

RESEARCH ARTICLE

Comparison in Efficacy between Fentanyl Continuous Infusion and Intrathecal Morphine for Pain After Caesarean Section Management

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ABSTRAK

Latar Belakang: Morfin intratekal efektif menghilangkan rasa nyeri pasca seksio sesar, namun mempunyai resiko depresi nafas tertunda. Infus kontinu fentanil dengan laju dasar infus tetap menggunakan *disposable elastomeric pump* merupakan alternatif namun belum terbukti efektif dibandingkan morfin intratekal. **Tujuan:** membandingkan efektifitas infus kontinu fentanyl dengan morfin intratekal pada nyeri pasca seksio sesar.

Metode: Uji klinis acak 56 pasien yang memenuhi kriteria inklusi dibagi menjadi 2 kelompok: Morfin (n=28): anestesi spinal Bupivacain Heavy 0,5% 10 mg + morfin 100 mcg dan Fentanyl (n=28): anestesi spinal Bupivacain Heavy 0,5% plain + infus kontinu fentanyl 0,5 mcg/kg BB/jam. Fentanil diberikan setelah bayi lahir menggunakan *disposable elastomeric infusion pump*. Penilaian skor nyeri menggunakan NRS dan OOAPS, sedangkan respon stress diukur dengan peningkatan kadar kortisol.

Hasil: Perbedaan skor NRS bermakna hanya pada pengukuran 6 jam pertama pasca operasi, $p=0,034$; nilai rerata skor NRS kelompok Morfin (0.68 ± 1.02) dan nilai rerata skor NRS kelompok Fentanyl (1.11 ± 0.832). Kedua kelompok sama efektifnya mencegah peningkatan kadar kortisol 6 jam pasca operasi; nilai rerata kelompok Morfin (15.053 ± 8.664) dan kelompok Fentanyl (12.162 ± 8.623), secara statistik berbeda tidak bermakna, $p=0.114$.

Kesimpulan: Infus kontinu fentanyl 0,5 mcg/kg BB/jam menggunakan *disposable elastomeric infusion pump* mempunyai efektifitas yang sama dengan morfin intratekal 100 mcg pada nyeri pasca seksio sesar.

Kata Kunci: nyeri, seksio sesar, morfin intratekal, infus kontinu fentanyl, *disposable elastomeric pump*, NRS, OOAPS, kortisol.

ABSTRACT

Background: Intrathecal morphine has been shown to be effective for pain after cesarean section with possible side effect including delayed respiratory depression, nausea vomiting and pruritus. Fentanyl continuous infusion fixed base infusion rate with disposable elastomeric pump is an alternative to intrathecal morphine but has not been widely studied. **Objective:** to compare the effectiveness between fentanyl continuous infusion fixed base infusion rate using disposable elastomeric pump and intrathecal morphine.

Methods: in a Randomized Controlled Trial (RCT), 56 patients meeting the inclusion criteria were divided into two groups: Morphine group (n=28): spinal anesthesia 10 mg Bupivacaine Heavy 0.5% + 100 mcg morphine; Fentanyl group (n=28): spinal anesthesia 10 mg Bupivacaine Heavy 0.5% + fentanyl continuous infusion 0.5 mcg/kg BW/hour using disposable elastomeric pump after delivery. Data analysis: Mann-Whitney test at the level of significance $p<0.05$.

Results: Analgesic effect of Fentanyl group was as effective as that of Morphine group. NRS score difference was significant only in measurement taken 6 hours after surgery ($p=0.034$). Mean NRS score for Morphine and Fentanyl were 0.68 ± 1.02 and 1.11 ± 0.832 , respectively. Both group were effective in preventing increased cortisol level measured 6 hours after surgery, mean value group Morphine and Fentanyl were 15.053 ± 8.664 and 12.162 ± 8.623 , respectively. There were no statistical significant difference between groups ($p=0.114$). No significant difference in side effect between the groups was found.

Conclusion: Fentanyl continuous infusion 0.5 mcg/kg BW/hour using disposable elastomeric pump is as effective as intrathecal morphine 100 mcg/kg BW/hour.

Keywords: pain, caesarean section, intrathecal morphine, fentanyl continuous infusion, disposable elastomeric pump, NRS, OOAPS, cortisol.

INTRODUCTION

Post-caesarean section patients suffer from moderate-severe pain up to 48 hours post section

leading to a delayed baby care (Verstraete S and Velde MVD, 2012). Ineffective management in post cesarean section pain may lead to various adverse

Putro, et al.

effects on the cardiovascular, respiratory, genitourinary, musculoskeletal neuroendocrine system resulting in the increased morbidity and mortality. (Man, 2014, Morrison et al., 2003, Escamilla RP et al., 1996). Postoperative pain management in caesarean section is often inadequate; parturient are often not treated as a patient because no illness (Vercauteren M, 2009).

Intrathecal Morphine is the gold standard of neuraxial opioids for pain after cesarean section, but it can cause side effects of delayed respiratory depression, nausea, vomiting, itching (pruritus) and sedation that can interfere the ability of the mother to immediately start taking care of her baby (Carvalho FAE and Tenorio SB, 2013). Breath depression, although rare (0.9%), could be fatal because it occur 6-18 hours after administration. Weinger M reported 16 cases of respiratory depression in neuroaxial opioid administration with mortality or permanent brain damage of 73% (Weinger M, 2007).

Fentanyl binds selectively to μ receptors in the central and peripheral nervous system so that side effects are minimal and do not have active metabolites. As a postoperative analgesia, Fentanyl effect lasting for only 30-45 minutes, requires continuous administration to maintain effective levels in plasma Effective concentration of plasma fentanyl for postoperative pain was 0.63 ng /ml (in the range of 0.23 to 1.18 ng /ml) The use of single use continuous infusion devices with disposable infuser elastomeric pump is an alternative for providing a simpler and cheaper infusion of fentanyl than a syringe pump.

The subjective clinical pain intensity could be measured using a standardized scale called numeric rating scale (NRS) (Coll Am et al., 2004). Kim et al used Observer Objective Assessment of Pain Scores which measures the intensity of pain objectively by an observer There is no biological marker of pain intensity that can be measured directly, but trauma or tissue damage due to surgery leads to hormonal and metabolic changes (stress response) in the form of increased secretion of pituitary hormones and sympathetic nervous system activation which releases corticotropin and stimulates the secretion of cortisol from the adrenal cortex that reaches its peak 4-6 hours after surgery begins (Desborough JP, 2000). This present study aimed to determine the difference in the effectiveness between continuous fentanyl infusion using a disposable infuser elastomeric pump fixed basal infusion rate and intrathecal morphine in postoperative cesarean section pain management with the parameters of pain scores (NRS and OOAPS), level of cortisol after 6 hours caesarian section and adverse events such as respiratory depression, sedation, nausea, vomiting and pruritus.

METHODS

This study was an experimental clinical trial with a randomized controlled trial design. The inclusion criteria of the study sample were caesarean section patients with spinal anesthesia, physical status of ASA I-II, aged 18-40 years. Exclusion criteria were contraindications to spinal anesthesia, inadequate sensory block after spinal anesthesia, surgery exceeding 90 minutes, patients with allergic history/hypersensitivity to study drugs and patient refuses to participate in the research. The sample size was calculated using an unpaired numerical analytic research formula with a sample size of 56 patients (28 per group). Sampling was done by consecutive sampling.

The Administration of Anesthesia

In the morphine (M) group, spinal anesthesia was performed with bupivacaine heavy 10 mg + 100 mcg intra thecal morphine. In the fentanyl (F) group, spinal anesthesia was performed only with bupivacaine heavy 10 mg and administered a continuous infusion of fentanyl using a disposable elastomeric infusion pump of 0.5 mcg/kgBW/hour for 24 hours started after the baby was born. In both groups were given non-steroidal anti-inflammatory drugs (NSAID) ketorolac 30 mg i.v per 8 hours to 24 hours postoperatively.

Measurements of NRS and Ooaps Pain Scores

Measurements of NRS and OOAPS pain scores in both groups were performed 6 hours postoperative and every 6 hours for 24 hours postoperative. If the pain score of NRS>5 or OOAPS>0, the additional analgesics (rescue dose) was administrated (petidin 0.5 mg/kg BW intravenous). Adverse events were recorded and reported using a sedation score, respiratory depression, Postoperative Nausea and Vomiting (PONV) scores and a pruritus score. The measurement of plasma cortisol was performed by sampling of vein 6 hours postoperative. Samples were then sent to the laboratory for processing and inspection.

Statistical Analysis

Data obtained were analyzed using chi-square test (categorical scale data baseline), independent T test (parametric) and Mann-Whitney test (nonparametric). Ethical clearance number: 313/XII/2015/Bioethical Commission was obtained from Bioethics Commission of Medical/Health Research of Medical Faculty of UNISSULA.

RESULTS

The result of independent T-test and Chi-Square

Table 1. Baseline data on age, body weight and physical status of preoperative ASA

VARIABLES	GROUP		P		
	MORPHINE MEAN ± SD	FENTANYL MEAN ± SD			
Ages (years)	28±7.045	26.93±5.04	0.516		
Weight (kg)	64.93±8.205	64.89±7.767	0.987		
ASA	N	%	N	N	%
ASA 1	15	53.57	18	15	53.57
ASA 2	13	46.43	10	13	46.43

* p <0.05, statistically different

Table 2. Numeric Rating Scale (NRS) Score 1-4, Observer's Objective Assessment of Pain Scores (OOAPS) 1-4, sedation score, Postoperative Nausea and Vomiting (PONV) scores, pruritus score, respiratory depression and cortisol levels.

NO	VARIABLES	GROUPS		P
		MORPHINE MEAN ± SD	FENTANYL MEAN ± SD	
1.	NRS 1	0.68 ± 1.02	1.11 ± 0.832	0.034 *
2.	NRS 2	1.11 ± 0.994	1.14 ± 0.356	0.743
3.	NRS 3	1.14 ± 1.044	1.36 ± 0.559	0.342
4.	NRS 4	0.89 ± 0.956	1.11 ± 0.497	0.293
5.	OOAPS 1	0.25 ± 0.518	0.32 ± 0.476	0.425
6.	OOAPS 2	0.32 ± 0.548	0.18 ± 0.476	0.215
7.	OOAPS 3	0.32 ± 0.476	0.32 ± 0.612	0.693
8.	OOAPS 4	0.25 ± 0.518	NO	0.01
9.	SEDATION SCORES	NO (0)	0.07 ± 0.378	0.317
10.	PONV SCORES	0.04 ± 0.189	0.11 ± 0.567	0.98
11.	PRURITUS SCORES	0.04 ± 0.189	NO (0)	0.317
12.	RESPIRATORY DEPRESSION	NO (0)	NO (0)	1
13.	CORTISOL LEVEL (µg/dl)	15.053 ± 8.644	12.162 ± 8.623	0.114

* p <0.05, statistically different

test to baseline showed that the two groups of patient's age, body weight and physical status of preoperative patients were comparable according to the classification of ASA (American Society of Anesthesiologists), p>0.05 (Table 1). While the NRS, OOAPS, PONV, and other scale was illustrated in Table 2.

NRS scores showed statistically significant differences in the first 6 hours. OOAPS scores, sedation score, PONV score, pruritus score, respiratory depression and cortisol levels were not significantly different in both groups.

The hypothesis of this study which states that there is no difference in effectiveness between a continuous infusion of fentanyl disposable infuser elastomeric pump fixed basal infusion rate with intrathecal morphine in post-caesarean section pain is accepted.

DISCUSSION

This study showed no side effects of respiratory depression. One of the risk factors for respiratory depression is the administration of a high dose of

intrathecal morphine. In this study, there was no respiratory depression might have been due to the use of a low dose of intrathecal morphine (100 mcg). This support findings of several studies showing that the optimal dose of intrathecal morphine for analgesia after caesarean in which there is a balance between analgesia and side effects that occur (Carvalho FAE and Tenorio SB, 2013, Wong JY et al., 2013, DeSousa KA and Chandran R, 2014, Irawan H et al., 2014).

NRS pain scores showed statistically significant differences only in the first 6 hours after caesarean section. The minimum effective concentration of fentanyl plasma that resulted in analgesia effect was 0.63 ng/ml. Research models of pharmacokinetics of fentanyl showed a delayed increase in the minimum effective concentration of plasma after the administration of continuous infusion with multiple dose regimens especially in the low background of infusion, resulting in insufficient plasma concentration to cope with the severity of the pain intensity in the initial phase of post-surgery in administration at a dose <1.1 mcg/kg/hr. The administration of a higher dose

Putro, et al.

of infusion (1.25-2.0 mcg/kg/hr) may increase the risk of adverse events such as ventilation depression. Some studies showed a relatively higher pain scores after the administration of intravenous fentanyl up to 4-6 hours postoperatively (Kim JY et al., 2013, Shafer SL et al., 1990, Choi SH et al., 2008). In this study, although pain scores with NRS in the first 6 hours were statistically significantly different between the two groups ($p = 0.034$), but it was not clinically significant. This is because the mean score of NRS in the first 6 hours in the fentanyl group and morphine group were 1.11 ± 0.832 and 0.68 ± 1.02 respectively. Both pain score were categorized as a mild pain (NRS score 0-3) so that the patient did not complain of pain and did not ask for additional analgesic (rescue dose). Assessment of pain scores with OOAPS showed a different results compared with NRS pain scores, this was due to difference in the technique. Numeric Rating Scale (NRS) was measured by asking the patient what the pain score was from the range between 0 (not feeling pain at all) and 10 (unbearable great pain). Thus, it was a subjective perceived pain. Measurement of pain score with OOAPS was done by objectively observing the patient's behavior including general condition, facial expression, groaning voice, body posture and patient's permission to additional analgesic evaluated by an observer. Nevertheless, the results of this study showed that NRS pain scores and OOAPS scores fell into the category of mild pain, resulting in no additional demand for analgesic by the patient. This suggests that the pain scores of NRS and OOAPS are clinically no different.

Surgical trauma leads to hormonal and metabolic changes called stress response. The stress response to surgery is characterized by hypophysis hormone and active sympathetic nervous system leads to corticotrophin release from the pituitary stimulating cortisol secretion from the adrenal cortex. Adrenal cortisol secretion is activated by stimuli such as pain, hypotension, and hypovolemia and tissue trauma. Normal cortisol levels are 6-23 $\mu\text{g}/\text{dl}$, starting to increase since the beginning of surgery and reaching its peak in the following 4-6 hours. In a surgery, there is a failure in the feedback mechanism (negative feedback) so that elevated levels of cortisol fail to inhibit the production of further adrenocorticotrophic hormone (ACTH). Presseau et al (2013) found an increase in salivary cortisol levels due to pain stimulation in studies on the contribution of acute stress responses to differences in perception of individual pain and brain activity associated with pain in healthy individuals and chronic pain sufferers (Burton D et al., 2004, Desborough JP, 2000, Presseau EV et al., 2013) In this

study, cortisol levels were found to be normal in the 6 hours postoperatively with an average value of $15.053 \pm 8.644 \mu\text{g}/\text{dl}$ in the group of morphine and $12.162 \pm 8.623 \mu\text{g}/\text{dl}$ in the fentanyl group, indicating the effectiveness of intrathecal morphine and a continuous infusion of fentanyl inhibiting postoperative pain stimulants that activate the sympathetic nervous system and stimulate cortisol secretion. There was no statistically significant difference in cortisol levels 6 h postoperatively between morphine k groups and fentanyl group 1.

This study has been limited to subjective pain properties and to date no definitive biological marker of pain has been found, so individual bias could not be prevented in the measurement of the score. Efforts to overcome this problem was by the use a more objective pain scores of OOAPS and measurement of plasma cortisol levels as an indicator of the body's stress response to surgery and pain. The use of cortisol to measure the body's stress response is an indirect indicator of pain intensity. The number of samples used in this study was also limited for time and cost effectiveness.

CONCLUSION

This study found that there is no difference in the effectiveness between continuous infusion of fentanyl using a disposable infuser elastomeric pump fixed base infusion rate and intrathecal morphine in post-cesarean section pain management.

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