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A randomized, clinical trial of ketorolac trometamine vs ketorolac trometamine plus complex B vitamins for cesarean delivery analgesia

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ABSTRACT

Background: Ketorolac is widely used for postoperative analgesia in patients who undergo cesarean delivery. In countries where the use of opioids is considerably restricted, alternatives to narcotics are required. **Aim:** We hypothesize that the addition of complex B synergize the analgesic effect of ketorolac in postoperative cesarean patients, thus requiring a smaller dose of the anti-inflammatory agent, and therefore decreasing the potential side effects of ketorolac. **Methods:** A randomized clinical trial with 100 patients undergoing a primary elective cesarean delivery enrolled in the study. Pain was assessed in the recovery room and then they were randomized to receive ketorolac 30 mg intramuscular (i.m.) or 15 mg of ketorolac plus complex B vitamin (CBV). The pain score with an analog scale was assessed 1, 2, 6, 12, 18, and 24 h after the baseline. The student's *t* test was performed to compare the demographic differences between the 2 means. **Results:** 100 patients were included in the study, showing no statistical differences in the demographics. The patient's pain score at 1, 2, 6, 12, 18 and 24 hours showed no statistical differences between the control group (ketorolac 30mg) compared to the group of ketorolac 15mg and complex B vitamins. No changes in the coagulation studies were found in both groups. **Conclusion:** The present study demonstrates that ketorolac 30 mg and ketorolac 15 mg plus complex B vitamins can provide acceptable analgesia in many patients with severe pain.

Key words: *B complex, cesarean, ketorolac*

INTRODUCTION

Ketorolac tromethamine is a pyrrole acetic acid nonsteroidal anti-inflammatory drug (NSAID) designed for either oral or parenteral administration. It has been evaluated to provide postoperative analgesia having a comparable effect to systemic opioids, but has a ceiling effect.[1]

Its bioavailability and dosage are similar for intramuscular (i.m.) and intravenous (i.v.) administration.[2] After cesarean delivery, the efficacy of i.m. ketorolac and meperidine are similar, but ketorolac produces fewer side effects.[3] Unfortunately, the quality of analgesia is variable and ketorolac alone is often inadequate.[3,4] When combined with an i.v. or i.m. opioid, ketorolac results in safe, effective analgesia after abdominal surgery, and may improve the response to patient-controlled morphine, reducing postoperative nausea and vomiting through an opioid sparing effect.[2,4]

The most common side effects of ketorolac are gastrointestinal bleeding and acute renal failure. This is one of the reasons why the dose is limited and there is the necessity to find other substances that can provide an additive effect to ketorolac to decrease the required dose of the medication.[1,2]

Previous studies have evaluated the observation that CBV is capable of potentiating the analgesic effect of ketorolac. Those findings demonstrated that patients required half of the dose of ketorolac to achieve the same analgesic effect; therefore, it is reasonable to believe that the use of CBV can decrease the required dose of ketorolac and in turn can decrease the chances of side effects.[5]

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CBV (thiamin, pyridoxine, and hydroxocobalamin) has been evaluated before as an analgesic in conditions, such as neuropathic pain and lumbago.[2] Those studies suggest that CBV produces an analgesic effect mediated by endogenous opioids or by the activation of the same receptors, and the release of nitric oxide.[5,6]

Several studies have shown that CBV can provide a potentiating effect with other NSAIDs, such as diclofenac. In addition, it is suggested that the same response can be seen when combining CBV with gabapentin, acetaminophen, or metamizol.[1,2] The association between ketorolac and CBV has even been shown to decrease the pain in animal studies.[5,6]

The purpose of this study is to compare the analgesic effect of ketorolac 30 mg versus ketorolac 15 mg plus CBV in the postcesarean recovery.

METHODS

The protocol was reviewed and approved by the Internal Review Board of the "Instituto Nacional de Perinatologia" and the ethics committee of the same institution. A detailed informed consent was obtained from all the eligible patients.

All the patients were scheduled for a primary elective low transverse cesarean delivery with a range of age between 18 and 40 years, had a weight greater than 50 kg, underwent preoperative complete blood count and coagulation studies and were capable of signing an informed consent. The exclusion criteria were bleeding disorders, renal disease, history of gastrointestinal ulcers/bleeding/perforation, asthma, or known allergy/hypersensitivity to the test medication, aspirin, or NSAIDs. All the patients must complete the assessments.

A bolus of 500 cc of Ringer's lactate solution was infused before starting the epidural procedure. Epidural is the analgesia standard of care during cesarean deliveries in Mexico, and a combination of 2% lidocaine plus epinephrine 1:200,000 was used. Analgesia was corroborated before starting the procedure and the patients who had a failed epidural and required spinal anesthesia or general anesthesia were not included in the study. All the patients had Pfannenstiel skin incision, and estimated fluid deficit and maintenance fluid requirements were infused as required during the case. All the epidural catheters were removed and discontinued at the end of the procedure as per standard protocol at our institution.

After finishing the cesarean delivery the patients did not receive any other analgesic medications. Sixty minutes after the surgery in the postanesthesia care unit (PACU), the pain was assessed with an analog visual pain scale [Figure 1].

Due to the oily nature of the CBV it was recommended by the internal review board to avoid administrating an oily placebo in the group receiving ketorolac alone, thus the reason why we did not perform a blinded randomized trial.

In the PACU the patients were allocated randomly into 2 groups (A and B) using envelopes with letters labeled as "A" and "B" that were placed by a nurse not participating in the trial. Group A received ketorolac 30 mg (1 mL preparation) i.m. every 6 h and the Group B patients received an injection of 15 mg ketorolac i.m. plus CBV (thiamin 100 mg, pyridoxine 100 mg, and cyanocobalamin) every 6 h (2 mL preparation). The pain was assessed at 1, 2, 6, 12, 18, and 24 h after the baseline. One patient from Group B was discontinued from the study due to required use of rescue medication (tramadol) as is shown in Table 1.

Data were obtained by 3 investigators who were trained to standardize the technique of using visual analog scores to assess pain. All the patients had a baseline biochemistry, coagulation profile, and complete blood count, and if any abnormalities were seen in any of the previously described studies the patients were disqualified from entering the study. New coagulation studies with complete blood count were obtained every 24 h for the subsequent 3 days. Any other complications, such as excessive vaginal bleeding, bleeding from the gums or urinary system were investigated and documented.

No pain	0
Mild pain	1–2
Moderate pain	3–6
Sever pain	7–9
Inconsolable pain	10

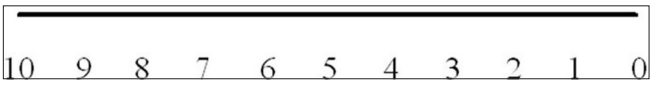

Figure 1: Visual pain analog scale

Table 1: Assigning the patients to the treatments

	Group A Ketorolac 30 mg	Group B Ketorolac 15 mg + complex B vitamin
Enrolled	50	50
Completed the treatment	50	49
Discontinuation	0	1
Motive		
Lack of efficacy (required rescue medication*)	0	1

*Rescue medication: Tramadol 1 mg/kg, one dose

All the information was documented in a database ad hoc. Statistical analysis was conducted using SPSS v9 for Windows. Two-sided tests were performed at the 5% level of significance using Student's *t* tests for normally distributed data. The pain intensity was assessed using the analysis of variance (ANOVA) test. Standard deviation and measures of central tendency were calculated. Statistical significance was calculated as *P* value equal or <0.05.

RESULTS

A total of 100 patients who met the inclusion and exclusion criteria were enrolled in the study. The patients did not represent any significant difference in age [Table 1]. The Student's *t* test was performed to compare the demographic differences between the 2 means. Table 2 shows that there were no demographic differences between the 2 groups (age, gravida, aborta, gestational age, and number of previous cesarean deliveries). From the pool of 100 patients, 3 patients in Group A and 2 patients in Group B had postepidural headache. No other complications were noted related to the use of epidural analgesia [Tables 2 and 3].

To compare the 2 means at each pain assessment between the 2 groups the Student's *t* test method was used. The ANOVA method was added after the measurement of pain at hour 6 through ANOVA [Figure 2]. There were no statistical differences for pain intensity for both medication groups up to 24 h.

The peak of the intensity of pain was calculated to be 6 h after the procedure due to lack of residual anesthetic effect. There were no statistical differences in the pain scale for both treatments at 1, 2, 6, 12, 18, and 24 h, respectively [Table 4].

No difference was noted between the 2 groups and the coagulation studies (prothrombin time and partial thromboplastin time) as outlined in Table 5.

Table 2: Demographic variables of the studied population

Variables	Group A Ketorolac 30 mg	Group B Ketorolac 15 mg + Complex B vitamin	Global	*P* value
Menarche (years)				
Mean	12.36	12.68	12.52	0.1748
Standard deviation	1.13	1.21	1.18	
Min–max	9–15	11–16	9–16	
n	50	50	100	
Gravid				
Mean	2.46	2.58	2.52	0.6258
Standard deviation	1.16	1.29	1.23	
Min–max	0–5	1–6	0–6	
n	50	50	100	
Para				
Mean	0.26	0.22	0.24	0.7603
Standard deviation	0.72	0.58	0.65	
Min–max	0–3	0–3	0–3	
n	50	50	100	
Aborta				
Mean	0.36	0.56	0.46	0.1922
Standard deviation	0.56	0.92	0.77	
Min–max	0–2	0–3	0–3	
n	50	50	100	
Cesarean deliveries				
Mean	0.86	0.86	0.86	1.0
Standard deviation	0.90	0.78	0.84	
Min–max	0–3	0–2	0–3	
n	50	50	100	
Gestational age (weeks)				
Mean	38.6	38.5	38.6	0.6181
Standard deviation	1	1	1	
Min–max	37.1–41.0	37.3–41.0	37.1–41.0	
n	50	50	100	

DISCUSSION

Despite the pharmacologic advances in postoperative pain management, this area still remains a relatively unexplored territory. The use of multimodal analgesia (using a combination of anti-inflammatory medications, local anesthetics, opioids, and antinarcoleptics) to address the various components of the nociceptive cascade at several sites along the sensory pathway is an important concept to explore as we struggle to manage postoperative pain while seeking to minimize adverse effects from traditional pharmacotherapy.

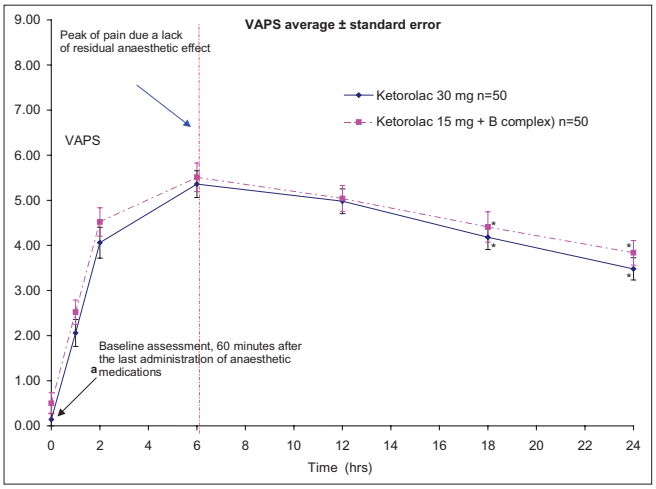

Figure 2: Pain score versus time

Pain control is probably one of the most important aspects of the postoperative period. In Mexico and several third world countries the use of opioids is very limited due to the general belief that they lead to dependence, and thus their use becomes only reserved for terminal stage patients with cancer.[7]

Although the cost of ketorolac is higher compared with morphine it has been widely adopted because it is easily and freely available in a relatively unrestricted market and not subjected to the same stringent regulations as morphine.[7,8]

Previous studies assessing the efficacy of i.m. ketorolac after a cesarean delivery have demonstrated similar efficacy to meperidine and epidural morphine, but there is a lack of evidence using only ketorolac as the sole analgesic.[4,8,9] Despite this it is a common practice in several countries to give ketorolac as the only source of analgesia and use a rescue medication, such as tramadol, should the patient require additional pain control.[4,9,10]

NSAIDs and ketorolac have been proven to be safe in breast-feeding, and some studies have found lower concentrations of this medication in breast milk compared with similar doses of ibuprofen.[11]

The side effects of the NSAIDs, such as ketorolac, are a significant issue in patients with peptic ulcer disease, renal failure, and bleeding tendencies. In our study coagulation studies were performed to rule out any bleeding tendencies,

Table 3: Distribution according the age of the patients

Characteristics	Group A Ketorolac 30 mg	Group B Ketorolac 15 mg + complex B vitamin	Global	*P* value
Age (years)				
Mean	29.3	28.7	29.0	
Standard deviation	6.89	6.47	6.66	
CV (%)	23.54	22.56	22.96	0.6545
Min–max	18–40	19–40	18–40	
n	50	50	100	

Note the homogeneity between the 2 groups according to the age

Table 4: Timed pain assessment after the surgery

	Time of assessment in hours													
	Baseline		1		2		6		12		18		24	
	GA	GB	GA	GB	GA	GB	GA	GB	GA	GB	GA	GB	GA	GB
Mean	0.14	0.5	2.06	2.52	4.06	4.52	5.36	5.51	4.98	5.04	4.18	4.41	3.48	3.84
Standard deviation	0.99	1.64	2.12	1.89	2.43	2.21	2.10	2.25	1.94	2.02	1.91	2.38	1.74	1.93
Standard error	0.14	0.23	0.3	0.27	0.34	0.31	0.3	0.32	0.27	0.29	0.27	0.34	0.25	0.28
Min	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Max	7	8	9	7	10	8	9	9	9	9	8	9	8	8
n	50	50	50	50	50	50	50	50	50	49	50	49	50	49
P value	0.1878		0.2549		0.3239		0.7316		0.8790		0.5999		0.3363	

GA - Group A; GB - Group B

Table 5: Changes in the coagulation studies

Coagulation studies	Group A Ketorolac 30 mg		Group B Ketorolac 15 mg + Complex B vitamin	
	Baseline	Control	Baseline	Control
Prothrombin time				
Mean	11.73	12.23	11.57	12.02
Standard deviation	0.65	0.79	0.87	0.84
Min–max	10.69–14.00	11.00–14.01	10.26–14.31	10.40–14.03
Prothrombin time %				
Mean	94.53	80.94	97.33	83.57
Standard deviation	16.96	13.29	16.65	12.39
Min–max	68.20–125.50	58.90–116.90	65.00–138.10	58.80–105.90
International normalized ratio				
Mean	1.02	1.05	1.01	1.03
Standard deviation	0.07	0.07	0.09	0.08
Min–max	0.90–1.30	0.93–1.23	0.87–1.30	0.88–1.20
Partial time of thromboplastin*				
Mean	25.94	26.78	25.57	26.61
Standard deviation	1.66	2.17	2.07	2.19
Min–max	22.00–30.20	22.00–33.80	22.50–31.72	23.00–32.90

and none of the patients in the study in either group had any major bleeding event, and no significant changes in terms of shift from baseline values, thus supporting the notion ketorolac is a safe medication, as previous studies have also concluded.[10-12]

Some suggestions as to this decreased rate of side effects in pregnant patients have been proposed by previous literature. This includes the idea that physiologic changes in the pregnancy, including increased volume of distribution and increased glomerular filtration rate lead to fewer side effects given the dose of drug described here.[12]

In terms of analgesia we understand that our study has limitations, such as the use of epidural analgesia instead of using spinal analgesia, that could help to reduce the costs of the procedure, but in most regions of Mexico the use of epidural analgesia is the standard of care (belief if the surgery will be too long, the patient would benefit from the epidural catheter avoiding general anesthesia). Another limitation for analgesia is the nonaddition of narcotics to the epidural.

In our study the inclusion of CBV using a lower dose of ketorolac (half of the usual dose), showed no differences in the pain scale and side effects, supporting the additive analgesic effect of CBV to ketorolac in the first 24 h of the postoperative period.

In Figure 2, it is important to notice that the efficacy at 6 h after the administration of both medications has no differences, and no statistical differences were noted in the pain evaluation at different times.

It should be noted that our study was done just measuring the pain in the first 24 h postoperatively and continuing with the parenteral administration of ketorolac will not be practical. This also opens the topic of a new study where the ketorolac and CBV could be administered orally.

CONCLUSION

The present study has demonstrated that ketorolac 30 mg and ketorolac 15 mg plus CBV can provide acceptable analgesia in many patients with severe pain. Although no serious complications were seen in both groups, there is a theoretic risk that at a higher dose of ketorolac it will be more common to see side effects. A trial is required to evaluate if ketorolac 30 mg plus CBV produces a better analgesia than ketorolac 30 mg alone. Due to the poor availability of opioids in developing countries the use of ketorolac 15 mg plus CBV makes it a relatively suitable drug combination for routine use.

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