Revista Mexicana de Anestesiología

ORIGINAL ARTICLE
Vol. 31. No. 3 July-September 2008
pp 172-178

Comparison between Buprenorphine and Peridural Morphine for Post-Operative Pain Management in Patients Subjected to Cesarean Section

Luz Adriana Templos-Esteban, MD;* Mirna Magali Delgado-Carlo, MD**

* Third year Resident of Anesthesiology.
** Anesthesia Medical of the Hospital Regional ISSSTE General Ignacio Zaragoza.

Reprints request:
Dra. Luz Adriana Templos Esteban
Calzada General Ignacio Zaragoza Núm. 1711, Colonia Ejército Constitucionalista.
Tel.: 57165200, ext.6783.
luzadrianatemplos@hotmail.com

Received for publication: 09-07-07
Accepted for publication: 27-09-07

SUMMARY

Objective: The postoperatory analgesia in the obstetric patient is controversial for the adverse effects that can happen with the elimination of medicaments in the breast milk. One must find a suitable line of managing, which can be provided by the peridural opioids. **Material and methods:** 60 patients submitted to Caesarean, 30 for the group A (peridural morphine) and 30 for the group B (peridural buprenorphine). Administering 2 mg of morphine or 300 μg of buprenorphine in the moment of the cut the umbilical cord, realizing measurements of the Visual Analogous Scale and adverse effects: nausea, vomit, pruritus, urinary retention and Ramsay to the moment of revenue to recovery, at 2, 4, 6, 12 and 24 h. **Results:** The group of morphine was top for presenting at 12 h, 56% of the patients with minor EVA of 5. One presented pruritus in 14% of the patients of the group A and nausea in 14% of the patients of the group B only to his revenue to recovery. **Conclusions:** The epidural morphine was effective for 8 to 12 h in average but not sufficiently in the only dose for the control of postoperatory pain. Analgesia of rescue was needed.

Key words: Postoperatory analgesia, morphine, buprenorphine, caesarean.

RESUMEN

Introducción: *La analgesia postoperatoria en la paciente obstétrica es controvertida por los efectos adversos que pueden ocurrir con la eliminación de fármacos en la leche materna. Debe encontrarse una línea adecuada de manejo, la cual puede ser proporcionada con los opioides vía peridural.* ***Material y métodos:*** *Sesenta pacientes sometidas a cesárea, 30 para el grupo A (Morfina peridural) y 30 para el grupo B (buprenorfina peridural). Se administraron 2 mg de morfina ó 300 μg de buprenorfina en el momento de pinzamiento del cordón umbilical, realizando mediciones de la Escala Visual Análoga y efectos adversos: náusea, vómito, prurito, retención urinaria y Ramsay al momento de ingreso a recuperación, a las 2, 4, 6, 12 y 24 h.* ***Resultados:*** *El grupo de morfina fue superior por presentar a las 24 h un 56% de las pacientes con EVA menor de 5. Se presentó prurito en el 14% de las pacientes del grupo A y náusea en el 14% de las pacientes del grupo B sólo a su ingreso a recuperación.* ***Conclusiones:*** *La morfina peridural fue eficaz por 8 a 12 h en promedio pero no suficiente en dosis única para el control de dolor postoperatorio. Se requirió analgesia de rescate.*

Palabras clave: *Analgesia postoperatoria, morfina, buprenorfina, cesárea.*

INTRODUCTION

Cesarean section is very common all over the world. In our country, we have over two million births a year; from them between 20% and 40% are performed through surgery, what indicates us that, in the area of anesthesiology, the management of obstetric patients is very habitual[1].

Neuroaxial anesthetic techniques are the elected ones in those cases; therefore, this study is based upon the use of peridural route for anesthesia and post-operative analgesia[2].

The evidence regarding the fact that opiates are excreted through mother's milk is forcible, but it is important to say that the amount of drug that is administered through peridural route is less than the one given intravenously.

POST-OPERATIVE PAIN MANAGEMENT IN OBSTETRIC PATIENTS

One of the areas that anesthesiologists usually face is the obstetric one, which, besides presenting a great number of patients, is very controversial with regard to management lines.

In our country, there are over two million births per year. These births are surgically solved in between 20% to 40% of the cases. Furthermore, pregnancies, births, and puerperiums constitute the first place in hospital admission.

The improvements in the area of anesthesiology have created several new and safe techniques in this field; therefore, post-operative pain management should not be the exception[1].

Local anesthesia is the technique preferred over general anesthesia. It is used in approximately the 8% of the cesareans. Among its advantages, it includes less exposure of the new-born to drugs, decrease of the risk of bronchoaspiration, immediate contact of the mother with her baby at the moment of the birth, and the option of using spine opiates in the post-operative period[2].

Pain control in the post-operative period in patients who have been practiced cesarean is an important matter, since it has been tried to introduce an analgesic technique that produces minimal side effects but provides good quality and length in order to achieve quick pain relief, good recovering and a significant decrease in hospital costs. There are studies that have shown cost reduction because of peridural analgesia when compared to analgesia controlled by the patient[3].

After the cesarean, the use of Non Steroidal Anti-Inflammatory Drugs (NSAIDs) (ketorolac, proparacetamol, etc.) is very common, but they present a limited efficacy. Besides this, when using more than one, we just potentiate side effects.

In the case of pain after cesarean surgery, the surgical section triggers the release of mediators, stimulating peripheral nocireceptors and activating A-delta and C afferent fibers. Secondary to surgery, uterus contractions activate mechanoreceptors, releasing mediators that are responsible for producing pain. Among them, we may find:

- Potassium.
- Hydrogen ions.
- Lactic acid.
- Serotonin.
- Bradicinin.
- Histamine.
- E1 and E2 Prostaglandins, thromboxanes.
- Cholinergic, adrenergic, dopaminergic systems, serotonin, etc., as well as cell immunity and inflammatory process mediators.

Either in the case of parturition or cesarean, there is a trigger of mechanisms of peripheral and central sensitization (there is an increase of the impulses arriving at the dorsal horn and there is a reduction in the gradient between the rest and the depolarization too) with allodynia and hyperalgesia.

The post-operative pain of the patient that has been subjected to cesarean is ruled by diverse factors: her experience in previous surgeries, anxiety, emotional changes, mother's expectations regarding the new childbirth, pain threshold, age, school level, etc. The pre-frontal cortex, the anterior part of the cingulum and the insular cortex regulate many of these phenomena.

The inadequate management of post-partum or post-operative pain may affect mother and newborn baby's welfare in a significant way. This last fact happens due to the delay in ambulation in the presence of pain, and the time of the beginning of food intake. Ventilation presents a restrictive pattern that conditions the gathering of secretions. In the whole, these alterations favor the development of complications such as ileum, atelectasies, pneumonia, embolisms. Furthermore, catecholamine secretion diminishes oxytocin secretion, what decreases or stops mother's milk secretion.

In the same way, it is suggested that breastfeeding should be practiced immediately, if it exists some contraindication. Therefore, the pharmacological approach must evaluate its safeness for both the mother and the child. Drug concentrations in mother's milk should be also be assessed along with the effects produced by these concentrations on the newborn baby during the suckle.

OPIATES IN THE OBSTETRIC PATIENT

The evidence about this fact is very strong with regard to opiate excretion through mother's milk. However, the American Academy of Pediatrics suggests that opiates may present certain compatibility with breastfeeding, if they are administered at low doses, during short periods of time, and at low blood concentrations in the mother.

It is important to take into account that in newborn babies opiate absorption through mother's milk experiences a first-step metabolism; therefore, alterations in renal or hepatic functions may favor the accumulation of certain metabolites and produce undesirable effects, such as depression, suppression of suckling reflex, delays in effective feeding, and neurobehavioral changes.

The opiates that may be used through peridural route (morphine and buprenorphine-type) fulfill the aforementioned requirements, since besides achieving a proper analgesia level, the present minimal hemodynamic and sensory changes and few adverse effects.

At the spine level, specifically at the dorsal horn level, there is an important concentration of opiate receptors (OR), which are three: mu, in a 70%; delta, in a 20%; and kappa, in a 10%. There are no reports about either sigma or epsilon receptors situated in Rolando's gelatinous substance in I and II Redex sheets, which is the site where A-delta and C afferent fibers converge.

These receptors, when joining their ligands, activate themselves and produce analgesia at two different pre-synaptic levels, diminishing the release of neuropeptides anti-inflammatory substances through the primary afferent fibers; and, at the post-synaptic level, theses receptors hyperbolize the neuron membrane of the medullary dorsal horn[4,5].

As the opiates join the receptors, it will be produced not only analgesia, but also a range of side effects. The most common of them are pruritus (itchy skin), nausea, vomits, respiratory depression, urinary retention (ischuria), etc. These symptoms are present when using higher doses than the habitually used ones; however, it is important to consider that the doses are lower through peridural route, the plasma concentrations decrease and, therefore, the adverse effects do.

Morphine and its derivates produce therapeutic effects over brain and medullary spinal cord; however, they also work over the digestive system, produce affective changes, respiratory depression, nausea, vomits, and changes in the pupil diameter. These are the reason why they produce adverse effects.

The main reason for giving opiate is that they present analgesic effects. Analgesia through morphine is caused by complex interactions at several sites of brain, spinal cord and, under certain conditions, in peripheral tissues. Morphine and its related opiates act in a selective way over neurons that transmit and modulate nociception without modifying the sensory or motor functions. At the level of the spinal cord, morphine acts in pre-synaptic sites over the principal afferent nociceptors in order to diminish the release of P substance through secondary messengers and G proteins, and it hyperbolizes interneurons in the gelatinous substance of the dorsal fascicle of the spinal cord in order to reduce the afferent transmission of the nociceptive stimuli. Rachidian analgesia by morphine is regulated by mu 2 receptors. Supraspinal analgesia emerges from the periaqueductal grey substance, the *locus ceruleus* and the nuclei of the rachidian bulb, specially the raphe nucleus, and it is mediated by the mu 1 receptors. Morphine spinal and brain administration increases its power up to tenfold. It has been observed that morphine may produce analgesia through peripheral route, especially when there is inflammation. After its administration through peridural route, it presents a 30-40-minute action and an effective average life of up to 12-24 hours. The dose consists of 0.1 mg/kg or it is standardized at 2 to 3 mg per dose. In studies on animals, it has been demonstrated that even the addition of adrenaline at commercial doses increases certain opiates lifetime average in the peridural space[6,7].

With regard to its pharmacology, buprenorphine is a derivate of thebaine, with great affinity for lipids, which in small to intermediate doses is 25 to 50-fold more powerful than morphine[8-10]. Buprenorphine is considered as an antagonist agonist with a mu agonistic activity with slow dissociation of receptors and mainly kappa antagonist. Buprenorphine presents a dose-effect curve in the shape of a bell. The IV (intravenous) doses go from 10 to 20 μg/kg of bodyweight and this drug presents a ceiling effect. At the beginning, this drug presents a slow action, its analgesic length through IV (intravenous via) lasts for over six hours; and through subarachnoid and peridural route, kinetics is modified lengthening average lifetime. The average dose through peridural route is of six hours. Buprenorphine is employed for the treatment of mild to severe post-operative pain.

Because of the aforementioned facts, we can conclude that analgesia in obstetrics is controversial. Therefore, it must be found a line of management that may result in minimal adverse effects for both the mother and the product with a good quality in pain treatment[11-14].

MATERIAL AND METHODS

With the previous approval of the Committee of Ethics in the General Ignacio Zaragoza Regional Hospital, under the registration number 181.2007, it was performed a longitudinal, prospective an randomized study, on 60 patients post-operated on cesarean. The patients had to fulfill the following inclusion criteria:

- Patients ASA I and ASA II physical condition, ages ranging from 15 to 45 years old, subjected to cesarean section under peridural anesthesia, without contraindications for peridural blockade, such as blood dyscracias, infections in the section site, lumbar pathology, etc.; without aller-

gies to the drugs to be given and without analgesic consumption in the 24 hours previous to the admission in the study under informed consent.
- Exclusion criteria: Added pathologies, such as diabetes or artery hypertension, rheumatic diseases, etc., evidence of product presenting malformations. Need for urgent cesarean: such as foetal suffering, eclampsia, placenta detachment, etc. Contraindication for local anesthesia or need to change into general anesthesia during the cesarean section.
- Elimination criteria: Hemodynamic instability or complications in the trans-surgical period (eclampsia, uterine atony, etc.), patient with duramater puncture, insufficient peridural blockade or hematic puncture. Presence of some anaphylactic reactions to the given drugs.

Two 30-patient groups were formed. Group A was given PV (peridural route) morphine, and Group B was administered buprenorphine through the same route.

Before the peridural blockade and the taking of basal vital signs, it was performed a pre-hydration by means of Hartmann or 0.9% NaCl solution at 15 a 20 mL per kg.

It was carried out a peridural blockade in L2-L3 with a Touhy 18 needle and a peridural cephalic catheter using the loss of resistance technique.

Two percent of lidocaine plus epinephrine was given at a dose of 5-7 mg/kg.

It was also performed a continuous monitoring with a cardioscope in DII, pulsioximetry, non-invasive artery blood pressure every 5 minutes and placing of a catheter of nasal oxygen at 3 liters per minute.

The patients that presented supine hypotension were managed in the following way: left dorsal decubitus, administration of volume or doses of ephedrine at 5 mg IV every 2 minutes (dose-response).

At the moment of clipping the cord, it was given:

- Group A: 2 mg of morphine to complete 10 mL in 0.9% physiological solution.
- Group B: 150 ìg of buprenorphine to complete 10 mL in 0.9% physiological solution.

Every patient was given 50 mg of ranitidine and 10 mg of metoclopramide as pre-medication.

Once the surgery had finished, the catheter was extracted.

Once both groups were in the recovery room, the following parameters were evaluated:

- *Vital signs at admission:* Arterial tension and cardiac frequency. The arterial tension was measured by an aneroid baumanometer, and cardiac frequency was measured by a precordial stethoscope.
- *Pain:* It was evaluated through the visual analog scale (VAS) at the moment of the admission to the recovery room and at 2, 4, 6, 8, 12, 18, and 24 after de admission. In the case of a higher value than five in the VAS, it would be administered 30 mg IV ketorolac as a rescue dose every 6 hours. Visual Analog Scale: 1-4, light pain; 5-7, moderate pain; 8-10, severe pain.
- *Pruritus (Itchy skin):* It was defined as light, moderate, and severe according to its localization: light, in face and rhinitis; moderate in upper thorax; and severe, if it were generalized. When pruritus was moderate, it was administered 0.5 mg/kg diphenhydramine as a single dose, and in an extreme case, 1 to 3 μg/kg of naloxone as a single and slow IV (intravenous) dose.
- *Nausea y vomits:* In case of presenting these symptoms, even with the use of metoclopramide, 4 mg of ondansetron were given every eight hours.
- *Sedation:* Through the Ramsay scale (which is as follows: 0, anxious, agitated or restless patient; 1, asleep or cooperating patient; 2 usually asleep and easy to awake patient; 3, sleepy and hard to awake patient; 4, unconscious patient with respiratory depression; 5 normal sleep. In case of presenting Ramsay 4 or 5, the patient was assisted by a mask and 100% with continuous monitoring and pulsioximetry until sedation was at 2 or 3 according to the aforementioned scale.
- *Urinary retention:* In case of presenting it, a #18 Foley catheter was placed through aseptic technique according to the necessities.

ANALYSIS OF THE RESULTS

It was performed a Student's "t" test in order to compare both groups of study. The p statistical significance was higher than 0.005 in favor of the use of morphine over buprenorphine through peridural route. The demographic variables of age and height were similar for the 60 patients in both groups (A and B), but weight variable was higher in the patients from the morphine group (A):

- Group A: Average weight, 81 kg; average height, 1.59 m; average age, 30 years old.
- Group B: Average weight, 68.3 kg; average height, 1.59 m; average age, 29 years old.

The hemodynamic variables for both groups at recovery admission did not show any significant differences:

- Group A: average MAP (Mean Arterial Pressure), 92 mmHg; respiratory frequency, 14; body temperature, 36.4-centigrade degrees.
- Group B: average MAP (Mean Arterial Pressure), 82

mmHg; respiratory frequency, 12; body temperature, 36.2-centigrade degrees.

ASA physical condition was of IIB for all the 60 patients included in the study.

At the evaluation of the VAS (Visual Analog Scale), it was found a longer anesthesia time for the Group A of peridural morphine, reporting just a 3% of the population with VAS of 1 (Figure 1) for morphine at recovery admission. At 24 hours after morphine administration, the 56.4% of the population presented a value of the VAS lower than 5 (light pain or painless) (Figure 2 and Table I), with need for 26 ketorolac rescues; the 30% of them occurred after 8 hours (the highest percentage of rescue from 100%). This is far different from Group B, which presented a 42.85% of the population with a value of the VAS lower than 5 at 24 hours, with need of 56 ketorolac rescues; the 43% of them occurred after 4 hours of the evaluation.

The most frequent adverse effect for Group A was pruritus, which was present, in a light form, in four patients (13.3%) at the moment of their admission to the recovery room, this effect was observed in only one patient up to 8 hours of evaluation.

Nausea was present in four (14.3%) patients from Group B at the moment of their admission to the Unit of Post-anesthetic Care, with the need of the administration of 4 mg of ondansetron in these patients (Figure 3). There were no cases of either vomits or urinary retention in any groups. The values from the Ramsay scale for all the patients and during all the monitoring were of 2, with the exception of one patient from the morphine group who presented a value of 3 at her admission to the recovery room.

DISCUSSION OF THE RESULTS

The reports from studies on peridural morphine as a single dose[3,7,11] mention between 12 and 24-hour length of analgesia with minimal adverse effects, one of which is usually pruritus (itchy skin). In our study, we observed effective analgesia between 12 and 24 hours with decreases in ketorolac rescues when compared to Group B. Pruritus was, in fact, the most frequent adverse effect, but it was mild in every case and it never reached the point of requiring diphenhydramine administration.

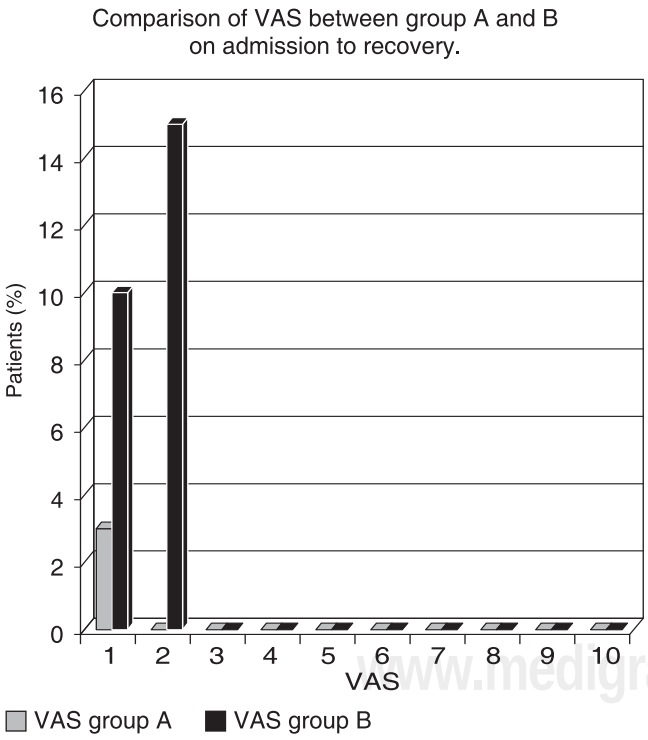

Figure 1. Shows comparison of visual analog scale (VAS) between the two study groups on admission to recovery. Group A 96.6% no pain, 3% VAS 1 presents (shows the graph). Group B 75% no pain, 10% VAS 1 and 15% VAS 2.

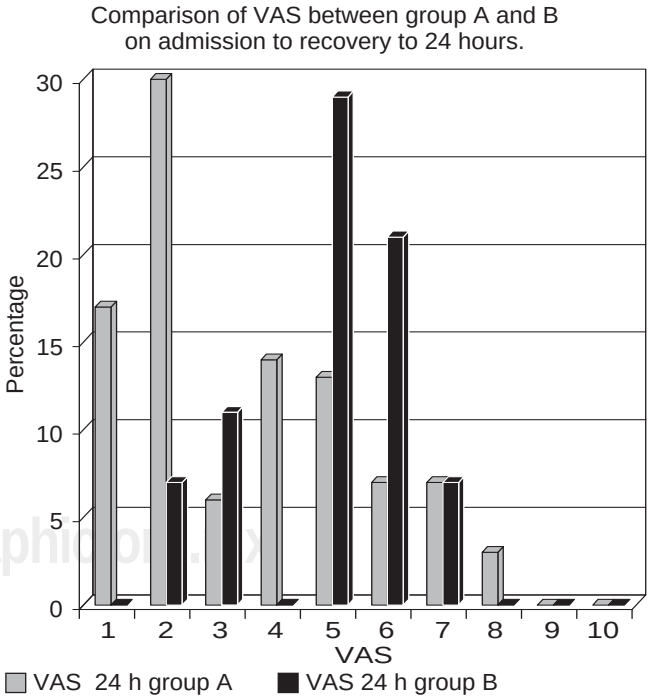

Figure 2. Shows comparison of visual analog scale (VAS) between the two study groups at 24 h of admission to recovery.

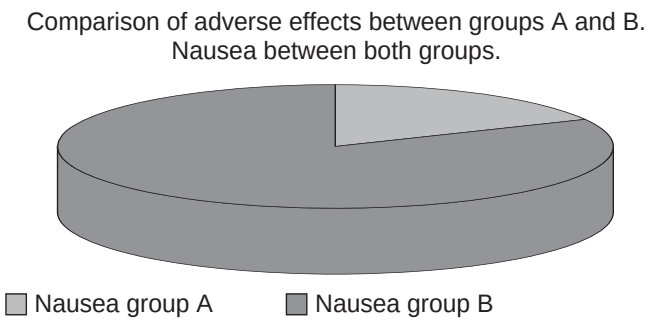

Figure 3. Comparison of adverse effects after administration of morphine or buprenorphine peridural route. Shown that it was more frequent presence of nausea in group B 14% than group A 3%.

Table I. VAS between the two study groups at 24 hours of admission to recovery.

VAS	Group A n = 30	Group B n = 30
Without pain	13 %	25 %
1	7 %	0
2	30 %	7 %
3	7 %	10 %
4	13 %	0
5	13 %	30 %
6	7 %	21 %
7	7 %	7 %
8	3 %	0
9	0	0
10	0	0

Shows VAS between the two study groups at 24 hours of admission to recovery and according to the percentage of patients. We observe that while the group B presented higher percentage of patients without pain, 60% of them presented moderate-severe pain (VAS of 4 to 6 moderate pain, 7 to 10 severe pain). The group A has the majority of their patients with mild pain 57% (VAS 1 to 3 mild pain) 24 hours.

Analgesia was very satisfactory but not good enough with a single dose. The administration of subsequent minimal doses (from 2 to 3 mg of morphine through peridural route) was a good option in order to achieve a good quality in pain control with no or few undesirable effects.

Its cost was another desirable effect from this opiate. Around one dose of 2 mg costs between 25 and 25 pesos, for a length of between 8 and 12 hours, it is compared to ketorolac, which presents a commercial cost of about 40 pesos per a 30 mg. In this last case, sometimes the dose may be of 60 mg every 8 hours (it is important to take into account that morphine through peridural route potentiates its effect up to tenfold); therefore, it is considered an excellent option because of its length and minimal adverse effects. Besides this, PV morphine has been approved by international drug review procedures, and it does not present any problems in lactation because it does not present metabolites in mother's milk when administered at the minimal doses and for the time and the administration route that we used in our study.

Moreover, morphine is an excellent post-operative analgesia option, not only for cesarean but also for any kind of major surgery.

With regard to buprenorphine, the literature reports a lifetime average of 6 hours[8,13]. In our population, it presented a lifetime average of between 4 and 6 hours, presenting nausea as the most important adverse effect, with the need for almost the double number of analgesic rescues due to the presentation of higher VAS in patients from this group. This last fact appears to be a little contradictory, since the latest reports consider buprenorphine up to 100-fold more powerful than morphine. Therefore, we consider it as an alternative choice for opiate peridural therapy.

CONCLUSIONS

Because of the aforementioned reasons, we reached the following conclusions: The use of morphine through peridural via in patients subjected to cesarean is safe and provides anesthesia of good quality with minimal adverse effects. These properties allow us to get a quick recovery and ambulation of patients and have less cost produced by the administration of other equipollent analgesics and the morbidity associated with the patient's slow mobilization.

REFERENCES

1. Covarrubias A, Silva A, Nuche E, Téllez E. Post-operative handling of pain in obstetrics: Is it safe? Rev Mex Anest 2006;29:231-239.
2. Olguín M. Post-caesarean analgesia: neuraxial opiates, route election. Rev Chilen Anest 2002;31:1-3.
3. Bartha E, Dualé C, Frey F, Bolandard A, Schoeffler PB. Evaluation of cost and effects of epidural analgesia and patient controlled intravenous analgesia after major abdominal surgery. B J Anaesth 2006;96:111-117.
4. Jaime A. Post-caesarean analgesia by morphine sulfate in epidural infusion. Rev Mex Anest 1999;22:238-242.
5. Villegas M, Segura G, Acevedo J. Comparison of pruritus (itch) incidence during the first 24 hours of post-operative period when using morphine and hydromorphine as epidural analgesics for caesarean section. Rev Col Anest 2001;XXIX:2:155-162.
6. Bernards CM, Shen D, Sterling S, Pharm D, Adkins J, Risler LS, Phillips B, Ummenhofer W. Epidural, cerebrospinal fluid and pharmacokinetics epidural opioids (part 2): effect of epinephrine. Anesth 2003;99:466-475.
7. Yukitoshi N, Tomoyuki N, Hitoshi S, Keiilchi O, Akiyoshi N. The addition of epidural morphine to ropivacaine improves epi-

dural analgesia after lower abdominal surgery. Can J Anesth 2005;52:181-185.
8. Rojas RA, Mendoza ME, Gutiérrez E, Velasco S, Murguía Y. Epidural buprenorphine *vs*. 0.125% bupivacaine for pain management in caesarean post-operated patients. Rev Mex Anest 2001;1(2):112-115.
9. Zaldívar VM, Ríos AV. Buprenorphine in post-operative period through epidural and sublingual: analgesia and side effects. Rev Mex Anest 2003;26(3):145-147.
10. Coda BA. Opiates. In: Barash PG. Clinical Anesthesia. McGraw-Hill Inter-Americana Editorial House. Third edition. Volume I:389-424.
11. Committee on Drugs. The transfer of drugs and other chemicals in to human milk. Pediatrics 2001;108:776-789.
12. Chestnut DH. Efficacy and safety opioids for postoperative analgesia. Anesth 2005;102:221-223.
13. Gómez JJ, Godínez H. Peri-operative epidural analgesia. Infusion *vs.* single analgesia in the peri-operative period at caesarean section. Rev Mex Anest 2003;26(4):194-197.
14. Pan P, Coghill R, Houle T, Seid M, Lindel W, Parker, Washburn S, Harris L, Eisenach J. Multifactorial preoperative predictors for postcaesarean section pain and analgesic requirement. Anesth 2006;104(3):417-425.