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Research Article

Hemodynamic Effects of a Single Dose Intravenous Ketamine Following Cesarean Section Under Spinal Anesthesia: A Randomized Control Trial

Naglaa Hussien[1*], Nagat El-Shmaas[2]

[1]Obstetrics and Gynecology Department, Tanta University. Tanta, Egypt
[2]Anesthesia, ICU, and Pain Medicine Department., Tanta University. Tanta, Egypt

[*]**Corresponding author**: Dr. Naglaa Hussien, Lecturer in Obstetrics and Gynecology Department, Faculty of Medicine, Tanta University. Tanta, Egypt.

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Abstract

Background: *There has been an increasing tendency in the frequency of cesarean delivery in the past 20 years, in both developing, and developed countries. We intended to evaluate the effect of a single dose intravenous Ketamine after cesarean section taken spinal anesthesia on hemodynamics.*

Methods: *A prospective randomized controlled trial enrolled 80 patients of pregnant women (40 patients in each group). Their age between 18-40 years, planned to go through an elective cesarean section operation. They were distributed haphazardly into two groups. The first group (Ketamine group (group A)) was taken 0.25 mg/kg Ketamine diluted with 20 ml normal saline intravenously, while the second group (Control group (group B)) was obtained intravenous 20 ml of normal saline, they terminated through 10 minutes. Pre-operative, all patients were evaluated then, received sub-arachnoid block without adding any adjuvants. Intra-operative, the patients were observed every 5 min at all through of operation for intraoperative hemodynamics (HR, BP), and side-effects postoperatively.*

Results: *As regard to hemodynamics (HR, SBP, DBP, and MBP), P value was insignificant >0.05 in 2 groups. According to post-operative side effects, dissociative analgesia experienced in 3 patients in group (A), while there was insignificant difference between 2 groups along with the other side-effects.*

Conclusions: *This study revealed that no hemodynamic changes in pregnant women undergo elective cesarean section, while administration of low dose 0.25 mg/kg (sub-anesthetic) of Ketamine.*

Keywords: Hemodynamic Effects, Low Dose Ketamine, Elective Cesarean Section

Introduction

There was an increasing in the rate of cesarean section in the last two decades not only in industrialized countries but also in developing countries. A trend analysisBased on data from 121 countries, showed that the global average CS rate increased by 12.4% between 1990 and 2014 (from 6.7% to 19.1%), with an average increase in annual rate of 4.4 % [1]. As regard to the latest data from 150 countries, CS was the main cause of 18.6% of all births, while in the least and most developed regions, between 6% and 27.2%. Latin America and the Caribbean region have the uppermost CS rates (40.5%), subsequently North America (32.3%), Oceania (31.1%), Europe (25%), Asia (19.2%) and Africa (7.3%) [2,3].

This increase in CS is caused by multifactorial reasons. From the possible reasons is the preference of patients and obstetricians. An increase in emergency caesarean sections was qualified to more advanced maternal fetal monitoring, which enabled obstetricians to take an earlier decision to more effective diagnosis of intra-partum fetal compromise. The frequency of caesarean sections in regional anesthesia is more than in general anesthesia [4].

New techniques for regional anesthesia, such as combined spinal epidural (CSE) anesthesia and continuous spinal anesthesia, provide specific advantages. Nowadays, the use of supraglottic airway devices for caesarean section under general anesthesia has the interest, particularly when a difficult airway is faced. Maternal comorbidities such as pre-eclampsia and obesity also present a challenge to obstetric anesthesiologists [2].

During pregnancy, there are profound changes in the cardiovascular system. These changes start early in pregnancy, as cardiac output increases by 20% after only eight weeks of pregnancy. Peripheral vasodilation is probably the main event. This is caused by endothelium-dependent factors, including nitric oxide synthesis, which is mediated by estradiol and probably by vasodilating prostaglandins (PGI2). Peripheral vasodilation causes a 25-30% decrease in systemi\c vascular resistance, so the cardiac output during pregnancy increases by about 40% to compensate for this. This is mainly done by increasing the stroke volume but increasing the heart rate has a lesser effect. At about 20 to 28 weeks gestation the cardiac output becomes the maximum [5].

Ketamine "Special K", is a dissociative drug. It is used commonly in veterinary medicine, in emergency medicine for severe trauma, for nerve pain treatment, and as in pediatric anesthesia. Because of hallucinogenic properties of Ketamine, it may be abused. It can be very sedative and sometimes make the patient unable to move [6].

Therefore, authors supposed this randomized controlled trial to evaluate the effect ofa single low dose intravenous Ketamine on the hemodynamics following cesarean section under spinal anesthesia.

Methods

This study was a double blinded prospective randomized clinical trial and, was executed in Tanta University hospital, Obstetrics and Gynecology Department, in the period from August 2016 to December 2017. The study was conducted after obtaining approval from Tanta University hospital. Informed written consent was taken from pregnant women. The study involved 80 ASA status I patients, aged between 18 and 40 years old, who were planned for elective CS taken spinal anesthesia with Bupivacaine.

Patients with Body mass index ≥40 Kg/m2, Known allergy to any of the study medication, Contraindication to spinal anesthesia, History of substance abuse, History of hallucinations, chronic opioid therapy, and chronic painwereexcepted.

Preoperative evaluation

All patients went through pre-anesthetic checkup the day before surgery. This involve detailed history, thorough general, physical, systemic examination and, laboratory investigation includes CBC and coagulation profile.

Intra-operative assessment

No pre-medications were given, and all patients were checked by ECG, non-invasive arterial blood pressure, and pulse oximetry once came in the operating room. All patients were preloaded with 10 ml/kg of ringer lactate arrived over 20 min after insertion period 18-gauge IV cannula.

A computer-generated randomization list was formed prior to commencement of the study. This list was arranged in serially numbered, closed envelopes. On the morning of surgery, one of the Anesthesiologists not included with the study opened the sealed envelope and equipped the drug solution.

Anesthesia plan

All participants had spinal anesthesia using Bupivacaine, 10mg (2 cc 0.5%), in the level of L4-L5 space byneedle 25G, midline, with the pregnant woman in a sitting position. The height of the sensory block was evaluated bilaterally after administering Bupivacaine, and before surgery (complete loss of sensation to ice) in a ascending manner starting from T12 dermatome. The operation was permitted to begin when adequate anesthesia to at least T6 dermatome was achieve Five minutes after delivery of the baby, all participants were randomly distributed into two equal group (n=40 in each group). The first group (Ketamine group (group A)) was received 0.25 mg/kg Ketamine diluted with 20 ml normal saline intravenously, while the second group (Control group (group B)) was taken intravenous 20 ml of normal saline, they finished through 10 minutes. Duration of operation, estimation of blood loss, drugs given (Ampicillin 1.5 gm for each, and Syntocinon 20 units for each, and "Ephedrine, and Metoclopramide" when the patient complaint), any intra-operative side-effects (vomiting, pruritus, hallucination nausea, and disturbance in conscious level "Dissociative analgesia"), and vital signs(HR, BP"SBP, DBP, and MBP", SaO2) were data collected through intra-operative evaluation which measured 5 min before spinal anesthesia (baseline measurement) then every 5 min until the operation end.

Post-operative assessment

Following surgery, patients were monitoring for 24 h in the post-anesthesia recovery unit by recovery room nurses who were blinded to the used technique. Side effects such as nausea, vomiting, headache, hallucination, and itching were documented allover 24 hours post-operative. Nausea and vomiting were evaluated using categorical score (0 = none, 1 = slight, 2 = moderate, 3 = severe/request treatment).10mg of IV Metoclopramide was administrated when moderate or severe nausea or vomiting was present.

Statistical analysis

Data was summarized and analyzed by SPSS program (v.20); and the resultswere described as mean -+SD, ordinal data was reported as median and range. ANOVA test makes comparison of the means of the two groups. Nonparametric variables were compared using Mann Whitney test. P-value < 0.05 indicate significant differenceall statistical tests.

Results

We involve 80 patients in the study randomized into 2 groups 40 patients in each. All the patients completed the study period (24 hrs) in both groups, according to patient flow.

Regarding demographic data (age, weight, height, gestational age, number of CS, and parity) in study groups. It was found that there was insignificant difference between two groups (insignificant P value / P>0.05). Table (1, 2).

	Group A (n=40)		Group B (n=40)		P. value
	Range	Mean±SD	Range	Mean±SD	
Age	18 – 40	28.13±5.91	18 – 40	28.33±6.54	0.886
Weight	55 – 100	74.05±10.39	60 – 100	76.03±9.90	0.387
Height	150 – 183	164.5±7.13	155 – 177	166.55±5.7	0.160
Gestational age (weeks)	37 – 40	38.05±1.01	37 – 40	38.13±0.88	0.725

Data presented as range, mean ±standard deviation

Table 1: Demographic data.

	Group A (n=40)		Group B (n=40)		P. value
	No.	%	No.	%	
Parity					
Primigravida (1st pregnancy)	5		10		0.354
Multi paragravida (3-5 pregnancy)	33		28		
Grand multi para (more than 5 pregnancy)	2		2		
Number of CS	24	60.0	24	60.0	1.000
1.oo(previous1)	*13*	*54.2*	*10*	*41.6*	
2.00(previous2)	*8*	*33.3*	*5*	*20.8*	
More than 2(more than previous2)	*3*	*12.5*	*9*	*37.5*	

Data presented by number (%)

Table 2: Patients characteristics.

According to anesthesia data (anesthesia time, time from anesthesia to delivery, time from operation to delivery, time from uterine incision to delivery, and level of sensory and motor block) with insignificant P value in both groups (P>0.05).Table (3, 4).

	Group A (n=40)		Group B (n=40)		P. value
	Range	Mean±SD	Range	Mean±SD	
Anesthesia time (minutes)	1 - 5.17	2.09±1.15	0.5 – 9.0	2.01±1.65	0.803
Time from anesthesia to delivery (min)	8 – 31	13.98±5.90	9 – 30	14.68±3.85	0.532
Time from operation to delivery (min)	4 – 17	10.98±3.2	4 – 25	10.88±4.4	0.901
Time from uterine incision to delivery (sec)	30 – 420	65±68.43	15 – 180	49.93±27.39	0.202

Data presented as range, mean ±standard deviation

Table 3: Anesthesia data.

	Group A (n=40)		Group B (n=40)		P. value
	No.	%	No.	%	
Level of sensory and motor block					
T2 (at level of axilla apex)	1	2.5	3	7.5	0.305
T4 (at level of nipple)	39	97.5	37	92.5	

Data presented by number (%)

Table 4: Anesthesia data.

Intra-operative drugs taken showed no significant p value in two groups (P>0.05). Table (5).

Drugs given	Group A (n=40)		Group B (n=40)		P. value
	No.	%	No.	%	
Ephedrine	**24**	**60**	**24**	**60**	**1.000**
Dose (mg)					
4	0	0	1	2.5	
5	1	2.5	1	2.5	
6	7	17.5	5	12.5	
9	5	12.5	4	10	
10	0	0	3	7.5	
12	4	10	4	10	
15	1	2.5	2	5	
17	1	2.5	0	0	
18	1	2.5	2	5	
20	1	2.5	0	0	
24	2	5	0	0	
25	0	0	2	5	
30	1	2.5	0	0	
Syntocinon(Oxytocin)	**40**	**100**	**40**	**100**	**1.000**
Dose (units)					
20 unit	38	95	39	97.5	
30 unit	2	5	1	2.5	
Ultracillin (Ampicillin)	**40**	**100**	**40**	**100**	**1.000**
Dose (1.5 g)	40	100	40	100	
Primperan (Metoclopramide) 10 mg	**1**	**2.5**	**3**	**7.5**	**0.601**

Data presented by number (%)

Table 5: Intra-operative drugs given.

Intra-operative hemodynamics as (HR, SBP, DBP and MBP). There was no significant difference among the study groups (P value > 0.05). Figure 1,2,3.4.

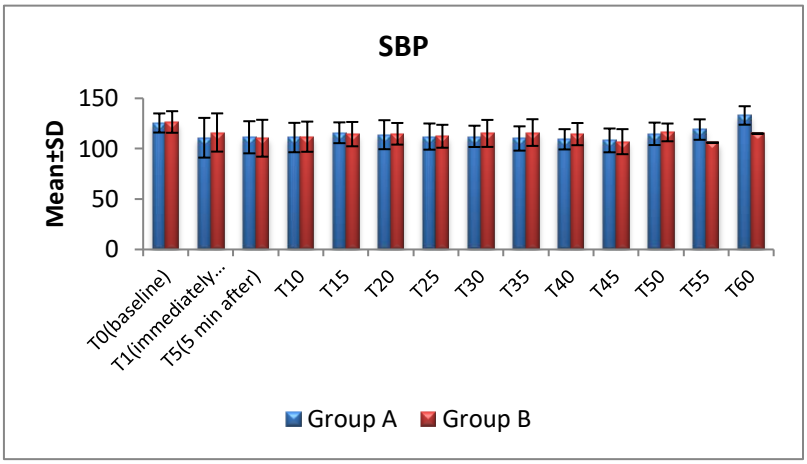

Figure 1: Intra-operative systolic blood pressure (SBP).

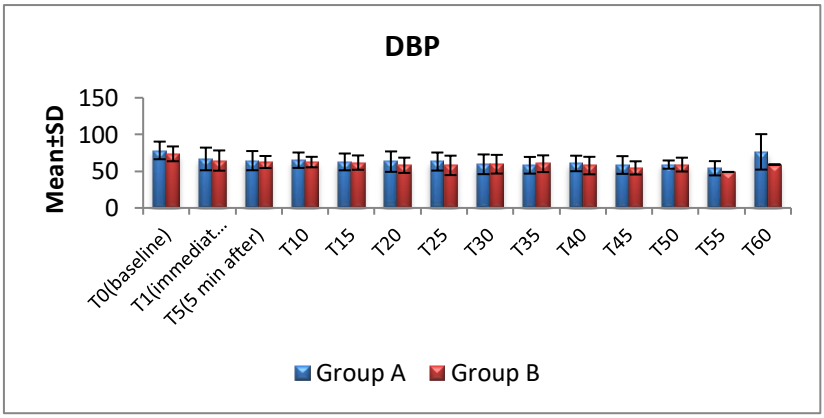

Figure 2: Intra-operative diastolic blood pressure (DBP).

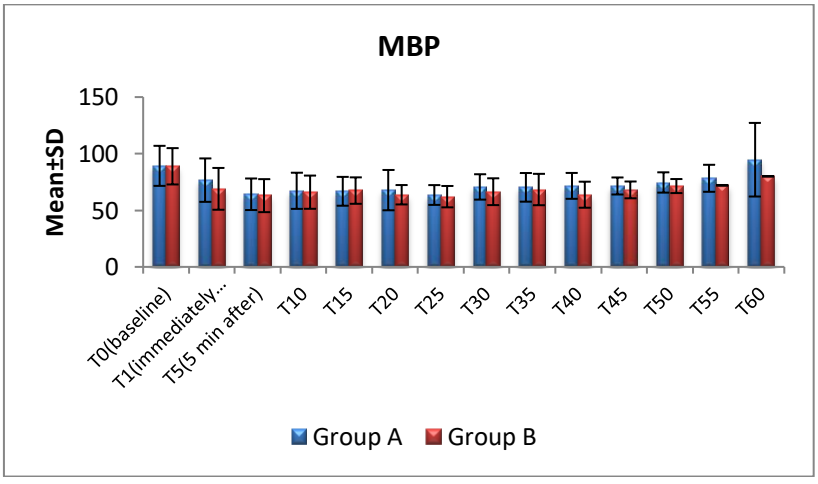

Figure 3: Intra-operative mean blood pressure (MBP).

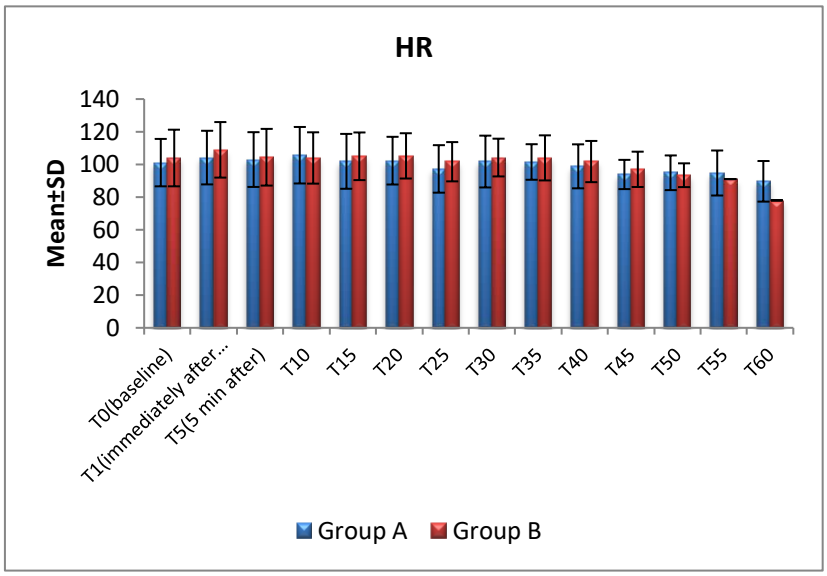

Figure 4: Intra-operative heart rate (HR).

Post-operative side-effects showed no significant difference, but there was positive data for dissociative analgesia in group A (Ketamine side-effect). Figure 5.

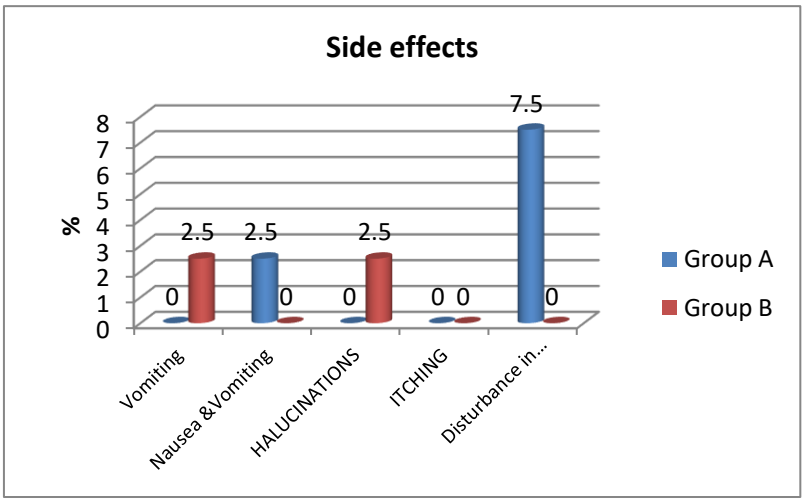

Figure 5: Post-operative side-effects.

Discussion

It is reported that IV administered ketamine elicits analgesic effects as a non-competitive NMDA receptor antagonist. However, incidence of undesirable effects of ketamine, it remains a controversial drug [6]. It is imperative to differentiate between high-dose ketamine as anesthetic and low-dose ketamine as anti-hyperalgesic. Low-dose ketamine is a bolus dose of <2 mg / kg taken intramuscularly or <1 mg / kg given through intravenous way or epidural [7].

Our study was prospective randomized double blind and carried on 80 patients ASA status I patients, aged between 18 and 40 years old, who were listed for elective cesarean section. patients were distributed into two groups. One was received sub anesthetic dose of ketamine 0.25 mg/kg (group A) 5 min after baby delivery, while the other wasgiven 20 ml of normal saline (group B).

Along with our results, there was no significant difference concerning two groups (insignificant P value, P>0.05) in demographic data (age, weight, height, gestational age, parity, and number of previous CS of each patient), and anesthesia data.

According to intra-operative data analysis, P value P>0.05 was found in 2 groups as regard to operative time, so no effect on the end results of the study.

In relation to side-effects, at group (A) 26 patient's complaint of nausea and vomiting, and 3 patients suffered from dissociative analgesia, on other hand group (B) 22 patient's complaint of nausea and vomiting. With this data, no significant P value >0.05 for 2 groups was detected.

Drugs were provided intra-operative when the patients complaint (Metoclopramide, and Ephedrine), but there were drugs were given to all patients (Ampicillin 1.5gm, and Syntocinon 20 or 30 units). This was with no significant difference.

About hemodynamics (HR, SBP, DBP, and MBP), there was insignificant P value >0.05 of 2 groups because we utilized a low dose (sub-anesthetic dose) of Ketamine that has irrelevant effect.

Concerning about complication in our study, no significant difference in post-operative complication (nausea, vomiting, hallucination, and itching), but in group A, three patients experienced disturbance in CL (dissociative analgesia) as apart from Ketamine mechanisms of pain control.

In a study by Richard Mwase and colleagues (2017), the effect of low dose ketamine on the postoperative course of intravenous administration prior to incision following spinal anesthesia in patients undergoing caesarean section was examined. This study was performed in 88 patients randomized equally into 2 groups. The ketamine group obtained intravenous ketamine (0.25 mg / kg) and the placebo group had normal saline before surgery. Postoperative pain was evaluated by the self-reporting Numerical Rating Scale (NRS). This was observed every 30 minutes for 24 hours or till the first pain complaint called "time to first breakthrough pain", which meant a pain in need of treatment (NRS ≥ 3). At this time, administration of intramuscular diclofenac (75 mg) was initially taken as rescue analgesia, then by standard treatment followed by tramadol as a secondary drug or meperidine / pethidine (100 mg) as a tertiary drug in continuous pain. The results demonstrated that ketamine, 0.25 mg / kg before incision, extended the first demand of pain treatment by 30 minutes. Low pain level and lowcumulative analgesic consuming was found in ketamine group at 24 hours, although not statistically significant. This was encouraging for the postoperative clinical benefit of ketamine, especially in the resource-constrained environment [8].

In a study by ShekoufehBehdad and colleagues (2012), the analgesicbenefits of ketamine recommendation in women go through elective caesarean section were compared to low-dose intravenous ketamine and midazolam and intravenous midazolam spine anesthesia in 60 patients alone. Patients were randomized into two study groups. The first group "Ketamine (30 mg) + midazolam (1 mg = 2CC) ", while the other group " 1 mg midazolam (2CC) alone "were givendirectly after spinal anesthesia. Pain scores in the 1st, 2ndand 3rd hour after CS surgery, analgesic request and adverse drug reactions were noted in all patients. The resultsrevealed that the ketamine group had significant pain-relieving properties in the first few hours following Caesarean section related to the control group. The total dose of meperidine consumption in women of the ketamine group was substanially lower than in women in the control group. There were no significant drug effects in participating patients [9].

In a study by SarvjeetKaur and colleagues (2015), the impact of intra-operative infusion of low dose ketamine on the treatment of postoperative analgesia was arranged randomly into two equal groups in a total of 80 patients scheduled for open cholecystectomy under general anesthesia through blind way. The general anesthesia technique was uniformed in both groups. Patients in group K (n = 40) received 0.2 mg / kg ketamine bolus intravenously, followed by an infusion of 0.1 mg / kg / h before skin incision, which continued till the surgery end. An equal volume of saline was infused into group C (n = 40). The pain assessment at numerous intervals and the collective morphine consumption over 24 hours were documented. Secondary outcomes for instance"hemodynamic parameters, patient satisfaction and prevalence of adverse events were also recorded. The results showed that effective analgesia in the first 6 hours of the postoperative period was achieved, resulting in diminished pain level and reduced opioid requirements (P value = 0.001). The incidence of adverse effects and patient satisfaction were the same in both groups [10].

Conclusion

The current study explained that administration of low dose 0.25 mg/kg (sub-anesthetic) of Ketamine in pregnant women undergo elective cesarean section provides no hemodynamic changes.

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