รายงานวิจัย ฉบับสมบูรณ์

เรื่อง

ผลการใช้ ropivacaine 12 มิลลิกรัม ร่วมกับ Fentanyl 25 ไมโครกรัม เปรียบเทียบกับการใช้ bupivacaine 10 มิลลิกรัม ฉีดเข้าช่องไขสันหลังสำหรับระงับความรู้สึกเฉพาะส่วน ในการผ่าตัดบริเวณต่ำกว่าสะดือ

(Effect of spinal anesthesia with the combination of 25 μg of fentanyl and 12 mg of ropivacaine in comparison with 10 mg bupivacaine alone for surgery at region below umbilicus)

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เสนอต่อ

กองทุนพัฒนาคณะแพทยศาสตร์ ฝ่ายส่งเสริมการวิจัย มหาวิทยาลัยเชียงใหม่

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Title: Effect of spinal anesthesia with the combination of 25 μg of fentanyl and 12 mg of ropivacaine in comparison with 10 mg bupivacaine alone for surgery at region below umbilicus

Key words: spinal, intrathecal, anaesthesia, ropivacaine, bupivacaine, fentanyl

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Abstract

A double blinded randomized controlled trial was conducted in 50 patients undergoing urologic procedures to determine the quality of analgesia, onset and duration of motor block after spinal anaesthesia with a combination of isobaric ropivacaine at 12 mg and fentanyl at 25 µg compared to spinal anaesthesia with 10 mg of isobaric bupivacaine. The patients were allocated randomly to receive spinal anaesthesia with either a combination of isobaric ropivacaine and fentanyl (Group 1, n=25) or isobaric bupivacaine (Group 2, n=25). The median (Q1,Q3) of onset time to Bromage 2 motor block was 9 (6, 12) min and 6 (3, 9) min in Group 1 and Group, respectively. The faster recovery of motor block was statistically significant in Group 1when compared to Group 2, with a median (95% CI) of total duration of 97 (84.76, 109.24) and 183 (171.58, 194.52) min, respectively. The quality of anaesthesia was acceptable in 92% and 96% of patients in Group 1 RF and Group 2 , respectively. It can be concluded that a combination of isobaric ropivacaine at 12 mg and fentanyl at 25 µg for spinal anaesthesia could maintain the quality of analgesia adequately in the majority of patients undergoing endoscopic urologic procedures, and shorten the duration of motor block in the lower extremities during the recovery period when compared to spinal anaesthesia with isobaric bupivacaine at 10 mg.

Introduction

Concern about transient neurologic symptoms (TNS) related to spinal lidocaine (1) has led to the search for alternative spinal local anesthetics, particularly for short operative procedures or ambulatory surgery. Because of its differential sensorimotor block (2,3), ropivacaine could be an alternative. However, a study by Malinovsky et al. (4) failed to demonstrate the advantage of spinal ropivacaine at 15 mg over spinal bupivacaine at 10 mg in terms of adequate analgesia and shorter duration of motor block in endoscopic urologic procedures. The use of a relatively high dosage of intrathecal ropivacaine could produce prolonged motor blockade (5). A reduction in the dose of spinal ropivacaine might shorten motor blockade duration, but the quality of intraoperative analgesia could be reduced (6). Because of evidence supporting enhancement of the spinal analgesic effect on local anaesthetics by fentanyl (7), we conducted this study to prove whether or not the addition of fentanyl (25μg) to a relatively small dose of ropivacaine (12 mg) could provide sufficient anaesthesia and shorten the duration of motor blockade compared to the standard dose of spinal bupivacaine (10mg) in endoscopic urologic procedures.

Method

This study was a double blinded randomized controlled trial.The protocol was approved by the institutional review board of the Faculty of Medicine, Chiang Mai University. The study population consisted of 50 ASA physical status I and II patients, who were 18-75 years old and scheduled for an elective urologic surgery (TURP, URS and litholapraxy) under spinal anesthesia. Patients with partial (on ASA, NSAID) or full coagulopathy; or cardiovascular instability, e.g. uncorrected hypotension, severe pulmonary diseases, pregnancy, neurologic disorders, myopathy and mental disorders; were excluded.

After obtaining written informed consent, each of the 50 eligible patients was randomly assigned to one of two anesthetic treatment groups based on a computer generated envelope-sealed random number.

Group 1 (RF group) received 12 mg of isobaric ropivacaine and 25μg of fentanyl for spinal anesthesia.

Group 2 (B group) received 10 mg of isobaric bupivacaine for spinal anesthesia.

The spinal anaesthetic solution was prepared by the anesthesiologist, who was not involved in caring for the patients or assessing the outcome. To make the volume of 3 ml, 0.9 % NaCl was added to each solution. Spinal block procedure: on arrival in the operating theatre, continuous monitoring with non-invasive arterial blood pressure, pulse oximetry and ECG were commenced and followed by preloading fluid via a suitable vein with 300 ml of Lactate Ringer or 0.9% NaCl solution. The patient was placed in the lateral position. An appropriate lumbar intervertebral space was located. The skin at the site of lumbar puncture was prepared by using the aseptic technique. After removing excess antiseptic solution, the skin at the lumbar puncture area was anesthetized with 0.5-1 ml of 1% lidocaine. A 27 Whitacre needle (Vygon^{R},

UK) was inserted by a midline or lateral approach at the selected intervertebral space (usually at the 3rd and 4th interspace).

When cerebrospinal fluid (CSF) appeared at the distal end of the needle, 3 ml of the study solution was injected over 10-15 s. The patients were placed in supine position immediately after the injection.

Outcome assessment: a blinded investigator, who did not know which solution had been injected, observed the developing block. The extent of sensory block (analgesia to pinprick), degree of lower limb motor block (modified Bromage scale: 0=full movement; 1=inability to raise extended leg, but can bend knee; 2=inability to bend knee, but can flex ankle; and 3=no movement), arterial pressure and heart rate were recorded at 0, 1, 2, 3, 6, 9, 12, 15, 20, 25 and 30 min, and at 30 min intervals thereafter until the regression of the sensation and motor blockade was observed. The pinprick sensation test was carried out every 10 min until complete regression. Hypotension, defined as a decrease of > 30% from baseline systolic blood pressure, was treated with 3-12 mg of intravenous ephedrine. Fluid was replaced as necessary. During the operation, inadequate anesthesia (a patient that complained of pain) was treated with an additional bolus of intravenous fentanyl at 0.75-1.0 μg /kg. The conversion to general anesthesia (GA) was allowed, as deemed necessary by the attending anesthesiologist. During the surgical procedure, the quality of anaesthesia score was recorded by using the following criteria (i.e. 0 = no sensation during procedure, 1 = sensation at the site of surgery, but no pain, 2 = painful sensation and supplemental analgesics required, and 3 = severe painful sensation and GA required. Confirmation of the assessment was tested by using Kappa statistics. (>0.7). After the operation, patients were transferred to the post anaesthetic area. Postoperative pinprick and motor tests were performed every 10 min until complete regression. For those who had not retained a urinary catheter, the time from block placement to first urination was recorded.

Follow up was carried out for 5 days by post anaesthesia follow up nurses, who looked for symptoms of pruritus, urinary retention, headache, transient neurological symptom, backache, other neurological complications and a satisfactory visual analogue score. A case report form was recorded for any symptoms and signs developing after the block and follow up period. Patients who had been discharged from hospital earlier were contacted by phone or mail when appropriate.

Data Management: characteristics of all eligible patients were recorded on the enrollment forms. The random assigned code did not appear in all of the recorded forms. The protocol allowed only the investigator who prepared the drug solutions to disclose the random assignment for each patient. Then, all of the codes were kept in security until the sample size was completed. All records were checked and cleaned for validity before entering into the computer. All of the relevant data were recorded twice into the computer. The random assignment was recorded into the computer in a separated file and then merged with the main file according to the corresponding serial number of each patient. Finally, all of the records were examined by a range and logic check and corrected before further analysis.

Statistical Analysis: the data were summarized by using appropriate statistics (i.e. either mean, sd. or median, interquartile range) to estimate the onset time , quality anaesthesia score, duration of sensory block, maximal motor block and total duration of motor block. An appropriate statistical test, i.e. either the unpaired t-test or Mann Whitney U test, was used to detect the difference in time to recovery from motor block and quality anaesthesia score between the two groups at $p<0.05$. Furthermore, the Chisquare test or Fisher exact test (with an expected value of <5) was used to detect the difference between the two groups in categorical variables at $p<0.05$. Those who violated the protocol

were retained in the assigned group and the intention to treat was used to analyze the data.

Kaplan-meier estimates were used to describe the recovery of motor block (Bromage score = 0).The Log rank test was used to compare the survival curve of motor block between the two groups.

The sample size was calculated to detect the difference in a motor blockade duration of at least 45 min between the two groups at $\beta = 0.10$ and $\alpha = 0.05$.The data were analyzed by using STATA ™ 7.0 (Stata Corporation, Texas ; USA).

Result

Fifty patients were enrolled in this study. Table 1 shows the demographic characteristics and duration of surgery in each group of treatment. The two groups were comparable with respect to age, weight, height and duration of surgery. The average duration (mean±sd.) of surgery was 52.52± 33.76 and 49.08±28.64 min in Group 1 and Group 2, respectively. The spinal anaesthesia was performed with a 27 Whitacre needle (Vygon^{R}, UK) for all patients in each group. All patients were followed up until the end of the study.

Characteristics	Group1 (RF) N = 25	Group2 (B) N=25	P value
Sex male/female (n)	16/9	12/13	0.254*
Age (yr)	53.02 ± 15.96	53.88 ± 14.12	0.84**
Weight (kg)	56.63±11.95	57.45±9.20	0.80**
Height(cm)	160.47±7.34	160.15±8.28	0.90**
Type of procedure (n)			
URS	10	11	0.77*
TURP, TURBT	12	10	
Others	3	4	
Duration of procedure (min)	52.52±33.76	49.08±28.64	0.69**

* Chisquared test

**unpaired t test

Data are presented at mean ± sd or n

Table 1. Demographic data, types of procedure and duration of urologic procedures

Variables	Group 1 (RF)	Group 2(B)	P value
Onset of sensory block to T10 (min)			
Median	9	6	0.08 *
Interquartile range (Q1,Q3)	6,12	3,9	
Duration of sensory block from T10 onset and T10 offset (min)			
Mean±sd.	101.75± 52.65	107.4±36.84	0.77 *
95%CI	77.11, 126.39	90.15, 124.64	
Onset time of motor block, Bromage score =2 (min)			
Median	9	6	0.03 *
Interquartile range	6, 14	3, 8	
Maximal motor block (Bromage score)			
Median			
Min, max	3	3	0.10 *
	0,3	3,3	

*Mann Whitney U test

**unpaired t test

Table 2. Onset of sensory block, duration of sensory block, onset of motor block and degree of motor block.

Table 2 shows the onset times of sensory and motor block, the duration of sensory block from T10 onset to T10 offset, and maximal motor block. The median onset time (Q1,Q3) of the sensory block to T10 was 9 (6,12) and 6 (3,9) in Group 1 and Group 2, respectively. The average duration

time (95% confidence intervals) from T10 onset to T10 offset was 101.75 (77.11, 126.39) min and 107.4 (90.15, 124.64) in Group 1 and Group 2, respectively. The onset of motor block developed significantly sooner in Group 2 than in Group 1 (p =0.03). Complete motor block occurred in all of the patients in Group 2 and in 18/25 (72%) in Group 1.

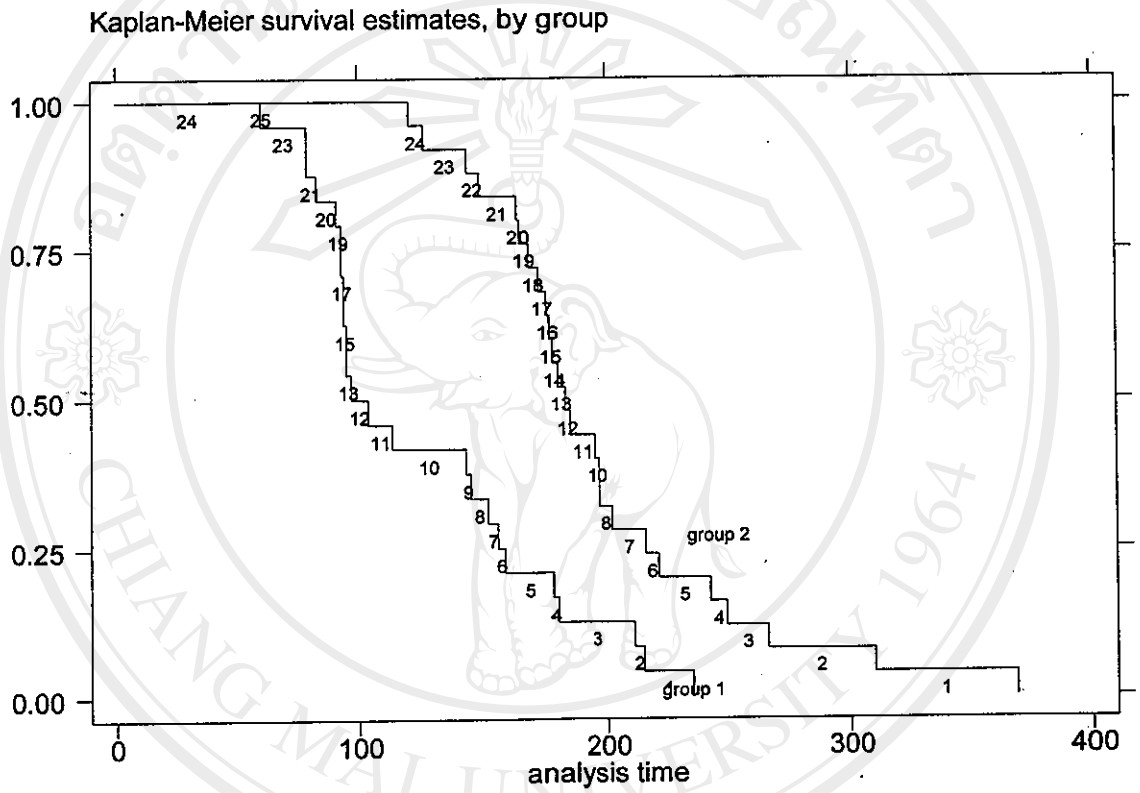

Figure 1. Kaplan-Meier curves of motor block. Group 1 received 12 mg of ropivacaine + 25μg of fentanyl. Group 2 received 10 mg of bupivacaine. This curve demonstrates the probability of motor block (y axis) at time (min, x axis) after spinal anesthesia in each group.

Figure 1 shows the Kaplan-meier curve of the motor block during the recovery period. The median time (95% confidence intervals) to recovery from the motor block was 97 (84.76, 109.24) min and 183 (171.58, 194.52) min in Group 1 and Group 2, respectively. Recovery from the motor block was significantly faster in Group 1 than in Group 2 (p =0.00, log rank test).

Variables	Group 1 (RF) N = 25	Group 2 (B) N =25	P value
Quality anesthesia score during procedures (n)			
0 = no sensation during procedure	17	19	0.52*
1 = sensation at the site of surgery but no pain	6	5	
2 = painful sensation and analgesic/sedatives supplemented	1	1	
3 = severe painful sensation and GA required	1	0	
Satisfaction score			
Median	10	9	0.26**
Min, max	4,10	4,10	

* two tailed, Chisqured test

** Mann Withney-U test

Table 3 Distribution of patients according to various levels of quality anaesthesia score and median of satisfaction score.

The result of the quality of anaesthesia score is shown in Table 3. Seventeen from 25 (68%) patients in Group 1 and 19/25 (76%) in Group 2 felt no pain during the uorologic procedures. Some of the patients (i.e. 6/25 in Group 1 and 5/25 in Group 2) had the sensation of visceral stimulation, but did not request any supplementary sedatives or analgesics. Hence, the quality of anaesthesia was acceptable in 92% and 96% of patients in Group 1 and Group 2, respectively. Although the level of sensory block was high up to T6, two patients (one in each group) still required supplementary sedative and analgesic agents during the urologic procedures (i.e. bilateral orchiectomy in Group 1 and URS in Group 2). The sensory level was not high enough (the maximal sensory block was at L1) in one patient belonging to Group 1 and general anesthesia was therefore given. All patients in each group were followed up until the end of this study.

Table 4 shows the relevant adverse events during the study. Intraoperative hypotension occurred in 4/25 (16%) patients in each group. Six out of twenty five patients in Group 1 developed pruritus in the recovery room, while only 2/25 patients in Group 2 did. However, the difference did not reach a statistically significant level ($p = 0.08$). In the recovery room, 2/25 (4%) patients in Group 1 and 9/25 (24%) patients in Group 2 experienced pain (VAS > 3), and the difference reached a statistically significant level ($p=0.0187$, one sided Fisher's exact test). There was no report of transient neurological symptoms in either group. There was no statistical difference in median satisfaction score between the two groups, with a median (min,max) of 10 (4,10) and 9 (4,9) in Group 1 and Group 2, respectively.

Event	Gr 1 (RF) N=25	Gr 2 (B) N=25	P value
Hypotension (n)			
During procedure	4	4	n.s
Nausea/vomiting (n)			
During procedure	0	0	n.s
At PACU	1	0	
Pruritus (n)			
During procedure	2	0	n.s
At PACU	6	2	0.12*
Pain (VAS > 3) at PACU (n)	2	9	0.02*
Day 1-5 adverse events (n)			
Headache	1	0	
TNS	0	0	
Nausea /vomiting	1	1	
Pruritus	4	0	
Urinary retention	1	0	
Respiratory complications	0	0	

* One sided, Fisher's exact test

Table 4 Adverse events in the operating theatre, the recovery room and ward

Discussion

It can be assumed that the recovery and mobilization of the patients could be faster if the motor block from spinal anesthesia is less intense. In the study by Buckenmaier et al. (8), spinal anesthesia with a small-dose of hyperbaric ropivacaine at 4 mg and fentanyl at 20 μg could provide adequate intraoperative analgesia with minimal motor block . However, this low dose would not be enough to provide adequate intraoperative analgesia and motor block for endoscopic urologic procedures, which require at least a T10 level of spinal anesthesia. Spinal anesthesia with bupivacaine at 10 mg could provide adequate anaesthesia for transurethral resection of the bladder or prostate (4, 9), but the duration of motor blockade could be prolonged for up to 3.5 hours (9). In our study, the duration of motor blockade after spinal anesthesia with bupivacaine at 10 mg was up to 3.1 hours (upper limit of the 95% confidence intervals). This prolonged duration of motor blockade could make patients feel uncomfortable during anaesthesia recovery . Concerning this problem, we took an interest in the motor recovery of the lower extremities after spinal anesthesia with a combination of ropivacine at 12 mg and fentanyl at 25 μg. Our result of ropivacaine having faster recovery from the motor block when compared with bupvacaine is in accordance with a recently published study (10). The faster motor recovery could allow patients to position themselves during the recovery period.

In our study, spinal anesthesia with the combination of plain ropivacaine at 12 mg and fentanyl at 25 μg resulted in a slower onset and less intense motor blockade than spinal bupivacaine at 10 mg. It should be pointed out that an incomplete motor block may increase the risk of lower extremity movements, which can lead to bladder perforation during instrumentation. However, no patient moved or experienced such a complication, despite less intense motor blockade in our study.

Spinal ropivacaine is less potent than spinal bupivacaine by about one half to two thirds.(6, 11). This could explain why 15 mg of spinal ropivacain was less effective than 10 mg of spinal bupivacaine for endoscopic procedures of the lower urologic tract in a previous study by Malinovsky et al. (4). Because of evidence supporting enhancement of the sensory block of spinal local anesthetics by fentanyl (9,12,13), we added fentanyl to spinal ropivacine. In our study, spinal anesthesia with the combination of ropivacaine at 12 mg and fentanyl at 25 μg appeared to be nearly as adequate as spinal bupivacine at 10 mg in endoscopic urologic procedures. However, a larger sample size is needed to detect the small difference. Furthermore, we found that the proportion of patients receiving spinal ropivacaine plus fentanyl, with postoperative pain (VAS score > 3), was significantly lower than the proportion of those who received spinal bupivacaine. This finding is consistent with the result from the study of Dahlgren et al.,(14) , which reports the effect of added sufentanil in hyperbaric bupivacaine spinal block on early postoperative analgesia. Pruritus is a common side effect when intrathecal opioids are used(15). Our study reported pruritus in 24% of patients receiving additional fentanyl for spinal anaesthesia. The administration of spinal opioid may carry a risk of respiratory depression (16). However, there was no report of respiratory depression in our study. Concerning transient neurologic symptoms after spinal ropivacaine (17), our team followed up on all of the studied patients after spinal anesthesia for five days and found no report of transient neurologic symptoms.

In conclusion, the combination of isobaric ropivacaine at 12 mg and fentanyl at 25 μg for spinal anaesthesia could maintain the quality of analgesia in the majority of patients undergoing endoscopic urologic procedures, and shorten the duration of motor block of the lower extremities during the

recovery period when compared to spinal anaesthesia with isobaric bupivacaine at 10 mg.

Acknowledgements:

We would like to thank the faculty research fund of the Faculty of Medicine, Chiang Mai University for supporting this research.

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