Original Article

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Anaesthesia Section

Effect of Ketofol on Pain and Complication after Caesarean Delivery under Spinal Anaesthesia: A Randomized Double-blind Clinical Trial

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ABSTRACT

Introduction: Pain is the key concern of women after caesarean delivery that may interfere with breastfeeding.

Aim: The aim of this study was to assess effect of ketofol (ketamine/propofol combination) on pain and complication after caesarean delivery under spinal anaesthesia.

Materials and Methods: In this randomized double-blind clinical trial, 92 parturient scheduled for elective caesarean delivery under spinal anaesthesia were included. The simple random sampling method was used to place subjects in four groups of ketamine (0.25 mg/kg), propofol (0.25 mg/kg), ketofol (25 mg ketamine plus 25 mg propofol) and placebo (saline). The drugs were administered intravenously immediately after clamping the umbilical cord. Visual Analog Scale (VAS) was used to determine the intensity of pain. Complications after surgery including shivering, nausea and vomiting as well as onset of breastfeeding were recorded.

Results: The mean score of pain, morphine consumption and time of breastfeeding in the ketofol group were significantly lower than other groups at various intervals ($p<0.05$, $p<0.001$). The frequencies of shivering, nausea, vomiting, retention and pruritus in the ketofol group were significantly lower than other groups ($p<0.001$, $p<0.05$)

Conclusion: The effective role of ketofol on reducing pain and complication after caesarean delivery indicated that it can be considered as a safe and alternative drug in these patients.

Keywords: Anaesthesia, Shivering, Vomiting

INTRODUCTION

Increasing rate of caesarean section is common among women in developing countries [1-3]. The caesarean delivery rate has been reported up to 31% of all births (>1 million caesarean deliveries per year) in the US [4]. The global rate of caesarean delivery was estimated as 32.0% of births in 2015 [2].

Pain is one of the most important challenges for the women and health care providers after caesarean delivery [5]. Postoperative pain after caesarean delivery may continue as chronic pain. The incidence of chronic pain after caesarean delivery was reported to be between 5.9 % to 33% [6-8]. The average morphine consumption after caesarean delivery has been reported to be 35.0 mg to 54.5 mg in the first 24 hours [9]. Acute pain after surgery leads to discomfort, morbidity, delayed healing and hospital costs [10,11]. Poor pain control after caesarean section may interfere with walking, breastfeeding, early attention and nutritional care of the newborn [9,12-14]. Therefore, effective pain management in women after caesarean delivery is vital [1] and improves the overall quality of life [13].

On the other hand, the prevalence of shivering in patients undergoing spinal or epidural anaesthesia has been reported up to 56.7% [15-17]. Postoperative Nausea and Vomiting (PONV) range from 9% to 56% [18] which is a common post-anaesthetic complication. PONV increase cost of care and prolonged stay in the recovery room [19], while shivering can interfere with electrocardiogram, oxygen saturation monitoring and blood pressure. In addition, shivering increases oxygen consumption, carbon dioxide production, and metabolic rate by up to 400% [15]. The opioids complication included respiratory depression, nausea, vomiting, excessive sedation, pruritus, and drowsiness. The use of opioids in caesarean section is limited due to mother-infant relationship [3,10]. Recently, it is emphasized to use non-opioid analgesic drugs [20,21].

Propofol and ketamine are sedative and hypnotic anaesthetic agents [19]. Propofol is an anaesthetic drug with rapid induction and recovery time with, low side effects and easy titration [22,23]. Ketamine can protect airway reflexes and spontaneous respiration due to characteristic analgesic, sedative and amnestic properties. The use of ketamine alone is associated with complication such as postoperative dysphoria, emergence phenomena, vomiting, or laryngospasm. However, administration combined with propofol leads to less respiratory and haemodynamic effects [24].

The aim of this study was to investigate the effect of ketofol on pain, shivering, nausea and vomiting after caesarean delivery under spinal anaesthesia. We hypothesized that effect of ketofol on pain and complications after caesarean section is different than propofol and ketamine alone.

MATERIALS AND METHODS

This clinical trial was conducted at the Shahid Mostafa Khomeini Hospital (center of women's surgery) affiliated with Ilam University of Medical Sciences, Ilam, Iran, during April 2015 to Jan 2016. The statistical population included all of the patients undergoing caesarean section.

Patients with the following criteria were excluded from this study: drug abuse, history of allergic reaction to any of the study drugs, contraindication to regional anaesthesia such as local infection or bleeding disorders, contraindication to spinal anaesthesia, under use of non-steroidal anti-inflammatory drugs, peptic ulcer, cardiovascular, metabolic, respiratory, and renal failure, or coagulation abnormalities.

The sample size was calculated according to data from a pilot study with 10 patients using the following formula.

$n= (z_{1-\alpha/2}+z_{1-\beta})^2 (2s^2)/d^2 = 23$

Z for $_{\alpha}$ = 95% = 1.96

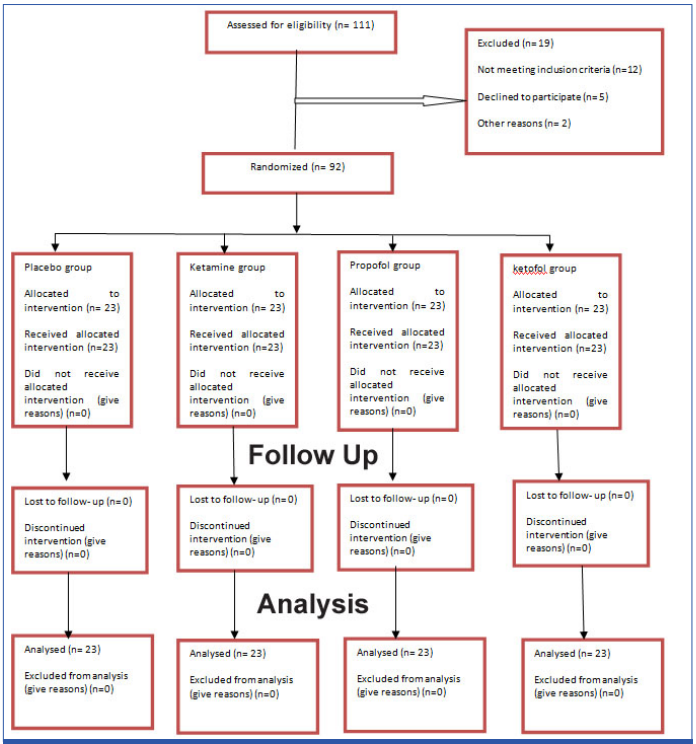
Z for $_{\beta}$ = 80%= 0.84 (test power)

S (an estimate of the standard deviation of VAS in the groups) 1.67 was obtained in a pilot study.

d (The minimum of the mean difference of VAS between the groups which showed a significant difference) was obtained 1.4.

Randomized double-blind clinical trial, included 92 patients having American Society of Anaesthesiologists (ASA) grade I or II, aged 20-35 years, gravid 1, scheduled for elective caesarean delivery under spinal anaesthesia. Patients were randomized into four groups. In each Group, there were 23 patients: Group A (propofol), Group B (ketamine), Group C (ketofol) and Group D (placebo). A simple random sampling method was used to assign subjects to four groups [Table/Fig-1].

A re-determined code was assigned to each group (code 1= propofol, code 2= ketamine, code 3= ketofol and code 4 =placebo) and each code placed in a sealed envelope. In order to determine which group the patient is going to be placed, a sealed envelope randomly was taken. The patients, anaesthesiologists and surgeons were blinded to the drug administered. Coding and sealed envelope technique was performed by a nurse who did not participated in this study. The patients in the Group A (propofol) received 0.25 mg/kg propofol, Group B (ketamine) received 0.25 mg/kg ketamine, Group C (ketofol) received 25 mg ketamine plus 25 mg propofol and Group D (placebo) received saline intravenously, immediately after clamping of the umbilical cord. Surgeon and anaesthesiologist were same in all patients. Standard monitoring included electrocardiogram, noninvasive blood pressure, and pulse oximetry. All parturient before induction of spinal anaesthesia received an infusion of lactated ringer's solution (1000 ml). The block was carried out with a 25-gauge quincke needle in the left lateral position at the L3-L4 interspace. Fentanyl was given in the operation room according to patient need and clinical discretion.



[Table/Fig-1]: CONSORT diagram of participant in the clinical trial.

The VAS was used to determine intensity of pain. The pain severity was assessed on first, fourth, eighth, 12th and 24th hour after caesarean section. The patient's vital signs, complications, morphine consumption and the time of breastfeeding were recorded. Shivering was evaluated on a tool with 0=no shivering observed, 1=shivering observed [25]. This study was approved by the Vice chancellor for research at the Ilam University of Medical Sciences, Ilam, Iran, (EC: 94/H/277) and informed consent was obtained from all participants. This study was registered at the Iranian Registry of Clinical Trials (IRCT2015061514668N4).

STATISTICAL ANALYSIS

Data were analyzed using the statistical software SPSS, Version 16.0. (SPSS Inc, Chicago, IL, USA). Descriptive statistics, one-way ANOVA, Least Significant Difference (LSD) test and repeated measurement was carried out to analyze the results. The $p<0.05$ was considered as significant.

RESULTS

According to Kolmogorov-Smirnov test, data were normally distributed and therefore parametric tests were used ($p>0.05$). Subject's characteristics were not different among the groups ($p>0.5$) [Table/Fig-2]. One-way ANOVA showed that the mean score of pain severity score in the ketofol group significantly was less than those of the placebo, propofol and ketamine groups respectively at various intervals ($p<0.001$) [Table/Fig-3]. The LSD test confirmed these results ($p<0.001$) [Table/Fig-4].

The means of morphine consumption and mean time of breast feeding after surgery in the ketofol group were significantly lower than those of the propofol, ketamine and placebo groups respectively ($p<0.001$) [Table/Fig-2,5]. Repeated measurement analysis showed that the mean pain score in the ketofol, ketamine, propofol and placebo groups were significantly different in various intervals ($p<0.001$) [Table/Fig-6].

The frequencies of shivering, nausea, vomiting, retention and pruritus in the ketofol group were significantly lower than those of the propofol, ketamine, and placebo groups respectively ($p<0.001$,

Patients Characteristics	Placebo (n=23) (mean±sd)	Propofol (n=23) (mean±sd)	Ketamine (n=23) (mean±sd)	Ketofol (n=23) (mean±sd)	p-value
Age/year	26.5±1.7	27.5±2.5	27.9±1.6	28.1±2.4	0.06*
Surgery duration/min	67.5±2	65.4±3.7	67.1±5.1	66.1±2.4	0.17*
Anaesthesia duration/min	84.3±4.3	83.1±3.5	85±5.6	85.6±5	0.31*
Morphine consumption/mg	14.1±2.1	8.4±2.3	4.3±0.9	0.3±0.2	<0.001
Breastfeeding time/min	58±5.5	42.6±5.4	31.9±6.6	25.8±3.5	<0.001
Nausea (n%)	8 (34.8%)	3 (13%)	2 (8.7%)	0.00	0.006**
Vomiting (n%)	6 (26.1%)	2 (8.7%)	1 (4.3%)	0.00	0.01**
Shivering (n%)	15 (65.2%)	8 (34.8%)	4 (17.4%)	0.00	0.00***
Retention (n%)	7 (30%)	4 (17.4%)	2 (8.7%)	0.00	0.02**
Drowsiness (n%)	2 (8.7%)	3 (13%)	9 (39.1%)	8 (34.8%)	0.03**
Dizziness (n%)	3 (13%)	5 (21.7%)	9 (39.1%)	5(21.7%)	0.2*
Pruritus (n%)	3 (13%)	4 (17.4%)	2 (8.7%)	2 (8.7%)	0.7*

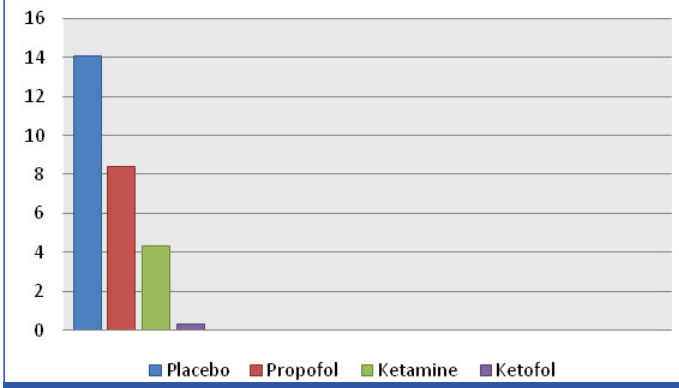
[Table/Fig-2]: Baseline characteristics and adverse effects in the patients.
Statistical test: Mean, Standard deviation, frequencies
* Not significant, ** Significant, *** Highly significant

Pain score by VAS, h	Placebo (n=23)	Propofol (n=23)	Ketamine (n=23)	Ketofol (n=23)	p- value
1 hr after intervention	8.6±0.4	5.6±0.4	2.3±0.4	1.4±0.7	0.001
4 hr after intervention	7.6±0.4	5±0.1	2±0.2	1±0.2	0.001***
8 hr after intervention	6.3±0.4	4±0.2	2±0.6	1±0.1	0.001***
12 hr after intervention	4.3±0.4	3.3±0.4	1.3±0.4	0.6±0.3	0.001***
24 hr after intervention	3±0.1	2±0.1	1±0.1	0.3±0.2	0.05

[Table/Fig-3]: Severity of pain at various intervals in the groups.
Statistical test: Mean, Standard deviation
** Significant, *** Highly significant

Outcome parameters	Between group	Drugs	p-value*
1 hr after intervention	Placebo	Propofol	<0.05
		Ketamine	<0.05
		Ketofol	<0.05
4 hr after intervention	Placebo	Propofol	<0.05
		Ketamine	<0.05
		Ketofol	<0.05
8 hr after intervention	Placebo	Propofol	<0.05
		Ketamine	<0.05
		Ketofol	<0.05
12 hr after intervention	Placebo	Propofol	<0.05
		Ketamine	<0.05
		Ketofol	<0.05
24 hr after intervention	Placebo	Propofol	<0.05
		Ketamine	<0.05
		Ketofol	<0.05

[Table/Fig-4]: Outcome of severity of pain between groups according to Post-hoc test.
* Highly significant



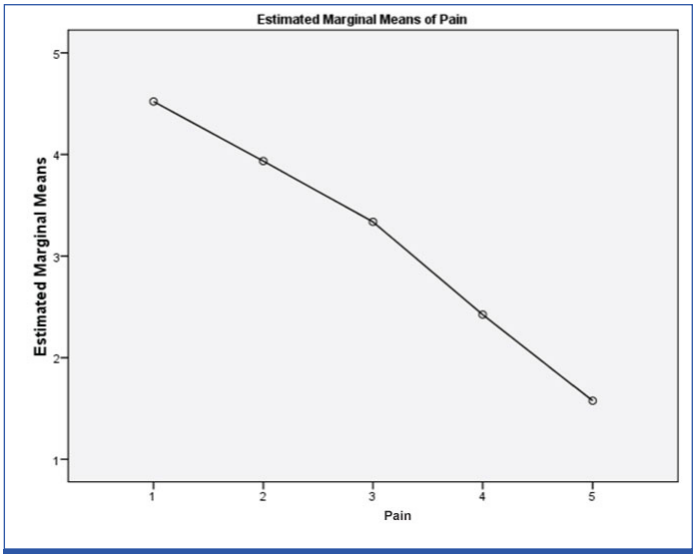
[Table/Fig-5]: Morphine consumption in the groups

p<0.05) [Table/Fig-2]. The frequency of drowsiness (42.1%) in the ketamine group was significantly higher than that of the propofol, ketofol and placebo groups (p<0.05). Although the frequency of dizziness in the ketamine group was higher than that of the placebo, propofol and ketofol group, no statistically significant difference between groups was observed (p>0.05) [Table/Fig-2].

DISCUSSION

Management of pain and complications after caesarean delivery such as shivering, nausea and vomiting are common challenges in care process, facilitated breastfeeding and satisfaction of mother. On the other hand, insufficient analgesia leads to catecholamine release, resulting in adverse effect on all organ systems [20,26]. Postoperative pain, shivering, nausea and vomiting are common complications impairing the quality of postoperative recovery such as readmissions after discharge, chronic pain after surgery and increasing morbidity and costs [20,21].

Opioids are the first choice to manage pain after surgery but they are associated with some complications [20]. Recently, there is an



[Table/Fig-6]: Repeated measurement analysis of pain between groups.

increasing trend of use of multimodal analgesia, using two or more analgesics and modalities with multi-mechanisms to treat analgesia and decrease the prevalence of complication [20].

Our finding suggested that ketofol significantly reduced pain, overall morphine consumption, postoperative shivering, nausea and vomiting in patients following caesarean delivery under spinal anaesthesia. This finding was consistent with the previous studies on the effects of ketamine on postoperative pain and complications [27-30].

Nejati A et al., found that ketamine/propofol versus midazolam/fentanyl in emergency patients significantly reduce pain. However no significant differences in sedation time between the groups were observed [24]. Behaeen K et al., concluded that injection of low dose ketamine at the incision site in caesarean delivery significantly reduce pain intensity and request of analgesia in 2, 4, 6 and 12 hours after surgery [5]. Himmelseher S et al., showed that ketamine administration both before induction of anaesthesia and during surgery significantly reduced the pain intensity and need for opioids [31].

Mizrak A et al., in a study on strabismus surgery of children concluded that the morphine consumption and the use of antiemetics in the ketamine group were significantly lower than propofol group [19]. Besides, Rasooli S et al., found that the combination of propofol and midazolam during caesarean section under spinal anaesthesia significantly decreases nausea and vomiting [32].

Dal D et al., concluded that ketamine and pethidine significantly reduce shivering and morphine consumption in patients after general anaesthesia [33]. On the other hand, Bilgen S et al., in their study on the effect of three different doses of ketamine on postoperative pain following caesarean delivery found no significant differences in pain, morphine consumption and side effects among the groups [1]. Becke K et al., found that intraoperative low-dose ketamine had no effect on morphine consumption and pain intensity during the first 72 hour after surgery [34].

Naghibi KH et al., compared effect of propofol, remifentanil and ketamine on postoperative pain scores and analgesic requirements in elective lower abdominal surgery under general anaesthesia and found that the pain scores were significantly lower in remifentanil group than the propofol and ketamine group. The morphine consumption in the first 24 hour after surgery was significantly high in the remifentanil and ketamine group than the propofol group [35].

Previous researches emphasized on the use of non-opioid analgesic drugs to control pain after surgery [20,21]. Propofol and ketamine inhibits N-methyl-d-aspartate (NMDA)-receptors in hippocampal neurons thereby reducing the postoperative pain [19]. Ketamine has several pharmacological effects including κ opioid agonist, blocking amine uptake in the descending inhibitory monoaminergic

pain pathways, having a local anaesthetic action and interacting with muscarinic receptors. Therefore, it may control shivering using non-shivering thermogenesis either by affecting hypothalamus or by the β-adrenergic effect of norepinephrine [33]. Ketamine in sedative doses can lead to electroencephalographic activation and in small doses increase thalamic sensory output and arousal. Emergence delirium occurs more often in adults than children and is an adverse effect of ketamine [24].

LIMITATION

The limitations of the current study include relatively small sample size and measuring self-reported subjective perception of pain by patients.

CONCLUSION

In general, ketofol significantly reduced pain and morphine consumption after caesarean delivery under spinal anaesthesia compared to ketamine and propofol. Our finding showed that ketofol had less adverse effects compared to other groups.

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