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Effects of intraoperative intravenous administration of analgesic dose of Ketamine during spinal anesthesia for cesarean section

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Abstract

Background and objectives: The most common anesthetic technique in the cesarean section is spinal anesthesia. Our objectives were to identify the patient's status by the use of analgesic dose of ketamine given intravenously during the first hour of spinal anesthesia for cesarean section operation.

Methods: This case control study was performed on 100 full term pregnant ladies, undergoing elective cesarean section by spinal anesthesia, in Erbil Maternity Teaching Hospital between the period of May 2021 until October 2021. Randomly 50% of them selected to give ketamine in an analgesic dose (0.35 mg/kg IV). Arterial blood pressure, heart rate, intra operative nausea and vomiting, peripheral capillary oxygen saturation, hallucination, shivering and anxiety were checked at 5 minutes before the spinal injection, and every 5 minutes interval after the injection. The use of ephedrine, rescue antiemetics was written.

Results: Mean arterial pressure in selected group where ketamine was used was significantly higher $p<0.001$ (100.3±13.9mmHg) with a more stable heart rate compared to that in the control group (99.4±15.4mmHg). Statistically significant ($p<0.001$) less ephedrine (total dose) used in the ketamine group (6 patients versus 39 patients in control group) as well as rescue antiemetics (2 versus 9, $p=0.025$). Shivering ($p>0.999$), and anxiety ($p=0.102$) had no statistically significant difference between the two groups.

Conclusion: Analgesic dose of ketamine intravenously can be beneficial in inhibiting hypotension after spinal anesthesia (less need for vasoconstrictors) and less intraoperative nausea and vomiting in parturient undergoing cesarean section.

Keywords: Analgesia, Cesarean section, Intravenous, Ketamine, Spinal Anesthesia

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Introduction

Spinal anesthesia is mostly used for operations below the umbilicus (including cesarean section), lower extremities, perineal and pelvic surgeries. Patient counseling for the procedure is essential, and she or he must sign the informed consent.[1] Proper patient selection should be made to prevent complications associated with spinal anesthesia. The incidence of the complications is infrequent; it is worth being aware of those complications. Critical complications might be rare, but the frequency is underestimated.[2] Most common complications are hypotension, intraoperative nausea and vomiting (IONV), shivering, total spinal anesthesia, post dural puncture headache (PDPH), backache, spinal hematoma and neurological injury. Local anesthetics inhibit conduction of impulses in the central and peripheral nervous system. A higher concentration leads to interruption of the transmission of nerve impulses result in paralysis, loss of sensation, and autonomic nervous system dysfunction.[3] Differential sensory nerve block would be the ideal property of a local anesthetics for regional anesthesia or pain management by selective inhibition of pain while preserving other functions intact. Nevertheless, sensory blockade alone is difficult to obtain without motor blockade.[4,5]Ketamine is a water-soluble derivative of phencyclidine which cause "dissociative anesthesia" and strong analgesia. The mechanism of dissociative anesthesia and analgesia induced by ketamine is unclear. It interacts on various CNS receptors, but its action was unclear. Ketamine act on N-methyl-d-aspartate (NMDA) receptors non-competitively. It also acts on neuronal nicotinic acetylcholine, L-type calcium channels, voltage-sensitive sodium, muscarinic, monoaminergic, and opioid receptors can exert the effects of ketamine.[6,7] By suppressing neutrophil production by the inflammatory mediators, ketamine enhances blood flow and prevents vasoconstriction. The analgesic effect of ketamine can be explained by direct inhibition of cytokines in blood.[8] Small doses of ketamine (0.2- 0.5 mg/kg IV) can cause strong analgesia.[9] This effect is more significant for somatic than for visceral pain. Its effects on thalamic and limbic systems can explain its analgesic effects.[10] This analgesic effect is useful in labor with no effect on the neonate. Apgar scores of neonates delivered by ketamine analgesia are higher than the scores in neonates delivered by thiopental nitrous oxide anesthesia.[3] The effectiveness of extradural ketamine is controversial, and intraspinal injection of ketamine cause variable and short analgesia.[8]Patients with ischemic heart disease might get complicated due to increased myocardial oxygen demand and sympathomimetic effects of ketamine on the heart. Its effects on airway resistance and bronchodilation properties of ketamine make it a potentially effective agent for anesthetic induction in patients with asthma. Patients suffering from hypertension or raised ICP and Nystagmus ketamine must be avoided or used with caution.[3] Emergence from ketamine anesthesia is the most undesired effect, limiting its clinical use as the sole induction agent characterized by confusional, proprioceptive, auditory and visual illusions, may lead to delirium postoperatively, even 24 hours after drug injection. The dreams usually have morbid content.[3,11] Inhaled anesthetics agents, diazepam and midazolam will suppress sympathetic nervous system outflow from the CNS, preventing ketamine's effect on increasing systemic BP and HR, which usually happens when ketamine is administered alone.[3,12]The aim of this study was to describe the effect of using an intravenous analgesic dose of ketamine on the vital signs and development of anxiety, hallucination, shivering, IONV in the parturient, and the need for adjunct therapies.

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Patients and methods

Two groups of 50 patients enrolled and compared who are scheduled for elective CS operation. The first group underwent spinal anaesthesia (Control group) and the second group underwent spinal anaesthesia with an IV analgesic dose of Ketamine within the first minute after the spinal injection (Ketamine group). The vital signs of HR, non-invasive BP, SpO_2 were recorded as pre-injection parameters. Without any premedication, preloading done by 1litre crystalloid fluid (normal saline 0.9%), the spinal anaesthesia is done in the sitting position for all cases. Under full aseptic condition, the spinal needle of 24-gauge pencil-point Whitacre was used to inject a bupivacaine 0.5% hyperbaric solution into the spinal canal (intrathecally). After the needle withdrew and patient repositioned to supine position, the vital signs recorded as minute zero and effects of spinal anaesthesia was confirmed with the patient by losing the sensation and ability to move the lower extremities. In ketamine group the analgesic dosage of ketamine (0.35 mg/kg) given intravenously and the patient was monitored for HR, BP, SpO_2, hallucination, IONV, shivering and anxiety for the first hour of operation in some cases patient required vasoconstrictors (Ephedrine) and/or antiemetics (Metoclopramide) given intravenously. Inclusion criteria include primigravida, multigravida, age from 14- 45 years, elective surgeries, previously operated for caesarean section under general anaesthesia or spinal anaesthesia, previous history of abortion, history of smoking, American society of anaesthesiologists (ASA) class 2, and history of the previous infection with covid-19. Exclusion criteria involve emergency cases, age above 45 years, morbid obesity, other ASA classes, drug history of (unfractionated and low molecular weight heparin, thrombolytic therapy, antiplatelets, and anticoagulants), thrombocytopenia or coagulopathy, preexisting neurological diseases, elevated ICP (primarily due to intracranial mass), severe hypovolemia, previous spinal surgery, infection at the site of the procedure may lead to meningitis, absence of consent from the patient. Patients having hypertrophic obstructive cardiomyopathy, left ventricular outflow obstruction, severe mitral and aortic stenosis, glaucoma, and failure of spinal anaesthesia and change to GA.Data collection started after obtaining the approvals from the supervising committee of the Arab Board for Health Specializations. Oral consents obtained after explaining the different types of anaesthesia and each type's side effects and advantages. Written consents were taken after explaining the procedure as standard clinical practice. A version of 25 of statistical package for social sciences is used to process the data. Comparing the proportions done by Chi square test of association, and when the expected frequency (value) was less than 5 of more than 20% of the cells of the table Fisher's exact test was used. For the normality of the data Shapiro-Wilk test was applied; accordingly, the Wilcoxon signed rank test (non-parametric test) was done when applicable for comparing the median of the same sample in 2 different periods. For comparing the means of two samples the student's t test (unpaired t test) of two independent samples was used. Statistically significant considered when a p value of ≤ 0.05.

Results

About 4.0% of patients of the ketamine group required rescue anti-emetics during the operation compared with 18% of the control group ($P = 0.025$), while 78% of the control group required ephedrine compared with 12% in ketamine group ($P < 0.001$). More than one third (38%) of patients of the ketamine group developed hallucination, while none of the patients of the control group had such a side effect ($P < 0.001$).

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About 16% of parturient in the ketamine group developed IONV while more than half (54%) of the parturient in the control group developed IONV ($p < 0.001$). The two groups had insignificant differences in developing shivering ($p > 0.999$) and anxiety ($p = 0.102$), as demonstrated in Figure (1).

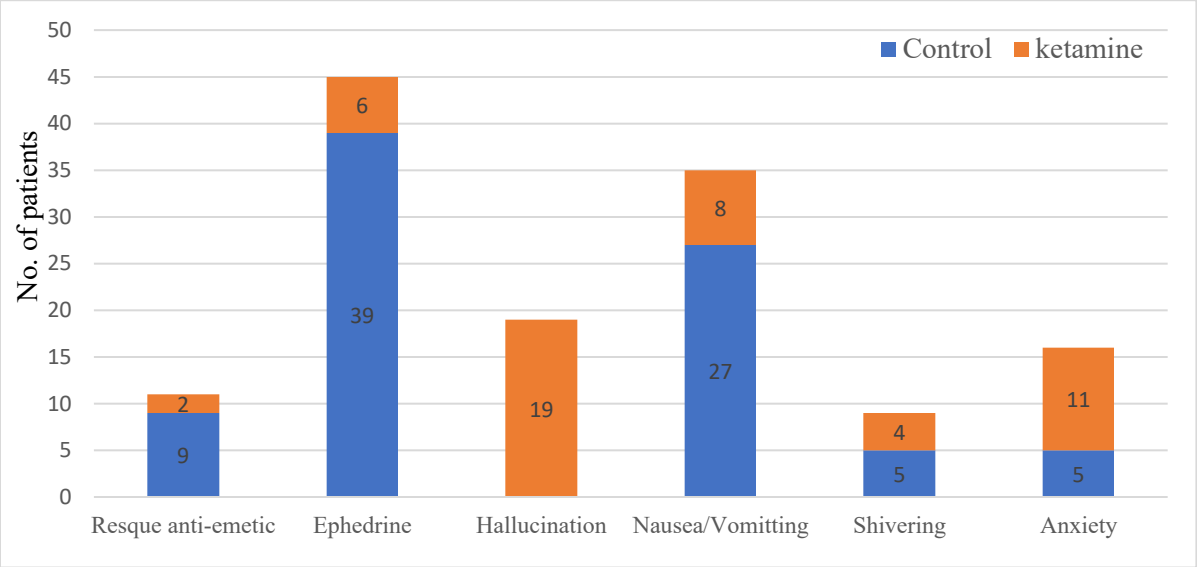

Figure (1): Side effects and adjuncts therapy.

The mean (± SD) pre-operative HR of the Control group was 97.2 ± 13.8 beat/minute, as presented in table (1). No significant differences were detected between the pre-operative mean and the means measured at different periods of the operation. The mean (± SD) pre-operative HR of the Ketamine group was 102.0 ± 10.3 beat/minute. It is evident in table (1) that up to 30 minutes after the start of the operation, there was insignificant difference between the pre-operative mean HR and the means measured up to 30min., while there was a significant decrease in the mean HR at 40, 50, and 60 minutes after induction of spinal anesthesia ($p = 0.002$, $p < 0.001$, $p = 0.039$ respectively), but still remains within the normal ranges and more than that of the control group.

Table (1): heart rate monitoring during 60 minutes

	Control				Ketamine			
Time Minutes	Mean HR	(±SD)	Median	*p**	Mean HR	(±SD)	Median	*p**
Pre-Op.	97.2	(±13.8)	105.0		102.0	(±10.3)	102.0	
0	97.1	(±14.3)	97.0	0.550	103.4	(±13.9)	101.0	0.660
5	100.4	(±17.5)	96.5	0.278	103.7	(±17.2)	110.0	0.242
10	96.1	(±19.8)	96.5	0.358	104.1	(±17.9)	98.0	0.194
15	99.6	(±19.4)	93.0	0.146	104.4	(±14.1)	107.0	0.233
20	94.4	(±22.7)	97.0	0.577	98.3	(±12.8)	102.0	0.296
25	94.9	(±17.6)	96.0	0.435	99.1	(±11.3)	100.5	0.294
30	92.8	(±19.0)	84.0	0.148	99.2	(±11.4)	100.0	0.292
40	95.9	(±15.1)	89.0	0.551	96.5	(±8.8)	95.0	0.002
50	94.8	(±16.6)	88.0	0.267	95.6	(±9.1)	96.0	<0.001
60	95.0	(±13.1)	93.0	0.226	98.3	(±7.5)	99.0	0.039

*By Wilcoxon signed rank test. HR=Heart Rate

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The pre-operative mean SpO_2 of the Control group was 98.9 (± 1.2). Up to the 25th min. after the operation, the differences were insignificant in SpO_2 values ($p > 0.147$), while after 30 minutes onwards, there was a significant decrease in the mean ($p < 0.012$). In the Ketamine group, the pre-operative mean SpO_2 was 98.0 (± 1.1). Significantly increase in the mean at different periods occur ($p < 0.001$), except at 30 minutes ($p = 0.065$). The MAP of the Control group was 99.4 ± 15.4 mmHg, and that of the ketamine group was 100.3 ± 13.9 mmHg. All the means were less significantly than the pre-operative means in both groups ($p < 0.001$), figure (2).

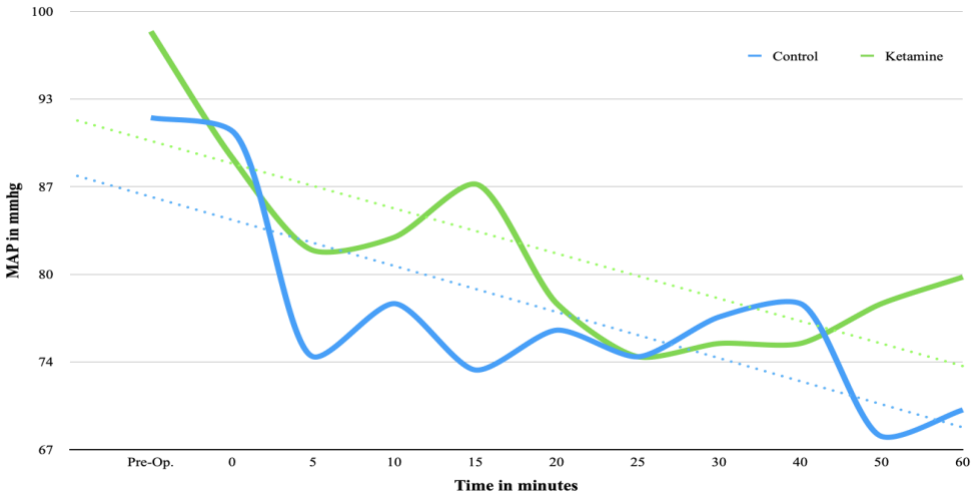

Figure (2): Mean arterial pressure readings during 60 minutes.

In each of the studied groups, all the mean systolic blood pressure (SBP) measured after the start of the operation were significantly ($p < 0.001$) less than the pre-operative mean, table (2). The same can be applied for the Diastolic blood pressure (DBP), where it is evident that the mean DBP decreased significantly after the start of the operation compared with the pre-operative mean in each of the studied groups ($p < 0.001$), table (3).

Table (2): Systolic blood pressure during 60 minutes

	Control				Ketamine			
Time Minutes	Mean SBP	(±SD)	Median	*P**	Mean SBP	(±SD)	Median	*P**
Pre-Op.	137.8	(±18.6)	131.5		136.2	(±14.8)	136.0	
0	127.3	(±22.5)	116.0	<0.001	129.8	(±18.9)	136.5	<0.001
5	126.5	(±32.8)	119.0	<0.001	126.3	(±18.9)	125.0	<0.001
10	118.7	(±17.8)	116.5	<0.001	121.6	(±15.1)	121.0	<0.001
15	114.9	(±21.7)	111.0	<0.001	123.5	(±13.7)	125.5	<0.001
20	115.2	(±19.1)	118.0	<0.001	116.1	(±11.8)	118.0	<0.001
25	112.7	(±17.8)	107.5	<0.001	112.0	(±13.4)	106.0	<0.001
30	116.4	(±13.7)	123.0	<0.001	114.4	(±8.4)	114.0	<0.001
40	115.6	(±17.2)	119.0	<0.001	111.4	(±10.0)	110.0	<0.001
50	111.4	(±18.9)	112.5	<0.001	115.2	(±12.0)	113.0	<0.001
60	118.7	(±28.9)	110.0	<0.001	115.3	(±11.4)	114.5	<0.001

*By Wilcoxon signed rank test. SBP=Systolic blood pressure.

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Table (3): diastolic BP during different periods of operation

	Control				Ketamine			
Time Minutes	Mean DBP	(±SD)	Median	*P**	Mean DBP	(±SD)	Median	*P**
Pre-Op.	80.1	(±15.1)	75.5		82.3	(±15.5)	89.0	
0	74.1	(±17.7)	71.5	<0.001	71.8	(±16.5)	71.5	<0.001
5	63.0	(±20.6)	53.5	<0.001	63.8	(±17.4)	61.0	<0.001
10	58.0	(±15.5)	57.5	<0.001	64.4	(±9.3)	66.0	<0.001
15	59.9	(±16.8)	55.5	<0.001	64.0	(±11.2)	65.0	<0.001
20	56.8	(±15.2)	58.0	<0.001	58.6	(±11.2)	58.5	<0.001
25	52.7	(±15.6)	52.0	<0.001	57.8	(±8.9)	57.0	<0.001
30	51.7	(±9.8)	52.0	<0.001	52.8	(±7.3)	54.0	<0.001
40	53.3	(±7.1)	54.0	<0.001	55.9	(±9.5)	56.5	<0.001
50	47.4	(±8.7)	46.0	<0.001	57.7	(±10.5)	58.0	<0.001
60	48.0	(±7.5)	47.0	<0.001	57.9	(±9.5)	58.5	<0.001

*By Wilcoxon signed rank test. DBP=Diastolic Blood pressure

The difference (diff.) between the pre-operative measurement and the minimum measurement during the operation was calculated for each of the studied parameters. The difference between the studied groups was not significant regarding the mean diff. of HR and DBP, while the mean diff. (±SD) of SpO_2, MAP, and SBP was significant between the studied group, as shown in table (4).

Table (4): comparison between the two studied groups regarding the means of the difference between the readings of the pre-operative measurements and the minimum values.

	Control		Ketamine		
	Mean	(±SD)	Mean	(±SD)	*p**
Diff. HR Pre-Minimum	17.90	(±17.71)	14.98	(±11.87)	0.336
Diff. SpO_2 Pre-Minimum	1.50	(±1.37)	0.36	(±0.78)	< 0.001
Diff. MAP Pre-Minimum	39.68	(±8.86)	34.24	(±12.42)	0.013
Diff. SBP Pre-Minimum	43.70	(±11.35)	33.78	(±12.77)	< 0.001
Diff. DBP Pre-Minimum	39.30	(±8.63)	36.16	(±13.85)	0.177

*By t test of two independent samples.

Discussion

The IV analgesic dose of ketamine given in spinal anesthesia for elective CS in parturient result in a significant decrease in the IONV, rescue anti emetic drugs, and the need to the vasoconstrictors (ephedrine). The spinal anesthesia was safer for maternal and fetal compared to general anesthesia. But unfortunately, intraoperative hypotension, shivering, and IONV are spinal anesthesia's disadvantages and irritating drawbacks.[13,14] Intraoperative nausea and vomiting are troublesome for parturient, anesthetists and obstetricians, and during the surgery may lead to visceral injury due to the uncontrolled involuntary movements of the abdomen. A lot of studies used different drugs to decrease IONV in spinal anesthesia for parturient undergoing CS; Balki and his colleagues saw that granisetron was not useful in the inhibiting of IONV in spinal anesthesia given

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for CS, and they conclude that managing the causative agents may be more beneficial like treating the reduction in the blood pressure. [15] The vagolytic effect of glycopyrrolate was used to prevent IONV, and it decreased it from 68% to 42% (in the placebo and the studied groups respectively).[16] Fujii, studied the sub hypnotic doses of propofol; they conclude that a dose of 0.5 mg/kg/h was not useful, while 1 and 2 mg/kg/h compared to placebo significantly decrease IONV. [17] Hassanein, used 0.4 mg/kg ketamine for group 1 versus 8mg dexamethasone for group 2 and 5ml normal saline in group 3. [18] They found that the incidence of IONV was less in the first two groups than group 3 regarding rescue antiemetics; only 4 patients received antiemetics in group 1 while 9 patients in group 3 received antiemetics. Shabana et al. used ketamine 0.5 mg/kg/20min intravenously compared to normal saline as a placebo; in result IONV and hypotensive episodes decreased significantly among ketamine group patients, 6 patients among group 1 have received antiemetics, while 9 patients needed antiemetics in group 2. [19] In this study there was a high difference ($P < 0.001$) between the two groups. In the control group, twenty-seven cases had IONV, while in the ketamine group, only eight patients developed IONV. Rescue antiemetics were administered to 9 patients in the control versus two patients in the ketamine group with a significant difference ($P = 0.025$). Spinal anesthesia led to hypotension and gastrointestinal hyperactivity due to relative vagal hyperactivity result in IONV, ketamine by its unique sympathomimetic and vagolytic effect may decrease the incidence of IONV in cesarean section under spinal anesthesia.

Concerning shivering this study showed control group and ketamine group with slight difference at ($p > 0.999$). But in Seyam's study showed 18 patients from Ketamine group, 28 patients in tramadol group and 35 patients in saline group have shivering with a significant difference, can be explained by dose and time of ketamine injection.[20] Shivering might develop due to unpressed spinal reflexes, exaggerated sympathetic activity, postoperative agony, adrenal abolition, and respiratory alkalosis.[21] Ketamine causes dissociative anesthesia, in analgesic doses which antagonizes N-methyl-D- aspartate receptors (NMDA) non-competitively and may take a role in thermoregulation. N-methyl-D- aspartate receptors act on thermoregulation lead to modulation of the serotoninergic and noradrenergic neurons in the locus coeruleus, which might share in heat control. Ketamine may have a role in shivering restriction either by its act on the hypothalamus or the β - adrenergic effect of norepinephrine.[22]In the postoperative period ketamine may cause confusion, proprioceptive, auditory, and visual illusions, sometimes up to delirium. The content of the hallucination some time may be morbid. And often, these side effects usually disappear within a few hours. In this study, 19 patients from ketamine group experienced hallucination, which is significant at ($p < 0.001$) compared with zero patients from control group. Shabana et al.[19] which was discussed above, showed that only one patient out of 110 experienced hallucinations in the ketamine group while zero patients from the second group, which can be explained by the dose and infusion time rate. The most typical side effect of spinal anesthesia is a reduction in blood pressure in more than 80%, which may have harmful effects on the fetal well-being and neonatal outcome due to reducing uterine blood flow, measured by Apgar scores and umbilical artery pH.[23] In spinal anesthesia for parturient hypotension may occur because of the compression on the aorta and inferior vena cava and blocking of the sympathetic nervous system. It is managed by IV fluid, left lateral tilt, and ephedrine (sympathomimetic drugs). Many methods

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used to eliminate hypotension in spinal anesthesia for parturient, but the better and effective technique is not defined yet. Methods are IV fluid as a pre-hydration, and co-hydration, medications like sympathomimetics, and physical methods like compression stockings or pneumatic leg compression.[24, 25] Ketamine can preserve arterial BP and systemic vascular resistance by increases the secretion and prevent the reuptake of catecholamines in the circulation. In a study comparing fentanyl to ketamine in the osteosynthesis of hip fractures done under spinal anesthesia, 0.7 mg/kg before intrathecal injection, then 15 and 30 min after that (0.35 mg/kg) ketamine given, compared to1.5 µg/kg fentanyl given before spinal injection, the ketamine makes the hemodynamics of the patient more stable. But in this study, there was a lesser benefit which can be explained by a lower dose (0.35mg/Kg) and frequency (one time after spinal anesthesia) of ketamine injection, and the significant decrease in HR at 40, 50, and 60minutes can be explained by the duration of action of ketamine. In this study, although the incidence of hallucination in ketamine group was high (one third of the patients), the parturient maintained the SpO_2 and airway reflexes. Salah and his colleagues[24] used 0.5 mg/kg ketamine in 3ml normal saline for 40 patients, while in the control group of 40 patients, they only received 3 ml normal saline. The result was that the HR and mean arterial pressure were significantly higher in the Ketamine group, and there was a significant decrease in ephedrine use in the ketamine group. Periods of mild and severe hypotension were substantially minimal among the ketamine group. In this study, in ketamine group there was a significantly less difference in comparing preoperative systolic blood pressure with a minimum value during the operation, with significantly less ephedrine use. The same is true for MAP; by comparing the preoperative MAP with the lowest readings during the course of 60 minutes of the operation, and it can be noticed that the difference between baseline reading before induction and the lowest MAP reading is much smaller in the ketamine group versus the control group with a ($P = 0.013$) the same calculation is made for SpO_2 and the ($P < 0.001$) in favor of ketamine group.

Conclusions

According to the present study, there are desirable effects of IV administration of ketamine in an analgesic dose including avoidance of sever drop in MAP which results in less ephedrine administration. Another beneficial effect is less IONV with decreasing the need of rescue anti-emetics. The only limitation of this practice might be its significant hallucination effect.

Conflicts of interest

The authors reports that there were no any conflicts of interest.

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