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Comparison of two concentrations of bupivacaine by continuous paravertebral infusion after thoracotomy with pulmonary resection: a double-blind, randomized clinical trial

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ABSTRACT

Background and objectives: Post-thoracotomy pain management should be based on a multimodal approach that includes continuous regional analgesia. The objective of this study was to compare the analgesic efficacy of two concentrations of bupivacaine (0.2 % and 0.3 %) through a paravertebral catheter, both group plus fentanyl 2 mcg/ml.

Methods: We conducted a randomized double-blind clinical trial to compare these two concentrations in patients undergoing pulmonary resection by thoracotomy in Donostia University Hospital between November 2010 and May 2011 (n = 59). The paravertebral catheter was placed prior to the surgical intervention, with the patient awake and sitting upright. Data were analyzed on an intention-to-treat basis. The Chi-squared test was used for qualitative variables and Student's t-tests or Mann-Whitney-Wilcoxon tests for quantitative variables, depending on the distribution of the variables. Statistical analysis was performed using IBM SPSS software (Version 17).

Results: We did not find statistically significant differences in postoperative pulmonary function (p = 0.49), self-perceived pain (VAS; p = 0.28) or cumulative morphine consumption (p = 0.101) in the two groups. We observed adverse effects in 8 patients in group 1 (29.6 %) and in 12 patients (37.5 %) in group 2, the difference not being statistically significant (p = 0.52).

Conclusions: Continuous thoracic paravertebral block for 48 hours is a good technique for the management of postoperative pain after pulmonary resection by thoracotomy. With moderate doses of local anesthetics (bupivacaine 0.20 %) we achieved good pain control and observed few systemic complications than major doses (bupivacaine 0.30 %).

Key words: Postoperative pain, thoracotomy, paravertebral blockade, analgesia, bupivacaine.

RESUMEN

Antecedentes y objetivos: El manejo del dolor post-toracotomía debe basarse en un enfoque multimodal que incluye la analgesia regional continua. El objetivo de este estudio fue comparar la eficacia analgésica de dos concentraciones de bupivacaína (0,2 y 0,3 %) a través de un catéter paravertebral, ambos grupos más fentanilo 2 mcg/ml.

Material y métodos: Se realizó un ensayo clínico aleatorizado, doble ciego, para comparar estas dos concentraciones en pacientes sometidos a resección pulmonar por toracotomía en el Hospital Universitario Donostia entre noviembre de 2010 y mayo de 2011 (n = 59). El catéter paravertebral se colocó antes de la intervención quirúrgica, con el paciente despierto en posición sentada. Los datos se analizaron sobre la base de intención de tratar. Se utilizó la prueba de Chi cuadrado para variables cualitativas y la t de Student o pruebas de Mann-Whitney-Wilcoxon para las variables cuantitativas, en función de la distribución de las variables. El análisis estadístico se realizó utilizando el software de IBM SPSS (versión 17).

Resultados: No se encontraron diferencias estadísticamente significativas en la función pulmonar postoperatoria (p = 0,49), la percepción subjetiva de dolor (VAS; p = 0,28) o el consumo

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de morfina acumulada (p = 0,101) en los dos grupos. Hemos observado efectos adversos en 8 pacientes del grupo 1 (29,6 %) y en 12 pacientes (37,5 %) del grupo 2; la diferencia no fue estadísticamente significativa (p = 0,52).

Conclusiones: El bloqueo paravertebral torácico continuo durante 48 horas es una buena técnica para el manejo del dolor postoperatorio después de la resección pulmonar por toracotomía. Con dosis moderadas de anestésicos locales (bupivacaína 0,20 %) se logró un buen control del dolor y observamos un número menor de complicaciones sistémicas que el grupo de dosis mayores (bupivacaína 0,30 %).

Palabras clave: Dolor postoperatorio, toracotomía, bloqueo paravertebral, analgesia, bupivacaína.

INTRODUCTION

Thoracotomy is one of the surgical interventions associated with most pain in the postoperative period (1). During the acute period after surgery, 45-65 % of patients report severe pain at rest and as many as 60-70 % on movement (1). Hence, one of the main goals for the postoperative period after thoracic surgery is to develop an effective analgesic regimen that enables patients to have adequate ventilation and, thereby, shorten the recovery period after surgery and avoid the development of perioperative complications (2,3).

It is already well recognized that postoperative analgesia requires a multimodal approach to pain and to postoperative recovery, routinely including respiratory physiotherapy and rehabilitation (4,5). Post-thoracotomy pain management should be based on continuous regional analgesia, either via thoracic epidural block (TEB) or paravertebral block (PVB), preferably started before surgery and maintained for 48-72 hours. The block should be used in combination with intravenous anti-inflammatory drugs and paracetamol, as well as neuromodulators (gabapentinoids), with opioids as rescue analgesia depending on the intensity of pain assessed using a visual analoge scale (VAS) throughout the postoperative period (6).

The objective of this randomized clinical trial was to compare the analgesic efficacy of two concentrations of bupivacaine, 0.20 *versus* 0.30 %, for PVB. For this purpose, we assessed postoperative pain (concerning VAS scores 24, 48 and 72 hours after extubation) and cumulative intravenous morphine consumption as rescue analgesia), pulmonary function 24, 48 and 72 hours after extubation, and morbidity and mortality 30 days after surgery.

METHODS

Recruitment

The study was approved by the Clinical Research Ethics Committee of Gipuzkoa and the Spanish Agency of Medicines and Medical Devices, with reference number EudraCT nº: 2010-021534-55. All patients who underwent pulmonary resection by thoracotomy in Donostia University Hospital between November 2010 and May 2011 were included in the study provided that they agreed to participate by signing an informed consent form.

Procedure

PVB was placed with the patient awake and sitting upright, using the loss of resistance technique and selecting the site for insertion in the middle of the dermatomes that were to be affected by the surgery (at the T5-T6 level). In all cases, an anesthesiologist with extensive experience in thoracic surgery carried out the procedure.

Doses of anesthetic drugs used

Pre- and intraoperative management was the same for all patients. First, they received a fractionated dose of bupivacaine 0.5 % plus adrenaline 1:200000 in a total volume of 0.25 ml/kg. During surgery, they were given bupivacaine 0.33 % plus adrenaline 1:200000 at a rate of 0.2 ml/kg/hour with a final bolus of bupivacaine 0.5 % and adrenaline 1:200000 in a total volume of 0.25 ml/kg administered at the end of the surgical intervention.

At the end of the surgery, randomization was carried out by research pharmacists using computer-generated lists to allocate patients to one of the two groups. Patients in group 1 were then administered a continuous infusion of bupivacaine 0.20 % plus Fentanest® 2 µg/ml at a rate of 10 ml/hour, while patients in group 2 were given a higher dose, bupivacaine 0.30 % plus Fentanest® 2 µg/ml at a rate of 10 ml/hour.

Regimen for multimodal and rescue analgesia

As part of the analgesic regimen, patients in both groups were also given alternating intravenous doses of metamizole (2 g) or paracetamol (1 g) every 4 hours, from the intraoperative period onwards. Rescue analgesia was provided with morphine on demand delivered by a patient-controlled intravenous analgesia (PCIA, Gemstar-Hospira®) system, programmed to release one bolus of morphine (0.02 mg/kg) (1-2 mg) with a 5-minute lockout time and up to a maximum of 20 mg in 4 hours. The PCIA pump was connected to patients on their arrival at the post-anesthesia care unit.

Data collection

The assessment consisted of measuring pain in terms of VAS scores at rest and on coughing at 24, 48 and 72 hours

after surgery. In addition, spirometry was carried out using a MicroGP portable spirometer (Care Fusion). The sensory block was assessed using the pin prick method and motor block with the Bromage scale. A record was kept from the cumulative amount of morphine consumed via the PCIA device at 24, 48 and 72 hours after surgery.

Statistical analysis

The required sample size was estimated to be 29 patients per group, on the basis of the Kotzé study (7). Data were analyzed on an intention-to-treat basis, that is, all the randomized patients were kept in their allocated group for the analysis. Chi squared tests were used for qualitative variables and Student's t-tests or Mann-Whitney-Wilcoxon tests for quantitative variables, depending on the distribution of the variables. Differences were considered to be statistically significant when $p < 0.05$. Statistical analysis was performed using IBM SPSS (version 17).

RESULTS

Cumulative doses of local anesthetic administered in each group

Assuming a mean body weight of 70 kg and that the mean duration of surgery was 3 hours, we calculated the amount of the bupivacaine (in mg) administered to the patients in each group. During the surgery, patients in both groups received 348.6 mg (divided between initial and final boluses and the intraoperative infusion). Patients in groups 1 and 2 were then given 768.6 mg and 978.6 mg respectively in the first 24 hours after the starting the surgery, and 480.6 mg and 720.6 mg respectively in the following 24 hours.

Composition of each group

We included 59 patients: 27 in group 1 and 32 in group 2. Table I summarizes the main characteristics of the patients by group.

Outcome variables studied: pulmonary function, pain and sensory block

In order to compare postoperative pulmonary function in the most objective way, we calculated the difference between the expected and observed values for each patient. For this purpose, we calculated the expected pulmonary function on the basis of test results before surgery and the number of functional lung segments resected. In this way, by comparing the difference between the expected and observed forced expiratory volume in 1st second (FEV1) in the two treatment groups, we avoid the potential bias that could be introduced by one group performing better than the other preoperatively.

In group 1, the mean preoperative FEV1 was 2.21 liters, compared to 2.72 liters in group 2 ($p = 0.02$). The

TABLE I
MAIN CHARACTERISTICS OF THE PATIENTS BY STUDY GROUP

	Group 1	*Group 2*	*P value*
Males	21 (77.8 %)	30 (93.8 %)	0.07
Harmful habits: Alcohol Smoking	 18 (66.7 %) 5 (18.5 %)	 15 (46.9 %) 5 (15.6 %)	 0.13 0.77
Mean age (years)	65 (SD 7)	61 (SD 12)	0.07
Mean BMI (kg/m^2)	26.3 (SD 4.6)	27 (SD 4.7)	0.60
Broken ribs	12 (44.4 %)	17 (53.1 %)	0.51
Right side approach	12 (44.4 %)	18 (56.3 %)	0.40
Difficult pneumolysis	9 (33.3 %)	13 (40.6 %)	0.56
Need for fraction of inspired oxygen at 100 %	18 (66.7 %)	22 (68.8 %)	0.55
Duration of surgery (hours)	3 (SD 1)	3 (SD 1)	0.80
Lung exclusion (hours)	2 (SD 1)	2 (SD 1)	0.66
Pneumonectomy	4 (14.8 %)	5 (15.6 %)	0.73

expected FEV1was 1.73 *vs.* 2.9 liters (p = 0.094) and the expected forced vital capacity (FVC) 2.59 *vs.* 3.01 liters (p = 0.110) in groups 1 and 2, respectively. The differences between the observed and the expected results are illustrated in Figures 1 and 2 for each group at 24, 48 and 72 hours after surgery.

Table II compares the perceived pain (regarding VAS scores) and the cumulative consumption of morphine in the first 72 hours in both groups, no statistically significant differences being found.

Motor block was not observed in any patients. As for sensory block, there were no significant differences between the groups. At 24 hours after surgery, sensory block had worn off in 7.7 % of patients in group 1, compared to 9.4 % in group 2 (p = 0.97). Subsequently, at 48 and 72 hours after surgery respectively, we observed a lack of sensory block in 8.7 and 13 % of patients in group 1 and in 9.7 and 10 % in group 2.

Detection of adverse effects

We detected adverse effects in 8 patients in group 1 (29.6 %) and 12 patients (37.5 %) in group 2, the difference not being statistically significant (p = 0.525). These events are detailed in Table III. No patients died within 30 days of their surgery.

DISCUSSION

The use of continuous regional analgesia techniques been shown to have greater efficacy in controlling pain and the recovery of pulmonary function after thoracotomy surgery than other analgesic techniques, such as intravenous opioids or intrapleural local anesthetics (LAs) (7). PVB has been compared to TEB after thoracotomy surgery in four systematic reviews. Detterbeck et al. (8) (17 studies

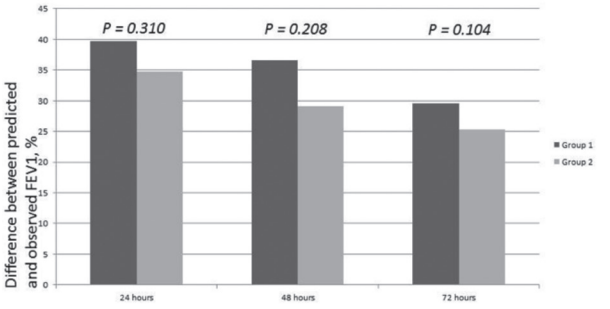

Fig. 1. Comparison of the differences between predicted and observed forced expiratory volume in 1 second (FEV1) in the two groups.

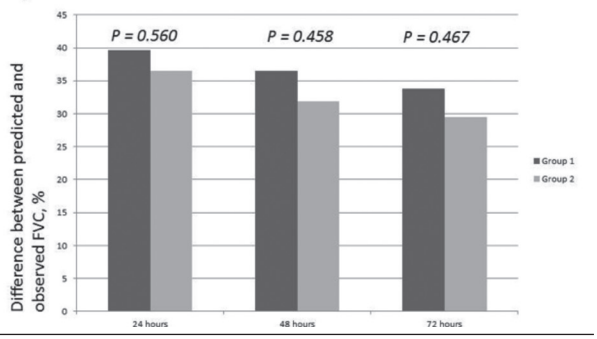

Fig. 2. Comparison of the differences between predicted and observed forced vital capacity (FVC) in the two groups.

TABLE II
PAIN VISUAL ANALOG SCALE (VAS) SCORES AND USE OF MORPHINE IN THE POSTOPERATIVE PERIOD BY GROUP

	Group 1	*Group 2*	*p*
	Mean (SD)	*Mean (SD)*	
VAS score at rest at 24 h	0.95 (1.53)	0.58 (1.17)	0.28
VAS score at rest at 48 h	0.82 (2.02)	0.71 (1.29)	0.92
VAS score at rest at 72 h	1.18 (2.02)	1.06 (2.12)	0.91
VAS score on coughing at 24 h	4.14 (2.78)	3.84 (2.31)	0.76
VAS score on coughing at 48 h	4.05 (2.47)	4.03 (2.18)	0.87
VAS score on coughing at 72 h	3.82 (2.48)	4.23 (2.82)	0.45
Cumulative morphine consumption, < 24 h	16.44 (11.19)	22.90 (16.65)	0.10
Cumulative morphine consumption, 24-48 h	12.08 (11.08)	9.75 (11.10)	0.44
Cumulative morphine consumption, 48-72 h	7.04 (7.52)	6.00 (10.55)	0.69

TABLE III
ADVERSE EFFECTS OBSERVED
IN THE POSTOPERATIVE PERIOD

	Group 1	*Group 2*
Pruritus	3	7
Nausea	3	2
Urine retention	0	1
Renal failure	0	1
Acute pulmonary edema	1	0
Atrial flutter	1	0
Anemia	0	1

and 619 patients) concluded that PVB achieved good pain control, similar to TEB. Consistent with this, Davies et al. (2) (10 studies and 520 patients) found that PVB achieved similar levels of analgesia to TEB but also that it was associated with lower rates of adverse effects, technical problems, and unsuccessful nerve block attempts, as well as 64 % fewer postoperative pulmonary complications. In the systematic review by Joshi et al. (9) (7 studies between 1966 and 2004), PVB was also found to achieve similar levels of analgesia to TEB but only when LAs were used alone, TEB being associated with better quality analgesia when LAs were combined with major opioids epidurally. On the other hand, the rate of pulmonary complications was lower among those receiving PVB than systemic analgesia for post-thoracotomy pain management. In 2010, Norum and Breivik (10) (10 clinical trials) concluded that PVB was not better than TEB for pain management after thoracotomy surgery in terms of efficacy or safety. Further, in a recent short communication, these same authors warned about a risk of systemic toxicity due to the high doses of LAs used in the PVB to achieve a good level of analgesia (11). Overall, given the results mentioned above, in our hospital PVB is highly recommended as an analgesic technique for thoracic surgery and is considered an excellent alternative to epidural analgesia (12).

To date, however, the ideal combination of drugs for paravertebral analgesia has not been established. In a systematic review, Kotzé et al. (7) found that high doses of bupivacaine (890-990 mg/day) were associated with lower pain scores and better recovery of pulmonary function, than observed with low doses (325-472.5 mg/day). In addition, the continuous infusion of LAs was a predictive factor for lower pain scores, compared to their administration as boluses. No clinical trials identified in that review (7) directly compared two concentrations of bupivacaine or considered moderate doses of this drug (473-880 mg/day).

To our knowledge, ours is the first clinical trial comparing PVB with two different concentrations of bupivacaine for providing analgesia after thoracotomy. We compared moderate doses (768.6 mg in group 1) with high doses (978.6 mg in group 2) of bupivacaine, to explore the minimum analgesic concentration of LAs required to provide the best *efficacy and side effect* profile (7). First, in agreement with previous meta-analyses (2,8-10), we have found that PVB performed at the thoracic level prior to lung resection surgery is highly efficacious for post-thoracotomy pain management, providing a good level of analgesia in both groups at rest (VAS score < 1.2) and on coughing (VAS score < 4.1), with no significant differences between the groups. Further, the use of intravenous rescue morphine did not differ significantly between the groups, along 72 h post-surgery (group 1 35.56 mg *vs.* group 2 38.65 mg) suggesting that they provide a similar quality of analgesia. Second, we have not found any significant differences between groups in observed compared to expected FEV1 values or vital capacity (FVC) measurements. Accordingly, we consider that lung function is not affected differently by the two doses of paravertebral bupivacaine. Third, we did not find significant differences in the observed adverse effects as a function of the concentration of LAs used.

Our results are consistent with those published by Kotzé et al. (7), and provide additional information regarding a new effective dose range for bupivacaine (moderate doses) for paravertebral analgesia. Taking all these data together, the two concentrations of LA providing similar levels of analgesia and having similar efficacy/tolerability profiles, leads us to suggest that it would be better to use moderate doses of bupivacaine (means in our study of 768.6 mg over the first 24 h and 480.6 mg over the second 24 h) in routine clinical practice; this approach would decrease the cumulative doses of LAs consumed and, hence, the risk of potential severe toxic adverse effects on the nervous and cardiovascular systems.

Adverse effects associated with PVB have been well documented in the past, especially when this type of procedure became highly popular, 60-70 years ago (13). However, new cases of systemic toxicity associated with this type of block are being reported, some resulting in death (14). This underlines that the total dose of LAs administered should be a key issue in the planning of multimodal analgesia after thoracotomy surgery. To date, the pharmacokinetic parameters of bupivacaine administered as a continuous paravertebral infusion have not been studied in detail, but it has been shown that in some cases there may be toxic levels (2-4.5 mg/l) even in asymptomatic patients (15,16). This is due to the greater doses and volumes of LA required to reach a good level of analgesia at the paravertebral level compared to at the epidural level and, hence, the systemic absorption of LA (11). In our study, we did not observe either neurological or cardiovascular event concerning LA, such as hypotension (defined as less than 20 % from basal BP), after surgery at the PACU or hospitalization wards.

Regarding strengths and weaknesses of this study, we should recognize that the results may not be easily reproduced, as in all patients the paravertebral catheter was placed by an anesthesiologist specialized in analgesia for thoracic surgery using the loss of resistance technique and catheter placement under ultrasound guidance seems to increase the success rate of the PVB technique (17,18). On the other hand, the combination of fentanyl and LA in the analgesic mixture does not seem to improve success rates into the paravertebral space, but it's an advantage for epidural analgesia, wich cannot be excluded after PVB diffusion. This mixture is what we routinely use in our hospital and it's also our general pain unit practice due to it's prepared under steryl conditions by the Pharmacy Hospital Service (7).

CONCLUSIONS

To conclude, continuous thoracic paravertebral block for 48 hours provides a good level of postoperative analgesia after pulmonary resection surgery by thoracotomy. Moderate doses of local anesthetics (bupivacaine 0.2 %) plus fentanyl 2 mcg/ml have an excellent analgesic profile, with good control of pain and a low rate but not statistically significant of systemic complications, than higher doses (bupivacaine 0.3 %).

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