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The safety and acceptability of intravenous fentanyl versus intramuscular pethidine for pain relief during labour

M. Rezk[1], E.S. El-Shamy[1], A. Massod[1], R. Dawood[1], R. Habeeb[2]

[1] Department of Obstetrics and Gynecology, [2] Department of Anesthesiology, Faculty of Medicine, Menoufia University, Menoufia (Egypt)

Summary

Objectives: This trial aimed to ascertain the relative efficacy, adverse effects, and acceptability of fentanyl versus pethidine for pain relief during labour. *Materials and Methods:* Parturients (n=80) in the active phase who requested analgesia were randomly assigned to receive either intravenous fentanyl (n=40) or intramuscular pethidine (n=40). Pain scores hourly, maternal and fetal adverse effects, neonatal outcome, and maternal acceptability were assessed. *Results:* Pain scores decreased in both groups, the decrease varying from mild to moderate, average pain scores remaining above 3.5 in both groups. Pain scores returned towards baseline over time; three hours after the initiation of treatment in the fentanyl group. Pethidine was associated with more maternal nausea and vomiting ($p < 0.05$) while fentanyl was associated with more neonates with low Apgar scores at one minute and more need for neonatal resuscitation and naloxone administration when compared to pethidine ($p < 0.05$). Both drugs were acceptable for pain relief during labour. *Conclusion:* Fentanyl is comparable to pethidine for pain relief during labour regarding efficacy and acceptability, but with more neonates with low Apgar scores at one minute and higher need for neonatal resuscitation and naloxone administration. Further larger trials are needed to confirm its safety.

Key words: Fentanyl; Pethidine; Pain relief during labour.

Introduction

Labour is a painful experience and analgesia is often required. It is emphasized that request for pain relief be considered as a sufficient medical indication for the use of labour pain relief methods [1].

Pain intensity is influenced by numerous factors such as anxiety, environmental factors, culture, support from caregivers, focus of attention, and previous experiences [1, 2].

Pethidine, otherwise known as meperidine, is a widely used analgesic for labour pain worldwide. Research has demonstrated that pethidine provides variable pain relief in labour; much of its effect is sedation rather than analgesia [3]. Pethidine also has adverse effects in both the mother and neonate. It crosses the placenta and may cause reduced fetal heart rate variability and fewer heart rate accelerations. Neonatal adverse effects include respiratory depression, impaired breastfeeding, and altered crying [4, 5]. Systematic reviews comparing parenteral opioids in labour have suggested the need for well-designed and adequately powered trials of pethidine versus other opioids [6, 7].

Fentanyl, a phenyl piperidine derivative, is a short-acting and potent synthetic narcotic. Several comparative studies have shown that analgesic effects of intravenous fentanyl are better than pethidine [8-10].

The aim of this study was to assess the efficacy, safety, and acceptability of intravenous fentanyl versus intramuscular pethidine for pain relief during labour.

Materials and Methods

This was a single center balanced randomized parallel group study carried out at the Department of Obstetrics and Gynecology, Menoufia University Hospital, Egypt between April 2013 and April 2014. The institutional review board approved the study protocol and an informed consent was obtained from all participants prior to commencing the study.

Based on previous trials, power was set at 0.8, alpha level at 0.05, and the confidence interval (CI) at 95%. A total sample size 80 subjects was needed for this trial (40 subjects in each group), after adding a 10% to compensate for possible drop out of cases.

Participants

The study was conducted on 80 healthy nulliparous women who requested analgesia for labour pains. Inclusion criteria included women who were in the active labour (defined as regular uterine contractions of at least two in ten minutes), with a singleton pregnancy, cervical dilatation of at least four cm, with gestation of 37–41 weeks, and reactive non-stress test.

Exclusion criteria included allergy or previous adverse reaction to opioids or opioid dependency, use of parenteral opioids within the previous 24 hours, presence of severe systemic or mental disease, maternal respiratory rate ≤ 8 or maternal bradycardia (pulse rate less than 60), and women requesting additional dosage of analgesia. The authors excluded women requesting additional analgesia in order to test the specific single dosing for a particular opioid.

Randomization

Enrolled women were randomly assigned into two groups according to the method of treatment. Randomization in 1:1 ratio was carried out using computer-generated simple random tables.

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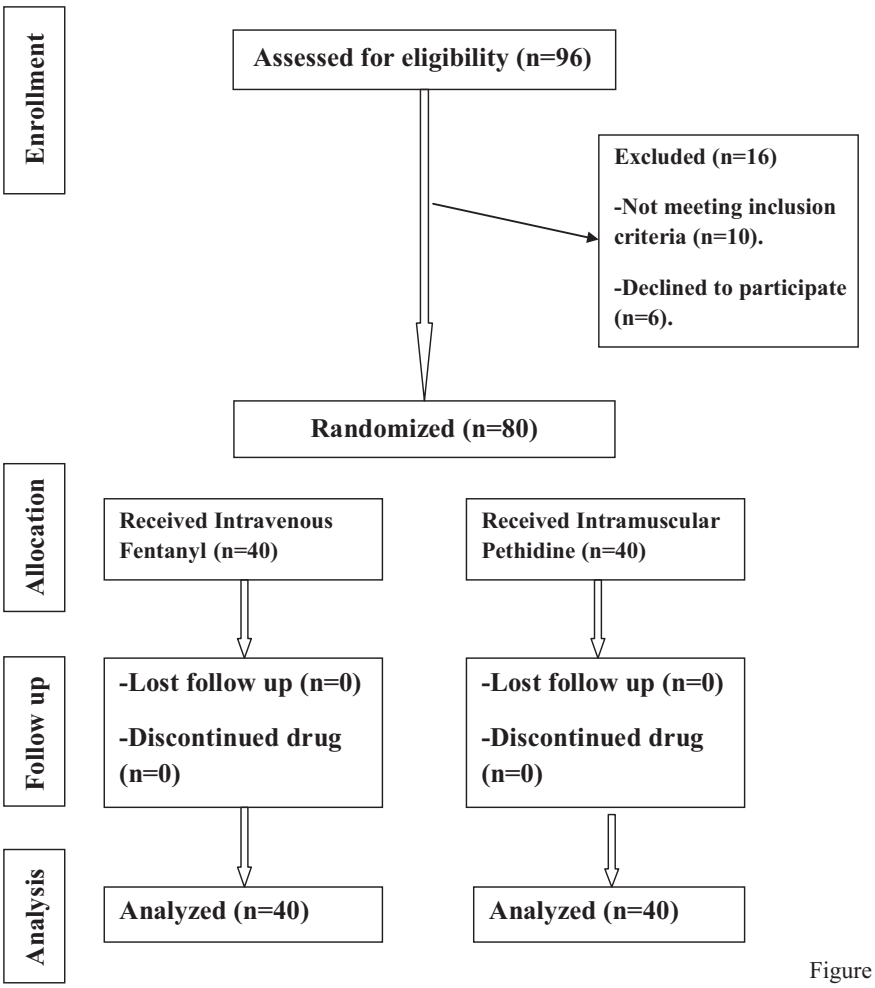

Figure 1. — Flow diagram.

It was not possible to blind the study participants from knowledge of which drug was received because methods of administration were clearly different.

Intervention

Group 1 (Fentanyl group): 40 pregnant women in whom 50 micrograms fentanyl was given after being diluted in 18 ml normal saline (total volume 20 ml - 50 µg /20 ml) during ten minutes intravenous infusion according to the present hospital policy.

Group 2 (Pethidine group): 40 pregnant women in whom 100 mg of pethidine was given by intramuscular injection.

Vital signs were monitored every ten minutes. Artificial rupture of membranes (AROM) was performed for all women with intact membranes and intravenous oxytocin infusion was started if there was no efficient uterine contractions. An oxytocin infusion was started at two mU/min and increased in increments of one to two mU/min at 15-30 minutes intervals as needed to achieve adequate uterine contraction pattern (≥ 200 MVU). Continuous cardiotocography (CTG) was done during delivery and the modified WHO partograph was followed up for the labour management. An anesthesiologist and resuscitation equipments were available at all times.

Outcome measures

Primary outcome measure included changes in pain scores. Pain severity during the last contraction was assessed using a Visual Analogue Scale [VAS] (with anchor points of 0 = no pain at all and 10 = the most excruciating pain) every 60 minutes during the three-hour period after administration of the trial drug. Pain severity was estimated four times (before and one, two, and three hours after drug intake). This information was used to derive measures of pain relief at each time-point using absolute change in pain intensity (on a 10-cm VAS) from pre-analgesia (score 0).

Maternal adverse effects [fainting, nausea and vomiting, respiratory depression, hypotension (blood pressure < 90 mmHg), bradycardia (heart rate < 60 beats min)], post-delivery maternal acceptability and neonatal outcome (Apgar scores at one and five minutes, need for resuscitation, and admission to neonatal intensive care unit) were recorded as secondary outcomes (Figure 1).

Statistical analysis

Data entry and analysis was carried out using SPSS version 16.

1) Descriptive statistics: quantitative data were expressed to measure the central tendency of data and diversion around the mean, mean (x) and standard deviation (SD). Qualitative data expressed in number and percentage.

2) Analytic statistics: *t*-test was used for comparison of two groups of normally distributed variables. Fisher exact test was used to compare categorical outcomes when expected cell or more in 2x2 tables was less than 5.

All these tests were used as tests of significance at:

Table 1. — *Maternal characteristics.*

	Fentanyl group n=40	Pethidine group n=40	*p*-value
Age (years)	21.72±2.63	21.70±1.69	> 0.05
Gestational age (weeks)	39.00±1.43	39.22±1.25	> 0.05
Weight (kg)	69.40±5.68	70.00±5.52	> 0.05
Duration of active phase (hours)	5.25±0.86	5.31±0.85	> 0.05
Need for oxytocin	26 (55%)	23(57.5%)	> 0.05

Table 2. — *Maternal pain scores using visual analogue scale (VAS).*

	Fentanyl group n=40	Pethidine group n=40	*p*-value
Score at inclusion (0)	8.50±1.13	8.25±0.84	> 0.05
Score at 1 hour *p* Score 1 *vs* Score 0	4.50±1.13 ***p* < 0.05**	4.80±1.09 ***p* < 0.05**	> 0.05
Score at 2 hours *p* Score 2 *vs* Score 0	5.10±1.13 ***p* < 0.05**	4.70±1.32 ***p* < 0.05**	> 0.05
Score at 3 hours *p* Score 3 *vs* Score 0	6.5±1.13 ***p* > 0.05**	4.85±0.86 ***p* < 0.05**	**< 0.001**

Table 3. — *Maternal adverse effects.*

	Fentanyl group n=40	Pethidine group n=40	Chi square test	*p*-value	Odds ratio (CI 95%)
Hypotension	4 (10%)	5(12.5%)	0.125	> 0.05	1.28 (0.32-5.18)
Bradycardia	1 (2.5%)	0 (%)	*1.013	> 0.05	-
Fainting	2 (5%)	3 (7.5%)	*0.213	> 0.05	1.54 (0.243-9.75)
Headache	2(5%)	5 (12.5%)	*1.41	> 0.05	2.714 (0.494-14.901)
Nausea and vomiting	4(10%)	11 (27.5%)	4.02	**< 0.05**	0.293 (0.084-1.12)
Need for anti-emetics	4 (10%)	5 (12.5%)	0.125	> 0.05	1.28 (0.32-5.18)

* Fisher exact test.

- *p* value > 0.05 was considered statistically non significant.
- *p* value ≤ 0.05 was considered statistically significant.
- *p* value ≤ 0.001 was considered statistically highly significant. [*p* values in **bold** in the tables are significant].

Results

Table 1 displays the maternal characteristics and the duration of the active phase of labour in the two groups. Table 2 reveals the maternal pain scores. There was a significant reduction of pain scores at one and two hours after administration of the analgesic drugs in both groups with return of pain intensity after three hours in the fentanyl group. Table 3 shows the maternal adverse effects. There was a significant number of women suffering from nausea and vomiting in the pethidine group ($p < 0.05$). Table 4 reveals the fetal-neonatal outcome. There was a significant low Apgar score at one minute and the need for neonatal resuscitation and naloxone administration in the fentanyl group ($p < 0.05$). Table 5 displays the post-delivery maternal acceptability. There was no significant difference between the two groups.

Table 4. — *Fetal-neonatal outcome.*

	Fentanyl group n=40	Pethidine group n=40	Chi square test	*p*-value	Odd's ratio (CI 95%)
Abnormal FHR	6 (15%)	4 (10%)	0.457	> 0.05	0.630 (0.163-2.42)
Apgar score at 1 minute	5.5±1.13	6.35±1.37	3.026	**< 0.05**	-
Apgar score at 5 minutes	8.00±1.43	8.20±1.18	0.681	> 0.05	-
Need for resuscitation	11 (27.5%)	4 (10%)	4.02	**< 0.05**	0.293 (0.084-1.12)
NICU admission	2 (5%)	1 (2.5%)	*0.346	> 0.05	0.487 (0.042-5.59)
Need for Naloxone	10	3	*4.501	**< 0.05**	-

* Fisher exact test, FHR=fetal heart rate, NICU=neonatal intensive care unit.

Table 5. — *Post-delivery maternal acceptability.*

	Fentanyl group n=40	Pethidine group n=40	Chi square test	*p*-value
Overall satisfaction with analgesia:				
1. Good	26 (55%)	23 (57.5%)	0.493	> 0.05
2. Neutral or somewhat satisfied	11 (27.5%)	13 (32.5%)		
3. Not satisfied	3 (7.5%)	4 (10%)		
Would choose the same analgesia in future labour and/or would recommend the analgesic to other women:				
1. Highly or somewhat agree	35 (87.5%)	33 (82.5%)	0.392	> 0.05
2. Neutral or somewhat disagree	5 (12.5%)	7 (17.5%)		

Discussion

The present study showed that intravenous administration of fentanyl decreased pain intensity similar to pethidine; the authors used the VAS for pain intensity [11]. Overall, the decrease in pain scores varied from mild to moderate, average pain scores remaining above 3.5 cm in both groups in the present study, which is comparable to previous studies concluding that intravenous patient-controlled analgesia with either remifentanil or fentanyl provides a moderate degree of labour analgesia [12-14].

Some have suggested that the minimum difference in pain that can be subjectively measured by women using the VAS is 1.3 cm, 1.4 cm or 1.8 cm [15-17].

In the fentanyl group, pain scores no longer differed significantly from baseline three hours after treatment was

started. Similar results of analgesia have been shown in other studies [10, 12, 14]. The short half-life of fentanyl (30-60 minutes) may explain the increasing pain score in third hour. Also, pain scores tended to increase with the progress of labour [12].

In the present study, more women suffering from nausea and vomiting in the pethidine group which is familiar with previous studies [9, 10].

There were a significant differences in the neonatal primary outcomes of the need for resuscitation and Apgar scores < 7 at one minute between the two groups as fentanyl was associated with lower Apgar scores at one minute and higher need for neonatal resuscitation which was confirmed in previous results [9, 10]. Also, fentanyl administered by subcutaneous route for pain relief during labour in a previous trial [18] was associated with significant need for naloxone during neonatal resuscitation which was confirmed in the present study.

Overall satisfaction scores were similar in both groups and approximately 85% of women in both groups would choose the same analgesia in a future labour and would recommend it to another women, when questioned within 24 hours of delivery.

Inability to design a double blinded trial and the small number of the present patients are the main limitations of our study. Further larger trials are needed to examine the safety of intravenous fentanyl on the neonatal outcome over longer periods of time.

In conclusion, under the conditions of the present study, intravenous fentanyl was effective as pethidine in providing pain relief during labour, but it was associated with significantly more depressed Apgar scores at one minute and a higher need for neonatal resuscitation and naloxone administration. Its effectiveness was time-limited (two hours); therefore, the authors would recommend the use of fentanyl only in the last phase of cervical dilation with the availability of neonatologists during delivery.

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Address reprint requests to:
M. REZK, M.D.
Kafr Manawhla, El-Bajour
20 Al-Takwa Mosque Street
Menoufia (Egypt)
e-mail: m_rezk9207@yahoo.com