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Comparative study of the efficacy and side effects of oral rofecoxib, intrathecal morphine with local anesthetics and intrathecal local anesthetics in patients undergoing anorectal surgery in first 24 hours

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Objective : *To assess the effectiveness and side effects of rofecoxib and compare them with intrathecal morphine in patients undergoing anorectal surgery.*

Setting : *King Chulalongkorn Memorial Hospital*

Design : *Prospective, randomized, controlled study*

Patients : *One hundred and twenty ASA I and II patients undergoing hemorrhoidectomy or fistulectomy were recruited into the study.*

Methods : *Control group received only spinal anesthesia with 1.2 mL of 0.5 % hyperbaric bupivacaine. Group R was given 50 mg of rofecoxib in the morning and Group M was added intrathecal morphine 0.15 mg. Pain verbal numeric scale among three groups along with nausea/vomiting score, pruritus score and other side effects were recorded at 2, 6 and 24 hours.*

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Result : *VNS at 6 hr was better in Group M and at 24 hr both Group M and Group R were better than Group C. The incidences of all side effects were significantly lower in Group C and Group R compared with Group M.*

Conclusion : *This study shows that rofecoxib can reduce post anorectal surgery pain nearly equal to intrathecal morphine and is better than control at 24 hour. The side effects are found less in rofecoxib group.*

Keywords : *Post operative pain, COX-2 selective inhibitors, Intrathecal morphine.*

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สถาบันวิทยบริการ
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ปกรณ์ อุรุโสภณ, พรอรุณ สิริโชติวิทยากร, วัชริน สินธวานนท์, สมรัตน์ จารุลักษณานันท์. การศึกษาเปรียบเทียบผลแก้ปวด และอาการข้างเคียงของการรับประทานยา Rofecoxib การฉีดยา Morphine เข้าไขสันหลังสำหรับผู้ป่วยที่มารับการผ่าตัดบริเวณทวารหนักใน 24 ชั่วโมงแรก. จุฬาลงกรณ์เวชสาร 2547 ม.ค; 48(1): 23 – 30

วัตถุประสงค์ : *เพื่อศึกษาเปรียบเทียบประสิทธิผลและอาการข้างเคียงของยา Rofecoxib กับการฉีด Morphine เข้าไขสันหลัง สำหรับผู้ป่วยที่มารับการผ่าตัดบริเวณทวารหนัก*

ประเภทโรงพยาบาล : *โรงพยาบาลจุฬาลงกรณ์*

รูปแบบการวิจัย : *การศึกษาไปข้างหน้าแบบสุ่ม โดยมีกลุ่มควบคุม*

การคัดเลือกผู้ป่วย : *ผู้ป่วย 120 รายที่มารับการผ่าตัด Hemorrhoidectomy หรือ Fistulectomy ณ โรงพยาบาลจุฬาลงกรณ์ ที่มี ASA physical status I และ II*

วิธีการทำวิจัย : *กลุ่มควบคุม C จะได้รับยาชา 0.5 % hyperbaric bupivacaine 1.2 มล. ฉีดเข้าไขสันหลังสำหรับการผ่าตัด กลุ่ม R จะได้รับประทานยา Rofecoxib 50 มก. ในตอนเช้าก่อนผ่าตัดร่วมไปกับการฉีดยาชาเข้าไขสันหลัง และกลุ่ม M จะได้รับยา Morphine 0.15 มก. ผสมไปกับยาชาฉีดเข้าไขสันหลัง บันทึกอาการปวดหลังผ่าตัดที่เวลา 2, 6 และ 24 ชั่วโมง โดย Verbal Numeric Scale (VNS) และบันทึกอาการข้างเคียง คลื่นไส้อาเจียน อาการคัน*

ผลการทดลอง : *ที่ 6 ชั่วโมง กลุ่ม M มี VNS น้อยกว่ากลุ่ม C และที่ 24 ชั่วโมง กลุ่ม M และ R มี VNS น้อยกว่ากลุ่มควบคุม นอกจากนั้นพบอาการข้างเคียงทุกประเภทในกลุ่ม C และ R น้อยกว่ากลุ่ม M อย่างมีนัยสำคัญทางสถิติ*

สรุป : *จากการศึกษานี้แสดงให้เห็นว่ายา Rofecoxib สามารถลดอาการปวดแผลหลังผ่าตัดทางทวารหนักได้ใกล้เคียงกับการผสมยา Morphine ฉีดเข้าไขสันหลังที่เวลา 24 ชั่วโมง และพบว่ามีอาการข้างเคียงน้อยกว่า เหมาะสมที่จะนำมาใช้ทางคลินิก*

คำสำคัญ : การระงับปวดหลังผ่าตัด, การฉีดยา morphine เข้าในน้ำไขสันหลัง

Anorectal surgery seems to be a minor operation, but it can cause a miserable postoperative period due to its severe unbearable pain. Most of the patients are prescribed opioid analgesics either by parenteral or oral for pain control. Some may receive neuraxial opioids if they are performed under regional anesthesia. Opioids are well known for their side effects such as nausea, vomiting, decreased bowel movement and urinary retention which can lead to delayed discharge from hospital. Recently, there has been a development in new analgesics, COX-2 selective inhibitors have a promising efficiency and decreased side effects compared with conventional NSAIDs.[1] This drug group may be an alternate for the management of postopertive pain especially in ambulatory procedures or others that allow the patient to take oral medication. We, therefore, designed a prospective, randomized, controlled study to assess the effectiveness of rofecoxib and compare it with intrathecal morphine in patients who were undergoing anorectal surgery.

Methods

After the Ethics Committee of the Faculty of Medicine approval and written, informed consent, 120 ASA physical status I and II scheduled for hemorrhoidectomy or fistulectomy at King Chulalongkorn Memorial hospital were enrolled in this study. Patients with any of the following were excluded: contraindication for spinal anesthesia, reaction with conventional NSAIDs and currently chronic use of opioids.

The patients were divided into 3 groups by random table. In Group R (n = 40), 50 mg of rofecoxib was administered orally 2 hours before the procedure and then 25 mg in the next morning. In Group M (n=40), 0.15 mg of morphine was added intrathecally with local anesthetics. In Group C (n=40), only local anesthetics was given intrathecally. Every subject received spinal anesthesia at L 3-4 level in lateral position with 1.2 mL of 0.5 % hyperbaric bupivacaine. Then the patients turned prone, position was adjusted and the surgery was started after losing pin prick sensation around the perinium. Only subcutaneous adrenaline in normal saline was injected around incisional area to provide bloodless field for the operation. All patients stayed in the recovery room for 2 hours and transferred to observatory ward for 24 hours. Diclofenac was ordered as 75 mg intramuscularly every 6 hours as needed.

Another independent anesthesiologist visited the patients and recorded data at 2, 6 and 24 hours after spinal anesthesia. Pain was assessed by verbal numeric scale (0 = no pain, 10 = the worst unbearable pain). Side effects were recorded as follow: nausea and vomiting (0 = no, 1 = nausea, 2 = vomiting, 3 = severe nausea or vomiting and needed medication), pruritus (0 = no, 1 = mild itching, 2 = moderate itching, 3 = severe itching and needed medication). Urinary retention and catheterization were noted as yes or no and times. Bleeding tendency and other GI symptoms were also assessed. The patients who required diclofenac were marked, along with the total dose of diclofenac received. Patient's satisfaction for postoperative pain management was assessed by verbal numeric scale (0 = totally unsatisfaction, 10 = the highest satisfaction).

The sample size as 120 was estimated for this study to detect a 50% reduction in pain score at α = 0.05, β = 0.01. Data were expressed as mean$\pm$

SD or range. Ordinal variables were analyzed by χ^2 test. Continuous variables were analyzed by ANOVA. For multiple comparison between groups, t-test and Mann-Whitney-U test with Bonferroni correction were used. A p value < 0.05 was considered statistically significant.

Results

There was no difference among the groups in demographic data, ASA physical status and operation time (Table 1).

The pain verbal numeric scale (VNS) was not different at 2 hours after spinal anesthesia. At 6 hours, VNS in Group M was significantly lower than Group C ($p < 0.01$). And at 24 hours, VNS in Group R and M were not difference, and both were significantly lower than Group C ($p < 0.01$). Ranges of VNS were demonstrated as in Table 2. The number of patients who required diclofenac was significantly different among the three groups (Table 3); however, there was no difference in total dose received (108 $\pm$ 54, 113 $\pm$ 53 and 101 $\pm$ 44 mg respectively).Table 3 showed the number of patients who experienced side effects including nausea and vomiting, pruritus, urinary retention and urinary catheterization. They were significantly higher in Group M compared with Group R and C in all aspects. The patients who needed medication for nausea and vomiting and pruritus were demonstrated only in Group M. All patients who complained of difficult voiding, needed one time of intermittent catheterization, except two patients in Group M needed 2 and 4 times. None of patients had bleeding tendency or other GI symptoms.

Patient's satisfaction scores were high in acceptable level (> 7) and there was significant difference in Group R and M compared with Group C (Table 4).

Table 1. Demographic and base line data.

	Group R (n = 40)	Group M (n = 40)	Group C (n = 40)
Age (yr)	43 $\pm$ 11	44 $\pm$ 14	42 $\pm$ 13
Weight (kg)	67 $\pm$ 11	67 $\pm$ 16	67 $\pm$ 15
Height (cm)	165 $\pm$ 9	165 $\pm$ 9	164 $\pm$ 9
Sex (M/F)	34 / 6	33 / 1	29 / 11
ASA status I/II	35 / 5	29 / 11	29 / 11
Operation time (min)	45 $\pm$ 30	38 $\pm$ 22	41 $\pm$ 22

Data are shown as number of patients or mean $\pm$ SD

No significant intergroup difference was observed.

Table 2. Verbal Numeric Scale Pain Scores (VNS).

	Group R (rofecoxib)	Group M (IT morphine)	Group C (control)
At 2 hrs - mean±SD	0 ± 0.2	0	0.1 ± 0.8
- min-max	0 - 1	0	0 - 5
At 6 hrs - mean±SD	2.1 ± 2.6	0.7 ± 1.6*	3.4 ± 3.0
- min-max	0 - 10	0 - 6	0 - 10
At 24 hrs - mean±SD	2.1 ± 2.5*	1.1 ± 1.9*	4.0 ± 2.4
- min-max	0 - 8	0 - 7	0 - 9

*p <0.01 Compared with group C

Table 3. Number of patients who required diclofenac and had side effects.

	Group R	Group M	Group C	P value*
● Required diclofenac	9 (22.5 %)	2 (5 %)	20(50 %)	P < 0.001
● Nausea/vomiting	0	10 (25 %)	4(10 %)	P = 0.002
Nausea	0	4	4	
Vomiting	0	3	0	
Severe vomiting	0	3	0	
● Pruritus	1 (2.5 %)	18 (45 %)	1 (2.5 %)	P < 0.001
Mild	1	17	1	
Moderate	0	0	0	
Severe	0	1	0	
● Urinary retention	4 (10 %)	15 (37.5 %)	8 (20 %)	P = 0.012
● Urinary catheterization	4 (10 %)	15 (37.5 %)	8 (20 %)	P = 0.012

* Group M compared with group R and C

Table 4. Satisfaction scores.

	Group R	Group M	Group C
Satisfaction scores (0-10)	8.5 ± 1.5*	9.1 ± 1.3*	7.5 ± 1.8

* p < 0.001 compared with group C

Discussion

Parenteral opioids are commonly used to alleviate pain after anorectal surgery[2] and their side effects are unavoidably noted. There have been studies on the use of other methods to control the pain. Vinson-Bonnet *et al*. showed that local infiltration with ropivacaine in anesthetized patient improved pain control after hemorrhoidectomy during the first 6 hours.[3] Morisaki *et al*. reported that local infiltration prolonged postoperative analgesia in patients undergoing hemorrhoidectomy with spinal anesthesia.[4] And, in his study, continuous epidural analgesia was used for pain control. At our institution, however, spinal anesthesia is usually performed for this type of surgery and some anesthesiologists add 0.1-0.15 mg of morphine intrathecally. Apparently, there is some disadvantage of the technique due to its high rate of side effects despite its effective pain control. From the study by Charuluxananan *et al*., intrathecal morphine prolonged the effect of analgesia as long as 36-48 hours after cesarean section [5]; however, the later studies by the same group showed a high rate of side effects that included 63 % of itching[6] and 25 % of nausea and vomiting.[7] Moreover, urinary retention and catheterization could occur which might cause hospital-acquired infection.[8]

COX-2 selective inhibitors gain more recognition in the management of postoperative pain especially in orthopedic surgery. Reuben *et al*. reported that rofecoxib reduced pain score during the postoperative period after total knee replacement in both resting and ambulating positions without any effect on coagulation.[9] Therefore, we chose rofecoxib for our study to avoid all the side effects mentioned above, especially bleeding tendency, which could lead to a major problem in patients after hemorrhoidectomy.

This study showed no difference in pain control at 2 hours after spinal anesthesia, which may be explained by the residual effect of intrathecal bupivacaine. At 6 hours, there was no significant difference when compared to VNS in rofecoxib group with either morphine or control group. However, at 24 hours, VNS in rofecoxib group was not different from the morphine group and both were lower than the control group. The numbers of patients who required diclofenac were less in the rofecoxib and morphine groups. These evidences supported that rofecoxib reduced pain after anorectal surgery nearly as effective as intrathecal morphine at 24 hours and better than control. Side effects were found less in rofecoxib group compared with morphine group and they were no need of medication. Also, there was no report of bleeding problem or other GI symptoms, which confirmed the advantage of COX-2 selective inhibitors.[10]

Patient's satisfaction scores were equally high in both the rofecoxib and the morphine groups, even though VNS in rofecoxib group was not comparable with the morphine group at all times. This may indicate the degree of dissatisfaction of the patients toward the side effects of morphine.

Conclusion

For post anorectal surgery, rofecoxib is nearly as effective as intrathecal morphine in pain control at 24 hrs with less unfavorable side effects. Since it is safe and simple to administer, it may be suitable for ambulatory settings.

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