KLINIKINIAI TYRIMAI

Effects of ketamine on precipitated opiate withdrawal

Tomas Jovaiša, Giedrius Laurinėnas, Saulius Vosylius, Jūratė Šipylaitė, Robertas Badaras, Juozas Ivaškevičius
Clinic of Anesthesiology and Intensive Care, Vilnius University, Lithuania

Key words: *ketamine, opiate withdrawal, anesthesia, opiate antagonists, cortisol.*

Summary. *Objective. N-methyl-D-aspartate antagonists were shown to be effective in suppressing the symptoms of opiate withdrawal. Intravenous anesthetic, ketamine, is the most potent N-methyl-D-aspartate antagonist available in clinical practice. The present study was designed to evaluate the effects of subanesthetic ketamine infusion, as little human data are available on ketamine in precipitated opiate withdrawal.*

Materials and methods. A total of 58 opiate-dependent patients were enrolled in a randomized, placebo-controlled, double-blind study. Patients underwent rapid opiate antagonist induction under general anesthesia. Prior to opiate antagonist induction patients were given either placebo (normal saline) or subanesthetic ketamine infusion of 0.5 mg/kg/h. Further evaluations were divided into three phases: anesthetic, early postanesthetic (48 hours), and remote at 4 months after procedure. Cardiovascular, respiratory, renal, and gastrointestinal responses to opiate antagonist induction were monitored during anesthesia phase. Changes in plasma cortisol concentrations were measured as stress-response markers. Evaluations during early postanesthetic phase were based on Subjective and Objective Opiate Withdrawal Scales. Remote effects were assessed according to questionnaire based on Addiction Severity Index.

Results. Altogether, 50 patients were included in the final analysis. Ketamine group presented better control of withdrawal symptoms, which lasted beyond ketamine infusion itself. Significant differences between Ketamine and Control groups were noted in anesthetic and early postanesthetic phases. There were no differences in effects on outcome after 4 months.

Conclusion. In this study, subanesthetic ketamine infusion was an effective adjuvant in the correction of acute precipitated opiate withdrawal although it had no long-term effects on treatment of opiate dependence.

Introduction

A number of recent publications support the hypothesis that N-methyl-D-aspartate (NMDA) antagonists attenuate the signs of opiate withdrawal and diminish progression or reverses existing opiate tolerance. Majority of these facts are shown on animal studies and experimental data using selective NMDA antagonists or clinically available substances (1–3). NMDA antagonists are shown to have an effect on opiate-induced behavioral changes in animal models (4, 5). Existing human data obtained from studies with clinically available NMDA antagonists, memantine and dextromethorphan, also prove the beneficial effects (6, 7).

Ketamine is another clinically available NMDA antagonist. A recent study found that electroencephalographic changes during rapid opiate detoxification are reversed by ketamine (8). Animal studies show that ketamine not only suppresses opiate withdrawal symptoms but also produces different and more extensive effects when compared to other anesthetic agents (9, 10). The use of ketamine in treatment of opiate withdrawal is limited mainly because of psychotropic effects and abuse potential (11). Considering this, we decided to evaluate the effects of ketamine during rapid opiate antagonist induction (RAI) under general anesthesia. In anesthesia community, RAI is regarded as a controversial procedure because of pronounced stress response effects, possible pulmonary, cardiovascular, and other complications (12–14). But if performed by experienced team in well-equipped

Correspondence to T. Jovaiša, Clinic of Anesthesiology and Intensive Care, Vilnius University, Šiltnamių 29, 04130 Vilnius, Lithuania. E-mail: tjovaisa@yahoo.co.uk

facilities, it presents the safe and acceptable model for evaluation of ketamine effects (15–18). At this stage, the effects and safety of ketamine anesthesia should be primarily questioned. Although initially designed to explore this issue only, the study was prolonged beyond the hospital period to evaluate the possible long-term effects.

Materials and methods

The study was approved by the National Bioethics Committee of Lithuania and the National Drug Control Agency. Each patient gave written informed consent at the beginning of the study. The study ran over the period of 18 months and took place at the Vilnius University Emergency Hospital, Lithuania.

Patients' groups. A total of 58 patients were enrolled in the study. Inclusion criteria were opiate dependence according to the 10th Revision of International Classification of Diseases (ICD-10) and 4th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM IV), the duration of substance abuse more than one year, age of 18–35 years, no or minor comorbidities, grade I–II according to physical status classification system of American Society of Anesthesiologists. We excluded patients with a current history of long acting opiate or polysubstance abuse, acute medical or surgical condition, and pregnancy. In the later phase, patients that required less than 30 mg of morphine during stabilization phase were excluded from final analysis. Patients were randomly assigned to Ketamine or Control group on the day of procedure.

Study plan. A randomized, placebo-controlled, double-blind study was performed. Patients were admitted to the hospital two days before the anesthesia for morphine stabilization. Intramuscular morphine hydrochloride was administered at doses of 5–10 mg as needed, based on Subjective and Objective Opiate Withdrawal Scales (SOWS and OOWS).

General anesthesia was induced uniformly at 9:00 a.m. on the in-patient day 3. A strict timing has been urged due to circadian rhythm in plasma cortisol concentration. A separate anesthetic chart and the set of algorithms were developed for uniform management of cardiovascular, respiratory, or muscle relaxant-related issues. The same RAI protocol was used as previously published (16). Withdrawal severity during anesthesia was measured according to Wang modified scale (OOWS-A) (19). Measurements were made every 10 minutes and summed up at the end of each hour following opiate antagonist induction. Anesthesia medications, interventions, and monitors are shown in Table 1.

Patients were required to have an aftercare plan before RAI. Following discharge from the hospital, patients entered the aftercare program of their choice: either abstinence-based, naltrexone-supported outpatient counseling or residential rehabilitation programs. All patients were contacted after 4 months to fill in the questionnaire based on Addiction Severity Index. Questionnaire focused on health and socio-legal issues: remote anesthesia complications, changes in health status, new onset of psychopathology or compulsive behavior, initiation and retention in naltrexone maintenance or rehabilitation program, changes in social life, family relations, and legal status. Retention in treatment and abstinence were confirmed by urine toxicology tests.

Statistical methods. Data are presented as means± standard deviation (SD). Statistical analyses were performed using "Microsoft Excel" and "SPSS for Windows" software. The Student's t-test was used to assess the difference between group means. The paired samples t-test was used to compare plasma cortisol concentration at baseline and following time points. The chi-square method was used to compare non-parametric values. A p-value of <0.05 was considered statistically significant.

Results

Complete profiles were obtained for 50 patients. Eight patients were excluded because of failure to comply with study protocol and incomplete data collection. Outcome data four months after the procedure were obtained for 45 patients. Five sets of blood samples were excluded due to processing-related issues.

Patients' characteristics. Demographic and clinical characteristics of 50 patients were comparable. Randomization resulted in very similar and equal distribution of main patients' characteristics (Table 2).

Anesthesia phase. Ketamine infusion significantly suppressed the expression of precipitated opiate withdrawal and prevented significant rise in cardiovascular, respiratory, and neuroendocrine response. The majority of recorded variables followed the same pattern, as differences between two groups were more pronounced during the acute phase of opiate antagonist induction.

Differences in cardiovascular response were more pronounced during the first two hours after opiate antagonist induction. Ketamine infusion resulted in more stable hemodynamic profile (Table 3). Mean arterial pressure and heart rate during the peak response to opiate antagonist induction and throug-

Table 1. **Anesthesia medications, interventions, and monitors. Timing of cortisol samples**

Medication	Intervention/Monitor	Cortisol samples
Preanesthesia Clonidine 5 μg/kg, orally Octreotide 100 μg, IV infusion Heparin 5000 U, IV		1st sample – baseline level
Induction of anesthesia Preoxygenation Propofol 2.5 mg/kg Lidocaine 1.5 mg/kg Pipecuronium 0.1 mg/kg	Standard anesthesia monitoring (Datex-Engstrom AS/3) Endotracheal intubation Insertion of oro-gastric tube	
Maintenance of anesthesia Isoflurane ≥0.8 MAC in oxygen/air* Pipecuronium as needed Ketamine or placebo**	Anesthetic gas analyzer Myoneural block monitor	
Opiate antagonist induction Naloxone 1.6 mg, IV Naloxone 0.8 mg/h, IV infusion Naltrexone 100 mg, via oro-gastric tube		2nd sample – 20 minutes after naloxone bolus
Emergence from anesthesia Reversal of myoneural blockade	Tracheal extubation Transfer to postanesthesia care unit	3rd sample – at the end of anesthesia phase
48-hour postanesthesia phase Clonidine 2 μg/kg, orally, twice daily Carbamazepine 200 mg, orally as needed Clonazepam 2 mg, orally at night Naloxone challenge test 1.2 mg, IV	Subjective and Objective Opiate Withdrawal Scales	4th sample – following morning after RAI at 8 a.m.

* adjusted if cardiovascular response exceeded 30% of the baseline values. Minute ventilation was targeted to maintain the constant $etCO_2$ at the level of 5%;

** started 5 minutes before the opiate antagonist induction, initial 0.5 mg kg^{-1} bolus, followed by infusion of 0.5 mg kg^{-1} h^{-1}.

Table 2. **Patients' characteristics**

Characteristic	Ketamine group (n=22)	Control group (n=28)
Age (years)	22.7±3.0	23.4±3.1
Weight (kg)	71.8±8.2	67.7±11.1
Sex (female/male)	2/20	5/23
Morphine stabilization dose (mg)	57.7±16.4	54.6±15.8
History of opiate abuse (years)	3.7±2.0	4.2±1.9
Number of previous medical detoxifications	2.2±2.1	2.4±2.3

Data are presented as mean±SD and total number for sex. Differences between groups are not significant for all variables, $p>0.1$.

hout the procedure were lower in Ketamine group (Fig. 1).

The peak rise in the requirement of respiratory minute volume following opiate antagonist induction was lower in Ketamine group. Differences between mean baseline volume and mean peak volume were 0.712±0.6 and 1.486±0.7 l in Ketamine and Control groups, respectively ($p<0.001$).

Table 3. **Cardiovascular response during rapid opiate antagonist induction under general anesthesia**

Variable	Control n=28	Ketamine n=22	95% confidence interval of the difference	p
Mean arterial pressure				
Baseline	71.6±10.9	69.6±5.2	–3.2; 7.04	0.450
Peak	96.6±13.8	79.4±10.8	9.9; 24.4	<0.001
1st hour	86.5±10.9	74.2±7.9	6.7; 17.9	<0.001
2nd hour	83.5±10.7	76.2±7.3	1.9; 12.6	0.009
3rd hour	82.2±10.4	79.2±7.3	–2.3; 8.3	0.255
Heart rate				
Baseline	69.1±15.5	64.3±9.7	–2.9; 12.4	0.216
Peak	95.5±12.8	75.6±13.0	12.5; 27.3	<0.001
1st hour	86.5±12.9	71.6±10.5	8.1; 21.7	<0.001
2nd hour	88.6±12.1	74.6±11.8	7.1; 20.8	<0.001
3rd hour	87.6±11.5	77.9±11.4	3.2; 16.3	0.005

Data are presented as mean±SD. Baseline – time point following induction of general anesthesia when hemodynamically steady state is achieved. Peak – single reading representing the maximum increase of the variable following opiate antagonist induction.

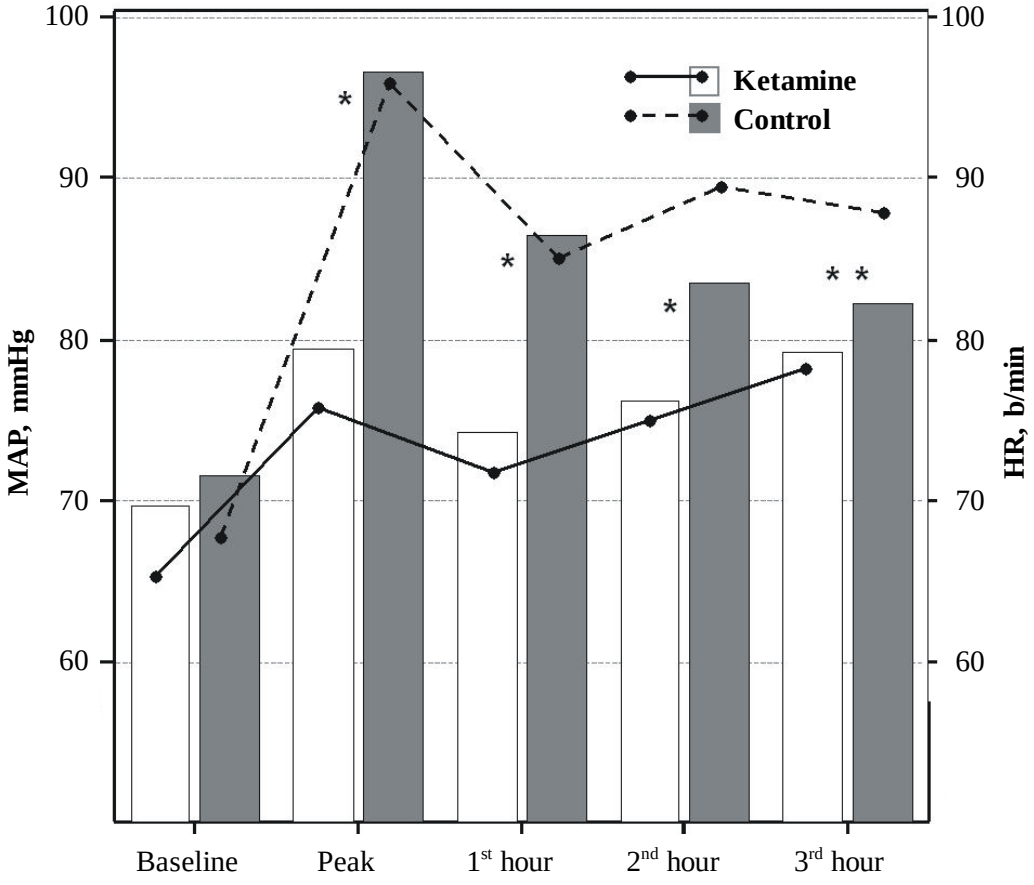

Fig. 1. **Cardiovascular response during rapid antagonist induction**

Bars show means of mean arterial pressure (MAP), lines show means of heart rate (HR).
* difference between groups significant for MAP and HR, p<0.01;
** difference between groups significant for HR only, p<0.05.

There were no significant changes or differences between groups in hourly urine output and gastrointestinal reaction.

Opiate withdrawal scores on OOWS-A scale were significantly higher in Control group, despite significantly higher mean hourly minimum alveolar concentration (MAC) of isoflurane (Fig. 2 and 3).

Baseline cortisol levels were comparable between groups. Mean concentrations for Ketamine and Control groups were 496±120 and 468±160 nmol/l, respectively ($p>0.5$). During general anesthesia phase, ketamine infusion significantly suppressed cortisol level even after opiate antagonist induction. Concentration decreased by 165±125 nmol/l when compared to baseline in Ketamine group ($p<0.05$); no significant changes were found in Control group – 62±92 nmol/l ($p>0.1$). A significant increase in morning cortisol levels was noted in both groups on the following day: 154±141 nmol/l for Ketamine group ($p<0.05$) and 302±210 nmol/l for Control group ($p<0.001$). The extent of increase was significantly higher in Control group patients compared to Ketamine group ($p<0.05$) (Fig. 4).

Early postanesthetic phase. Patients in Ketamine group required significantly less additional carbamazepine and clonazepam to maintain the same level of opiate withdrawal symptoms during the first 48 hours following RAI. Mean total clonazepam dose was 5.0±2.7 and 8.6±3.7 mg for Ketamine and Control groups, respectively ($p<0.001$). Mean total carbamazepine dose was 473±335 and 957±423 mg ($p<0.001$). There were no significant differences in SOWS and OOWS scores on days 3 to 5 ($p>0.1$). Naloxone challenge test was negative in all cases. There were no complications related to anesthesia phase or opiate antagonist induction.

Outcome results after four months. Five patients were lost to follow-up. Altogether, 13 out of 21 pa-

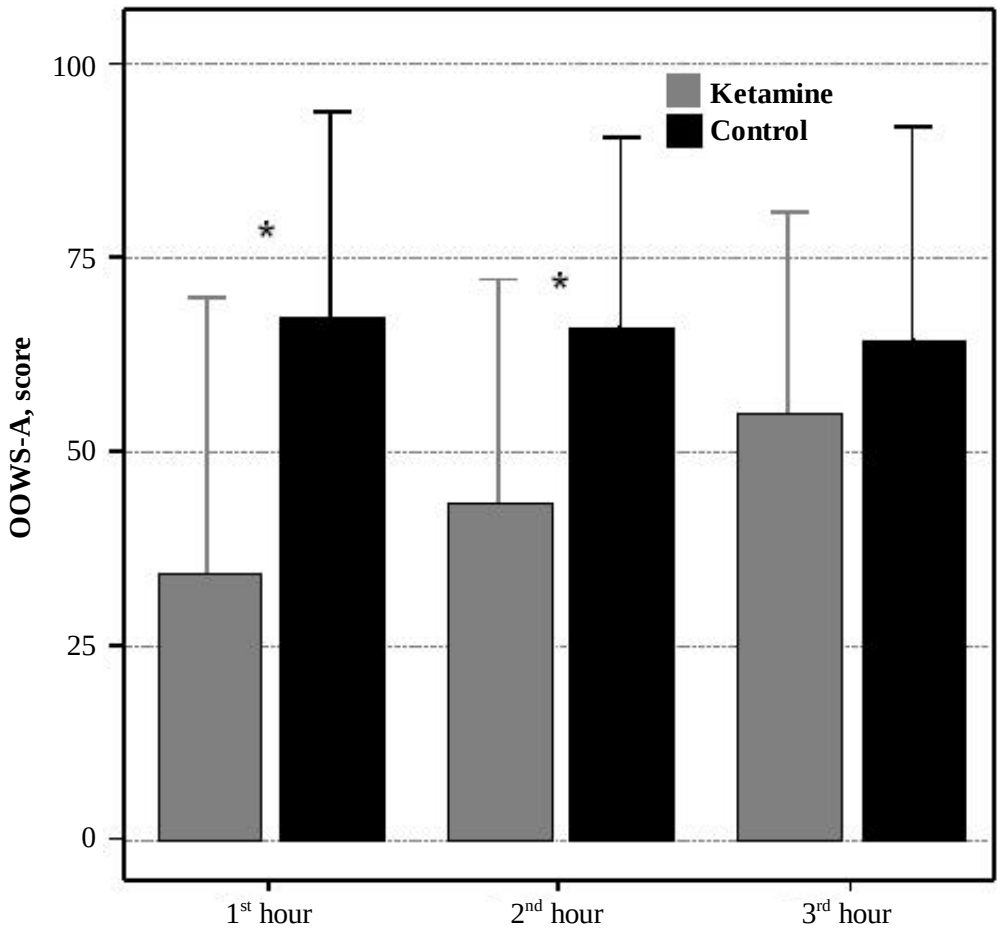

Fig. 2. **Severity of opiate withdrawal during anesthesia phase according to Objective Opiate Withdrawal Scale (OOWS-A) score**

Bars show means of hourly OOWS-A score, error bars show standard deviation.
* difference between groups significant for hourly OOWS-A score, $p<0.05$.

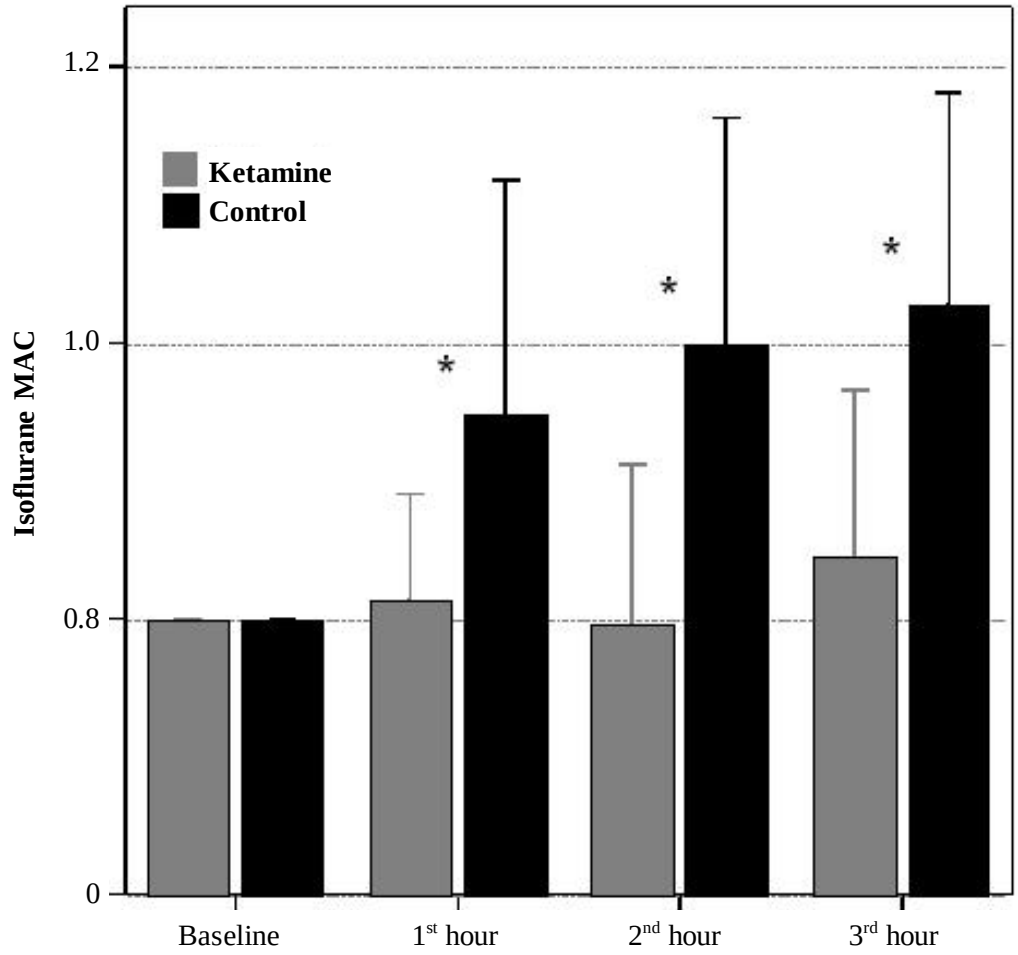

Fig. 3. **Minimum alveolar concentration (MAC) of isoflurane during anesthesia phase**
Bars show mean minimum alveolar concentrations of isoflurane, error bars show SD.
* difference between groups significant, $p<0.05$.

tients in Ketamine group and 19 out of 24 patients in Control group entered outpatient counseling programs; other patients entered residential rehabilitation programs. Difference between groups is statistically insignificant. The patients in Ketamine and Control groups were opiate free on average for 9.4±6.6 and 8.0±7.0 weeks, respectively ($p>0.05$). The summary of outcome data is presented in Fig. 5. Differences between groups are statistically insignificant. No remote complications related to RAI were reported. Four patients were admitted to hospital in a 4-month period for trauma, acute pancreatitis, and ulcerative colitis. One more patient returned to regular opiate use, developed injection-related sepsis, and later died in hospital.

Discussion

This is the first randomized, placebo-controlled, double-blind trial evaluating effects of subanesthetic infusion of ketamine during RAI. Our data support the hypothesis that NMDA antagonists may selectively interfere with expression of opiate withdrawal. Although it is known that different doses of ketamine may produce different effects (9, 10), but there are few studies indicating the target infusion rate or dose. Doses of 1.5 mg/kg and higher were used in the studies mentioned above. The protocol of our study was aimed at maintaining equianesthetic conditions during opiate antagonist induction. None of routinely used methods for monitoring or assessing the depth of anesthesia are suitable for ketamine-induced general anesthesia (20, 21). This makes it impossible to compare it with other anesthetic agents (mainly gamma-aminobutyric acid (GABA)-acting) without questioning the comparability of anesthetic protocols. We chose subanesthetic infusion of 0.5 mg/kg/h as it is likely to produce NMDA antagonistic effects and have minimal effect on overall depth of anesthesia. Ketamine, as a single agent, administered at infusion rates of 0.3 and 0.5 mg/kg/h was used in the studies evaluating neuroen-

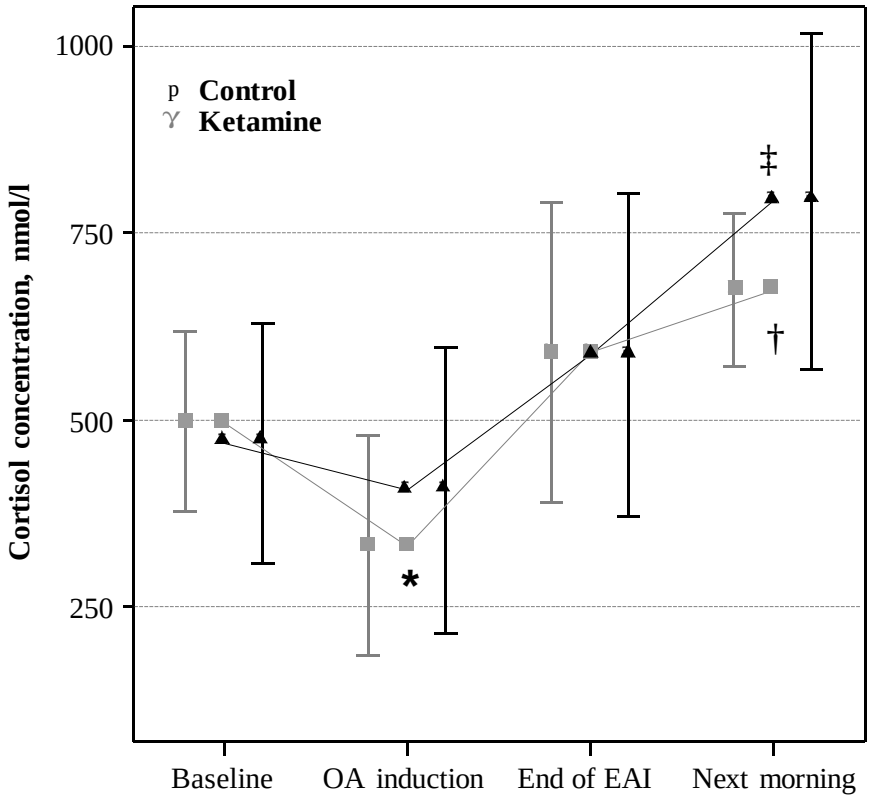

Fig. 4. **Trends of plasma cortisol levels during the first 24 hours following rapid opiate antagonist induction**

Bars show means and error bars show SD. OA – opiate antagonist.
* a statistically significant difference as compared to baseline for Ketamine group only; p<0.05;
† and ‡ – a statistically significant difference as compared to baseline for both groups; p<0.05.

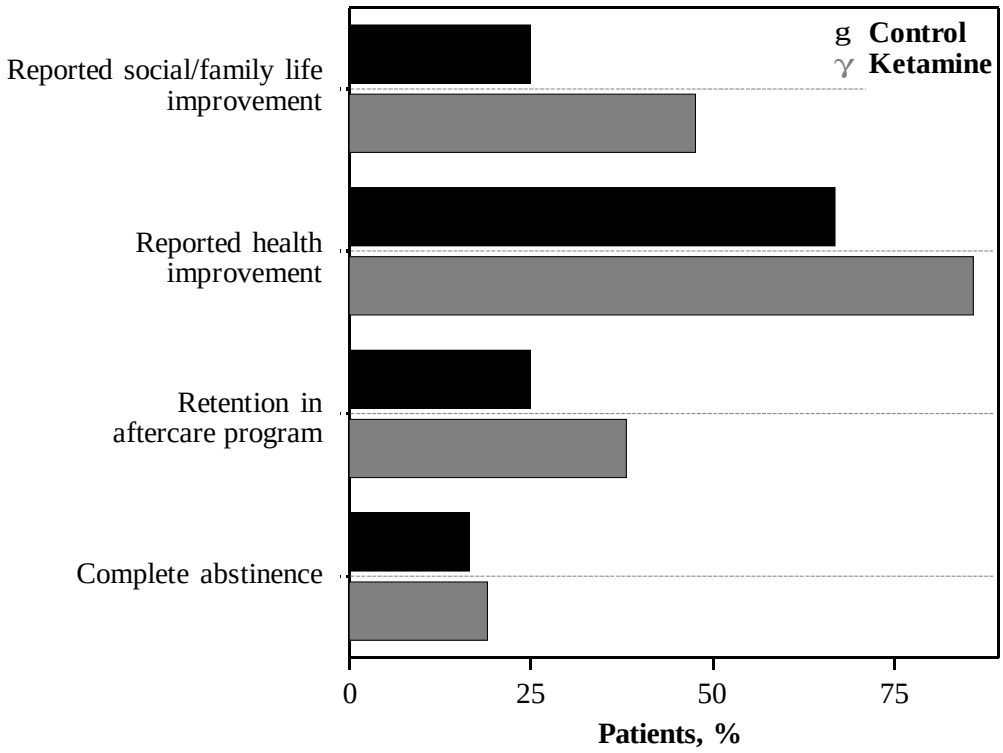

Fig. 5. **Summary of outcome at 4 months following rapid opiate antagonist induction**

docrine response (22). It was shown that this dose regimen did not induce general anesthesia and complex hallucinations.

In the number of analyzed variables, we noticed the same pattern – more significant differences between Ketamine and Control groups during the acute phase of RAI and minor or no differences at the end of procedure. This trend may be attributable directly to changes in plasma ketamine concentration – peak of concentration following bolus and later steady state following continuous infusion. To some extent, this pattern may be caused by non-NMDA-mediated activation of hypothalamo-pituitary-adrenal axis. Many neurons express simultaneously two or more isotypes of glutamate receptors, so pharmacological modulation of more than one receptor may be necessary to abolish completely neuroendocrine response (23).

Ketamine is the only anesthetic which stimulates the cardiovascular system, and even a dose of 0.5 mg/kg can cause this effect. It causes an increase in plasma concentrations of catecholamines and cortisol as well (22). Contrary to basic pharmacodynamics of ketamine, in this study ketamine infusion resulted in lowered blood pressure, heart rate, and cortisol levels. We can hypothesize that in precipitated opiate withdrawal, NMDA blockade produced by ketamine outweighs the stimulant effects of ketamine.

Known effects of ketamine on respiratory system are minimal; the only clinically important feature is bronchodilation. Ketamine neither suppresses the respiratory minute volume nor alters the respiratory response to an increase in carbon dioxide. Opiate antagonist induction is shown to increase ventilatory requirement (24). Considering the above facts, lower peak respiratory minute volume in Ketamine group is more likely to be due to more effective suppression of opiate withdrawal rather than anesthetic effects of ketamine.

In this study, differences in cardiovascular and respiratory response between groups are attributable solely to ketamine infusion. There is no doubt that higher dose of other general anesthetic agents may suppress these responses, but this study demonstrates that NMDA receptor antagonist may result in very specific effects, at least comparable to those of GABA-acting anesthetic agents. Isoflurane MAC was significantly higher in Control group as a result of more pronounced withdrawal symptoms during the anesthetic phase. Even if we speculate that difference in MAC was attributable to different depth of anesthesia because of ketamine, then isoflurane and ketamine mixture may be regarded as more effective, considering significant differences in OOWS-A scores.

More importantly, this study demonstrates the preemptive effect of ketamine. Lower doses of clonazepam and carbamazepine on days 3–5 and significantly lower concentration of cortisol 24 hours after procedure represent the lower intensity in the residual symptoms of opiate withdrawal. This effect cannot be attributed to any of the residual effects of anesthetic, and it demonstrates complex processes underlying interference with opiate withdrawal. It is generally accepted that opiate withdrawal induces a significant rise in plasma and salivary cortisol levels. This effect may last for weeks after detoxification (25). Neurobehavioral effects of addiction and withdrawal may correlate to neuroendocrine changes (26). Modulation of this response during rapid opiate antagonist induction may be promising, but clinical significance of this effect remains unclear, as the differences in long-term outcome results were insignificant. Similar outcome results were published in a recent Cochrane review (27).

This dose of ketamine may be used in other protocols of RAI under anesthesia or deep sedation. It may also offer some advantages in cases of polysubstance abuse when tolerance to GABA-acting substances is very likely. Nevertheless, contraindications should include cases of concomitant cocaine intake and alcohol withdrawal.

Considering the recent publication by E. Freye and colleagues (8) and available animal model data, this trial adds to growing body of evidence that ketamine may be a promising adjuvant in RAI. Further studies are needed for a better understanding of ketamine effects on opiate withdrawal.

Conclusion

In this study, subanesthetic ketamine infusion was an effective adjuvant in the correction of acute precipitated opiate withdrawal although it had no long-term effects on treatment of opiate dependence.

Acknowledgements

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Ketamino įtaka sukeltai opioidinei abstinencijai

Tomas Jovaiša, Giedrius Laurinėnas, Saulius Vosylius, Jūratė Šipylaitė, Robertas Badaras, Juozas Ivaškevičius
Vilniaus universiteto Anesteziologijos ir reanimatologijos klinika

Raktažodžiai: ketaminas, opioidinė abstinencija, anestezija, opioidų antagonistai, kortizolis.

Santrauka. N-metil,D-aspartato receptorių antagonistai slopina opioidinės abstinencijos simptomus. Į veną vartojamas anestetikas ketaminas yra stipriausias N-metil,D-aspartato receptorių antagonistas, net anestezijos nesukeliančios ketamino dozės veikia gliutamato receptorius.

Tyrimo tikslas. Įvertinti subanestetinės ketamino infuzijos sukeliamus poveikius, nes klinikinių duomenų apie ketaminą, vartojamą opioidinei abstinencijos būklei gydyti, yra labai mažai.

Metodai. Prospektyviajame, atsitiktinių imčių, dvigubai koduotame tyrime dalyvavo 58 tiriamieji. Ketamino poveikiai tirti atliekant opioidų antagonistų ankstyvąją indukciją bendrosios anestezijos metu. Prieš opioidų antagonistų indukciją pacientams buvo skiriama pastovi ketamino infuzija 0,5 mg/kg/val. arba placebo (fiziologinis tirpalas). Tyrimas suskirstytas į tris fazes: anesteziją, ankstyvąjį laikotarpį po anestezijos (48 valandos) ir vėlyvąjį laikotarpį. Anestezijos metu buvo stebimi širdies ir kraujagyslių, kvėpavimo sistemų, inkstų ir virškinamojo trakto funkcijų pokyčiai. Atsakui į stresą vertinti buvo tiriama kortizolio koncentracija. Vėlyvieji rezultatai buvo vertinami po keturių mėnesių remiantis priklausomybės sunkumo indeksu, pagrįstu klausimynu.

Rezultatai. 50 pacientų duomenys įtraukti į tolesnę analizę. Ketamino infuzija veiksmingiau slopino opioidinės abstinencijos simptomus, šis poveikis užfiksuotas ir pabaigus infuziją. Reikšmingų skirtumų nustatyta tarp tiriamosios ir kontrolinės grupių anestezijos metu ir ankstyvuoju laikotarpiu po anestezijos. Reikšmingo skirtumo tarp tiriamosios ir kontrolinės grupių po keturių mėnesių nenustatyta.

Išvada. Papildoma subanestetinė ketamino infuzija padeda efektyviau koreguoti sukeltos opioidinės abstinencijos simptomus, tačiau neturi įtakos vėlesniems opioidinės priklausomybės gydymo rezultatams.

Adresas susirašinėti: T. Jovaiša, Vilniaus universiteto Anesteziologijos ir reanimatologijos klinika, Šiltnamių 29, 04130 Vilnius. El. paštas: tjovaisa@yahoo.co.uk

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