gutiérrez CI, Ortiz-Gómez GA, Valencia-Ríos JF, Arango-Gómez F. Comparison among subarachnoid opioid mix for cesarean section – An observational study. *Colombian Journal of Anesthesiology*. 2021;49(1):e940.

Introduction

Classically, the local anesthetic (LA) has been combined with one lipophilic and another hydrophilic opioid for neuraxial anesthesia in cesarean section. In Colombia, the practice has been the use of morphine hydrochloride with fentanyl, but the occasional shortage of the former triggered an interest in new options. In response to the shortage of morphine in 2017-2018, a contingency plan was developed at the SES Hospital in Caldas, prefilling syringes at the hospital compounding central, with: bupivacaine, morphine and fentanyl (BMF); bupivacaine, fentanyl and hydromorphone (BFH); and bupivacaine and hydromorphone (BH). Hydromorphone has a rapid onset of action, long-lasting effect and is indicated for spinal administration in the safety data sheet; therefore, the advantages of adding fentanyl to this mix are questionable.

Objective

To compare the clinical analgesic efficacy at the time of the incision and during the first 12 hours after surgery.

Methods

An observational, analytical study was conducted, using the mixtures BMF, BFH and BH in patients receiving subarachnoid anesthesia for cesarean section. Pain was assessed at the time of the incision, as well as any adverse effects and the pain visual analogue scale over the following 12 hours.

Results

Of the 71 patients participating in the study, 40.9 % received BMF; 22.5 %, BFH; and 36.6 %, BH. None of the patients experienced pain at the time of the incision. There was no difference in terms of adverse effects among the three groups. The mean difference in the visual analogue scale (VAS) for postoperative pain at 3, 6 and 12 hours was lower in the groups in which hydromorphone was used.

Conclusion

BFH and BH combinations are comparable to the original preparation in terms of adverse effects, with the advantage of being more effective in controlling postoperative pain.

Keywords

Caesarean section; analgesics, opioid; subarachnoid space; injections, spinal.

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Resumen

Introducción

Para anestesia neuroaxial en cesárea, se ha combinado clásicamente el anestésico local (AL) con un opioide lipofílico y otro hidrofílico. En Colombia se ha usado clorhidrato de morfina con fentanilo, pero el ocasional desabastecimiento del primero despertó el interés por nuevas alternativas. En SES Hospital de Caldas se generó un plan de contingencia frente a la escasez de morfina en 2017-2018, prellenando jeringas en su central de mezclas con: bupivacaína, morfina y fentanilo (BMF); bupivacaína, fentanilo e hidromorfona (BHF); y bupivacaína e hidromorfona (BH). La hidromorfona tiene inicio rápido de acción, efecto prolongado e indicación en ficha técnica por vía espinal, por lo tanto, las ventajas que pudiera generar la adición del fentanilo a esta mezcla son cuestionables.

Objetivo

Comparar la eficacia analgésica clínica al momento de la incisión y en las primeras 12 horas postoperatorias.

Métodos

Se realizó un estudio observacional analítico, empleando las mezclas BMF, BHF y BH en pacientes que recibieron anestesia subaracnoidea para cesárea. Se evaluó el dolor a la incisión, los efectos adversos y la escala visual analógica de dolor en las 12 horas siguientes.

Resultados

De las 71 pacientes del estudio, 40,9 % recibieron BMF; 22,5 %, BHF; y 36,6 %, BH. En ninguna paciente se observó dolor a la incisión. No hubo diferencia en efectos adversos entre los 3 grupos. La diferencia de medias de la escala visual analógica (EVA) para dolor postoperatorio a las 3, 6 y 12 horas, fue menor en los grupos en los que se usó hidromorfona.

Conclusiones

Las mezclas BHF y BH son equiparables a la preparación tradicional en cuanto a efectos adversos, con la ventaja de ser más efectivas para el control del dolor postoperatorio.

Palabras clave

Cesárea; analgésicos; opioides; espacio subaracnoideo; inyecciones espinales.

INTRODUCTION

The *Clinical practice guidelines for obstetric anesthesia* of the American society of Anesthesiology and those of the American Society of Pain, recommend the routine use of neuraxial anesthesia for cesarean section (1), because it reduces the maternal risk, has improved fetal outcomes, and provides better postoperative analgesia. (2)

The classical regimen for cesarean section is based on a combination of the local anesthetic (LA), one lipophilic opioid — for instance, fentanyl — and one long-acting hydrophilic opioid — for instance morphine —. (3)

The erratic availability of morphine is a real challenge in Colombia and in other countries. (4,5) Reasons such as the lack of stimulus for the pharmaceutical companies to produce molecules with expired patents, and shifts in the demand for the product, may result in drug shortages. On the other hand, excipient-free morphine sulphate is the preparation endorsed for intrathecal

use; however, it is not available in Colombia, so morphine hydrochloride has been used, although this preparation is not registered for this route of administration. Hydromorphone in contrast, does have a safety data sheet for spinal administration.

With regards to fentanyl, there are no studies available assessing the relevance of removing it from the preparations with hydromorphone for spinal injection. The academic discussion among anesthesiologists to remove fentanyl was based on two aspects: 1. The maximum effect of fentanyl is achieved after 10-20 m and that of hydromorphone is achieved after 20-30 m, which is not a clinically significant difference in the context of neuraxial anesthesia. (6–8). 2. The duration of the effect of fentanyl is 130 m, which is very similar to the local anesthetic (LA). (9)

The results of this study are consistent with those claiming a lower pain score in anesthesia for cesarean section with hydromorphone, but disagree with the

studies describing an equivalence to morphine. This may be due to variations in the doses studied (10), and suggest that the effective dose described in the literature may approach the cut-off point for such effect. (5)

As a contingency mechanism in 2017, due to the shortage of morphine, the SES Hospital in Caldas, prepared bupivacaine, morphine and fentanyl (BMF) and bupivacaine, fentanyl and hydromorphone (BFH) prefilled syringes for subarachnoid anesthesia at its compounding central, based on the available publications (4,5), and one without fentanyl bupivacaine and hydromorphone (BH). The objective of this paper is to compare the clinical analgesic efficacy of these three anesthetic mixtures used in cesarean section, at the time of the incision and over the first 12 hours after surgery.

METHODS

Type of study: Observational, analytical.

Ethical approval: This study received the approval of the two committees: Ethics Committee of the Universidad de Caldas (Ethics Committee CBCS-032, May 7, 2018) and Ethics Committee of the SES Hospital of Caldas (Ethics Committee DC-048-18, May 7, 2018), both in Manizales, Colombia. Moreover, each patient surveyed completed their informed consent.

Setting: SES Hospital of Caldas is a third-level referral center for highly complex obstetric care in the Department of Caldas, located in Manizales city, Colombia.

Population: Full term pregnant women over 15 years old, with an indication for cesarean section and subarachnoid anesthesia, from June 2018 and May 2019. Patients with multiple pregnancies, chronic use of opioids, allergies to any of the drugs of the prefilled syringes, suspicion of maternal-fetal abnormalities, and patients who received any additional medication or a lower dose than the intrathecal premix, as prescribed by their treating physician, were all excluded.

Exposure: Subarachnoid anesthesia for cesarean section is a standard practice at the hospital. The preparations of the packaged prefilled syringes in the compounding central are:

- Hyperbaric Bupivacaine 0.5 % 2 mL + morphine 100 µg and fentanyl 10 µg (2.3 mL) (BMF)
- Hyperbaric Bupivacaine 0.5 % 2 mL + hydromorphone 80 µg and fentanyl 10 µg (2.4 mL) (BFH)
- Hyperbaric Bupivacaine 0.5 % 2 mL + hydromorphone 80 µg (2.1 mL) (BH)

Data collection: All data were collected by the team of investigators. The instrument to measure postoperative pain at 3, 6 and 12 hours was standardized, the reviewers received a preliminary training to use of the SES Hospital of Caldas rule, which is based on the numerical visual analogue scale (VAS). The electronic medical records and the anesthesia records were reviewed to identify any missing data. Patients were followed for 24 hours in the hospital.

Biases: A convenience sampling was conducted between June 2018 and May 2019, regardless of the anesthesiologist in charge, or of the reason for choosing the premix, in order to control the selection bias. All patients remained hospitalized for at least 24 hours to control for the non-response bias. All outcome variables were objectively measured, and pain was directly scored by each patient. All of the patients receiving care accepted to participate in the study.

Statistical analysis: The information obtained was logged into a previously designed Excel database and was analyzed using the SPSS version 25 software. The results are shown on frequency distribution charts. The normal distribution continuous variables are summarized as averages and standard deviation. The continuous variables with non-normal distribution are summarized with median and interquartile range. The Kruskal-Wallis non-parametric test was used at all time points in which the VAS was analyzed. The variance analysis for repeated measurements was not used due to the small sample size. A bi-variate analysis was conducted to identify the association between pain at the time of the cesarean section incision, adverse effects, and postoperative pain with the intrathecal mixture used. The categorical variables were compared using Chi square or the exact Fisher's test, as needed. A new stratified analysis was conducted to control for any confounding variables, such as having received prophylactic antiemetics during the trans-operative period, and adjuvant analgesia during the intra and post-operative periods.

RESULTS

71 patients were studied (figure 1), of which 40.9 % (*n*: 29) received the usual BMF combination; 22.5 % (*n*:16), BFH; and 36.6 % (*n*: 26), BH. No patients were lost to follow-up. The characteristics of the population are shown in Table 1. The reason for the

anesthesiologist to prescribe one or other combination is described in Table 2.

Regardless of the mixture used, none of the patients experienced pain during the incision, or required changing the anesthetic technique. There were no statistically significant differences in terms of the incidence of pruritus (*p* 0.64) and hypotension (*p* 0.10), none of the patients experienced respiratory distress and there was no difference in the duration of the motor block (table 3).

Forty two patients received a prophylactic antiemetic (16 BMF, 11 BFH y 15 BH), 16 patients received two prophylactic antiemetics (7 BMF, 4 BFH and 5 BH) and 12 patients did not receive any of those drugs. There were no statistically significant differences among the groups in terms of nausea or vomiting (table 4).

All patients that received BMF and experienced hypotension (*n*: 16), had nausea; on the contrary, among those receiving BFH or BH, only 50 % of those that experienced hypotension, presented nausea during the trans-operative period.

There were group differences in the pain record at 3 and 6 hours. As seen in Figure 2, the mean difference was smaller among patients who received the BFH and BH mixtures, as compared to those receiving the BMF combination; according to the clinical manifestation, this suggests less postoperative pain in the groups of patients receiving hydromorphone.

Adjuvant analgesia during the trans-operative period included sodium dipyrone, 2 g IV; diclofenac, 75 mg IV; or both, upon removing the fetus. During the postoperative period, patients received – as instructed by the ObGy service – sodium dipyrone, 2 g IV every 8 hours; diclofenac, 75 mg IV every 12 hours; and oral acetaminophen, 1 g every 8 hours; the use of diclofenac was only avoided in patients with any presentation of renal impairment (*n*:13).

DISCUSSION

The usual institutional mix is prepared with 10 mg of hyperbaric bupivacaine,

in accordance with a meta-analysis conducted in 2011 by Arzola and Wiczorek (4), showing that although the low doses of bupivacaine (< 8 mg) are associated with a lower risk of hypotension, nausea, and vomiting, they compromise the effectiveness of the anesthetic block, which is evidenced by the increased need of additional analgesia during surgery and higher conversion rates to

general anesthesia, as compared to the conventional doses (> 8 mg).

The liposolubility of the opioid is inversely proportional to the time or residence and diffusion into the cerebrospinal fluid (CSF). (7) With regards to the intrathecal puncture site, the rostral spread of the drug, and the analgesic effect of fentanyl – with an octanol:buffer (O:B) partition coefficient of 955 in contrast to morphine (7,11) — which

has a barely metameric and short-lived spread; morphine O:B of 1 (11,12) has a high and late spread, which accounts for the risk of respiratory depression up to 24 hours after its injection. Hydromorphone, with a comparative O:B of 525 (11,12), has a long-acting effect as do all hydrophilic opioids, but an intermediate diffusion over time, and a higher dermatomeric extension than fentanyl, but lower than morphine (7) (Figure 3).

TABLE 1. Characteristics of the population.

	BMF (n: 29)	BFH (n: 16)	BH (n: 26)	p
Age in years (SD)	28.6 (6)	30.6 (7.4)	27.5 (6.4)	
Gestational age, weeks (IR)	39 (38-39)	39 (38-40)	39 (38-39)	
ASA Classification				
ASA 2	96.5 %	93.8 %	92.3 %	0.82
ASA 3	3.5 %	6.2 %	7.7 %	
Pregnancy				
Pregnancy 1	34.5 %	37.5 %	45.8 %	0.74
Pregnancy 2	37.9 %	43.8 %	25 %	
Pregnancy ≥ 3	27.6 %	18.7 %	29.2 %	
Previous cesarean sections				
Cesarean sections 0	48.3 %	62.5 %	50 %	0.51
Cesarean sections 1	34.5 %	37.5 %	41.7 %	
Cesarean sections 2	17.2 %	0 %	8.3 %	
Indication				
Previous cesarean section	27.6 %	25 %	16.7 %	0.82
Failed induction	10.3 %	6.2 %	16.7 %	
Dysfunctional labor	6.9 %	6.2 %	8.3 %	
Unsatisfactory fetal status	6.9 %	6.2 %	0 %	
Fetopelvic disproportion	13.8 %	0 %	4.2 %	
Abnormal presentation	20.7 %	31.3 %	25.0 %	
Maternal pathology	10.3 %	25.0 %	20.8 %	
Maternal wish	3.5 %	0 %	8.3 %	

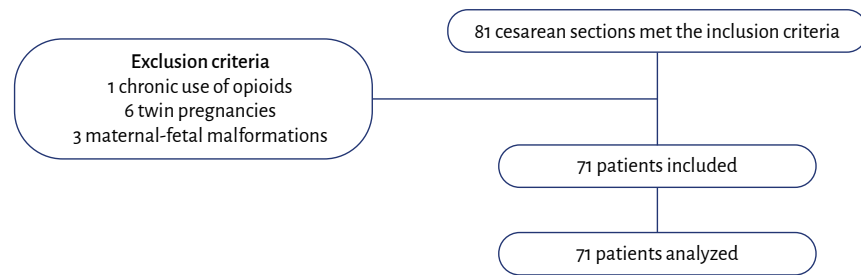
ASA: American Society of Anesthesiologist, BFH: bupivacaine, fentanyl and hydromorphone, BH: bupivacaine and hydromorphone, BMF: bupivacaine, morphine and fentanyl, IR: interquartile rank SD: standard deviation. **SOURCE.** Authors.

TABLE 2. Reason for selecting the anesthetic mixture.

Preference	BMF		BFH		BH	
	n	%	n	%	n	%
Is the one I have always used	21	72.4	0	9	0	0
I think a new option is interesting	2	6.9	16	100	24	92.4
I believe there is less vomiting	0	0	0	0	1	3.8
Only option available	1	3.5	0	0	1	3.8
By chance	4	13.7	0	0	0	0
Syringe allocated by nurse	1	3.5	0	0	0	0
Total	29	100	16	100	26	100

BFH: bupivacaine, fentanyl and hydromorphone, BH: bupivacaine and hydromorphone, BMF: bupivacaine, morphine and fentanyl. **SOURCE.** Authors.

FIGURE 1. Patient selection.



SOURCE. Authors.

TABLE 3. Recovery of motor block.

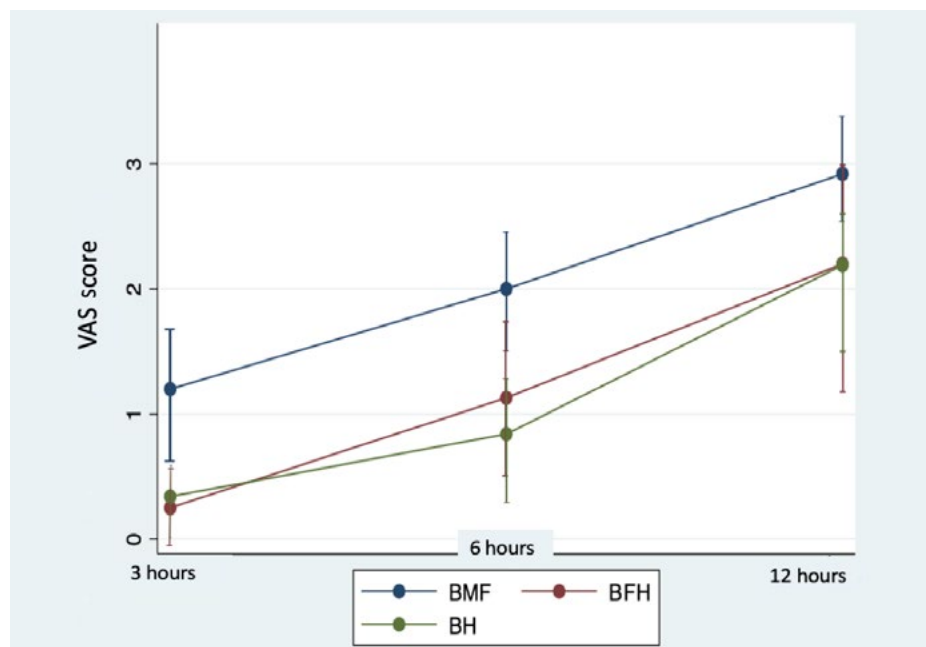
	BMF (n: 29)	BFH (n: 16)	BH (n: 26)
Time in minutes (SD)	155 (8.35)	153.6 (7.12)	152.5 (8.12)
95 % CI	137.8- 172.1	138.3- 168.9	135.8- 169.2

BFH: bupivacaine, fentanyl and hydromorphone, BH: bupivacaine and hydromorphone, BMF: bupivacaine, morphine and fentanyl, CI: Confidence interval, SD: standard deviation. **SOURCE.** Authors.

TABLE 4. Stratified analysis of nausea and vomiting.

Prophylactic antiemetics		BMF		BFH		BH		p*	
		n	%	n	%	n	%		
1 antiemetic	Nausea								
	Yes	11	68.7	4	36.3	5	33.3	0.10	
	No	5	36.3	7	63.7	10	66.7		
	Total	16	100	11	100	15	100		
	1 antiemetic	Vomiting							
		Yes	4	25.0	5	45.5	1	6.7	0.07
No		12	75.0	6	54.5	14	93.3		
Total		16	100	11	100	6	100		
2 antiemetics	Nausea								
	Yes	5	71.4	2	50.0	2	40.0	0.55	
	No	2	28.6	2	50.0	3	60.0		
	Total	7	100	4	100	5	100		
	2 antiemetics	Vomiting							
		Yes	1	14.3	1	25.0	2	40.0	0.61
No		6	85.7	3	75.0	3	60.0		
Total		7	11.1	4	0	5	0		

* Kruskal-Wallis Test. BFH: bupivacaine, fentanyl and hydromorphone, BH: bupivacaine and hydromorphone, BMF: bupivacaine, morphine and fentanyl. **SOURCE.** Authors.

FIGURE 2. Postoperative pain

BFH: bupivacaine, fentanyl and hydromorphone, BH: bupivacaine and hydromorphone, BMF: bupivacaine, morphine and fentanyl, VAS: visual analogue scale. **SOURCE.** Authors.

Morphine has a pK_a of 8.21 (13,14) and a pH of 7.32, corresponding to the CSF; it has an 11.4 % of non-ionized fraction (*Non-ionized fraction* = $10^{(pH-pK_a)} \div 1 + 10^{(pH-pK_a)}$). Morphine in the neuraxial scale has an onset of action of 15-30 minutes, a peak effect at 60-90 minutes (8) and an average duration of 17 hours without the need to administer any rescue opioids, at doses of 200 μ g (4). Hydromorphone also has a pK_a of 8.2 (13,14), but due to its additional pharmacokinetic characteristics has an onset of action at 10-15 m, a peak effect at 20-30 m (8) and a mean duration of 14.6 hours with no need to administer any rescue opioids, at an intrathecal dose of 60 μ g. (4)

Johansen et al., discovered that intrathecal hydromorphone is faster in accessing the dorsal horn neurons and a faster onset of analgesia. (15) Moreover, due to its intermediate liposolubility, hydromorphone has a lower rate of adverse effects with an epidural administration. (16,17). The current reference ED 90 is 75 μ g for hydromorphone and 150 μ g for morphine. (5). The decision to do the hydromorphone preparations with 80 μ g was a joint decision adopted by the team

of anesthesiologists of the SES Hospital of Caldas and the compounding central, in order to avoid mistakes during preparation.

In our study, there was improved pain control over the first 12 postoperative hours in the BFH and BH groups. Beatty et al., compared 38 pregnant women in labor that received 0.04 mg of spinal hydromorphone and 76 who received 0.1 mg of spinal morphine, and found no differences in terms of analgesia or incidence of side effects. (18) The disparity with our study, in terms of analgesia, may be due to the higher dose of hydromorphone. (5) Rauch et al., found that the patients receiving hydromorphone experienced significantly lower pain levels after 4, 12 and 24 hours, as compared to other combinations (LA and LA plus). The conclusion was that intrathecal hydromorphone seems to be more effective in providing analgesia during the intra and post-operative period in cesarean section than other opioids, including morphine. (11) There is however one yet unanswered question regarding the physical and affinity characteristics for the dorsal horn receptors.

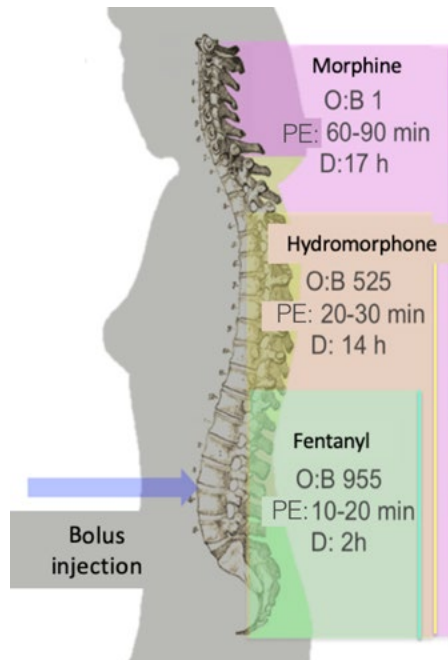
Regarding the recovery time of the anesthetic block, it has been widely known

that thinner nerves are more sensitive to the effects of LA agents, due to the high relationship between the surface area of the membrane and the unit volume of the axon. (19). This may lead us to believe that the LA may result in a visceral analgesic effect (non-myelinated C 0.3-1 μ m fibers) long after the motor recovery (myelinated A- δ , 1-4 μ m fibers), in average 153 minutes in our study, giving hydromorphone enough time to start acting.

One of the arguments to use fentanyl in the subarachnoid mix is that phenylpiperidine-derived opiates exhibit close structural similarities of the LA agents, and this may result in a synergistic effect of its action on the C sensory fibers and the possibility to lower the LA dose (20), in order to reduce hypotension, nausea and vomiting in the transoperative period. (15,16) However, no studies have yet been conducted to forcefully proof this fact. (16) Moreover, the anatomic variations in pregnant patients must be taken into consideration, i.e.: reduced CSF volume as a result of the distention of the epidural veins, cephalic movement of hyperbaric anesthetics in supine position, and the huge sensitivity of the nerve fibers that result in lower intrathecal anesthetic requirements versus the non-pregnant population. (21) Furthermore, the duration of analgesia with intrathecal fentanyl is approximately 130 minutes (8,9,22), very similar to the duration of LA agents, which further questions the actual benefit of such drug. (9)

The effects of fentanyl and morphine, alone and in combination, as adjuvants for spinal anesthesia in elective cesarean section, were examined in a clinical trial. The conclusion of the trial was that the opioid combination adds no further advantages versus the mix with morphine only. (23) Specifically, the trial failed to show a difference in the incidence of adverse effects between the groups. It may be reasonable to believe that by reducing the burden of opioids, their side effects will be less. Maybe larger studies could specifically show the clinical benefit of removing fentanyl from the hydromorphone mix.

FIGURE 3. Spread of opioid analgesia following spinal administration.



D= Duration, O:B= octanol:buffer, PE= peak effect .**FUENTE.** Modified by the authors, based on Mugabure, et al (7,8).

With regards to hypotension, it is clear that its incidence in this group of patients is multifactorial in origin, and increases when raising the dose of operative bupivacaine, while decreases only when doses of < 6 mg are used. (21) However, the deleterious effect of using such low doses is well known. The anesthesia guidelines for cesarean section recommend the simultaneous loading with crystalloids, the prophylactic use of a vasopressor (ephedrine, phenylephrine, norepinephrine) and the lateralization of the uterus, to prevent this frequent outcome of neuraxial anesthesia. (21,24). In our hospital in particular, phenylephrine as a vasopressor is not available, and instead, norepinephrine is used in boluses of 8 µg or etilefrine 1 to 2 mg, in accordance with the preference of the anesthesiologist; this is a limitation in this study. Along these lines, the presence or absence of hypotension may be more related to the sympathetic block caused by the LA agent, rather than by the combination of opiates.

According to the literature, the incidence of respiratory depression is of 0.03-7 %. (6)

Lipophilic intrathecal opiates may cause early respiratory depression (0-1 hour), whilst the more hydrophilic opiates may result in either early or late respiratory depression (up to 24 hours). Specifically morphine may induce respiratory depression between 3.5 and 12 hours after the injection, with a peak at 6 hours. (6) It should be mentioned that the clinical monitoring of the hospitalized patients was performed for a minimum of 24 hours, and no incidents of this nature were experienced.

The presence of pruritus in this study is consistent with the current literature. It is known to be more frequent in pregnant women, probably due to disruptions in gestational hormones in the opioid receptors. Its incidence according to previous reviews ranges from 0 and 100 %, and predominantly affects the face, the neck, and the upper chest. (6)

These results should be carefully interpreted, since this is an observational analytical study, with some limitations such as convenience sampling, imbalanced groups, and no sample size calculation which probably resulted in indication and selection biases, since the intervention was not randomized. No minors were exposed to any risks on behalf of the investigators, since the allocation of the premix is part of the autonomous and usual clinical practice of each treating anesthesiologist.

The external validity of this study is limited to high complexity obstetric centers that have available a compounding central pharmacy for preparing medications. This study may be the basis for designing future randomized, controlled clinical trials with a more rigorous methodological approach and adequate sample sizes, able to contest or reaffirm the results, and generate significant impact on clinical practice.

CONCLUSION

Mixtures with hydromorphone may be a valid option to replace the usual mixtures with bupivacaine, morphine and fentanyl, in subarachnoid anesthesia for cesarean

section. Hydromorphone has the advantage of having a safety data sheet that authorizes its intrathecal use, and apparently results in improved postoperative pain control after 3, 6 and 12 hours.

ETHICAL RESPONSIBILITIES

Protection of humans and animals

The authors declare that no experiments were conducted in human beings or in animals for this research project.

Confidentiality of the information

The authors declare that all of the institutional protocols regarding the publication of patient data were followed.

Right to privacy and informed consent

The authors have obtained the informed consents of all patients and/or subjects mentioned in this article. The corresponding author is the custodian of these documents.

Ethical approval

This study received the approval of the two committees: Ethics Committee of the Universidad de Caldas (Ethics Committee CBCS-032, May 7, 2018) and Ethics Committee of the SES Hospital of Caldas (Ethics Committee DC-048-18, May 7, 2018), both in Manizales, Colombia. Moreover, each patient surveyed completed their informed consent.

ACKNOWLEDGEMENTS

Contributions by authors

CIOG and GAOG: Original project design, planning of the study, data collection, interpretation of the results, and initial and final approval of the manuscript.

JFVR: Planning of the study, data collection, interpretation of the results and final approval of the manuscript.

FAG: Planning of the study, analysis and interpretation of the results and approval of the final manuscript.

Assistance for the study

None declared.

Financial support and sponsorship

None declared.

Conflict of interests

None declared.

Presentations

None declared.

Acknowledgements

We want to acknowledge Gloria Andrea González Ibáñez, pharmacist, for her work, and her team of the compounding central of SES Hospital of Caldas, for their constant interest and for ensuring the adequate preparation and availability of the premixed syringes.

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