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Epidural ropivacaine infusion as part of a multimodal postoperative pain treatment following thoracolumbar spinal fusion surgery, a randomised controlled trial

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Abstract : *Background* : Pain management after posterior thoracolumbar interbody fusion surgery remains a challenging problem. Epidural analgesia with local anesthetics as an adjuvant treatment might prove beneficial.
Objective : To evaluate the effects of continuous epidural analgesia with a ropivacaine solution as an adjuvant treatment after posterior thoracolumbar interbody fusion.
Study design : A prospective double-blind, randomized, placebo-controlled clinical trial. *Setting* : University Hospital Brussels, a tertiary academic health science centre.
Methods : Thirty-three patients undergoing spinal fusion surgery were randomized into two groups. One group was administered a continuous epidural infusion of a 0.9% saline solution. The other group was administered a continuous epidural infusion of a 0.2% ropivacaine solution. The primary outcome measure was the level of pain experienced by the patients, which was assessed using the visual analogue scale (VAS). Secondary outcomes were time to mobilisation, total length of stay and opioid consumption on patient demand.
Results : The mean VAS score postoperatively the day of surgery was scored as 3,5 for the patients receiving the ropivacaine infusion. The placebo group scored 5 on the VAS scale, thus suggesting a beneficial effect of ropivacaine infusion (p-value 0.02). The mean VAS score at post-op day 1 of surgery differed between 2 for the ropivacaine group and 2,8 for the placebo group (p-value 0.05). Length of stay was shorter for patients who had received ropivacaine infusion (mean difference 1,8 days ; p-value 0,02). No other significant differences were withheld.
Conclusion : The use of a continuous epidural ropivacaine infusion after posterior thoracolumbar spinal fusion surgery could improve postoperative VAS scores and may also result in faster hospital discharge rate. *Trial registration* : registered and approved in the EudraCT registry (2014-004713-91).

Keywords : Epidural anesthesia ; spinal surgery ; back surgery ; spinal fusion ; pain medicine ; orthopedic surgery ; ropivacaine**.**

Introduction

Many different therapeutic interventions thought to reduce postoperative pain after posterior thoracolumbar spinal fusion surgery have been investigated (1). A multimodal strategy for pain management can consist of a combination of different interventions, but even so pain management after posterior thoracolumbar spinal fusion surgery remains challenging (2, 3). Better pain management has been associated with less incidence of chronic back pain, less postoperative complications, better surgical outcome, faster time to mobilisation and shorter length of stay, thereby also reducing financial cost (4, 5, 6).

Traditionally opioids are the agents of choice for pain management (6, 7). The role of opioids has

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Authors contribution : *Maurizio Tosi and Jigme Bhutia designed the study. Maurizio Tosi and Jigme Bhutia recruited the patients and collected the data. Maurizio Tosi performed the analyses. Jigme Bhutia interpretated the data. All the authors contributed to scientific discussion, the draft redaction and approved the final version.*
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been investigated thoroughly as well as their many different administration routes : oral, subcutaneous, intramuscular, intravenous, epidural and intrathecal (8). However, use of opioids is associated with many side effects including respiratory depression, urinary retention, hypotension, nausea and cognitive impairment, thus limiting their usefulness (6). When used via an epidural route, these side effects can be partially overcome (8, 9).

Epidural analgesia, when compared to other modalities in postoperative pain control, provides a greater potency and efficacy of the administered drugs. As a result, drug load can be limited, which diminishes the severity and incidence of side effects (6, 8).

The use of epidural local anesthetics is a well-established practice, however the advantages of this approach in the setting of spinal surgery have only been suggested over the course of the last few years (2, 6, 10). The main action of local anesthetics is to block neural transmission of pain signals. Used via the epidural route local anesthetics may prevent central pain sensitization, a key factor in chronic pain (6). For this study we chose to examine the effect of ropivacaine, since this drug permits the preservation of motor function and has limited cardiovascular and neurological toxicity (11).

The primary objective of this study is to examine the effect of a continuous epidural infusion of ropivacaine on postoperative pain after spinal surgery, assessed by a visual analogue scale (VAS). Secondary objectives include time to first mobilisation, total length of stay and the use of opioids as rescue medication on patient demand.

Patients and methods

A double-blind, randomised, placebo-controlled, clinical trial was set up at the University Hospital Brussels (Brussels), a tertiary academic health science centre. The study protocol was approved by the local ethics committee (Medical Ethics Committee UZ Brussel - VUB, Laarbeeklaan 101, 1090 Brussels ; head of the ethics committee : A. Van Steirteghem ; date of approval 4/12/2014) and registered and approved in the EudraCT registry (2014-004713-91). Forty patients were included, they all provided written informed consent prior to inclusion.

Patients who were scheduled to undergo thoracic or lumbar posterior interbody fusion surgery were eligible for the study, provided they be adults fitting the American Society of Anesthesiologists physical status (ASA) I-III. The exclusion criteria included the inability to provide informed consent, minors (patients under the age of 18 years) and a history or suspicion of allergy to local anesthetics.

Randomization of the subjects into two groups was performed by blocks. A patient-list sorted by date of scheduled surgery was used to associate subjects a unique number. Those numbers were randomized using an online form (www.randomization.org), to generate two groups of equal size. Patients in group 1 were given placebo (saline), patients in group 2 were administered ropivacaine. The randomized list was kept confidential by the principal investigator (MT). Allocation of the patient to either group was concealed from surgeons, anesthesiologists, participants and all other personnel involved in data collection. An epidural catheter was placed during the procedure, an infusion system was installed to enable the continuous infusion of a clear fluid (NaCl 0.9% for group 1, ropivacaine 0.2% for group 2). Both these products were stored in the operating theatre and prepared by the principal investigator during the surgical intervention. The infusion fluid was introduced in elastomeric pumps and labelled as study medication. Infusion fluid for bolus injection was prepared in syringes, also labelled as study medication. In this manner the products were handed over to the attending anesthesiologist so as to ensure full blindness.

All patients received standard preoperative care as per protocol used in our hospital. Patients were premedicated with transdermal fentanyl (patches, 25 mcg per hour) and oral administration of gabapentin (300 mg) the evening before the intervention. Patients already on opioids, saw their daily dose added in fentanyl patches. A first VAS score was determined the evening before surgery as reference. On the day of surgery oral administration of gabapentin (300 mg) was repeated and acetaminophen (1000 mg) was added.

General anesthesia was induced with propofol and sufentanyl. Muscle relaxation was achieved witch rocuronium, unless the patient presented chronic kidney or liver dysfunction ; in these cases cisatracurium was used. The trachea was intubated and ventilation was controlled at the discretion of the anesthesiologist. General anesthesia was maintained with sevoflurane. Perioperative pain was managed with ketamine infusion (bolus of 1 mg per kg and maintenance of 0.2 mg per kg per hour) and sufentanyl also at the discretion of the attending anesthesiologist.

At the end of the procedure, the epidural catheter (Perifix® Epidural Anesthesia Catheter, B. Braun) was introduced by the spine surgeon. The

catheter was placed four to five cm in the epidural space, in the centre of the surgical field so its placement could be confirmed visually. Afterwards a bolus of 10 ml NaCl 0.9% or ropivacaine 0.2% was administered. Continuous infusion was started at the Post Anesthesia Care Unit (PACU) through an elastomeric pump at a basal rate of 7 ml per hour for 72 hours after surgery.

At the PACU, pain scores were determined every 10 minutes. Piritramide was administered, 2 mg per bolus, until a VAS score ≤3 was achieved. At the surgical ward, VAS scores were determined every 8 hours and oxycodone was administered on patient demand in case of pain. Standard postoperative pain treatment consisted of 1000 mg acetaminophen every 6 hours, and gabapentin (300 mg) every 12 hours. Side effects were recorded if any and when they occurred.

We aimed to detect a 40% reduction in VAS score in the treatment group as compared with the control group. Assuming a standard deviation of 2, a minimum of 16 patients per group would be required. We set type I error $\alpha = 0.05$ (two-sided) and type II error b = 0.2. For statistical analysis SPSS Statistics® version 23 was used. The normality of the distribution was assessed using the Kolmogorov-Smirnov test. The student T-test was used for analysing the differences between the two groups. The chi-square test was used for analysis regarding the occurrence of side effects. P values <0.05 were considered to be statistically significant. No post-hoc correction was used.

This report is redacted according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (consort-statement.org).

Results

Since our power analysis indicated we needed two groups of at least 16 patients, we proposed to include 40 patients between December 2014 and December 2015 in the study (Fig. 1). Seven patients

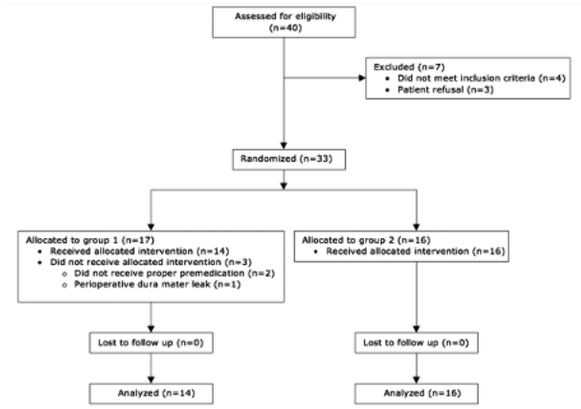

Fig. 1. — Consort diagram. n = number of patients, group 1 = placebo group, group 2 = ropivacaine group.

were excluded because of refusal to participate or because they did not meet the inclusion criteria. The included patients were monitored in hospital until they were discharged. Seventeen patients were randomized into group 1 and 16 into group 2. 3 patients from group 1 had to be removed from the study. Two patients were excluded because they did not receive the correct premedication in accordance with the study protocol. A third patient was excluded because of a dura mater leak that occurred during surgery. The leak could not be properly sealed during surgery so the desired epidural anesthesia could not be guaranteed. In total then, 14 patients were assigned as treatment group and 16 patients as control group.

There were no significant differences between the two groups concerning age, weight, height, gender, BMI (Body Mass Index), ASA physical status, duration of the surgical procedure, preoperative VAS score or preoperative mean daily morphine consumption (Table 1).

The mean VAS scores are detailed in Table 2. The VAS scores at day 0 and day 1 were significantly lower in group 2 (p-value 0.02 and p-value 0.05). Intraoperative opioid administration and supplemental opioid consumption on patient

Table 1

Patient characteristics

	Group 1	Group 2	Difference (95% CI)	P
Average age, years	62 ±16	55 ± 18	-6.8 (-19.2 to 5.6)	NS
Weight, kg	70 ± 12.7	79.8 ± 18.6	9.8 (-2.2 to 21.7)	NS
Height, cm	165.9 ± 7.7	171.7 ± 11.7	5.3 (-2.2 to 12.8)	NS
BMI, kg/cm²	26.5 ± 3.7	24.9 ± 10.2	1.7 (-1.8 to 5.3)	NS
ASA I/II/III, n	3/9/2	4/10/2	-0.1 (-0.5 to 0.4)	NS
Preoperative VAS	3 ± 3.1	3.4 ± 2.8	0.4 (-1.8 to 2.6)	NS
PMDM[a]	0	0	/	NS

[a] Preoperative mean daily morphine, mg.

Table 2

VAS score (mean ± SD) at each collection time

Time	Group 1	Group 2	Difference (95% CI)	P
First PACU	7.2 ± 3.7	4.5 ± 3.9	2.7 (-1.8 to 2.6)	NS
Mean PACU	5.7 ± 0.9	3.6 ± 3	1.5 (-1.5 to 5.6)	NS
Day 0	5 ± 2.9	3.5 ± 1.5	1.6 (-0.1 to 3.6)	0.02
Day 1	2.8 ± 1.5	2 ± 0.7	0.8 (0 to 1.7)	0.05
Day 2	2.1 ± 0.8	1.7 ± 1.2	0.4 (-0.4 to 1.2)	NS

Day 0 = day of surgery.

Table 3

Supplemental opioid consumption (mean ± SD) at each time

Time	Group 1	Group 2	Difference (95% CI)	P
OR	41.4 ± 14.2	55.5 ± 23.5	14.1 (-1 to 29.1)	NS
PACU	14.8 ± 10.9	9 ± 7.5	5.7 (-1.2 to 12.6)	NS
Day 0	10.5 ± 11.4	6.9 ± 7.3	3.6 (-3.4 to 10.6)	NS
Day 1	11.4 ± 10.5	6.8 ± 7.9	4.5 (-2.3 to 11.4)	NS
Day 2	11.8 ± 15.9	6 ± 7.5	5.8 (-3.3 to 14.9)	NS

OR: mg sufentanyl. PACU: mg piritramide. Otherwise: mg oxycodone.

Table 4

Day of mobilisation, length of stay (mean ± SD)

Parameter	Group 1	Group 2	Difference (95% CI)	P
Mobilisation, days	1.5 ± 1	0.8 ± 0.8	0.8 (0 to 1.4)	NS
Hospitalisation, days	9.6 ± 5.6	6.7 ± 3.9	1.8 (-0.7 to 6.5)	0.02

Table 5

Occurrence of side effects

	Group 1 vs. Group 2			
	PACU	**Day 0**	**Day 1**	**Day 2**
Nausea/vomiting, %	14.3 vs. 6.3[b]	0 vs. 6.3[b]	0 vs. 6.3[b]	0 vs. 0[b]
Abdominal discomfort, %	0 vs. 0[b]	7.1 vs. 0[b]	7.1 vs. 0[b]	7.1 vs. 0[b]
Constipation, %	14.3 vs. 6.3[b]	21.4 vs. 25[b]	28.6 vs. 21.3[b]	21.4 vs. 12.5[b]
Pruritus, %	0 vs. 0[b]	0 vs. 0[b]	0 vs. 0[b]	0 vs. 0[b]
Respiratory depression, %	0 vs. 0[b]	7.1 vs. 0[b]	0 vs. 0[b]	0 vs. 0[b]
Paresthesia, %	0 vs. 18.9[b]	0 vs. 18.9[b]	0 vs. 12.5[b]	0 vs. 12.5[b]
Motor blockade, %	0 vs. 0[b]	0 vs. 0[b]	0 vs. 0[b]	0 vs. 0[b]

[b] P-value non-significant, n = number of patients.

demand is detailed in Table 3. Opioid use is expressed in mg sufentanyl during the OR, mg piritramide at the PACU and mg oxycodone at the ward.

The mean time to mobilisation and mean length of stay are detailed in Table 4. Patients in the ropivacaine group presented a shorter length of stay. The occurrence of side effects is detailed in Table 5. There were no significant differences between the two groups concerning side effects.

Discussion

In this trial, significantly lower VAS scores were observed postoperatively at day 0 and day 1 in the ropivacaine group when compared to the placebo group. Other mean VAS scores did not differ significantly. The lack of significance for the other VAS scores could be attributed to an inadequate sample size or by our means of data collection. Gottschalk et al. (2) also compared epidural ropivacaine 0.1% with placebo and found significant reduction of more postoperative VAS scores. This study measured VAS scores at fixed time intervals, which we could not achieve.

For our study we used a ropivacaine 0.2% solution, whereas Blumenthal et al. (12) used a solution of 0.3% ropivacaine. Their choice was based on a single pilot study, which demonstrated

superior pain control with a 0.3% ropivacaine solution compared to a 0.2% solution. However, a more concentrated solution might also make the patient more prone to motor blockade, which is an undesirable effect in spinal surgery.

In the study of Blumenthal et al. (12) the authors investigated the effect of epidural infusion of ropivacaine in comparison to intravenous morphine as pain management after scoliosis surgery. The VAS scores in this study were significantly in favour of the ropivacaine group.

Opioid consumption did not differ significantly, although patients in the treatment group seemed less likely to ask for additional opioid administration. This lack of significance is in accordance with a study conducted by Choi et al. (10) who used a combination of epidural bupivacaine and hydromorphone administration after lumbar spinal fusion. The authors suggested that the observed wide confidence intervals may fail to detect a significant difference. Studies with larger sample sizes than this study or our own may resolve this issue.

The availability of rescue medication is a possible confounding variable. Any medication had to be requested by the patient. Patients may be holding back to ask for rescue medication when needed. The use of patient controlled analgesia (PCA) is a possible solution for this problem. Gottschalk et al. (2) used this approach and provided their patients with an intravenous PCA pump. This way they could demonstrate lower opioid requirements in the ropivacaine group.

The time to mobilisation was not significantly shorter in the ropivacaine group. This is in accordance with other studies in the literature. Fisher et al. (13) conducted a study to compare patient controlled intravenous analgesia (PCIA) to PCEA after lumbar spinal fusion. Their epidural solution contained a combination of fentanyl, bupivacaine and epinephrine. They also found no difference in time to mobilisation between groups. The major difference with our study is that we use a placebo (epidural infusion of NaCl 0.9%) whereas the control group in the study of Fisher et al uses PCIA. Choi et al. (10) failed to detect a difference in mobilisation as well.

In summary, a continuous epidural analgesia infusion with ropivacaine 0.2% after posterior thoracolumbar spinal fusion resulted in significantly lower pain scores at day 0 and day 1. It also resulted in significantly faster discharge rates in the ropivacaine group. Based upon these results, a beneficial effect of the use of epidural local anesthetics post thoracolumbar spinal fusion surgery can be suggested.

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