THE EFFECT OF INTRAVENOUS KETAMINE ON PREVENTION OF HYPOTENSION DURING SPINAL ANESTHESIA IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA

Fatih Özkan Assist. Prof MD,[1] Ziya Kaya Assist. Prof MD,[2] Mustafa Süren Assist. Prof MD[2]

[1] Ondokuzmayıs University Faculty of Medicine, Department of Anesthesiology, Samsun, Turkey

[2] Gaziosmanpaşa University Faculty of Medicine, Department of Anesthesiology, Tokat, Turkey

ABSTRACT

Objective: *Hypotension is a common complication during spinal anesthesia. The elderly are at an increased risk of developing complications from hypotension due to reduced physiological reserves. Ketamine induces activation of the sympathetic nervous system, thus often increasing heart rate and blood pressure. The aim of our study was to determine protective effects of ketamine on hemodynamic changes under spinal anesthesia in the elderly patient.*

Material and Method: *Sixty patients (ASA I-III) scheduled to undergo spinal anesthesia for transurethral resection were randomly allocated to receive either ketamine or placebo intravenously (i.v.) during the procedure. Immediately before spinal anesthesia, 500 ml of an isotonic NaCl solution was administered i.v. Patients received either placebo 2 cc NaCl solution i.v. before anesthesia or ketamine 1 mg/kg in 2 cc i.v. before spinal anesthesia.*

Results: *In both groups, spinal anesthesia resulted in a reduction in Mean Arterial Pressure (MAP). MAP was lower in the placebo group than in the ketamine group at all times. There was a significant change in heart rate in placebo group compared to ketamine group ($p<0.05$).*

Conclusion: *We concluded that ketamine 1 mg/kg i.v. given before spinal anesthesia resulted in greater hemodynamic stability in elderly patients undergoing transurethral resection compared with placebo.*

Key Words: *Ketamine, spinal anesthesia, blood pressure, hypotension, transurethral resection, benign prostatic hyperplasia.* ***Nobel Med 2011; 7(3): 82-88***

BENİGN PROSTAT HİPERPLAZİLİ HASTALARDA UYGULANAN SPİNAL ANESTEZİ SIRASINDA İNTRAVENÖZ KETAMİNİN HİPOTANSİYONU ÖNLEME ÜZERİNE ETKİSİ

ÖZET

Amaç: Hipotansiyon spinal anestezi sırasında sık olarak görülür. Yaşlı hastalar fizyolojik rezervlerinin azalmış olmasından dolayı hipotansiyondan kaynaklanan artmış komplikasyon riski altındadırlar. Ketamin sempatik sinir sisteminin aktivasyonunu artırarak sıklıkla kalp hızını ve kan basıncını yükseltir. Bu çalışmanın amacı yaşlı hastalarda spinal anestezi altında ketaminin hemodinamik değişimleri önleyici etkilerini belirlemektir.

Materyal ve Metod: Spinal anestezi altında transuretral rezeksiyon planlanan 60 hasta (ASA I-III), randomize şekilde ya intravenöz ketamin ya da intravenöz placebo almak üzere ayrıldı. Spinal anesteziden hemen önce 500 ml izotonik NaCl intravenöz (i.v.) olarak uygulandı. Hastalar spinal anestezi öncesinde plasebo olarak ya 2 cc NaCl i.v. ya da 2 cc içinde 1 mg/kg ketamin i.v. aldılar.

Bulgular: Her iki grupta spinal anestezi ortalama arteryel basınçta (OAB) azalma ile sonuçlandı. Tüm ölçümlerde OAB placebo grubunda ketamin grubundan daha düşüktü. Ketamin grubuyla karşılaştırıldığında placebo grubunda kalp hızında önemli değişiklik görüldü ($p<0.05$).

Sonuç: Transuretral rezeksiyon geçiren yaşlı hastalarda spinal anesteziden önce verilen 1 mg/kg i.v. ketaminin plasebo ile karşılaştırıldığında daha iyi bir hemodinamik stabilite sağladığı sonucuna varıldı.

Anahtar Kelimeler: Ketamin, spinal anestezi, kan basıncı, hipotansiyon, transuretral rezeksiyon, benign prostat hiperplazisi **Nobel Med 2011; 7(3): 82-88**

INTRODUCTION

Spinal anesthesia is widely used for transurethral resection of the prostate (TURP) because it allows earlier recognition of symptoms caused by occasionally seen complications of TURP—such as overhydration and hyponatremia.[1] However, hypotension is a common complication during spinal anesthesia and may result in serious adverse outcomes such as cerebral ischemia, thrombosis, reduced renal function, congestive heart failure and myocardial infarction. Elderly patients who have reduced physiological reserves and higher incidence of systemic disease are at an increased risk of developing hypotensive complications.[2]

The management of hypotension emerging during spinal anesthesia aims to reverse the vasodilatation with vasoconstrictor drugs and increase the circulating volume by hydration.[3] Fluid administration during spinal anesthesia in elderly patients implies an increased risk for post-operative cardiopulmonary complications due to cessation of the sympathetic block which results in increased pre-and–afterload.[3] Vasopressors including ephedrine, methoxamine and adrenaline are highly effective in preventing hypotension but may result in cardiac arrhythmias and myocardial ischemia.[4] Indeed preoperative hemodynamic instability is associated with a higher frequency of postoperative complications.

It is hypothesized that ketamine may be used as an anesthetic agent for poor-risk patients due to its relative safety of use and the beneficial effects on cardiovascular functions resulting from its sympathomimetic characteristics.[5] The indicators of ketamine's cardiovascular stimulation include increases in heart rate, cardiac index and arterial pressure. Although the principle of management for hypotension during spinal anesthesia is correct, ketamine is not known to be an efficient or useful vasopressor in patients with limited cardiovascular reserves. Some researchers emphasize that ketamine may represent a very rational choice for rapid sequence induction for these patients while several pharmacology textbooks state that ketamine at induction can be deleterious.[6-8] Since establishment of cardiovascular stability is crucial in elderly patients undergoing TURP, we evaluated the effects of a phenylcyclidine derivative ketamine within the sedation dosage.

MATERIAL and METHOD

Our study was approved by the Ethics Committee of our hospital, verbal and written informed consent was obtained from all subjects, and the study was performed in accordance with the Helsinki Declaration. We studied 60 ASA I, II and III patients (aged 61-87 year) scheduled for TURP under spinal anesthesia. Patients were randomly allocated to either the ketamine (n=30) or placebo (n=30) group. Patients were not admitted to the study if any of the following criteria were present: less than 60 years of age, ASA IV or V patients, congestive heart failure, hypertension, respiratory illness, coronary artery or cerebral disease, and those in whom spinal anesthesia was contraindicated. →

Table 1: Patient Characteristics. Data are frequencies, median (range) or mean (SEM).

	Ketamine (n=30)	Placebo (n=30)	P
ASA I/II/III	9/14/7	7/13/10	NS
Age (year)	70(65-83)	71(61-87)	NS
Height (cm)	173.60 (3.47)	171.81 (13.45)	NS
Weigh (kg)	75.37 (4.20)	76.40 (4.60)	NS

NS: Non-significant

Table 2: Mean values of Mean Arterial Pressure (MAP) in two groups

	Ketamine (mmHg)		Placebo (mmHg)		P
	Mean	SEM	Mean	SEM	
MAP (Premedication)	92.10	1.045	90.41	1.22	NS
MAP 3.min.	86.10	1.281	79.49	1.24	<0.002
MAP 6.min.	84.25	1.66	81.15	1.13	NS
MAP 9.min.	83.50	1.176	74.15	0.922	<0.01
MAP 12.min.	82.04	1.59	77.10	1.803	NS
MAP 15.min.	82.95	1.45	76.01	0.534	<0.01
MAP 20.min.	80.25	1.615	76.75	0.36	NS
MAP 25.min.	82.80	0.704	76.90	0.764	<0.01
MAP 30.min.	84.35	1.31	79.75	0.907	<0.03
MAP (Recovery)	85.40	1.23	83.80	1.287	NS
	p<0.0001*		p<0.0001*		

SEM: Standard error of mean, NS: Non-significant
* Friedman Two-Way Analysis of Varians test result of comparison among 10 measures within group

Table 3: Mean values of Systolic Arterial Pressure (SAP) in two groups

	Ketamine (mmHg)		Placebo (mmHg)		P
	Mean	SEM	Mean	SEM	
SAP (Premedication)	136.30	2.101	127.50	3.614	NS
SAP 3.min	12.50	2.628	104.27	2.96	<0.01
SAP 6.min.	11.60	2.88	97.5	1.78	<0.01
SAP 9.min.	11.10	1.532	99,.0	1.697	<0.01
SAP 12.min.	11.55	1.280	10.35	1.38	<0.01
SAP 15.min.	111.65	1.159	101.735	0.968	<0.01
SAP 20.min	115.05	2.04	105.43	1.327	<0.01
SAP 25.min	120.45	1.143	111.35	1.17	<0.01
SAP 30.min.	122.70	1.99	111.65	1.33	<0.01
SAP (Recovery)	132.50	3.23	122.74	3.23	<0.04
	p<0.0001*		p<0.0001*		

SEM: Standard error of mean, NS: Non-significant,
* Friedman Two-Way Analysis of Varians test result of comparison among 10 measures within group

Premedication comprised of midazolam 0.03 mg/kg i.v. 5 min before commencement of the procedure. The order of drug administration was randomized by draw lots and patients were enrolled into study in order of admittance. The solutions were prepared aseptically immediately before intravenous injection by an anesthetist who was not one of the investigators. Study group patients received ketamine 1 mg/kg i.v. in 2 cc before assuming the correct lateral decubitus position for spinal anesthesia. Placebo was identically supplied as 2 cc NaCl solution except that it contained no ketamine. Three milliliters (15 mg) of bupivacaine were injected over 15 second into the subarachnoid space through L 4-5 intervertebral space. No prophylactic vasopressor was used. The patients were discharged from the recovery room if the motor block was completely resolved. Other discharge criteria were stable vital signs, minimal nausea or vomiting and no severe pain or bleeding. Systolic arterial pressure (SAP) and mean arterial pressure (MAP) were measured using an automated oscillotonometer (Siemens SC 7000, ENG) immediately before anesthesia, following administration of ketamine/placebo, 1 min after subarachnoid administration of bupivacaine, then every 3 min for 15 min, at 5 min intervals for the subsequent 30 min and during the recovery period. ECG monitoring was performed and heart rates (HR) were measured before anesthesia, following administration of ketamine/placebo, 1 min after the subarachnoid administration of bupivacaine, and then every 1 min for 10 min and then in 5 min intervals for 30 minutes. Patients received oxygen at a rate of 2 L/min through a nasal catheter during the procedure. Peripheral oxygen saturation and respiratory rates were measured peroperatively.

Patients were assessed by an investigator blinded to the solution administered for motor and sensory blocks, sedation and side effects-such as nystagmus, dizziness, nausea and vomiting, and psychomimetic effects. Sensory block was assessed by pinprick test. Motor block was assessed by modified Bromage scores (0: no motor loss; 1: inability to flex the hip; 2: inability to flex the knee; 3: inability to flex the ankle). Sedation was assessed every 15 min using a four-point scale (1 awake; 2, drowsy but responsive to verbal stimulus; 3, drowsy but responsive to physical stimulus; 4, unresponsive to verbal and physical stimulus). Offset of sensory block was assumed when bilateral sensation to pinprick test at the S2 dermatome was recovered. Complete motor recovery was assumed when modified Bromage score was zero. Duration of spinal analgesia was determined from the time of spinal bupivacaine administration to patient's first complaint of pain during the postoperative period.

An isotonic NaCl-solution was given at a rate of 500 ml/20 min i.v. as a rapid infusion when spinal anesthesia was induced and then at 7 ml/kg/h i.v. during the study period. The rate of infusion was increased upon reduction in MAP exceeding 20% of baseline value. If the reduction in MAP exceeded 30% of baseline or SAP decreased to less than 80 mmHg patients were considered hemodynamically unstable and treated with ephedrine.

Statistical analysis

A sample size of 29 patients per group would permit a 2-sided significance level of 5%, power of 90% →

and standardized effect size of 0.75. To allow for the possibility of patients lost to follow-up, incomplete data collection, and protocol violations, the planned sample size was 30 patients in each group. Power analysis was performed using G-Power Version 3.1.2. Data were analyzed using Statistical Package for Social Sciences (SPSS) for Windows software (SPSS Inc. Chicago, Illinois, USA), Version 15.0. Data were expressed as mean ± standard error with necessary median with interquartile ranges used. Distribution of the groups was analyzed with one-sample Kolmogrov–Smirnov test for all parameters. Mann-Whitney U test, Wilcoxon rank test, and Friedman test were performed for abnormal data. Student's t test was used for data showing normal distribution. P values of <0.05 were accepted as statistically significant.

RESULTS

Both ketamine (Group I) and placebo groups (Group II) consisted of 30 patients each. The groups were comparable according to age, height, body weight and ASA status (Table 1). All blocks were adequate for surgery and no patients were withdrawn due to technical failure.

Spinal anesthesia caused a fall in MAP in both groups. The MAP was lower in the placebo group at all time points. However, the difference was significant at t3, t9, t15, t25 and t30 time points. When compared with the preoperative MAP values, the decrease in the MAP values was significant for all measurements in ketamine and placebo groups (Table 2). None of the subjects experienced a decrease in their MAP exceeding 30% of the baseline value, which was accepted as a criteria for hemodynamic instability in both groups. Spinal anesthesia resulted in an SAP fall in both groups. SAP was lower in placebo group at all time points; the difference was significant for all measurements. Both ketamine and placebo groups showed a significant decrease in SAP at all measurements, outside of recovery periods when compared with preoperative SAP values. None of the patients developed SAPs below 80 mmHg–the threshold criteria for haemodynamic instability in both groups (Table 3). Spinal anesthesia resulted in decreased heart rate in both groups. Heart rate was lower in placebo group at all time points and the difference was significant at t2, t5, t6, t7, t8, t9, and t10 time points. In ketamine group, the decrease in the heart rate was significant from t3 to t20 when compared with the preoperative values. In placebo group, decrease in heart rate was significant at the first measurement and from t15 to t30 relative to preoperative values (Table 4). The cephalad spread of pinprick analgesia reached to T4 dermatomal level

Table 4: Mean values of Heart Rate (HR) in two groups

	Ketamine (Beat/Minute)		Placebo (Beat/Minute)		P
	Mean	SEM	Mean	SEM	
HR (Premedication)	75.70	2.70	73.80	2.728	NS
HR 1. min.	73.80	2.20	71.50	2.74	NS
HR 2. min.	71.85	1.958	64.90	2.471	<0.03
HR 3. min.	69.10	1.923	64.00	2.343	NS
HR 4. min.	68.45	1.855	60.34	2.103	NS
HR 5. min.	68.20	1.673	61.55	1.92	<0.01
HR 6. min.	69.50	1.716	58.35	1.884	<0.001
HR 7. min.	69.40	1.966	58.90	2.032	<0.001
HR 8. min.	68.85	1.68	58.80	1.38	<0.01
HR 9. min.	69.50	1.364	60.50	1.153	<0.01
HR 10.min.	68.65	1.17	60.60	1.32	<0.01
HR 15.min.	70.40	2.46	69.19	2.881	NS
HR 20.min.	70.45	1.243	69.52	2.012	NS
HR 25.min.	71.24	1.46	70.30	1.65	NS
HR 30.min.	71.25	1.782	70.25	1.508	NS
	p<0.0001*		p<0.0001*		

SEM: Standard error of mean, NS: Non-significant,* Friedman Two-Way Analysis of Varians test result of comparison among 15 measures within group

Table 5: Side effects in two groups

	Ketamine (n=30)	Placebo (n=30)
Nistagmus	17/30	0/30
Dizziness	11/30	0/30
Nausea and Vomiting	8/30	12/30
Psychomimetic Effects	0/30	0/30
Postdural Puncture Headache	0/30	0/30

in only one patients in the ketamine group. There was no significant difference between the groups in regard to level of spinal analgesia (p>0.05). In ketamine and placebo groups mean (±SD) duration of spinal analgesia was 146.35 ± 12.21 min and 151.50 ± 17.44, respectively. There was no significant difference between groups in duration of spinal analgesia (p>0.05). Additional analgesics were not administered in either group.

Preoperative sedation was provided by i.v. midazolam (1 to 3 mg). There was no significant difference between groups and no relation between dosages and decrease in MAP during the preoperative period. In ketamine group, median scores of sedation at 15th and 30th min were to 2.5(2-3) and 2(1-2) and in placebo group corresponding values were 1(1-1) and 1(1-1), respectively, which indicates a significant difference between groups (p<0.0001 and p<0.002, respectively)

No subject developed preoperative postdural puncture headache or psychomimetic side effects. Nistagmus and dizziness were seen in ketamine group (Table 5). The mean peroperative blood loss was below 250 ml in both groups. →

DISCUSSION

Spinal anesthesia was introduced into clinical practice by German surgeon Karl August Bier in 1898.[9] After more than a century, it is one of the most popular techniques for lower limb and lower abdominal procedures, including TURP today.[10,11] However, hypotension is one of its important and predicted physiological effects. Spinal anesthesia blocks efferent sympathetic fibers and reduces systemic vascular resistance by decreasing the sympathetic tone of arterial circulation. Peripheral venous pooling of blood also occurs which may reduce cardiac output.[12] Such changes frequently result in systemic hypotension which is the most common complication of spinal anesthesia with an incidence of 20% in the elderly.[13] Hypotension leads to insufficient global or regional perfusion that is not adequate to support normal organ function. This definition emphasizes the anesthesiologist's obligation to ensure adequate organ perfusion during the perioperative period. Severe hypotension can result in an altered mental state due to cerebral ischemia, thrombosis, or edema, especially in the elderly and arteriosclerotic patients. It can also result in reduced renal function, acute renal failure, congestive heart failure, myocardial infarction, and myocardial arrest.[14] If hemodynamic instability (especially hypotension) can be prevented, TURP can be favorably performed under spinal anesthesia.

Prevention of hypotension during spinal anesthesia is a contentious subject without a perfect method to prevent it. Mechanical methods, volume loading and vasopressors have been tried from time to time with variable results. Most studies have focused on the effects of preloading or vasopressors.[15,16] Hypotension during spinal anesthesia can partly be controlled by infusion of i.v. fluids. Excessive fluid administration during spinal anesthesia in elderly patients implies an increased risk of postoperative cardiopulmonary complications and may increase cardiac preload and afterload.[17] Vasopressors such as ephedrine, methoxamine, and epinephrine have been used in preventing hypotension. They cause peripheral blood vessels to constrict and raise the cardiac output by increasing the heart rate and the contractility of the myocardium.

On the other hand, they may also cause several complications such as hypertension, cardiac arrhythmia, and myocardial ischemia.[13] Peroperative hemodynamic stability is very important to prevent possible cardiovascular complications after the surgery. Ketamine is a phenylcyclidine derivative that causes a dissociative anesthesia and has a relatively strong analgesic effect. Its mode of action includes noncompetitive antagonism at *N*-methyl D-aspartate (NMDA) receptors and a local anesthetic effect.[18] Ketamine has an impact on the sympathetic nervous system; following i.v. administration, the effect will commence within 30 seconds and last for 10-15 minute. The peripheral adrenergic response to ketamine is characterized by catecholamine release and inhibition of norepinephrine reuptake. MAP is typically elevated by approximately 25 mmHg. Pulse rate, stroke volume, and cardiac output also increase, however, systemic vascular resistance is unaffected.[19] Thus, heart rate and blood pressure increase after activation of the sympathetic system. These two advantageous characteristics make ketamine a favored sedative agent for patients in shock. The drug also has other antidysrhythmic effects and has been shown to reduce reperfusion-induced ventricular fibrillation in animals.[20] In addition, ketamine blunts the myocardial response to catecholamines, making it a useful agent in decreasing epinephrine-induced dysrhythmias. Ketamine produces neither hypotension nor depression, which is why many medical centers use ketamine as an induction agent for potentially hypovolemic trauma patients undergoing rapid-sequence intubation.[7,21]

Other uses include sedation for hypovolemic or hypotensive patients undergoing emergency cardioversion, amputation, or chest tube placement. Patients sedated with ketamine appear to be awake and have little higher cortical depression.[22] Our aim was to keep the patient in a state of procedural sedation during spinal anesthesia supplemented with ketamine and to prophylactically prevent any expected signs of cerebral hypoxia due to bradycardia and hypotension. In agreement with the other authors, we suggested that ketamine is the proper supplement to spinal anesthesia due to its rapid onset and short-duration of action after i.v. injection, non-depressant respiratory effects, maintenance of pharyngeal and laryngeal reflexes, and desirable cardiovascular sympathetic stimulant effects. In the literature there are studies demonstrating the usage of ketamine with the intention of sedation at a dosage of 0.5 mg/kg in combination with another sedative agent like midazolam or propofol, some studies have also indicated its use at a dosage of ≥2mg/kg so as to provide i.v. sedation.[23-25] Szappanyos et al. tried ketamine cover for spinal and epidural anesthesia using an i.v. dose of 1 mg/kg.[26] Ozyalcın et al. used the same ketamine dosage via i.m. and epidural routes for control of postoperative pain.[27] Similarly, as an optimal supplementary sedative dosage we used a 1mg/kg i.v. ketamine dose in order to reveal the impact of spinal anesthesia on hemodynamic factors with satisfactory results. →

Many authors have praised this technique on the basis that while the factors involved in the fall of blood pressure during spinal anesthesia are purely depressor, ketamine has a purely pressor effect on the cardiovascular system. Yonou et al. concluded that 13 dementia patients with benign prostatic hyperplasia (BPH) who had undergone TURP operation under spinal anesthesia had been well managed postoperatively with i.v. ketamine.[28] On the other hand, Hemmingsen and Nielsen compared the effect of i.v. ketamine and fentanyl in patients who underwent TURP operation for BPH, and established that MAP was lower in the fentanyl group than in the ketamine group at all time points.[22] Consequently, authors concluded that during spinal anesthesia, patients should be maintained in a hemodynamically stable state by intravenous administration of ketamine. In our study, spinal anesthesia-related decreases in all arterial blood pressure measurements performed on ketamine group were observed to be comparatively lower. Especially most of the measurements of MAP and heart rates and all values of SAP obtained at 15. minutes after institution of spinal anesthesia were found to be significantly higher when compared with the placebo group. These findings suggest that these observations might be related to the alleviation of the effects of sympathetic blockage of spinal anesthesia on hemodynamic mechanism at their zenith by ketamine. Ketamine, rather than the combined effects of atropine and ephedrine, can decrease bradycardia and hypotension during spinal anesthesia and that the patient enters a state of procedural sedation during the operation as well.

There are no reports of ketamine-induced myocardial ischemia. Furthermore, the literature is replete with studies of ketamine use in the elderly including its use in coronary artery bypass grafting.[22,28,29] However, whereas the stimulation of cardiac output is an advantage in the hypotensive patient, the resulting increase in myocardial oxygen demand as an effect of sympathomimetic stimulation by ketamine can be consequential in patients known at risk for severe cardiovascular disease such as tachycardia, angina, heart failure, increase pulmonary pressures, malignant hypertension and coronary artery disease.[30] The patient with known severe atherosclerotic heart disease may not be an appropriate candidate for ketamine or any procedural sedation, depending on the urgency of the procedure.[29] Although our study suggests that ketamine can be considered as a safe alternative for the alleviation or prevention of hypotensive episodes encountered during spinal anesthesia applied for elderly patients with lower risk, in high–risk patients with systemic problems, the effects of ketamine on intraoperative hypotension should be comparatively analyzed. On the other hand, some studies have recommended usage of ketamine in combination and/or mixture with other anesthetic agents because of enhancement of its sedative effects and reduction of the effects of potential risk factors such as poor medical status and age (pediatric and geriatric patients) of the patients.[23-25,31,32] In our study as a premedication we used midazolam which is frequently employed in combinations with similar reasons. Recently studies investigating the effects of ketamine-propofol (ketofol) mixtures have emphasized that combinations provided more effective sedation, hemodynamic stability, faster recovery and lesser adverse effects when compared with propofol per se.[23,25,32] Most of these studies have underscored the necessity of reinforcing these outcomes obtained with larger scale trials comparing single and combined uses of ketamine.

Although it is well known that ketamine is a hallucinogenic agent, we did not observe such a hallucinogenic effect of ketamine.[31] This may due to routine use of midazolam as an adjunct. Also, the hallucinogenic factor was eliminated in the ketamine group where patients were hemodynamically stable.

CONCLUSION

Compared with placebo, ketamine 1 mg/kg i.v. given 5 min before spinal anesthesia resulted in greater haemodynamic stability in elderly patients undergoing TURP.

C **CORRESPONDING AUTHOR:** Fatih Özkan Assist. Prof MD. Ondokuzmayıs University, Medical Faculty, Department of Anesthesiology, Samsun, Turkey dr.fat.oz@hotmail.com

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REFERENCES

1. Ozmen S, Kosar A, Soyupek S, et al. The selection of the regional anaesthesia in the transurethral resection of the prostate (TURP) operation. Int Urol Nephrol 2003; 35: 507-512.
2. Togal T, Demirbilek S, Koroglu A, Yapici E, Ersoy O. Effects of S(+) ketamine added to bupivacaine for spinal anaesthesia for prostate surgery in elderly patients. Eur J Anaesthesiol 2004; 21:193-197.
3. Heidemann BH, Clark VA. Use of pre-emptive vasopressors for spinal anaesthesia-induced hypotension during caesarean section. Br J Anaesth 2001; 87: 320-321.
4. Brooker RF, Butterworth JF, Kitzman DW, et al. Treatment of hypotension after hyperbaric tetracaine spinal anesthesia. A randomized, double-blind, cross-over comparison of phenylephrine and epinephrine. Anesthesiology 1997; 86: 797-805.
5. Hoffmann VL, Baker AK, Vercauteren MP, Adriaensen HF, Meert TF.

Epidural ketamine potentiates epidural morphine but not fentanyl in acute nociception in rats. Eur J Pain 2003; 7: 121-130.
6. Morris C, Perris A, Klein J, Mahoney P.Anaesthesia in haemodynamically compromised emergency patients: does ketamine represent the best choice of induction agent? Anaesthesia 2009; 64: 532–539.
7. Stoelting RK. Nonbarbürate induction drugs. In: Stoelting RK, ed. Pharmacology and Physiology in Anesthetic Practice, 3rd ed. Philadelphia, Pennsylvania: Lippincott Williams and Wilkins 1999: 148-154.
8. White PF, Romero G. Nonopioid Intravenous Anesthesia. In: Barash PG, Cullen FB, Stoelting RK eds. Clinical Anesthesia, 5th ed. Philadelphia, Pennsylvania: Lippincott Williams and Wilkins 2006: 344-346.
9. Brill S, Middleton W, Brill G, Fisher A. Bier's block; 100 years old and still going strong! .Acta Anaesthesiol Scand 2004; 48: 117-122.
10. Govindan K, Krishnan R, Kaufman MP, et al. Intrathecal ketamine in surgeries for lower abdomen and lower extremities. Proc West Pharmacol Soc 2001; 44: 197-199.
11. Chander J, Vanitha V, Lal P, Ramteke VK. Transurethral resection of the prostate as catheter-free day-care surgery. BJU Int 2003; 92: 422-425.
12. Gogarten W. Spinal anesthesia for obstetrics. Best Pract Res Clin Anaesthesiol 2003; 17: 377-392.
13. Morgan P. The role of vasopressors in the management of hypotension induced by spinal and epidural anaesthesia. Can J Anaesth 1994; 41: 404-413.
14. Reich DL, Bodian CA, Krol M, et al. Intraoperative hemodynamic predictors of mortality, stroke, and myocardial infarction after coronary artery bypass surgery. Anesth Analg 1999; 89: 814-822.
15. Morgan PJ, Halpern SH, Tarshis J. The effects of an increase of central blood volume before spinal anesthesia for cesarean delivery: a qualitative systematic review. Anesth Analg 2001; 92: 997-1005.
16. Rout CC, Rocke DA, Gouws E. Leg elevation and wrapping in the prevention of hypotension following spinal anaesthesia for elective caesarean section. Anaesthesia 1993; 48: 304-308.
17. Holte K, Foss NB, Svensen C, et al. Epidural anesthesia, hypotension, and changes in intravascular volume. Anesthesiology 2004; 100: 281-286.
18. Ilkjaer S, Petersen KL, Brennum J, Wernberg M, Dahl JB. Effect of systemic N-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans. Br J Anaesth. 1996; 76: 829-834.
19. Sprung J, Schuetz SM, Stewart RW, Moravec CS. Effects of ketamine on the contractility of failing and nonfailing human heart muscles in vitro. Anesthesiology 1998; 88: 1202-1210.
20. Baczko I, Lepran I, Papp JG. Influence of anesthetics on the incidence of reperfusion-induced arrhythmias and sudden death in rats. J Cardiovasc Pharmacol 1997; 29: 196-201.
21. Hemmingsen C, Nielsen JE. Intravenous ketamine for prevention of severe hypotension during spinal anaesthesia. Acta Anaesthesiol Scand 1991; 35: 755-757.
22. Pfenninger E, Himmelseher S. Neuroprotection by ketamine at the cellular level. Anaesthesist 1997; 46: 47-54.
23. Da Silva PS, de Aguiar VE, Waisberg DR, Passos RM, Park MV. Pediatr Int. The use of Ketofol for procedural sedation and analgesia in children with hematological diseases. 2010 Jul 5. [Epub ahead of print]
24. Wang X, Zhou ZJ, Zhang XF, Zheng S A comparison of two different doses of rectal ketamine added to 0.5 mg x kg(-1) midazolam and 0.02 mg x kg(-1) atropine in infants and young children. Anaesth Intensive Care. 2010; 38: 900-904.
25. Singh R, Batra YK, Bharti N, Panda NB.Comparison of propofol versus propofol-ketamine combination for sedation during spinal anesthesia in children: randomized clinical trial of efficacy and safety. Paediatr Anaesth. 2010; 20: 439-444.
26. Szappanyos G, Gemperle M, Rifat K. Selective indications for ketamine anesthesia. Proc R Soc Med 1971; 64: 1156-1159.
27. Ozyalcin NS, Yucel A, Camlica H, et al. Effect of pre-emptive ketamine on sensory changes and postoperative pain after thoracotomy: comparison of epidural and intramuscular routes. Br J Anaesth 2004; 93: 356-361.
28. Yonou H, Kagawa H, Oda A, et al. Transurethral resection of the prostate for patients with dementia. Hinyokika Kiyo 1999; 45: 241-244.
29. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. Am J Emerg Med. 2008; 26: 985-1028.
30. Sinner B, Graf BM. Ketamine. Handb Exp Pharmacol. 2008; 182: 313-333.
31. Parker RI, Mahan RA, Giugliano D, Parker MM. Efficacy and safety of intravenous midazolam and ketamine as sedation for therapeutic and diagnostic procedures in children. Pediatrics 1997; 99: 427-431.
32. Rapeport DA, Martyr JW, Wang LP. The use of "ketofol" (ketamine-propofol admixture) infusion in conjunction with regional anaesthesia.Anaesth Intensive Care. 2009; 37: 121-123.