Preliminary Study: Comparation Study between Parecoxib 40 mg iv and Morphine 5 mg iv As Postoperative Analgesics Following Gynecologic Laparatomy Surgery

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Tujuan: Membandingkan efektivitas Parecoxib 40 mg iv dengan Morfin 5 mg iv dalam 24 jam pertama pascaoperasi laparotomi ginekologi.

Bahan dan cara kerja: Penelitian pendahuluan ini yang berupa penelitian acak tersusun dilakukan pada 20 pasien di RSCM, dibagi dalam kelompok eksperimen (40 mg iv Parecoxib) dan kelompok kelola (Morfin 5 mg iv). Pemantauan dilakukan selama 24 jam. Efektivitas diukur dengan t test dengan variabel VAS (Visual Analog Scale), MAP, denyut jantung, efek samping, dan dosis penanggulangan yang diperlukan pada efek samping.

Hasil: Tidak terdapat perbedaan bermakna antara kedua kelompok yang berhubungan dengan VAS, MAP, denyut jantung, nausea muntah, dan pethidin tang diperlukan.

Kesimpulan: Tidak terdapat perbedaan bermakna antara kelompok Parecoxib 40 mg iv dan Morfin 5 mg iv sebagai analgesik pascabedah pada laparotomi ginekologi.

[Maj Obstet Ginekol Indones 2006; 30-4: 223-8]

Kata kunci: ginekologi, laparotomi, analgesia, terapi

Objective: *To compare the efficacy of Parecoxib 40 mg iv (COX2 selective inhibitor) with Morphine 5 mg iv in the first 24 hours in post operative gynecologic laparotomy surgery.*

Materials and methods: *A preliminary study of clinical randomized controlled trial had been conducted involving 20 subjects in Dr. Cipto Mangunkusumo Hospital. Subjects were recruited according to independent parallel design, which were categorized as experimental group for parecoxib 40 mg iv treatment and control group fo morphine 5 mg iv treatment. The subjects were monitored for 24 hours (0 min, 10 min, 6 hr, 12 hr, 18 hr and 24 hr) respectively and the effectiveness were examined using independent T-test with variables of VAS (Visual Analog Scale), MAP, heart rate, side effects, and rescue dose needed (pethidine bolus IV) to those groups, $p < 0.05$ was significant.*

Results: *There were no significant difference were found between parecoxib 40 mg iv and morphine 5 mg iv treatment related to VAS, MAP, heart rate, nausea, vomitus, and pethidine needs in the postoperative gynecologic laparotomy surgery.*

Conclusions: *The difference between parecoxib 40 mg iv and morphine 5 mg iv as post operative analgesics were not significant in postoperative gynecologic laparotomy subjects.*

[Indones J Obstet Gynecol 2006; 30-4: 223-8]

Keywords: *gynecology, laparotomy, analgesia, treatment*

INTRODUCTION

Traditionally, pain had been defined as acute or chronic pain, pain that lasted for a short time, or pain that continued or recured for a longer period. But these division were not one hundred percent correct, because acute pain could become chronic when untreated and chronic pain could have acute exacerbations.[1,2] Many ways could effectively treat acute and chronic pain. Each of these options had its own benefits and risks, no single option was right for every patient.

Treatment options for acute and chronic pain:[3] 1) NSAIDs: nonselective and COX-2 selective; 2) Opioids; 3) Local anesthesia; 4) Adjuvant therapy, etc.

Opioid analgesics were usually considered a standard drugs for analgesic efficacy, but physician and patient concern about their side effects might contribute to the problem of under management of pain. Opioid analgesics were associated with adverse effects that limited their utility in the hospital, the most dangerous was respiratory depression. Nausea, vomiting, and constipation occurred frequently and were often intolerable.[4,5] The addition of nonopioid analgesic could improve pain control and minimize adverse effects while decreasing the needed dosage for opioids. COX-2 selective inhibi-

tion e.g. parecoxib reduced pain and inflammation without the adverse effects traditionally associated with COX-1 inhibition or opioids.[6,7]

Because pain was often under treated there was urgent need to educate both professionals and patients on effective safe management of pain and to investigate new analgesic treatments to fill this need.

Under treated pain could cause discomfort, fear, anxiety, sleeplessness, and increased blood pressure and heart rate, resulting longer recovery times and unnecessary use of health care resources. Patients needed to be educated about pain relief, what to expect and how to report both their pain and the degree of pain they were experiencing, and the healthcare professional should use analgesics that optimized pain relief while limiting side effects.

COX-2 selective inhibition reduced pain and inflammation without the adverse events traditionally associated with COX-1 inhibition.

Hypothesis: parecoxib had better efficacy as post operative analgesic in gynecologic surgery than morphine.

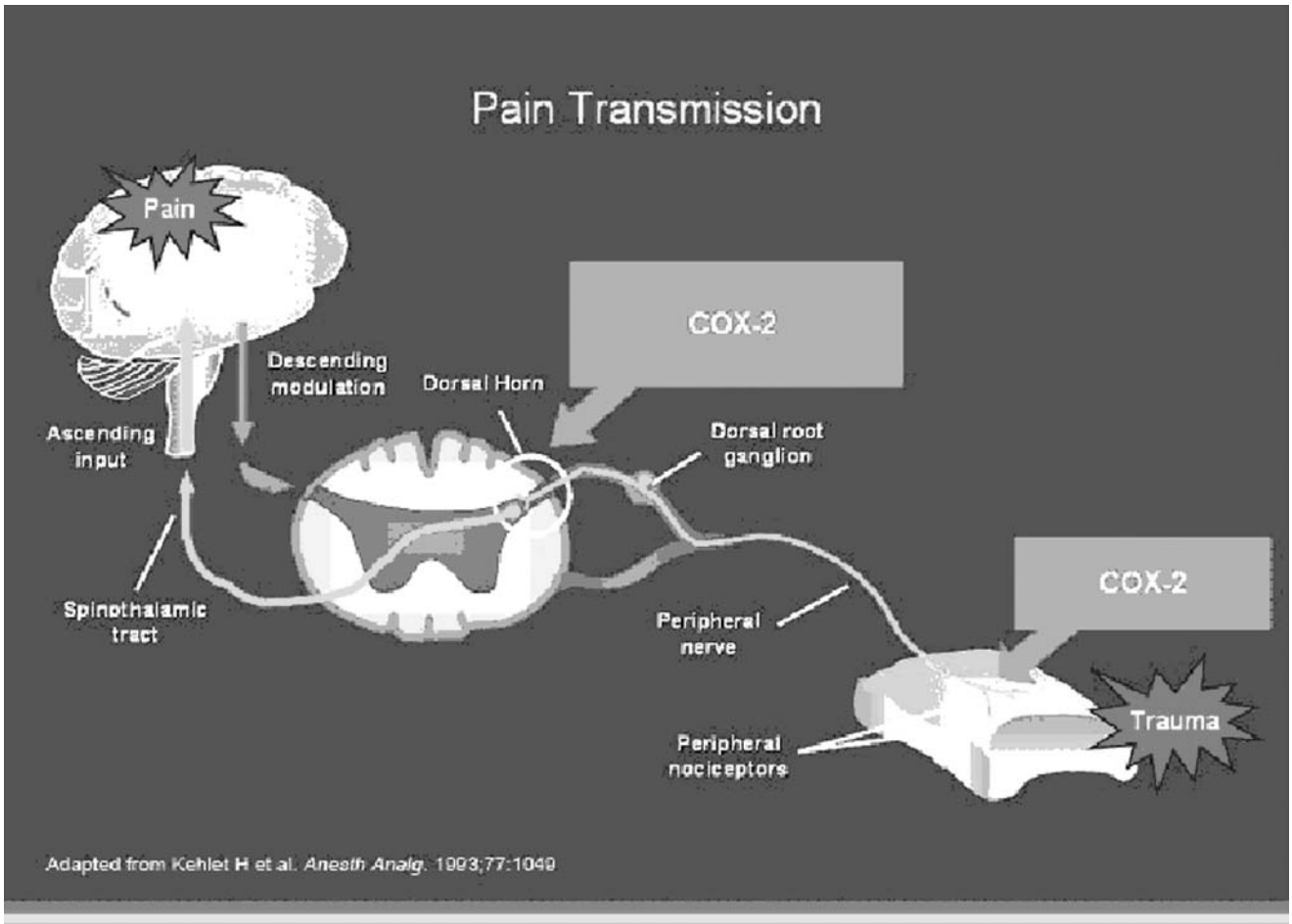


Figure 1. This figure illustrated the pathways of pain, pain was transmitted as a nerve signal, and pain response was a complex process that involves both peripheral nervous system (PNS) and central nervous system (CNS). The transduction of noxious stimuli typically began with peripheral nociceptors. Signals from these nociceptors travelled to the dorsal horn of the spinal cord and then along the spinothalamic tract to the thalamus and cortex of the brain. COX-2 contributed to increase pain sensitivity peripherally at the nociceptor as well as centrally at the dorsal horn.[8]

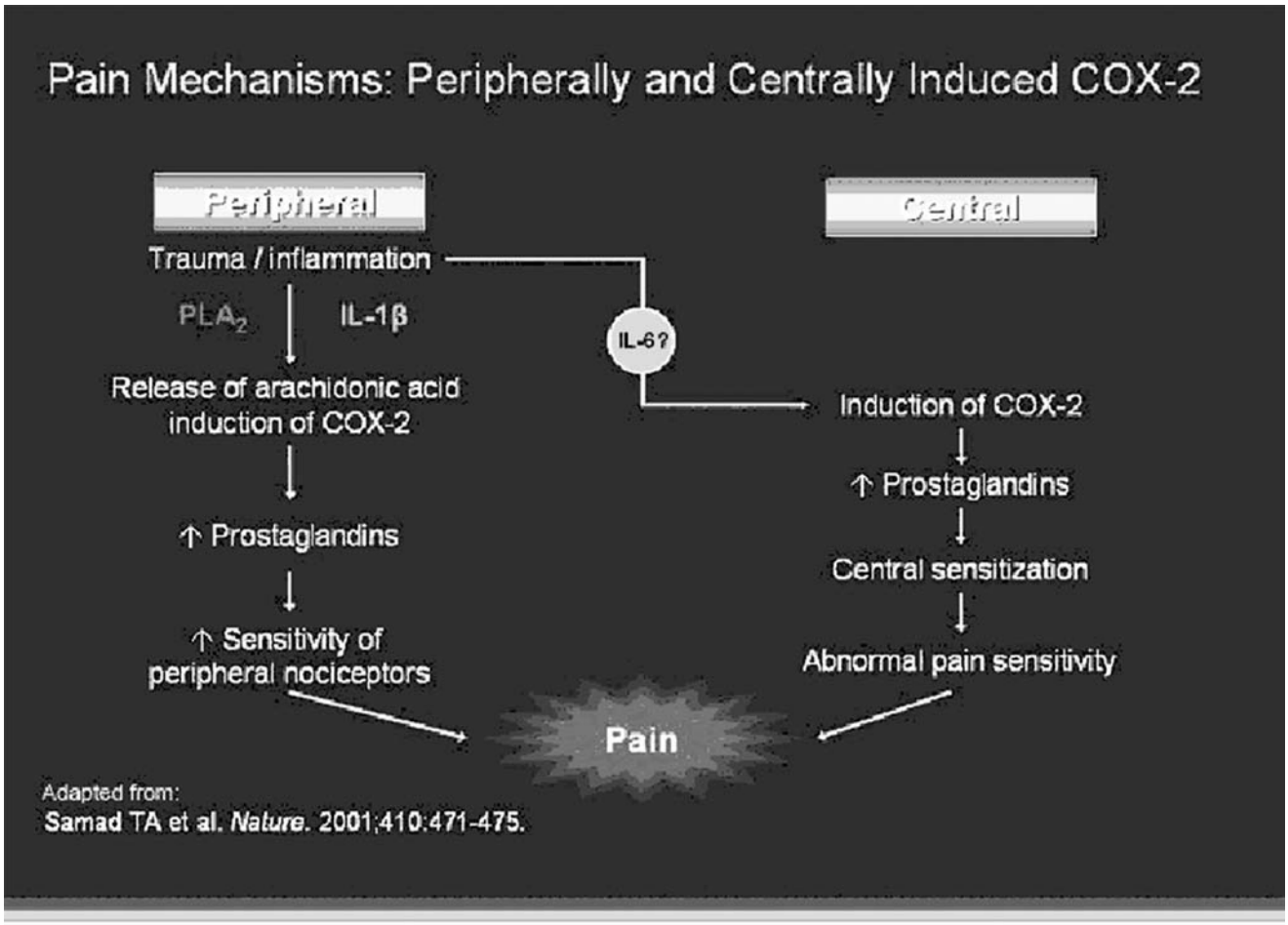


Figure 2. COX-2 played an important role in both peripheral and central mechanisms of pain, contributing to the development of inflammatory pain sensitivity. Induction of COX-2 in the CNS resulted in an increased production of central prostaglandins, which were involved in central sensitization.[9]

METHODS

Twenty patients scheduled for elective surgery were studied prospectively. After acquisition of ethical clearance and informed consent these patients were admitted to the study, age between 20 and 50 with normal body weight (± 20%), good general condition, underwent elective gynecologycal surgery with general anesthesia in Dr. Cipto Mangunkusumo Hospital, Jakarta.

They were divided into two groups in random: experimental group (Parecoxib group) and control group (Morphine group). All patients were premedicated with 2.5 mg midazolam and 50 mg pethidine. 10 patients received 40 mg Parecoxib IV post operatively; the other 10 patients received 5 mg morphine post operatively. All of the patients were monitored for 24 hours (0 min, 10 min, 6 hr, 12 hr, 18 hr and 24 hr respectively) started in the PACU and in the ward, asessment of the variables including: VAS (Visual Analog Scale), MAP, heart rate, side effects, and rescue dose needed (pethidine bolus IV).

Parecoxib and morphine were given to patients when they started complaining pain.

Pain Score (VAS)

Asessment start from the first 10 minute, 6 hr, 12 hr, 18 hr and 24 hr post operative respectively.

MAP and Heart Rate

MAP were computed using variable diastolic and systolic blood pressure. Studied in 24 hour in the same period as above as VAS and heart rate.

Side Effects

The side effects in the both group were noted: nausea, vomitus, and pruritus.

Pethidine Rescue Dose

Were given intravenously when the VAS value above 50.

Statistical Analysis

Statistical analysis for this clinical trial of parecoxib 40 mg iv and morphine 5 mg iv were using unpaired T-test, p value < 0.05 were considered significant.

RESULTS

Anthropometrical Characteristics

Twenty patients were included in preliminary study, the age average were 39.5 years in parecoxib and 41.2 years in morphine group. There were no differences in body weights between parecoxib (54.3 kg) and morphine (54 kg).

Table 1. Anthropometrical Characteristics between Parecoxib 40 mg iv and Morphine 5 mg iv Group (n = 20)

Variable	Mean (SD)			
	Parecoxib 40 mg iv		Morphine 5 mg iv	
Age (years)	39.5	(8.18)	41.2	(7.24)
Body Weight (kg)	54.3	(9.35)	54	(6.04)
Height (cm)	156.7	(6.11)	158.4	(3.20)
Systolic Blood Pressure (mmHg)	126	(11.74)	114.8	(9.85)
Diastolic Blood Pressure (mmHg)	81	(7.38)	72.5	(7.91)
Heart Rate (times/ minute)	81.3	(9.48)	84.2	(9.82)

Comparison between Parecoxib 40 mg iv and Morphine 5 mg iv in VAS, MAP, and Heart Rate

Table 2 showed the comparison of VAS, MAP, and heart rate that were monitored for 24 hours between patients who were treated with parecoxib 40 mg iv and morphine 5 mg iv. There were no significant differences between the groups, p value > 0.05.

Table 2. The Differences between Parecoxib 40 mg iv and Morphine 5 mg iv Group in VAS, MAP, and Heart Rate

Variable	Mean (SD)				95% CI		*p*
	Parecoxib 40 mg iv		Morphine 5 mg iv		Lower	Upper	
VAS							
0 minute	71	(23.78)	72	(14.76)	-19.59	17.59	0.276
10 minute	51	(20.66)	55	(7.82)	-18.67	10.67	0.077
6 hr	39.50	(22.29)	36.50	(12.70)	-14.05	20.05	0.191
12 hr	37	(14.76)	35.50	(14.42)	-12.21	15.21	0.812
18 hr	33.50	(12.92)	33.50	(11.07)	-11.30	11.30	0.601
24 hr	34.50	(11.17)	29.50	(10.66)	-5.26	15.26	0.682
MAP							
0 minute	92.20	(12.19)	85.07	(14.27)	-5.33	19.60	0.503
10 minute	91.60	(13.28)	88.7	(14.31)	-10.07	15.87	0.949
6 hr	91	(16.71)	83.83	(11.11)	-6.16	20.50	0.589
12 hr	90.33	(9.09)	83	(10.82)	-2.06	16.72	0.797
18 hr	85	(9.33)	85	(9.33)	-8.77	8.77	0.913
24 hr	87.67	(6.86)	86	(8.43)	-5.56	8.89	1.000
Heart Rate							
0 minute	89.1	(18.28)	89	(18.09)	-16.99	17.19	0.910
10 minute	87.4	(17.94)	84.8	(20.24)	-15.37	20.57	0.598
6 hr	84.5	(10.87)	89	(15.81)	-17.25	8.25	0.600
12 hr	88.4	(13.06)	88.4	(14.96)	-13.19	13.19	0.900
18 hr	88.4	(8.88)	87.6	(9.28)	-7.73	9.33	0.956
24 hr	85.4	(6.87)	87.4	(9.14)	-9.60	5.60	0.774

Nausea, Vomitus, and Pruritus between Parecoxib 40 mg iv and Morphine 5 mg iv

Both parecoxib and morphine groups had not significant difference in side effects of nausea, vomitus, and pruritus.

Table 3. The Differences Between Parecoxib 40 mg iv and Morphine 5 mg iv Group in Nausea, Vomitus, and Pruritus

Group	Parecoxib 40 mg iv n (%)	Morphine 5 mg iv n (%)	Total	*p*
Nausea				
Yes	7 (70)	7 (70)	14	> 0.05
No	3 (30)	3 (30)	6	
Vomitus				
Yes	3 (30)	2 (20)	5	> 0.05
No	7 (70)	8 (80)	15	
Pruritus				
Yes	0 (0)	0 (0)	0	> 0.05
No	10 (100)	10 (100)	20	

Rescue Drug Dose

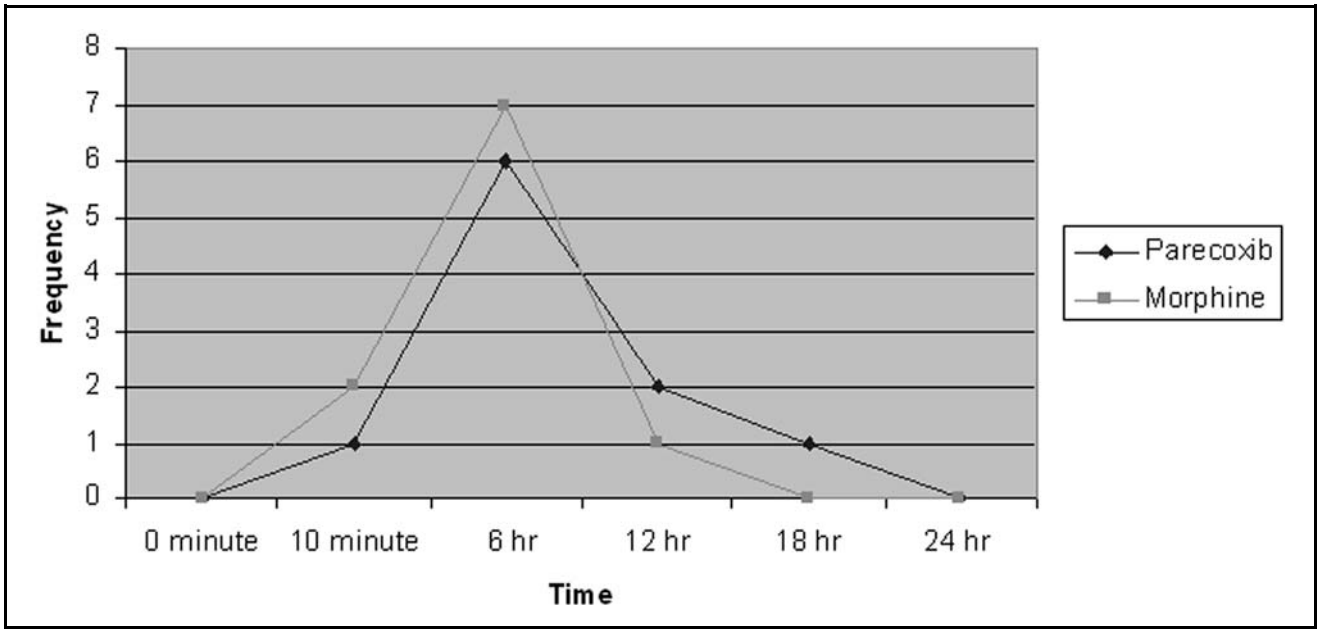
Studied the consumption of the pethidine. In 10 minutes, patients in the morphine group got more pethidine than parecoxib group but there were not significant difference. After 10 minutes until 24 hours there were not significant differences either.

DISCUSSION

In our hypothesis, we thought that parecoxib iv would have superior efficacy over morphine iv, as we could see from the studies by Barton et al and Rasmussen et al[10,11] that had demonstrated single dose parecoxib 40 mg iv had a rapid onset and magnitude of analgesia, and superior analgesic efficacy to a single dose morphine 4 mg intravenously, in our study we used parecoxib 40 mg iv comparable to 5 mg morphine (1 mg higher dose), that's why we found that the difference in analgesia and efficacy not significant in the statistic analysis.

In studies to date, parecoxib sodium had properties that were typical of COX-2 selective agents; it was nonulcerogenic and did not affect platelet function/bleeding.[12-14] In addition, parecoxib sodium was useful in combination with opioids as a part of a multimodal regimen to relieve pain. These opioid-sparing effects had been observed in patients who underwent total knee arthroplasty[15] and laparoscopic cholectystectomy.[16] In our study, the used of pethidine as rescue dose showed these phenomena in combination with parecoxib or morphine.

In conclusion, this study indicated that the COX-2-selective analgesic anti-inflammatory agent parecoxib was an effective analgesic in combination with opioids (pethidine) but we still needed bigger population to know more findings suggested parecoxib would be an effective and well-tolerated in-



Graphic 1. The Frequencies of Pethidine Needed in Parecoxib and Morphine Treatment Group

jectable analgesic for management of postoperative pain after gynecologic surgery.

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