ประสิทธิผลของยา buprenorphine เปรียบเทียบกับยา mepridine hydrochloride ในการบรรเทาอาการปวดระหว่างเจ็บครรภ์คลอด

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บทคัดย่อ การศึกษานี้ต้องการศึกษาประสิทธิผลของยา buprenorphine ในการระงับความเจ็บปวดระหว่างการเจ็บครรภ์เปรียบเทียบกับประสิทธิผลของยา mepridine ว่าแตกต่างกันหรือไม่ โดยการศึกษาแบบ blinded, random, prospective ในสตรีตั้งครรภ์ที่เจ็บครรภ์ระยะ early active จำนวน 325 คน พบว่า การใช้ยา buprenorphine เข้าทางหลอดเลือดดำสามารถระงับความเจ็บปวดระหว่างการเจ็บครรภ์ได้นานกว่าการให้ยา meperidine เข้าทางหลอดเลือดดำ แต่ประสิทธิผลของยา buprenorphine ชนิดอมใต้ลิ้นในการระงับความเจ็บปวดระหว่างการเจ็บครรภ์ต่ำกว่าการให้ยา meperidine เข้าทางหลอดเลือดดำ การให้ยา buprenorphine เข้าทางหลอดเลือดดำมีผลให้ช่วงระยะเวลารอคลอดยาวนานขึ้นเมื่อเปรียบเทียบกับกลุ่มที่ได้รับยา meperidine เข้าทางหลอดเลือดดำ (322.85 ± 185.69 VS. 257.62 ± 118.54 นาที) แต่วิธีการคลอดของทั้ง 2 กลุ่มไม่แตกต่างกัน ยา buprenorphine และ meperidine มีผลกดการหายใจทารกหลังคลอด แต่ไม่มีผลต่อการเกิดภาวะตกเลือดหลังคลอดหรือทารกน้ำหนักตัวน้อย การให้ยา promethazine ร่วมกับยาระงับปวดจะช่วยให้ประสิทธิผลของยาระงับปวดสูงขึ้น นอกจากฤทธิ์ในการช่วยลดการเกิดอาการคลื่นไส้อาเจียน

สรุป การให้ยา buprenorphine เข้าทางหลอดเลือดดำสามารถระงับความเจ็บปวดระหว่างการเจ็บครรภ์ได้นานกว่าการให้ยา meperidine เข้าทางหลอดเลือดดำ แต่ประสิทธิผลของยา buprenorphine ชนิดอมใต้ลิ้นในการระงับความเจ็บปวดระหว่างการเจ็บครรภ์ต่ำกว่าการให้ยา meperidine เข้าทางหลอดเลือดดำ

Abstract **Comparative study between buprenorphine and meperidine in relief of the labor pain**

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OBJECTIVE : The aim of the study was to assess the efficacy in relif of labor pain between buprenorphine and mepridine hydrochloride.

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STUDY DESIGN : Prospotive, randomized study.

SETTING : Department of Obstetrics and Gynecology, Vajira hospital.

PARTICIPANTS : Three handred and twenty five parturients were randomly allotted to 5 groups an received sublingual buprenorphine, intravenous meperidine, sublingual buprenorphine plus intravenous promethazine, intravenous meperidine plus promethazine, intravenous buprenorphine plus promethazine respectively.

MAIN OUTCOME MEASURES : The number of the parturients who felt better, time from active labor until giving the birth, method of delivery, and untoward or side effects on the parturients and newborns.

RESULTS : Intravenous buprenorphine could relieve labor pain longer and more efficacious than intravenous meperidine (38.46% versus 6.15% felt better for an interval more than thirty minutes). But sublingual buprenorphine was less efficacious than intravenous meperidine (38.46% and 49.23% versus 50.75% and 56.81%, $P<0.05$). For the adverse effects, intravenous buprenorphine prolonged an interval between active phase of the labor and giving the birth significantly compared with intravenous meperidine (322.85 ± 185.69 VS. 257.62 ± 118.54). However it remain no effect on method of delivery. Both buprenorphine and meperidine could depress on the infant's respiration but did not increase an incidence of post-partum hemorrhage of the partureints or low birth weight infants. The prescription of promethazine in combination with the analgesic agents could also improve the efficacy in relief of labor pain besides the prevention of nausea and vomit.

CONCLUSIONS : The efficacy of intravenous buprenorphine in relief of the labor pain was better than of intravenous meperidine but the efficacy of sublingual buprenorphine is less than intravenous meperidine.

KEY WORDS : buprenorphin, meperidine, relief, labor pain.

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Introduction

The most common analgesic agent used in most Thai hospitals is meperidine hydrochloride (Pethidine®). The purpose of this study is to search another alternative convenient or higher efficay analgesic agent. Buprenorphine (Temgesic ®) is an analgesic agent for which initial clinical studies indicated that it was extremely potent and had much longer duration of action for pain relief than established analgesia[1,2] Also, it was available in different form. (sublingual, intramuscular and intravenous forms), which makes it be convenient to administer.

The objective of this study is to compare meperidine with buprenorphine with reference to efficacy and side effects profile on the parturients, the progression of labor, and the depressant effect on the newborn.

Materials and Methods

This prospective comparative randomized study was carried out at the department of Obstetrics and Gynecology, Vajira hospital between September 1995 and April 1996 on a sample of three hundred and twenty five term pregnant women who had regularly visited the antenatal clinic of Vajira hospital with no known sensitivity to meperidine hydrochloride or buprenorphine hydrochloride, no respiratory of hepatobiliary system diseases and no history of suspicious of drug addiction and were in early active labor. The parturients were randomly allotted to five groups of 65 parturients in each group. During the active phase of labor, when the pain made them feel discomfort, meperidine hydrochloride 1-1.5 mg/kg. administered intravenously in the first group, buprenorphine hydrochlored 0.4 mg. sublingual form was given to the parturients in group 2, buprenorphine hydrochloried 0.4 mg. sublingual and intravenous promethzine hydrochloride 50 mg. (Phenergan ®) was given in group 3, meperidine hydrochloride 1-1.5 mg/kg. and promethazine hydrochloride 50 mg. was administrated intrave nously in group 4, and buprenorphine hydrochloride 0.3 mg. and promethzine hydrochloride 50 mg. was administrated intravenously in group 5. The pain prior to the administration of analgesic agents was assessed by means of the linear analgesic scale[3,4] and categorized into 5 levels according to pain intensity, namely, interval between 0-2 cm. long of the linear analgesic scale was equivalent to level 1, interval between more than 2 and 4 cm. long was equivalent to level 2, interval between more than 4 and 6 cm. long was equivalent to level 4, more than 8 to 10 cm. was equivalent to level 5, The assessment of the pain was blindly evaluated by the parturients and well trained observers every 5 minutes for he first half an hour, and then every 15 minutes. The relief of pain was graded as poor when the parturients did not feel better after giving the medication, as fair when the parturients felt slightly better for and interval of less than 15 minutes, as good when the parturients felt better for an interval of about 15-30 minutes, as very good when the parturients felt better for an interval of more than 30 minutes to an hour, and as outstanding when to parturients felt beter for an interval of more than one hour. The uterine contraction, progression of the labor, vital signs of the parturients, fetal heart rate, and untoword or side effects were also observed and recorded. Pelvic examination was evaluated every one to three hours. In case of poor uterine contraction, the oxytocin 5-10 IU was added to 5% dextrose in half strength normal saline 1000 ml. to keep good uterine contraction. The relief of pain, an interval between the early active phase of the labor and giving the birth, the method of delivery, birth weight, the neonate whose 5 minute apgar scores was less than 7 or naloxone (Narcan ®)[5] was given, and the parturients who vomited or got nausea orpostpartum hemorrhage between group 1 with group 2, group 3 with group 4, and group 4 with 5 were compared. The statistical comparison of the results included two tailed t-test, the significance of the difference between means of the samples and Chi-square test for contingency tables. For all analyses statistical significance was considered at a value of $P<0.05$. Averages were reported as mean $\pm$ 1 SD.

Results

Table 1 shows no significant difference in age, height, weight, gestational age, and the number of the parous women between group 1

(intravenous meperidine) with group 2 (sublingual buprenorphine), group 3 (sublingual bupenourphine plus intravenous promethazine) with group 4 (intravenous meperidine plus promethazine), group 4 with group 5 (intravenous buprenorphine plus promethazine). For the number of the parous women, only statistically significant difference between group 3 and group 4 was found.

Table 1 General characteristics.

	Age	Height	Weight	Gestational age
Group 1	24+6.14	156.60+6.07	65.12+8.31	39.17+1.29
	NS.	NS.	NS.	NS.
Group 2	24.31+4.90	155.98+5.31	64.20+7.57	38.28+1.96
Group 3	25.78+5.42	154.75+5.4	64.17+754	39.10+1.00
	NS.	NS.	NS.	NS.
Group 4	24.88+5.3	155.10+4.52	63.17+8.36	38.98+1.59
	NS.	NS.	NS.	NS.
Group 5	24.57+6.43	155.8+5.27	65.54+8.06	38.83+0.68

	Number of the parous women			
	0	1	2	3
Group 1	41 (63.08%)	16 (24.62%)	4 (6.15%)	4 (6.15%)
	NS.			
Group 2	41 (63.08%)	20 (30.77%)	0 (0.0%)	4 (6.15%)
Group 3	37 (56.9%)	12 (18.46%)	13 (20.0%)	3 (4.60%)
	P<0.05			
Group 4	53 (81.55%)	8 (12.30%)	4 (6.15%)	0 (0.00%)
	NS.			
Group 5	49 (75.38%)	8 (12.30%)	7 (10.78%)	1 (1.54%)

Table 2 shows the number of the parturients augmented with oxytocin. Only the deffence between the number of the parturients of group 3 with group 4 was found to be significant. 28 of 65 parturients (43.09%) in group 3 compared with 49 of 65 parturients (75.38%) in group 4 were augmented.

Table 2 The number of the parturients were augmented with oxytocin.

	Augmentation with oxytocin	
	Yes	No
Group 1	16 (24.62%)	49 (75.38%)
NS		
Group 2	12 (18.46%)	53 (81.54%)
Group 3	28 (43.09%)	37 (56.91%)
P<0.05		
Group 4	49 (75.38%)	16 (24.62%)
NS		
Group 5	41 (63.08%)	24 (36.92%)

Table 3 The level of labor pain before giving the analgesic agents.

	The level of labor pain before giving the medication				
	1	2	3	4	5
Group 1	0 (0.0%)	12 (18.46%)	37 (56.92%)	16 (24.62%)	0 (0.0%)
P<0.05%					
Group 2	1 (1.54%)	32 (49.23%)	24 (36.93%)	8 (12.3%)	0 (0.0%)
Group 3	0 (0.0%)	0 (0.0%)	37 (56.92%)	24 (36.93%)	4 (6.15%)
P<0.05					
Group 4	0 (0.0%)	0 (0.0%)	17 (12.16%)	40 (16.54%)	8 (12.3%)
NS.					
Group 5	0 (0.0%)	0 (0.0%)	16 (24.62%)	45 (69.23%)	4 (6.15%)

Table 4 The relief of babor pain

	the relief of labor pain				
	Poor	Fair	Good	Very Good	Outstanding
Group 1	32 (49.23%)	20 (30.77%)	13 (20.00%)	0 (0.0%)	0 (0.0%)
P<0.05					
Group 2	40 (61.54%)	25 (38.46%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Group 3	33 (50.77%)	16 (24.62%)	12 (18.46%)	4 (6.15%)	0 (0.00%)
P<0.05					
Group 4	28 (43.09%)	0 (0.0%)	12 (18.46%)	21 (32.20%)	4 (6.15%)
P<0.05					
Group 5	8 (12.3%)	0 (0.0%)	4 (6.15%)	28 (43.09%)	25 (38.46%)

Table 5 An interval between active phase of the labor and giving the birth (A), the number of the parturients who vomited (B) or got nausea (C) or postpartum hemorrhage (D), birth weight (E), the number of the neonate whose apgar scores less than 7 at 5 minutes (F) or was given the naloxone (G)

	Group 1	Group 2	Statistical significance
A (min.)	238.22+100.78	233.09+110.80	NS.
B (cases)	3 (4.62%)	0 (0.0%)	NS.
C (cases)	9 (13.85%)	0 (0.0%)	P<0.05%)
D (cases)	0 (0.0%)	0 (0.0%)	NS.
E (grams)	3184.62+271.42	3174.46+616.03	NS.
F (cases)	0 (0.0%)	0 (0.0%)	NS.
G (cases)	0 (0.0%)	0 (0.0%)	NS.

	Group 3	Group 4	Group 5
A (min.)	265.88+146.77	257.62+118.54	322.85+185.69
B (cases)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	NS	NS	
C (cases)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	NS	NS	
D (cases)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	NS	NS	
E (grams)	3262.92+301.93	3162.15+325.32	3188.77+226.04
	NS	NS	
F (cases)	0 (0.0%)	1 (1.54%)	1 (1.54%)
	NS	NS	
G (cases)	0 (0.0%)	1 (1.54%)	1 (1.54%)
	NS	NS	

Table 6 Method os delivery

	Method of delivery		
	Normal delivery	operative vg delivery	cesarean section
Group 1	50 (76.93%)	10 (15.38%)	5 (7.69%)
NS			
Group 2	50 (76.93%)	11 (16.92%)	4 (6.15%)
Group 3	49 (75.39%)	12 (18.46%)	4 (6.15%)
NS			
Group 4	42 (64.62%)	14 (21.54%)	9 (13.84%)
NS			
Group 5	49 (75.39%)	9 (13.84%)	7 (10.77%)

Table 3 shows at pre-medication administration, 81.54% of group 1 got the labor pain at or more than level 3 compared with 49.23% of group 2. (P<0.05) Also, 73.84% of the parturients in group 4 got the labor pain at or more than level 4, was higher than in group 3 (43.08%) (P<0.05). There was no statistically significant difference in the parturients who got the labor pain before giving the analgesic agents between group 4 with 5.

Table 4 shows 50.75% the parturients in group 1 felt better after reciving the analgesic agents compare with 38.46% of group 2 (P<0.05). No anyone in group 2 felt better more than 15 minutes. Between group 3, 4 and 5, the number of parturients felt better was statistically significant increase in ascending order of group. In group 3, 32 of 65 parturients (49.23%) felt better, 18.46% felt better for an interval of about fifteen minutes to half an hour and 6.15% felt better for an interval of more than thirty minutes. No one felt better for an interval more than one hour. In group 4, 37 of 65 parturients (56.81%) felt better. 38.35% felt better for an interval of more than half an hour and 6.15% felt better for an interval of more than hour. In group 5, most of the parturients (87.7%) felt better and 38.46% of them felt better for an interval more than one hour.

Table 5, 6 shows an interval between active phase of the labor and giving the birth, the number of the parturients who vomited or got nausea, an post partum hevmorrhage, birth weight, the number of the neonates whose apgar score less than 7 at 5 minutes and were given naloxone. No statistically significant difference in each group except for an interval bvetween active phase of the labor and giving the birth of group 4 and 5 (257.62+118.54 min. VS. 322.85 +185.69 min. respectively) and the number of the parturients who got nausea in group 1 (9 "subjects = 13.85%) compared with no anyone in group 2.

Discussion

In this research, comparative study of both sublingual and intraveous buprenorphine were designed. (no oral form of intravenous meperidine abvailable in Thailand). Because promethazine was usually prescribed in combination with meperidine in labor room also included in this study. Buprenorphine is a semisynthetic, highly lipophilic opioid derived from thebaine. It is a partialy uagonist and 25 to 50 times more potent than morphine. Its action is also longer lasting than morphine.[6,7,8]

In this study intravenous buprenorphine relieve labor pain longer and be more efficcious than intravenous meperidine (38.46% versus 6.15%) felt better for an interval more than thirty minutes) despite no difference of the level of labor pain before giving the analgesic agents and the number of the parturients with oxytocin augmentation. But sublingual buprenorphine was less efficacious than intravenous meparidine (38.46% of group 2 versus 50.75% of group 1 and 49.23% of group 3 versus 56.81% of group 4, P<0.05) in spite of lower level of labor pain prior to giving the analgesic agents and littler number of the parturients with oxytocin asugmentation. For the adverse effects, intravenous buprenorphine, compared with intravenous meperidine, prolonged an interval between active phase of the labor and giving the birth significantly (322.85 + 185.69 VS. 257.62 + 118.54). Presumably it might also influence the uterine contraction, however it remained no effect on method of delivery. Further studies of its influence on uterine contraction would be needed. In both medication, buprenorphine and meperidine, could

depress on the infant's respiration, even though no statistically significance in difference of the numbers of infants who got respiratory depression, However in case of buprenorphine, naloxone could not reverse its effect annd endotracheal intubation was needed. This result confirmed Jaffe JH. and Martin WR.'s description[6] that the respiratory depression and other effects of buprenorphine could be prevented by prior administraion of naloxone. but they were not readily reversed by high doses of naloxone once the effects had been produced. Both buprenor-phine and meperidine did not increase an incidence of post-partum hemorrhage of the partureints or low birth weight infants. In this study showed the prescription of promethazine in combination with the analgesic agents could also improve the efficacy in relief of labor pain besides the prevention of nausea and vomit.

In conclusion the efficacy of intravenous buprenorphine in relief of the labor pain was better than of intravenous meperidine. However its depressant effect on respiratory system of the infants should be aware of and its effect on prolongation of the labor needed more studies.

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