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Impact of caudal ropivacaine on non-depolarizing muscular relaxation

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SUMMARY

Objective: To determine whether ropivacaine for caudal blockade prolongs the effect of intravenously administered atracurium to patients undergoing anorectal surgery. **Methods:** Forty adult participants were randomly allocated to two groups of 20 each; Group A (with caudal block) and Group B (without caudal block). After intravenous induction, Group A received caudal blockade with ropivacaine of 0.1% with a 14 ml volume. Group B was the comparison group in which caudal blockade was not performed. The neuromuscular blockade was monitored by using a Train-of-four stimulus and the duration of blocking effect of atracurium was measured in both groups. **Results:** The average time to reach the Train-of-four of 80% was 70.59 ± 10.72 min, for group A, while for group B was 55.67 ± 10.72 min ($p < 0.001$). Administering neostigmine was necessary in 45% of group A patients and 25% of group B patients. **Conclusions:** Caudal blockade performed with ropivacaine increases significantly the duration of atracurium when compared with a group of participants in which ropivacaine was not administered.

Key words: Ropivacaine, atracurium, caudal blockade, neuromuscular blockade.

RESUMEN

Objetivo: *Determinar si la ropivacaína administrada mediante bloqueo caudal, prolonga el tiempo de acción del atracurio, administrado por vía endovenosa, en pacientes sometidos a cirugía anorrectal.* ***Material y métodos:*** *Se estudiaron 40 pacientes adultos, divididos aleatoriamente en 2 grupos de 20 sujetos cada uno. Después de la inducción vía endovenosa, al grupo A se le aplicó bloqueo caudal con ropivacaína al 0.1% con un volumen de 14 mililitros, el grupo B no fue bloqueado. Se monitorizó el bloqueo neuromuscular mediante estímulo tren de cuatro. Se evaluó el tiempo de duración del atracurio en ambos grupos: grupo A (bloqueo caudal) y B (sin bloqueo caudal).* ***Resultados:*** *El registro del tiempo estimado en minutos para alcanzar un tren de cuatro del 80% para el grupo A fue 70.59 ± 10.32; mientras que para el grupo B fue de 55.67 ± 10.72. (p < 0.001). En el grupo A fue necesario administrar neostigmina en el 45% de los pacientes, en el grupo B sólo 25%.* ***Conclusiones:*** *El bloqueo caudal con ropivacaína, produce un aumento estadísticamente significativo en la duración de acción del bloqueador neuromuscular no despolarizante atracurio, comparado con el grupo control en el cual no se aplicó ropivacaína.*

Palabras clave: *Ropivacaína, atracurio, bloqueo caudal, bloqueo neuromuscular.*

INTRODUCTION

In 1901, in Paris, Ferdinand Cathelin, an urologist, and Jean Sicard, a surgeon, described caudal epidural anesthesia (CEA) for the first time[1]. Early registries describing its use for cystoscopies in pediatric patients date from 1933[2]. Then, the reemergence of caudal anesthesia occurred in the early 1940's, when Hingson et al recommended caudal blockage to alleviate pain during delivery[3,4]. The relevance of this anesthetic technique has increased in the field of anorectal surgery for adults. CEA has the advantage of being more selective, lasting longer and having more potent analgesic qualities than other anesthetic techniques[5].

Deep inhalation anesthesia, regional nerve blockade or neuromuscular blockade produces skeletal muscle relaxation. In 1942, Harold Griffith published the results of a study in which he used a refined extract of curare during analgesia[6]. In 1949, Bovet synthesized succinylcholine, which in 1951 was approved for clinical use. Other muscle relaxants introduced to the anesthesia field were: galamine, decamethonium, metocurarine and alcuronium, although these were associated with unwanted adverse effects. Therefore, the search for the ideal muscle relaxant continues. Some that are close to reaching such an ideal and have been described recently are: doxacuronium, vecuronium, atracurium, cisatracurium and rocuronium.

For more than half a century, it has been well established that procaine, lidocaine, bupivacaine and other local anesthetics block neuromuscular transmission in human beings[7], and its interaction in the neuromuscular union has been described as well[8]. In 1961, Stranghan, and in 1968, Ususbiaga and Standaert described the effect of local anesthetics in the motor nerve terminal. In 1969, Katz and Gissen reported that neuromuscular blockade produced by local anesthetics was completely different from the blockage that d-tubocurarine produces. That is because edrophonium does not consistently revert neuromuscular blockage[7]. Ropivacaine is a long lasting anesthetic drug belonging to the amino amide group; its molecular structure is similar to bupivacaine, levobupivacaine and mepivacaine[9-11]. Ropivacaine was originally developed in the 1950's, although its clinical use began in the 1990's, as an alternative to bupivacaine, which had the disadvantage of causing cardiotoxic and neurotoxic adverse effects[12-16].

METHODOLOGY

A randomized-clinical trial was conducted in Centro Medico ABC. The local research and ethics committee approved the study, the surgical team gave its support and the patients gave their informed consent. The study included forty patients (men and women) scheduled for elective anorectal surgery. The ages ranged from 23 to 70 years; their physical status, according to the American Society of Anesthesiologists (ASA), was ASA I to II. Patients were randomly allocated to a group of 20 participants each. All patients received balanced general anesthesia. Monitorization of patients included: continuous electrocardiogram on derivations DII and V5, non-invasive blood pressure, SpO_2 (oxygen saturation) and $EtCO_2$ (carbon dioxide). Neuromuscular relaxation (NMR) was monitored by using Datex-Ohmeda AS/5 equipment (S/5^{tm} Neuromuscular transmission module – NMT MechanoSensor) and by train-of-four stimulus (TOF) to evaluate the time of latency and the amount of time that the non-depolarizing neuromuscular relaxant (ND-NMR) lasted in both groups. The measurements were taken every five minutes, until the surgical procedure was complete.

Intravenous anesthesia was induced with fentanyl 3.0 µg/kg, propofol, 2.5 µg/kg and atracurium 400 µg/kg (2ED95); before this, the patient received oxygen (O_2 at 100%) through a facial mask. Once the patient was unconscious, manual ventilation assistance began. A TOF stimulus with 2 Hz was used for the nerve *ulnar pollicis*. The stimulus was every 15 seconds, until optimal conditions of endotracheal intubation were reached. After respiratory automatism was lost, the ventilatory mechanic system began. This maintained $EtCO_2$ between 25 and 30 mmHg during the study. After intubation and adjustment of the ventilatory mechanic support (VMS), patients in Group A were set in a prone position, the site of puncture was located (sacral hiatus) and asepsis and antisepsis techniques were performed. The puncture was done with a 23G hypodermic needle at a 30° angle and after crossing the sacrococcygeal membrane, the position was corrected 15°; then, it was introduced to the sacral hiatus and after verifying the puncture site, 0.1 ropivacaine[4], 50 µg/kg fentanyl[14] and 14 mL of physiological solution[1] were administered. In Group B, after intubation and adjustment of the VMS, the surgical procedure continued. For the maintenance period of anesthesia, we used desfluorane 1 MAC and O_2-air with 70% fiO_2. Neuromuscular blockade was reversed with neostigmine 0.04 mg/kg and atropine 0.02 mg/kg when needed and based upon neuromuscular monitoring.

The statistical analysis was carried out by using Pearson chi- square test and Student t test.

RESULTS

Forty patients were included in the study. Tables I and II show the demographic characteristics. No statistically significant differences between groups ($p > 0.05$) were found on the variables of age, weight and height. The average age of Group A patients was 43.15 ± 10 years and that of Group B patients was 46.9 ± 12 years. Mean weight (kilograms) of Group A members was 72.7- ± 15 and for Group B was 80.25 ± 13. Mean height (meters) was 1.67 ± 0.09 for Group A and 1.73 ± 0.09 for Group B.

Table II shows that there were 11 women (55%) and 9 men (45%) in Group A and 3 women (15%) and 17 men (85%) in Group B. To make statistical comparisons between groups (age, weight and height), we used the student's t test and to compare sex, we used the Pearson chi-square test.

Neuromuscular monitoring by using TOF was registered every five minutes since the onset and until the end of the surgical procedure. Figure 1 shows the average of registries of TOF every 5 minutes in both groups, from minute 35 to minute 65. TOF shows $p < 0.0$. Student's t test was used to make statistical comparisons of TOF registries every five minutes.

Table III shows that the average time of surgery ± 1 standard deviation of Group A (caudal blockage) was 70.59 ± 10.32 min, while the average time of Group B was 55.67 ± 10.72 min ($p < 0.001$).

Table IV shows the time intervals in which recovery of muscular relaxation occurred (T0F = 80%), which was as follows: Group A, 7 patients (55-65 min); 6 patients (65-75 min); 5 patients (75-85) min and 1 patient (85-95 min). Group B: 5 patients (35-45 min); 4 patients (45-55 min); 7 patients (55-65 min); 3 patients (65-75 min) and 1 patient (75-85 min). Figure 2 shows the distribution per group of patients according to the time in which they reached TOF = 0.8. The Student's t test was used to make the statistical comparisons ($p > 0.05$). It was necessary to reverse the residual relaxant effect of atracurium in 9 patients (45%) of Group A while this was needed in 5 patients of Group B (25%) (Table V). We used Pearson Chi-square test ($p = 0.185$) to compare the reversion between groups.

Table I. Demographic characteristics.

	Group A Caudal blockage	Group B Without caudal blockage	value P
Age (years)	43.15 ± 10	46.90 ± 12	0.315
Weight (kg)	72.70 ± 15	80.25 ± 13	0.111
Height (m)	1.67 ± 0.09	1.73 ± 0.09	0.08

Average values ± 1 standard deviation
$p < 0.05$

Table II. Demographic data: Sex.

Gender	Group A Caudal blockage	Group B Without caudal blockage	Total (p = 0.008)
Women	11 (55%)	3 (15%)	14
Men	9 (45%)	17 (85%)	26
Total	20	20	40

$p < 0.008$

Table III. Average time to reach train-of-four (TOF) of 80%.

	Number of Patients	Average time	Standar deviation
Group A (Caudal blockage)	20	70.59	10.32
Group B (Without caudal blockage)	20	55.67	10.72

$p < 0.001$

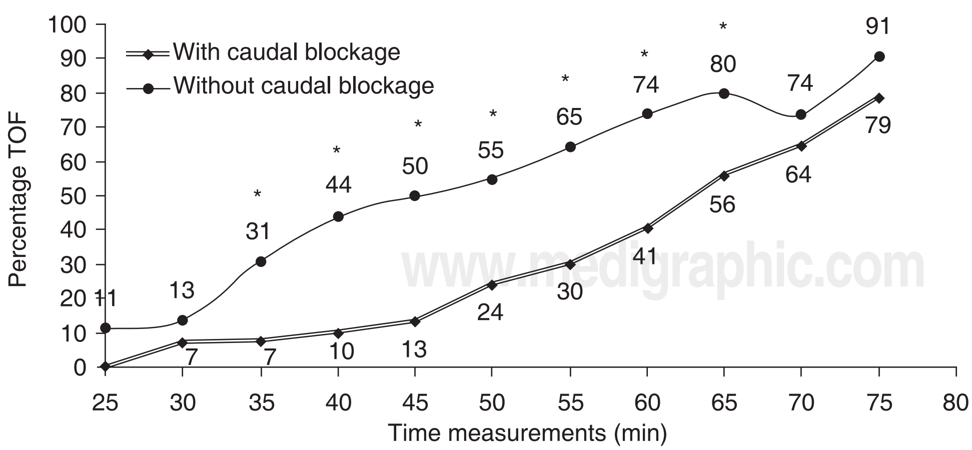

Figure 1. The figure shows the train-of-four (TOF) registers of both groups. The average of registries is shown in five-minutes intervals, starting at 35 minutes and until 65 minutes. p value < 0.05. Values outside this time range showed p > 0.05.
Student´s t test.
* p < 0.05

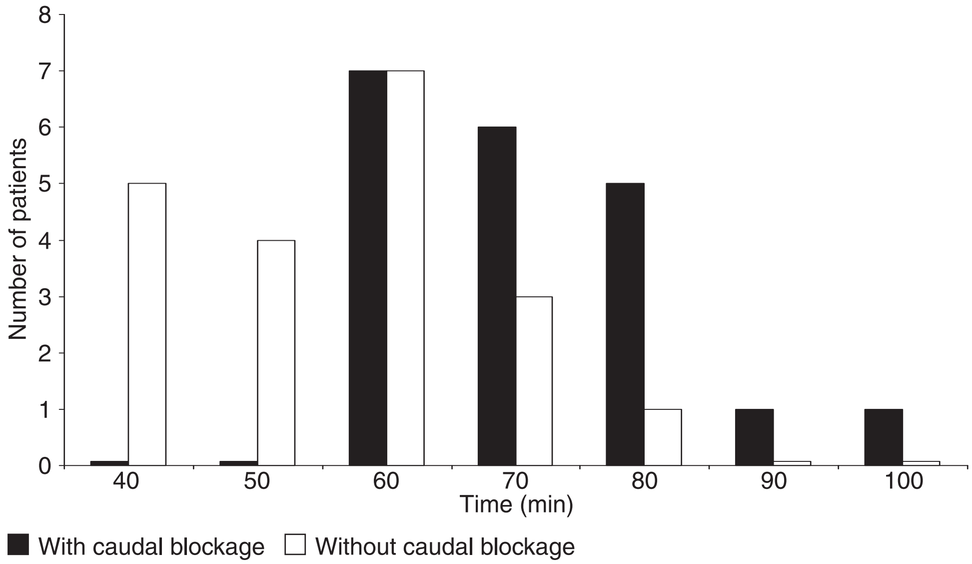

Figure 2. Distribution of patients according to the time in which they reached a train-of-four ≥ 80% and the distribution per group. Student's t test was used to make statistical comparisons, $p > 0.05$.

Table IV. Train-of-four recovery time intervals (80%).

Ranges Time (min)	Caudal blockade N	Without caudal blockade N
35 - 45	0	5
45 - 55	0	4
55 - 65	7	7
65 - 75	6	3
75 - 85	5	1
85 - 95	1	0
95 - 105	1	0

Figure 2 shows the group distribution of patients according to the time in which they reached train-of-four ≥ 80%.

Table V. Reversed patients.

	Group A Caudal blockade N (%)	Group B Without caudal blockade N (%)	Total N (%)
Reversed	9 (45%)	5 (25%)	14 (35%)
No revertidos	11 (55%)	15 (75%)	26 (65%)
Total	20 (100%)	20 (100%)	40 (100%)

The table shows all patients that were reversed at the end of the procedure because they did not show TOF of 80% or clinical data of neuromuscular relaxation. $p = 0.185$.

DISCUSSION

The present study shows that caudal-peridural blockage with ropivacaine, when compared with a control group not receiving ropivacaine, prolongs the duration of action and the time for reversal of the non-depolarizing neuromuscular blocker atracurium. Also, the study confirms that ropivacaine, when passing over to systemic circulation, influences the neuromuscular relaxing effect of atracurium. Several authors have addressed the interaction between local anesthetics and muscle relaxants[17,18]. When local anesthetics are administered intravenously alone, they do not show any effect on the neuromuscular relaxation. However, intravenous administration of these drugs partially increases the neuromuscular blockade that muscle relaxants induce[17,18].

It has been well established for more than half a century that procaine, lidocaine, bupivacaine and other local anesthetics block the neuromuscular transmission in human beings[7] and its interaction in neuromuscular union has been described as well[8,19]. In 1961, Stranghan and in 1968, Ususbiaga and Standaert described the effect of local anesthetics in the motor nerve terminal. In 1969, Katz and Gissen reported that neuromuscular blockade produced by local anesthetics was completely different from the blockage that d-tubocurarine produces. That is because edrophonium does not revert consistently the neuromuscular blockage[7]. As mentioned earlier, using a combined anesthetic technique (general anesthesia and caudal epidural blockage) makes it possible to observe interactions between the drugs used in both techniques. It is promising for analyzing the interactions and effects, despite the fact that the routes of administration are different (intravenous: general anesthesia; epidural: caudal blockade)[8]. The interaction between these drugs that come from different genre, can result in prolonging the effects of one or the other drug, as well as to decrease its requirements. It is worth mentioning the possibility of residual effects after the surgical procedure ends, as usually happens when using muscle relaxants. Depending upon its molecular weight and its liposoluble properties, local anesthetics can pass to the circulation through the epidural space and cause a systemic effect, thus potentiating the effect of non-depolarizing neuromuscular relaxants. The absorption of ropivacaine, as well as other local anesthetics is mainly through the venous system. The peak of plasma concentration of local anesthetics is influenced by the site of injection as well as by the individual pharmacological profiles of each drug[20,21]. The site of higher absorption to the lower absorption is as follows: intercostal > caudal > epidural, lumbar/thoracic > brachial plexus > sciatic-femoral[22,23].

Several mechanisms could explain the interaction of ropivacaine that is absorbed at a systemic level and atracurium on neuromuscular relaxation that this study demonstrates. The presynaptic area is where local anesthetics depress motor nerve terminals selectively and decrease release of acetylcholine (ACh) during nerve stimulation. The postsynaptic area is where local anesthetics attach to a variety of specific sites, but all are linked functionally to the sites where ACh binds. This promotes de-sensitization of ACh receptors. Furthermore, this action has an effect on the opening of ACh receptor channels[17]. In the study conducted by Taivainen et al[19] peridural bupivacaine was administered causing an increase in the duration of neuromuscular relaxation due to vecuronium administration. However, there were no significant differences in the clinical duration or recovery of the neuromuscular relaxation between the two groups in study that received pharmacologically equivalent dosages of muscle relaxant. In our study, the results showed that if the local anesthetic bupivacaine passed to the systemic circulation, then it would influence the efficacy of the neuromuscular agent by an estimated 20% persistence of the effect of vecuronium in the bupivacaine-neuromuscular blocker group. This is in comparison to the control group, which was using non-depolarizing neuromuscular relaxant. This is the same result that Tuft et al[2] notes, in which atracurium and peridural bupivacaine were administered.

Neuromuscular monitoring is used routinely to determine an adequate neuromuscular blockage during and after surgery and to ascertain adequate reversion of the relaxant effect. Since the publication of Ali et al, in 1971[26], the TOF ratio is still the standard method[24,25] for carrying out neuromuscular monitoring. The TOF method consists in the application of four stimuli (each stimulus of 0.12 mlseg) with an interval of 0.5 sec in a specific frequency (2 Hz); this means four stimuli in two seconds. Conventionally, the presence of 70% to 75% of TOF was considered as a recovery criterion of neuromuscular blockade (NMB), although a value of 80% or 90% is recommended to guarantee an adequate NMB.

In our study, the TOF from the 35th minute to the 65th minute showed a significantly lower value in those patients who received ropivacaine via caudal peridural ($p > 0.05$). This is different from the study that Taivanen conducted[9] in which vecuronium was demonstrated to be slightly more potent when peridural bupivacaine was administered. However, no statistically significant differences were found regarding clinical duration or recovery in both groups.

We made calculations to estimate the time to reach an ideal TOF to recover from neuromuscular blockade (80% or 0.8)[27,28]. In Group A the estimated time to reach TOF of 0.8 was 70.59 min ± 10.32 min, while the estimated time for Group B was 55.67 min ± 10.72 ($p < 0.001$). This finding highlights that the time to reach a TOF of 0.8 in the group receiving caudal peridural ropivacaine increased significantly. This difference of time between groups shows the direct effect of caudal ropivacaine on neuromuscular relaxation, when atracurium is administered as NDNMR.

The study showed that five patients in Group B had TOF of 0.8 after 35 min, while seven patients in Group A, had TOF of 0.8 in the range of 55-65 min. Thus, the time of recovery from NMR was longer in Group A. An added observation of our study was that atracurium had a residual effect, being more prevalent in Group A, in which nine patients (45%) were reverted by using neostigmine-atropine, than in Group B where only five patients required reversion (25%).

CONCLUSIONS AND RECOMMENDATIONS

We have presented, in a safe and pragmatic way, our experience using caudal peridural ropivacaine, including its effect on atracurium-induced NMR in adult patients undergoing anorectal surgical procedures. Because the time of reversion from NDNMR was longer in patients in whom we performed caudal blockage with ropivacaine, we recommend evaluating using lower doses of atracurium (< 2ED95 adjusted by TOF) for intubation and maintenance for this kind of surgical procedure, so as to avoid atracurium residual effects and to decrease the incidence of neuromuscular blockade reversion.

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