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RESEARCH ARTICLE

Morphine versus Fentanyl Used Spinally for Post Cesarean Section Analgesia: A Randomized Clinical Trial

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Abstract

Background: Finding appropriate analgesic for cesarean section with maximum pain relief and minimal untoward effects is very important to aid mother's recovery. So, this study was carried out to compare morphine and fentanyl given spinally in patients undergoing cesarean section.

Methods: Hundred and twenty one patients (aged 18-43 years) undergoing either elective or emergency lower-segment cesarean section were enrolled in this randomised, unmasked, parallel-group controlled trial, at Al Helal Al Emirati Hospital, Rafah, Gaza Strip, occupied Palestinian territory. Using manual-blocks formation based on the rolling of a die, women were randomly assigned into two groups. Morphine group (n=59) received 0.2mg preservative-free morphine combined with 2ml of 0.5% hyperbaric bupivacaine while Fentanyl Group (n=62) received 20μg fentanyl combined with 2ml of 0.5% hyperbaric bupivacaine for spinal anesthesia. Visual analogue scales (VAS; range 0–10, 0=no pain and 10=pain as bad as it could be) were used to record the pain 1 h after the after the end of surgical procedure and then at 6 h, 12 h, 18h and 24 h. Time from induction of spinal anesthesia to the first demand of other analgesia and the total amounts and types of analgesics used in 24 hours, were recorded (primary outcomes). The secondary outcomes were nausea and vomiting scores (NVS 0–3; 0=no nausea or vomiting and 3=severe, unresponsive to antiemetic drugs), sedation scores (SS 0–3; 0=patient awake and 3=severe sedation, patient difficult to rouse, unrousable) and pruritis scores {PS 0-2; 0= no pruritis, 2= severe pruritis (treatment required).

Findings: Greater analgesia was achieved in Morphine group as VAS for pain was reduced significantly ($p<0.05$) during the 24 hours study period and the time to first demand of other analgesia was also significantly longer compared to Fentanyl group (9.03 h vs. 2.46 h $p= 0.000$). In Morphine group 33.9% of patients didn't need additional analgesia, while all the patients of Fentanyl group needed analgesia (OR=2.590 [2.025-3.312] CI=95%). The incidence of nausea was seen more in Morphine group at the sixth hour while drowsiness was seen more at the 12th hour among the same group ($p<0.05$). Over the study period 15.3% of Morphine groups suffered from pruritis and needed treatment compared with 1.6% from Fentanyl group (OR=10.980 [1.345-89.624] CI=95%).

Conclusion: Spinally morphine in dose of 0.2mg for cesarean section provided satisfactory and long duration analgesia compared with 20μg fentanyl. Although morphine was associated with more side effects, they were treatable and didn't pose any danger to patients.

Keywords: Morphine; Fentanyl; Cesarean Section; Spinal Anesthesia; Postoperative Analgesia

Introduction

Management of postoperative pain relieves suffering and leads to earlier mobilization, shortened hospital stay, reduced hospital costs, and increased patient satisfaction [1]. So the major goal in the management of postoperative pain is minimizing the dose of medications to lessen side effects while still providing adequate analgesia. This can be accomplished with multimodal and preemptive analgesia [2]. In other side, intraoperative administration of spinal opioids reduces the need for systemic opioids postoperatively [3]. As, a single dose of spinally administered narcotic can provide substantial pain relief up to 18 to 24 hours postoperatively [4]. Morphine has been used spinally for postoperative pain management for long time [5]. Effective analgesia can be obtained with doses ranging from 0.1 to 2.5 mg [6]. But, it is preferable to use low doses of spinal morphine ranging from 0.1

to 0.25 mg to reduce side-effects and complications as for cesarean section and other surgical procedures such as tubal ligation, gynecological surgeries and so many others [7-11]. Fentanyl (approximately 100 times more potent than morphine) is used also for this purpose in doses of 10 to 20 μg during the placement of a spinal anesthetic [4]. Physicochemical properties of the drugs and, in particular, lipid solubility determine the duration of action of the drugs. Morphine is highly ionized and hydrophilic and reaches maximum effect in about 45 minutes and lasts for 18 to 24 hours when administered by the spinal route while fentanyl, which is more lipids soluble and penetrates into the lipid rich dorsal horn, acts more quickly, but its duration of action is shorter [12,13].

Therefore, because post-cesarean section pain relief is important and its good management will improve mobility and can reduce the risk of thromboembolic disease, which is increased during pregnancy and pain may also impair the mother's ability to optimally care for her infant in the immediate postpartum period and may adversely affect early interactions between mother and infant and pain and anxiety may also reduce the ability of a mother to breast-feed effectively, it is necessary pain relief to be safe and effective, that not to interfere with the mother's ability to move around and care for her infant, and that to result in no adverse neonatal effects in breast-feeding women.

In Gaza strip in 2013 there were about 38,000 deliveries in the governmental hospitals, 8,229 were cesareans [14]. The percentage of spinal anaesthesia is not documented in our settings but, it is growing worldwide. So, this trial was carried out to find the more effect analgesic which may reduce effectively pain with minimal unwanted side effects for mother and infant in our settings and to compare the efficacy and side effects of morphine and fentanyl used in spinal analgesia for post cesarean section pain relief.

Materials and Methods

Study population

Eligible participants were pregnant women registered in Al Helal Al Emirati Hospital (AHAEH) undergoing elective or emergency caesarian section under spinal anesthesia. Exclusion criteria were patients using anticoagulants, who had local septic sources, who were with increased intracranial pressure or patients with previous history of morphine or fentanyl allergy.

Study design and intervention

This randomized, controlled, and parallel clinical trial was approved by Helsinki Committee (number PHRC/HC/03/15). It was conducted at Al Helal Al Emirati Hospital which belongs to the Palestinian Ministry of Health in Gaza strip.

After completed an informed consent, recruited patients were randomly divided into two groups using manual-blocks formation based on the rolling of a die. Patients in Morphine group received 2ml 0.5% hyperbaric bupivacaine with 200μg preservative-free morphine (diluted in 0.5ml normal saline) and patients in Fentanyl group received 2ml 0.5% hyperbaric bupivacaine with 20μg fentanyl. Both groups received a total of 2.5ml local anaesthetic solution for each patient. Standard monitoring included noninvasive blood pressure, pulse oximetry and electrocardiography.

Patients were given 500ml of Hartmann's solution as a fluid preload which was carried out over 15 minutes prior to the procedure then spinal anaesthesia was performed with the patient in the sitting position under aseptic technique using 25-gauge spinal needle at either L3-L4 or L4-L5 interspace. After back-flow of clear cerebrospinal fluid, patients were given 2ml 0.5% hyperbaric bupivacaine with 200μg/0.5ml morphine (Group M) or 2ml 0.5% hyperbaric bupivacaine with 20μg/0.5ml fentanyl (Group F). After spinal anaesthesia, patients were placed supine position with 15º left uterine displacement and the level of sensory loss to temperature was determined. Surgery only started after a satisfactory blockade up to level of T4was achieved. Oxygen at 6 L/min flow was administered via a face mask to the patient. Blood pressure was monitored at 1-minute intervals until stable then continued every 5 minutes. Hypotension was defined as a 20% reduction from baseline systolic blood pressure. If this occurred, patients were treated with a rapid infusion of 100ml of Hartmann's solution and intravenous ephedrine 6mg boluses.

After surgery patient were sent to the obstetric surgery ward for observations. Data collection was done by trained staff nurses who were blinded to the procedure. Pain was assessed by using visual analogue score (VAS; range 0–10, 0=no pain and 10=pain as bad as it could be) 1 h after the end of surgical procedure and then at 6 h, 12h, 18h and 24 h. Time from induction of spinal anesthesia to the first demand of other analgesia and the total amounts and types of analgesics used in 24 hours, were recorded (primary outcomes). In this study pethedine was used as the standard opioid painkiller after surgery. Side-effects of morphine and fentanyl were recorded as the secondary outcomes: nausea and vomiting scores {NVS 0–3; 0=no nausea or vomiting, 1 = present of nausea without vomiting, 2 =mild to moderate vomiting (not requiring treatment) and 3=severe, unresponsive to antiemetic drugs}, sedation scores {SS 0–3; 0=patient awake, 1 = mild drowsiness, 2 = moderate drowsiness, easily awaken and 3=severe sedation, patient difficult to rouse, unrousable}and pruritis scores {PS 0-2; 0 = no pruritis, 1 = mild to moderate pruritis (not requiring treatment), 2 = severe pruritis (treatment required). Severe vomiting as more than two episodes, was treated with intravenous metoclopramide 10mg. Severe pruritis was treated with intravenous promethazine 50mg. In cases of unsuccessful treatment, unpleasant pruritis or occurrence of any life threatening event, an anesthetist would be called in to deal with the problem. Other secondary outcomes were time to pass first flatus, time to remove urine catheter, time to pass first urine and stay period in the hospital after surgery.

Data collection statistical analysis

Special data sheet forms were done to investigate and collect clinical data of recruited patients. Personal and demographic data of

the patients were collected from their casa notes. Data were stored and cleaned by Microsoft excel 2007. Statistical analysis of the data was performed using the Statistical Package for Social Sciences (SPSS) software version 22. Descriptive statistics, including χ^2 (chi square) and OR (odds ratio), were used to compare the categorical variables and risk association of subjects' characteristics in both groups. After the assumption of normality, continuous variables were presented as mean ± standard deviation. Independent t-student test was applied assess the difference between the two groups. Mann-Whitney U statistical test was used for non-normally distributed parameters. A P-value of < 0.05 was considered statistically significant at the level of confidence interval of 95%.

Findings

In this study, a total of 121 patients were recruited. Of these 59 patients (48.76%) were allocated in Morphine group and the remainders 62 (51.24%) were grouped in Fentanyl group. There were no significant difference between the two groups in terms of demographic data (age and weight), operation characteristics (duration and type) and hospital stay after surgery as shown in Table 1. There was no statistically difference in the incidence of intraoperative hypotension between Morphine and Fentanyl groups (OR=1.291 [0.372-4.479] CI=95%).

Variable	M group (n=59)	F group (n=62)	Test value	P-value
Demographic data				
Age (years) (mean ± SD)	28.23±6.12	28.58±5.41	t=0.333	0.739
Weight (kilograms) (mean ± SD)	80.53±16.87	82.64±13.50	t=0.682	0.497
Operation characteristics				
CS duration (minutes) (mean ± SD)	39.24±8.14	41.29±9.79	t=1.251	0.213
Elective CS (%)	31 (52.5%)	34 (54.8%)	χ^2=0.064	0.800
Urgent CS (%)	28 (47.5%)	28 (45.2%)		
Stay period after CS (hours) (mean ± SD)	38.61±13.68	39.71±13.01	t=0.450	0.654
Time to pass first flatus(hours) (mean ± SD)	10.54±4.15	10.62±4.39	t=0.087	0.931
Time to remove urine catheter (hours) (mean ± SD)	6.67±1.15	6.83±2.57	t=0.422	0.674
Time to pass first urine(hours) (mean ± SD)	8.08±2.52	7.44±2.55	t=1.344	0.182

M group: morphine group; F group; fentanyl group; SD: standard deviation; CS: cesarean section; t: independent-samples t-test; χ^2: chi-square test.

Table 1: Demographic data, operation characteristics and hospital stay after surgery

Over the 24-hours study period, twenty (33.9%) patients from Morphine group didn't need additional analgesia, while all the patients of Fentanyl group needed analgesia (OR=2.590 [2.025-3.312] CI=95%). In the other side, these patients in Morphine group needed more time to require additional analgesia than in Fentanyl group (9.03 hours vs. 2.46 hours p= 0.000). VAS values of Morphine group were significantly lower in study period compared with Fentanyl group and this was shown also with number of additional analgesics needed through the study period as stated in Table 2.

Variable	M group (n=59)	F group (n=62)	Test value	P-value
Comparison of postoperative pain scores (VAS)				
1st hour VAS (mean ± SD)	1.81±1.75	2.57±2.31	U=1420.0	0.039*
6th hour VAS (mean ± SD)	1.84±1.51	5.08±2.27	U=459.00	0.000**
12th hour VAS (mean ± SD)	1.45±1.06	3.30±1.76	U=644.00	0.000**
18th hour VAS (mean ± SD)	1.62±1.42	3.18±1.37	U=664.00	0.000**
24th hour VAS (mean ± SD)	1.61±1.03	2.68±1.07	U=883.50	0.000**
Comparison of type required analgesia				
No other analgesia required (%)	20 (33.9%)	0 (0%)	χ^2=51.535	0.000**
Required only non-narcotic analgesics (%)	18 (30.5%)	2 (3.2%)		
Required narcotic analgesics (pethedine) (%)	21(35.6%)	60(96.8%)		
Comparison of number of required analgesics				
No other analgesia required (%)	20 (33.9%)	0 (0%)	χ^2=40.806	0.000**
One other analgesic required (%)	23(39.0%)	13(21.0%)		
Two other analgesics required (%)	13(22.0%)	31(50.0%)		
Three or more other analgesics required (%)	3(5.1%)	18(29.0%)		

M group: Morphine group; F group: Fentanyl group; VAS: visual analogue scale; SD: standard deviation; U: Mann-Whitney U test; χ^2: chi-square test; *: Statistically significant at level P< 0.05, **: Statistically significant at level P< 0.01

Table 2: Postoperative analgesia characteristics

The incidence of nausea was seen more in Morphine group at the sixth hour but this was not associated with vomiting. There was no significant difference in the incidence of nausea and vomiting between the two groups in the rest times as shown in Table 3. Also, the need of antiemetic drugs was approximately the same between Morphine and Fentanyl groups (OR=1.052 [0.064-12.209] CI=95%).

Variable		M group (%)	F group (%)	Test value	P-value
1st hour NVS	No nausea or vomiting	93.2%	100.0%	χ^2=4.347	0.114
	Nausea without vomiting	5.1%	0.0%		
	Mild to moderate vomiting	1.7%	0.0%		
6th hour NVS	No nausea or vomiting	74.1%	93.5%	χ^2=9.222	0.010*
	Nausea without vomiting	24.1%	4.8%		
	Mild to moderate vomiting	1.8%	1.7%		
12th hour NVS	No nausea or vomiting	86.0%	96.7%	χ^2=4.350	0.114
	Nausea without vomiting	8.8%	1.7%		
	Mild to moderate vomiting	5.2%	1.6%		
18th hour NVS	No nausea or vomiting	96.5%	100.0%	χ^2=2.142	0.143
	Nausea without vomiting	3.5%	0.0%		
24th hour NVS	No nausea or vomiting	98.2%	100.0%	χ^2=1.100	0.294
	Nausea without vomiting	1.8%	0.0%		

M group: Morphine group; F group: Fentanyl group; NVS: nausea and vomiting scores; χ^2: chi-square test; *: Statistically significant at level P<0.05

Table 3: Incidence of postoperative nausea and vomiting

At the 12th hour the incidence of drowsiness among Morphine group was seen more than among Fentanyl group but in the rest times there were no significant differences is sedation scores among the two groups (Table 4).

Variable		M group (%)	F group (%)	Test value	P-value
1st hour SS	Patient awake	100.0%	98.4%	χ2=0.960	0.327
	Patient mild drowsiness	0.0%	1.6%		
6st hour SS	Patient awake	94.8%	100.0%	χ2=3.289	0.070
	Patient mild drowsiness	5.2%	0.0%		
12st hour SS	Patient awake	93.0%	100.0%	χ2=4.431	0.035*
	Patient mild drowsiness	7.0%	0.0%		
18st hour SS	Patient awake	96.5%	100.0%	χ2=2.177	0.140
	Patient mild drowsiness	3.5%	0.0%		
24st hour SS	Patient awake	98.2%	100.0%	χ2=1.079	0.299
	Patient mild drowsiness	1.8%	0.0%		

M group: Morphine group; F group: Fentanyl group; SS: sedation scores; χ^2: chi-square test; *: Statistically significant at level P< 0.05

Table 4: Postoperative sedation scores

Over the study period 15.3% of Morphine groups suffered from pruritis and needed treatment compared with 1.6% from Fentanyl group (OR=10.980 [1.345-89.624] CI=95%) detailed pruritis scores are shown in Table 5. There was no significant difference in the incidence of headache between the two groups (OR=1.607 [0.259-9.978] CI=95%).

Variable		M group (%)	F group (%)	Test value	P-value
1st hour PS	No pruritis	84.7%	96.8%	χ^2=4.347	0.114
	Mild to moderate pruritis	10.2%	3.2%		
	Severe pruritis	5.1%	0.0%		
6th hour PS	No pruritis	74.6%	100.0%	χ^2=17.993	0.000**
	Mild to moderate pruritis	18.6%	0.0%		
	Severe pruritis	6.8%	0.0%		

Variable		M group (%)	F group (%)	Test value	P-value
12th hour PS	No pruritis	81.4%	100.0%	χ^2=12.521	0.002**
	Mild to moderate pruritis	11.9%	0.0%		
	Severe pruritis	6.8%	0.0%		
18th hour PS	No pruritis	86.4%	100.0%	χ^2=8.862	0.012*
	Mild to moderate pruritis	11.9%	0.0%		
	Severe pruritis	1.7%	0.0%		
24th hour PS	No pruritis	93.2%	100.0%	χ^2=4.278	0.039*
	Mild to moderate pruritis	6.8%	0.0%		

M group: Morphine group; F group: Fentanyl group; PS: pruritis scores; χ^2: chi-square test; *: Statistically significant at level P< 0.05; **: Statistically significant at level P< 0.01
Table 5: Postoperative pruritis scores

Discussion

Spinal and epidural anesthesia for cesarean section have become a popular practice worldwide since 1980s. In England as example it was noticed that more than 60% of obstetric anesthetists used the spinal and epidural anesthesia during labour or caesarean section [15]. Spinal anaesthesia has the superiority over epidural because it takes less time to perform, has faster onset and provides a more consistent and reliable block [16]. The addition of an opioid to the local analgesic is essential because in cesarean section there is significant traction of peritoneum and intraperitoneal structures which raise the visceral pain and increase the demand of optimal analgesia respectively [17]. Therefore, the choice of suitable opioid is very important to obtain good analgesia for the longest time and minimal side effects. So, the comparison of both effects and side effect for the two drugs as morphine and fentanyl has its importance to give more choices for anesthesiologists to find the appropriate medication for their practice.

We found in this study the superiority of morphine over fentanyl in reducing post-operative pain. This was shown by significantly reducing mean VAS for the first 24 hours. This superior analgesic effect of morphine was shown also in reducing the demand of other post-operative analgesia and more time to request this analgesia if needed. These results are consistent with other studies were done by Sibilla, *et al.* in 1997 by using morphine and fentanyl alone or in combination for perioperative analgesia in caesarean section, and Salmah and Choy in 2009 who compared morphine and fentanyl for this purpose also but with different doses [18,19].

Although, Palmer et al in 1999 observed that the duration and effectiveness of used morphine spinally was dose-dependent, the ceiling effect was observed to be at above 0.1 mg [20]. In the other hand, the incidence of side effects always increases with the increase of the dose and may limit the quantity of morphine given dose. A significant incidence of respiratory depression above or at 0.2 mg spinally morphine has been described but in our study we didn't observe clinically-detectable respiratory depression with the dose of 0.2mg nor with the dose of 0.02 mg fentanyl [16,20]. The incidence of intraoperative hypotension was approximately the same between the two drugs. We observed that morphine caused slightly more sedation after 12 hours which can be explained that the delayed effect is due to slow transport of hydrophilic morphine by the cerebrospinal fluid circulation to the fourth ventricle, where it acts on opioid receptors and can cause drowsiness [20].

The risk of nausea and vomiting was seen more in Morphine group than Fentanyl group. The incidence of treatable moderate vomiting was the same after 6 hours in the two groups, but it was seen more among Morphine group after 12 hours but this was statistically insignificant. In Morphine group the incidence of nausea was remarkable but patients didn't need treatment. Vomiting may result either from rostral spread of the drug in CSF to the chemoreceptor trigger zone (CTZ) or the vascular uptake and delivery to the vomiting center and CTZ [21]. Few patients needed treatment with antiemetic drugs as metoclopramide and with ranitidine. Anyway, nausea and vomiting are easily treated side effects, as antiemetic treatment does not interact with analgesia [21].

Pruritis side effect was seen to be remarkable between patients of Morphine group. It is known that pruritis is one of the most common side effects of spinal morphine, especially in doses equal to 0.2mg or more. These findings were seen in a recent meta analysis done by Sultan et al who found pruritis to be associated with high doses of spinal morphine [22]. May be pruritis is more likely to occur in obstetric patients, due to interaction of estrogen with opioid receptors [19]. In our study promethazine was used for the treatment of pruritis, which has also antiemetic and sedative effect. Naloxone which is an opioid antagonist was not used because of concern to reverse the analgesic effect of morphine.

Although, only 30.5% of Morphine group and 3.2% of Fentanyl group required only non-steroidal anti-inflammatory drugs, it is essential to think about the importance of these medications in post-cesarean section pain relieve to avoid undesirable side effects of pethedine. The used dose of morphine was near the lower limit which ranges from 0.1 to 2.5 mg to have desired analgesic effect with minimal side effects, but pruritis was a remarkable side effect in our study [6]. In this study we aimed to reach more participants but because of lack of financial recourses and some study settings constrains as work load in the place and some local social believes limit our ability to have a larger sample size. We think all these constrain didn't have any impact on the results of the study.

Conclusion

Our conclusion, morphine in dose of 0.2mg used for spinal analgesia for cesarean section provided satisfactory and long duration analgesia compared with 20μg fentanyl in same route of administration. Although, it was associated with more side effect compared with fentanyl, these side effects were treatable and didn't pose any danger to patients.

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