EFFECT OF PETHIDINE VERSUS TRAMADOL ON LABOUR PAIN IN PRIMIPAROUS WOMEN

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ABSTRACT

Background

Labour has long been recognized as a very painful event. Meperidine or Pethidine is one of the most frequently used opiate agonists while Tramadol is a centrally acting analgesic. There are variable debates about their uses in labour and their effects on progress of labour, mother and her fetus.

Objective

To evaluate and compare the efficacy and adverse effects of intramuscular Pethidine versus Tramadol as an analgesic during labour.

Patients and Methods

A randomized controlled prospective study carried at Sulaimani Maternity Teaching Hospital throughout the period 1st of January to 1st of July 2010. Two hundred twenty five full terms parturient, were randomly assigned into: Group 1, included 75 cases received 100 mg Pethidine intramuscularly; group 2, included 75 cases received 100 mg Tramadol intramuscularly; and group 3, included 75 cases received 1ml distilled water intramuscularly as control group. Analgesic efficacy, maternal and neonatal side effects, duration of labour and maternal satisfaction were determined.

Results

Following drug administration, significant reduction in pain level achieved after 60 and 120min in the studied groups. Maternal side effects such as nausea, vomiting, drowsiness, and dry mouth occurred more frequently in Pethidine group than the others (p-value < 0.05). Both drugs caused shortening in the duration of active phase of 1st stage of labour. Regarding the neonatal outcome, infants of Pethidine group showed poorer feeding, poor reflex and drowsiness, but non of the neonates developed respiratory depression.

Conclusion

Pethidine seem to be better than Tramadol as obstetric analgesia because of its superiority in pain relief but with more side effects on the mother and her baby.

***Keywords*:** *Labour, Pethidine, Tramado, Aanalgesia, Dduration of labour.*

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INTRODUCTION

Pain and agony during childbirth is quiet unbearable and at times beyond description [1].The management of labour pain is a major goal of modern intrapartum care [2]. Epidural analgesia is the most effective analgesia for women in labour [3]. Unfortunately an epidural service cannot be made routinely available in most obstetric units in developing countries for reasons of cost and personnel. Most obstetric units therefore use systemic opioids for analgesia as they are cheap, simple to use and readily available [4].

Sources of pain in labour

In general 3 sources of pain are found; *Physical source*: include uterine contraction, cervical dilatation, descending of the fetus with associated vaginal stretching [5]. *Mechanical source*: this occurs due to poor body mechanics for the right way to use the muscles necessary for the labour task [5]. *Emotional source*: the 3rd source is maternal body natural response to stress. Anxiety and fear causes the uterine muscles to work to constrict the cervix, causing unproductive contractions and increasing pain [5]. Labour pain can affect the mother and the baby. These effects are principally due to maternal sympathetic autonomic system activation that cause increase cardiac output, pulse rate, blood pressure resulting in exhaustion, dehydration, misery, oxygen and glucose consumption, and even hyperventilation and hypocapnia which can be severe enough to produce tetany in painful labour [6]. Fear of childbirth has been associated with longer 1st and 2nd stages of labour and dissatisfaction with childbirth experience which may adversely affect the psychology of the patients [7]. On the fetal side, labour induces massive catecholamine surge in the fetus, particularly in the 2nd stage of labour. While this fetal stress response is favorable to the fetus, unmodified painful labour can decrease placental blood flow leading to fetal compromise [6].

Since its introduction in 1939, Pethidine has become the most commonly used opioids for obstetric analgesia throughout the world despite an unimpressive safety record [8]. It works best in 1st stage of labour when the pain is primarily visceral and less intense, but has limited efficacies for relief of pain in later labour [9]. All opioids readily cross the placental barrier and may cause neonatal respiratory depression depending on the dose and time relative to the delivery. They may also decrease fetal heart rate variability (not reflect fetal acidosis) and impair neonatal feeding [10]. Pethidine act on central nervous system by inhibiting the pain signals sent to the brain [11]. Pethidine through its action on central nervous system rather than spinal cord causes more sedation than pain relief in labour [12]. It can act as muscle relaxant which can in some cases result in faster dilatation of cervix [11]. Intramuscular Pethidine injection starts action within 15 min, reaches peak in circulation within 45-50 min, and lasts for 2-4 hours [13]. Advantages of Pethidine in labour include maternal relaxation during labour and easy administration by midwife with no need for a doctor [14]. Also, Pethidine use was associated with changes in the cervical proteases during labour [15].

Regarding the side effects of Pethidine: On the mother: the common side effect are sedation as well as nausea and vomiting so an antiemetic drug can be mixed with it to decrease these side effects [16]. Some women describe drowsiness and confusion [16, 17]. On the baby: the main problem to the baby is its ability to produce respiratory depression through its action on respiratory center. This effect is worse if the baby is born 1-3 h after injection of Pethidine and is the reason that Pethidine ideally not given when the birth is perceived to be closed [11, 12]. This effect of Pethidine can be readily reversible with Naloxone (a specific opioid antagonist). The neonatal dose is 10 mg/kg, repeated if necessary [17].

Repeated administration of Pethidine affects negatively the suckling of the infant [18]. It has been suggested that the course of behavioral maturation during certain period of infancy is influenced by Pethidine administration at birth [19].

Tramadol hydrochloride is a centrally acting drug that was first discovered in Germany in 1970. It is a synthetic analogue of codeine that binds μ-opioid receptor and inhibits nor-epinephrine and serotonin up-take thus giving dual mode of action. It has low affinity to opioid receptors [20, 21]. Tramadol can be administered orally, rectally, intravenously and intramuscularly. It is principally metabolized by liver and excreted by the kidney, so the dose should be adjusted in patients with impaired liver or kidney function [22].

Intramuscular Tramadol has rapid onset of action, usually within 10 min, reach peak within 45 min, and last for 4-6 hours [23]. The effect of Tramadol is not completely reversed by opioid antagonist (Naloxone); this is because of dual mode of action of this drug [24]. Tramadol has been found to have analogous analgesic efficacy to Pethidine but with less sedative effect on the mother, it is also associated with shorter duration of labour, a lower maternal side effects and less incidence of neonatal respiratory depression [25]. Regarding the side effects of Tramadol, it includes nausea, vomiting, dizziness and confusion. Titrating the dose slowly may improve tolerability [26].

PATIENTS AND METHODS

This study is a randomized comparative controlled prospective study. It was performed on 225 primigravida women admitted to the delivery suite in Sulaimani Maternity Teaching Hospital for the period between 1st of January and 1st of July 2010. Inclusion criteria included: primigravida, spontaneous onset of labour, term pregnancy, singleton pregnancy, vertex presentation (occiput anterior), active phase of 1st stage of labour with at least 3 regular painful uterine contractions over 10 min, 4 cm cervical dilatation and 70-90% cervical effacement. After taking full history from each woman and doing detailed physical examination, women who fit the inclusion criteria were randomly allocated to one of the methods of pain relief after obtaining verbal consent from them i.e patients were randomly divided into 3 groups: Group A: Included 75 cases who received 100 mg of Pethidine (hameln pharmaceuticals gmbh Langes Feld 13, 31789 Hameln, Germany) intramuscularly. Group B: Included 75 cases who received 100 mg of Tramadol (Brown and Burk (UK) LTD. Brentford, Middlesex, TW8 9JQ, London, U.K.) intramuscularly. Group C: Included 75 cases who received 1ml of distilled water (DW) as placebo intramuscularly. Pain score was assessed before administration of the drug and then 1/2, 1and 2 hours after the administration through using 4 points verbal rating scale (0- represent no pain or very little pain, 1- represent mild pain, 2- represent moderate pain, and 3- represent severe pain). Duration of active phase of 1st and 2nd stage of labour, the needs for oxytocin drug and mode of delivery were recorded. Maternal side effects such as nausea, vomiting, drowsiness, dry mouth, etc. were observed and recorded. Maternal satisfaction with method of pain relief during labour evaluated 2 hours after delivery. After birth neonatal examination performed and Apgar score at 1 min and 5 min were recorded. Naloxon (specific opioid antagonist) was available for any adverse effects. Patients were phoned 24 hours later asking them about any complications. Statistical analysis: Data were collected, coded, tabulated and then analyzed by computer using SPSS (Statistical Program for Social Science) version 18.

RESULTS

1. Demographic characteristics of the studied groups (table 1):

No statistical difference was found between the studied groups regarding demographic feature.

2. Mode of delivery (table 2):

Majority of the patients delivered by normal vaginal delivery [group A: 66 cases (88%), group B: 66 cases (88%), group C: 65 cases (86.7%)].

3. Pain relief (table 3):

Before drug injection: All the patients felt pain with the beginning of the active phase of 1st stage of labour. After 1/2h of drug injection: more pain relief was observed in group A compared to group B and C, however this difference was not significant. While after 1 hour significance statistical difference was achieved in favor of group A. After 2 hours of drug injection: Twenty one cases of group A, 26 cases of group B, and 8 cases of group C were delivered, so only 54 cases of group A, 49 cases of group B, and 67 cases of group C entered to the statistical analysis. Also more degree of pain relief recoded in group A than group B and C. Significant difference among these groups was found regarding pain score since the calculated p-value was (0 .000).

4. Satisfaction with method of pain relief (table 4):

More women experienced satisfaction with method of pain relief in group A [33 cases (44%)] as compared to group B [15 cases (20%)] and group C [3 cases (4%) and statistically were regard as significant as p-value equal to 0.000.

5. Maternal side effects (table 5):

Regarding maternal side effects, higher frequency of nausea, vomiting, drowsiness, and dry mouth occurred in group A than group B and C. There was significant statistical difference among these groups regarding the maternal adverse effects

since the calculated p-value was < 0.05, as recorded in table (5).

6. Babies outcome: table (6, 7 and 8):

The majority of babies in all the studied groups did not need admission to the neonatal care. Most of the babies' weight fell in the range between 2.5-3.7 kg, which is regarded as normal weight. No significant difference found in comparing the groups regarding their weights since the calculated p- value was above 0.05. All the above data are demonstrated in table (6).

Majority of the neonates were with good general condition and high Apgar score at 1 and 5 minutes after delivery. Statistically dealing with these groups, there were significant statistical difference among them regarding Apgar score at 1 minute, but it was not significant at 5 minutes (p-value =0.005,and o.444,respectively), as shown in table (7). In early neonatal period, 7 babies (9.3%) of group A suffered from poor feeding compared to only 3 cases (4%) of group B and none in group C, only 2 babies (2.7%) in group A had poor reflex.

Respiratory depression was not observed in any of the born infants and none of the neonates required opiate antagonist. Also this difference was statistically significant since the p-value was less than 0.05, as shown in table (8).

7. Duration of labour (table 9):

All the cases that need oxytocin for poor progression of labour excluded from statistical analysis for duration of labour [group A: 11 cases (14.7%), group B:9 cases (12%) and group C: 9 cases (12%)] and further three cases of group A, 4 cases of group B and only 1 case of group C were also excluded from statistical analysis at active phase of 1st stage of labour as all these cases ended by cesarean section during the 1st stage of labour without completing it (the duration can't be calculated). In spite of small differences in duration of labour between groups A and B, significant statistical value was obtained when comparing them with control group, since the calculated p-value was (0.000). In 2nd stage of labour, further 9 cases of group A, 7 cases of group B, and 7 cases of group C that ended by cesarean section excluded from statistical analysis. In 2nd stage of labour the result of group B seems to be shorter than the other groups, but despite these differences, the calculated p-value didn't reach statistical significance (0.059).

Table 1. Demographic distribution of the patients.

Variable Name	Class	Group A		Group B		Group C		*P-value
		N	%	N	%	N	%	
Age	<20	19	25.3	23	30.7	17	22.7	.941
	20-30	50	66.7	46	61.3	53	70.6	
	>30	6	8.0	6	8.0	5	6.7	
	Total	75	100.0	75	100.0	75	100.0	
Occupation	Housewife	58	77.3	62	82.7	64	85.3	.419
	Employee	17	22.7	13	17.3	11	14.7	
	Total	75	100.0	75	100.0	75	100.0	
BMI**	<18	1	1.3	1	1.3	2	2.7	.153
	18-25	40	53.3	38	50.7	43	57.3	
	26-30	21	28.0	22	29.3	22	29.3	
	>30	13	17.3	14	18.7	8	10.7	
	Total	75	100.0	75	100.0	75	100.0	
Blood group	Rh +	75	100.0	62	82.7	66	88.0	.001
	Rh -	0	0.0	13	17.3	9	12.0	
	Total	75	100.0	75	100.0	75	100.0	
Residence	Rural	20	26.7	18	24.0	29	38.7	.113
	Urban	55	73.3	57	76.0	46	61.3	
	Total	75	100.0	75	100.0	75	100.0	

***p-value < 0.05 statistical difference significant.**
**** BMI= weight/height ^{2}.**

Table 2. Mode of delivery of the studied groups.

Mode of delivery	Group A		Group B		Group C		P-value
	N	%	N	%	N	%	
NVD	66	88.0	66	88.0	65	86.7	.478
Instrumental *	0	0	2	2.7	3	4.0	
CS	9	12.0	7	9.3	7	9.3	
Total	75	100.0	75	100.0	75	100.0	

***p-value calculated by one way ANOVA test, statistically significant if p-value below 0.05**.

Table 3. Evaluation of pain scores of all studied groups (using 4 points verbal rating scale) before and after 1/2, 1 and 2 hours of drug injection.

Variable Name	Class	Pethidine		Tramadol		Control		P-value
		N	%	N	%	N	%	
before drug injection	no pain	0	0.0	0	0.0	0	0.0	.559
	Mild	2	2.7	7	9.3	4	5.3	
	Moderate	49	65.3	45	60.0	52	69.4	
	Severe	24	32.0	23	30.7	19	25.3	
	Total	75	100.0	75	100.0	75	100.0	
1/2h after injection	no pain	3	4.0	1	1.3	0	0.0	.179
	Mild	38	50.7	19	25.3	5	6.7	
	Moderate	32	42.6	47	62.7	49	65.3	
	Severe	2	2.7	8	10.7	21	28.0	
	Total	75	100.0	75	100.0	75	100.0	
1h after injection	no pain	3	4.0	1	1.4	0	0.0	.035
	Mild	44	58.7	17	23.6	6	8.0	
	Moderate	21	28.0	38	52.8	31	41.3	
	Severe	7	9.3	16	22.2	38	50.7	
	Total	75	100.0	72	100.0	75	100.0	
2h after injection	no pain	0	0.0	0	0.0	0	0.0	.000
	Mild	22	40.7	6	12.2	3	4.5	
	Moderate	15	27.8	8	16.4	12	17.9	
	Severe	17	31.5	35	71.4	52	77.6	
	Total	54	100.0	49	100.0	67	100.0	

Table 4. Maternal satisfaction with method of pain relief.

Maternal satisfaction	Group A		Group B		Group C		P-value*
	N	%	N	%	N	%	
Satisfied	33	44.0	15	20.0	3	4.0	.000
Not satisfied	42	56.0	60	80.0	72	96.0	
Total	75	100.0	75	100.0	75	100.0	

***p-value calculated by one way ANOVA test, statistically significant if p-value below 0.05.**

Table 5. Maternal side effects in the studied groups.

Maternal side effects*	Group A		Group B		Group C		P-value
	N	%	N	%	N	%	
No	11	14.7	22	29.3	67	89.3	.000
Nausea	54	72.0	37	49.3	2	2.66	
Vomiting	23	36.66	5	6.66	1	1.33	
Drowsiness	47	62.66	17	22.66	5	6.66	
Dry mouth	25	33.33	2	2.66	1	1.33	

***No cases of palpitation, urinary retention, constipation, respiratory depression, hallucination, post partum haemorrhage and allergic reaction.**

Table 6. Babies' outcome of the studied groups.

Variable Name	Class	Group A		Group B		Group C		P-value
		N	%	N	%	N	%	
baby sex	Male	38	50.7	35	46.7	28	37.3	.243
	Female	37	49.3	40	53.3	47	62.7	
	Total	75	100.0	75	100.0	75	100.0	
Admission to NCU	Yes	5*	6.7	14**	18.7	11***	14.7	.090
	No	70	93.3	61	81.3	64	85.3	
	Total	75	100.0	75	100.0	75	100.0	
Baby weight	< 2.5	1	1.3	3	4.0	2	2.7	.657
	2.5-3.7	46	61.3	48	64.0	46	61.3	
	≥3.8	28	37.4	24	32.0	27	36.0	
	Total	75	100.0	75	100.0	75	100.0	

*** Two babies admitted because of meconium, 1 had hydrocephalus, 1 had family history of congenital heart disease and1 had polydactyl.**
****13 babies of them were admitted because of Rh factor and one developed meconium staining of liquor. *** 9 babies of them were admitted because of Rh factor, one baby had low Apgar score and 3 babies because of instrumental deliveries (2 of them were Rh negative).**

Table 7. Apgar score at 1st and 5th minutes.

Variable Name	Class	Group A		Group B		Group C		P-value*
		N	%	N	%	N	%	
Apgar score (1min)	0-6	16	21.4	8	10.7	9	11.9	.005
	7-10	59	78.6	67	89.3	66	88.1	
	Mean±S.D	**7.29±0.941**		**7.53±0.890**		**7.89±1.429**		
Apgar score (5min)	0-6	0	0.0	0	0.0	1	1.3	.444
	7-10	75	100.0	75	100.0	74	98.7	
	Mean±S.D	**9.23±0.863**		**9.40±0.678**		**9.36±1.035**		

***p-value calculated by one way ANOVA test, statistically significant if p-value below 0.05.**

Table 8. Neonatal side effects.

Complication*	Group A		Group B		Group C		P-value
	N	%	N	%	N	%	
No	40	53.3	70	93.3	74	98.7	.000
Poor feeding	7	9.3	3	4.0	0	0.0	
Drowsy baby	29	38.7	2	2.7	0	0.0	
Poor reflex	2	2.7	0	0.0	0	0.0	
Neonatal death	0	0.0	0	0.0	1	1.3	

***No cases of respiratory depression.**

Table 9. Duration of labour.

Variable Name		Group A	Group B	Group C	P-value*
Active phase of first Stage	**N**	61	62	65	.000
	Mean±S.D	139.36±79.21	148.14±85.46	192.77±90.35	
Second Stage	**N**	55	60	59	.059
	Mean±S.D	24.49±18.48	22.94±16.49	29.31±15.14	

***p-value calculated by one way ANOVA test, statistically significant if <0.05.**

DISCUSSION

Labour pain is one of the most excruciating pain experiences that women encountered in their lives. The intensity of the pain affects maternal psychology, labour progression and fetal well being, so provision of analgesia regarded as one of the basic principle of modern obstetrics management [27]. About efficacy of analgesia, the result of present study indicates that pain intensity depending on 4 points verbal rating scale was lower in patients received Pethidine than those received Tramadol or placebo at all time intervals. However, only at 1h and 2h intervals it reached statistical significant value. Our findings are consistent with Keskin HL *et al*. [28] and F Seyed Alshohadaei *et al.* [29]. In both of these studies, they found significant lower pain score with the use of Pethidine than Tramadol at all stages of labour, while this was not achieved in study prepared by KHOOSHEDAEH *et al.* [25] from Iran, which found no significant difference between Pethidine and Tramadol in 1st stage of labour while significant level achieved in 2nd stage of labour. The result of the latter may be due to the lower dose of Pethidine used in their research. On the other hand, Viegas OAC *et al.* [30], and Fieni S *et al.* [31] reached dissimilar conclusions from us, in all these studies, they found that Tramadol produces equivalent analgesia to Pethidine when used in labour probably due to lower dose of Pethidine in their studies. In our study we found greater satisfaction with the use of Pethidine (44%) than Tramadol (20%) and placebo (4%). This result agreed with studies performed by Viegas OAC *et al.* [30], F Seyed Alshohadaei *et al.*[29] and KHOOSHEDEH *et al.* [25].

In our study, both Pethidine and Tramadol caused shortening of duration of labour, but the mean duration of active phase of 1st stage of labour was shorter in Pethidine than those in Tramadol and placebo groups, while it was longer in 2nd stage of labour than Tramadol group, but these differences were significant only at the 1st stage of labour. Viegas OAC *et al.* [30], Keskin HL *et al.* [28] and F Seyed Alshohadaei *et al.* [29] reached similar conclusion to us, in that both drugs caused shortening of duration of 1st stage of labour, but their calculated p-value was statistically not significant. Our result is in contrast to the result of KHOOSHEDEH *et al.* [25] with respect to duration of labour, which found longer duration of 1st stage of labour in patient received Pethidine than those received Tramadol. Regarding maternal side effects, our results reported high percentage of non serious side effects, like nausea, vomiting, drowsiness, and dry mouth in patients received Pethidine in labour and the difference among the 3 groups was statistically significant (p-value was <0.05). These were similar to studies demonstrated by Viegas OAC *et al.* [30], O. Kuti *et al.* [32], F Seyed Alshohadaei *et al.* [29], and KHOOSHEDEH *et al.* [25], and was in contrast to another study performed by Keskin HL *et al.* [28], showed high incidence of adverse effects in Tramadol than Pethidine group, but only the change of nausea and fatigue were statistically significant in latter study. The results of our study indicate that Pethidine significantly produce more side effects on the neonate than Tramadol and placebo, although most of these side effects are transient and not serious. These results consistent with results of studies done by Viegas OAC *et al.* [30] and Keskin HL *et al.* [28] , however, the results of S Mansoori *et al.* [33] disagree with our result, who found no significant side effects of Pethidine on neonatal outcome with exception of slight reduction of neonatal blood pH in the Pethidine group. Similarly other 2 studies performed by *Nagaria et al.*[34] and O Kuti *et al.* [32] found no significant side effects of Tramadol on neonatal outcome. Our finding of poor feeding agreed with the results of studies done by Richard L *et al.* [35] and Nissen E *et al.* [36], all these studies found significant poor feeding in neonates whose mother receive Pethidine in labour for the 1st 24h after delivery.

Regarding the Apgar score of the baby, our result showed significant lower mean Apgar score at 1st min in babies whose mother received Pethidine during labour than those received Tramadol or placebo, while very similar high Apgar score obtained in all groups at 5th min, which made the result non significant. Viegas OAC *et al.* [30], Keskin HK *et al.* [28] and F Seyed Alshohadaei *et al.* [29] studies didn't agree with our result at 1st min; however their results were similar to us at 5th min. Also Nagaria *et al.* [34] and O Kuti *et al*. [32] agreed with our result that no significant effect of Tramdol found on neonatal Apgar score. About the need for admission to the neonatal care unit, we found no significant statistical difference among the groups, this was similar to result of Viegas OAC *et al.* [30], Keskin HL *et al.* [28], and KHOOSHEDEH *et al.* [25]. In our study, there was

no significant difference among the groups regarding the birth weight which was agreed with result of study prepared by F Seyed Alshohadaei *et al.* [29].

CONCLUSIONS

Tramadol is a safer alternative to Pethidine in labour although it gives lesser degree of pain relief, but shortens labour and produce less maternal and neonatal side effects when compared to Pethidine. Neither analgesics produce adequate pain relief to provide maximum maternal satisfaction.

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