



Vasoactive stress hormone (adrenaline, noradrenaline and cortisol) concentration in plasma after administration of low doses of S-(+)-ketamine epidurally

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Abstract

Background and Purposes: The aim of this study was to investigate the effect of epidurally administered S-(+)-ketamine on vasoactive stress hormones. It was a prospective study conducted after approval of the Ethical Committee and informed consent of patients.

Materials and Methods: The study was performed on 80 patients: 40 patients in Group 1 (0.5% bupivacaine) and 40 patients in Group 2 (0.5% bupivacaine + 25 mg S-(+)-ketamine – 0.326 mg/kg-bm). All patients were adults aged between 18 and 45 years, ASA I and II with epidural anaesthesia for a surgical procedure. Vasoactive parameters: concentrations of adrenaline, noradrenaline and cortisol were measured 30 minutes before setting the vein pathway and 17–25 min. after application of anaesthetics.

Results: There were no statistically significant changes in vasoactive stress hormones (adrenaline, noradrenaline and cortisol) plasma concentrations after administering 0.5% bupivacaine, 0.5% bupivacaine + S-(+)-ketamine epidurally.

Conclusion: Setting central nervous block before skin incision, using local anaesthetic, and S-(+)-ketamine, leaves concentrations of stress hormones in plasma within referent values. Adding a low dose of S-(+)-ketamine into the epidural space in combination with 0.5% bupivacaine does not have an effect on the concentration of stress hormones in plasma.

INTRODUCTION

Anaesthetic primarily has an effect on the nervous system, but is undoubtedly related with effect on the endocrine system. Catecholamines adrenaline and noradrenaline and cortisol are important stress hormones which are excreted as the outcome of different stress stimuli. The organism's perioperative stress response is caused by more factors. Many patients have an increased sympathetic tonus caused by fear and uncertainty of the surgical intervention already perioperatively. This can be avoided by talking to the patient and explaining the planned course of anaesthesia and operation as adequate premedication (1).

Spontaneous changes of heart rate, blood pressure and other cardiovascular system parameters are well known (2, 3, 4). These changes are classified depending on their frequency and each frequency of change comes from the different activity of two branches of the autonomic ner-

vous system – sympathetic and parasympathic (5). Many studies have been made in order to determine the correlation between changes of heart rate and blood pressure with different changes of the autonomic nervous system.

Ketamine causes prominent cardiovascular stimulation increasing the minute volume of the heart, myocardial oxygen consumption, heart rate, mean arterial and pulmonary pressure and central venous pressure (4, 5, 6, 7, 13).

Adding S-(+)-ketamine to bupivacaine intrathecally did not cause significant changes in arterial pressure compared to a group which was given only bupivacaine (8).

Blood pressure stability is kept by negative feedback mechanism – decreased pressure is detected by sino-aortal baroreceptors that are stimulated by sympathetic nerves (9). Higher sympathetic activity above the place of block results in increased tonus and decreased compliance of cutaneous arterias (8, 13).

Bolus application of S-(+)-ketamine leads by itself, without surgical stress, to general stimulation of endocrine stress response, (except) apart from increasing ADH. »Dissociative anaesthesia«, caused by ketamine, represents endogene psychical stress and contributes to stress response (9).

Epidural anaesthesia prevents catecholamine secretion from the adrenal gland that occurs because of stimulation from the operation field. Epidural anaesthesia has no effect on secretion of cortisol, probably because afferent vagus paths are not blocked (12).

MATERIALS AND METHODS

Patient selection

A study/investigation of sympathetic activity was carried out in 80 patients aged 18 to 45 years ASA II who had undergone surgical intervention under epidural anaesthesia. Examinations were performed after administering drugs, but before skin incision. Patients were introduced to the course and aims of the study and drugs to be used throughout the study the day before the operation.

Patients were divided into two groups; Group 1, consisted of 40 patients who received an injection of 0.5% bupivacaine into the epidural space, and Group 2 who received an injection of 0.5% bupivacaine and low dose (25 mg) of S-(+)-ketamine into the epidural space.

Exclusion criteria were:

1. Contraindications for EDA anaesthesia.
2. Accompanying cardiovascular diseases (arteriosclerosis, hypertension, Raynaud syndrome), neuromuscular diseases, diabetes.
3. Preoperative cardiac therapy, particularly vasoactive drugs.

4. Patients older than 18 and younger than 45:

- 40 patients underwent surgical intervention under epidural anaesthesia with epidural catheter set at the level of L3–L4 in a lateral lying position.
- 0.5% isobaric bupivacaine, 1 ml per segment, plus 0.1 ml per segment for every 5 cm for patients taller than 150 cm was injected into the epidural space at the rate of 0.3 to 0.75 mL/s. Each patient was given 25 mg of S-(+)-ketamine.
- 40 patients, who composed the control group, underwent surgical intervention under epidural anaesthesia with the catheter set at the level of L3–L4.
- 0.5% isobaric bupivacaine, 1 ml per segment, plus 0.1 ml per segment for every 5 cm for patients taller than 150 cm was injected into the epidural space at the rate of 0.3 to 0.75 mL/s.

The night before the operation, patients were given 5 mg of diazepam perorally, as well as one hour before the operation.

Each patient took prescribed drugs up to the morning before the operation.

Vein pathway (cannula 16G) was set on the forearm before the anaesthesia.

500 mL of 0.9% NaCl was given several minutes before the operation in order to compensate expected decrease of arterial pressure.

Monitoring was performed by indirect measuring of the blood pressure using automatic (sphygmo)manometer before and every 5 minutes after epidural anaesthesia. ECG II lead, pulse oxymetry on fingers and temperature were also measured indirectly. Haemodynamic parameters were heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure

Epidural anaesthesia was performed by puncturing the epidural space and fitting the epidural catheter at the level of L3–L4 using hang drop technique. After identifying the epidural space, 2 mL of 0.9% NaCl were injected and thereafter, the catheter was set 2–3 cm into the epidural space. The catheter was then fixed and the filter was set. Correct position of catheter was checked using aspiration test and test dose. Position had to be checked in order to exclude subarachnoidal position of the catheter. The aspiration test is used to detect whether any blood or liquor are being aspirated, whilst the test dose is used to detect whether an injection of 3 mL of 0.5% bupivacaine caused spinal block. If both tests were positive, then the catheter would be in the subarachnoidal space.

Estimating vasoactive hormones

Blood was taken to determine concentrations of adrenaline, noradrenaline and cortisol 30 minutes before setting the vein pathway and 17–25 minutes after epidural injection.

Non-competitive (enzymeimmunochemistry?) method (Cat Combi ELISA) was used to determine the con-

centrations of catecholamines (adrenaline and noradrenaline). The sample should contain 1.1 mL of plasma or blood, taken by EDTA.

Referent value of adrenalin in plasma is <0.69 nmol/L, whilst for noradrenalin it is <3.55 nmol/L.

Cortisol was estimated by immunoenzymometric determination (IEMA) with luminescent substrate on a machine called Vitros Eci. The sample contained 0.2 mL of serum. Referent value for samples taken in the morning is 138–690 nmol/L.

Statistical methods

Data are shown in tables with median and belonging range.

Differences between the two groups of patients (Group 1 vs. Group 2) were tested by nonparametric test for independent samples (Mann-Whitney U-test). Differences between two measurements of single parameters of the same patients were tested by nonparametric test for dependent samples (Wilcoxon's test of pairs). Differences between three or more measurements of single parameters of the same patients were tested by nonparametric analysis of variance for dependent samples (Friedman ANOVA).

Differences in changes of values of single parameters in several measurements between both groups of patients were tested by variance analysis with repeated measurements.

$P < 0.05$ was taken as the limit of statistical significance.

Statistical processing was carried out on a PC using the programme Statistica 6.

RESULTS

There were no statistically significant ($p > 0.05$) differences between patients regarding age, body mass and height. Mann-Whitney U test ($p = 0.7234$).

TABLE 1

Age, body mass and height.

	Group 1 N = 40 Median (range)	Group 2 N = 40 Median (range)	Mann-Whitney U test
Age	41 (23–45)	42 (19–45)	$p = 0,7234$
Body mass	84 (60–102)	81,5 (50–102)	$p = 0,2910$
Height	179 (158–191)	176 (152–188)	$p = 0,1545$

DISCUSSION

Stress hormones are secreted after the adrenal gland has been stimulated by the sympathetic nervous system (15).

Cortisol and adrenaline secretion are connected. High plasma concentration of catecholamines leads to increased cortisol secretion.

Catecholamines released in stress activate the cardiovascular system (15).

Catecholamines in plasma do not have to be the cause of cardiovascular changes, they can be a result of direct sympathetic area stimulation.

S-(+)-ketamine, administered solely, leads without surgical stress to general stimulation of endocrine stress response, although antidiuretic hormone secretion is not stimulated (9). Bolus application of S-(+)-ketamine leads to an increase in adrenaline, noradrenaline and cortisol concentrations, whilst ACTH concentration increases insignificantly.

Low doses of S-(+)-ketamine, administered intravenously, stimulate endocrine stress response by blocking catecholamine re-uptake in the intrasynaptic cavity and extraneuronal catecholamine re-uptake.

Surgical stress was excluded in our study, measurements were performed before the skin incision. Low analgesic bolus doses of S-(+)-ketamine with 0.5% bupivacaine (Group 2) did not cause an endocrine stress response. Concentrations of adrenaline (Figure 1, 2, $p > 0.05$), noradrenaline (Figure 3, 4, $p > 0.05$) and cortisol (Figure 5, 6, $p > 0.05$) remained within referent values. Adrenaline and noradrenaline concentrations did not increase and, therefore cortisol concentration remained within referent values (Figure. 1–6, Table 2–6).

Togal *et al.* proved that adding S-(+)-ketamine to intrathecally administered bupivacaine, caused no statistically significant changes in arterial blood pressure, heart rate and mean arterial pressure compared to intrathecally administered bupivacaine alone (9).

In our study, adding S-(+)-ketamine to epidurally administered bupivacaine, caused no statistically significant changes in arterial blood pressure, heart rate and mean arterial pressure compared to epidurally administered bupivacaine alone (14).

In our study, administering low analgesic bolus doses of S-(+)-ketamine and 0.5% bupivacaine epidurally did not lead to a statistically significant increase in adrenaline, noradrenaline and cortisol, neither did it cause endocrine stress response with the following cardiovascular changes. The absence of cardiovascular changes noted in former reports agrees with our results (Figures 1–6, Tables 2–5).

Dahl (68) *et al.* proved that setting the epidural nervous block before the skin incision, administering only a local anaesthetic, does not change stress hormone concentrations in plasma.

There were no changes in stress hormone concentrations in plasma in both groups of patients. Only local anaesthetic was given to Group 1, while local anaesthetic with S-(+)-ketamine was given to Group 2.

Adrenalin, noradrenalin and cortisol

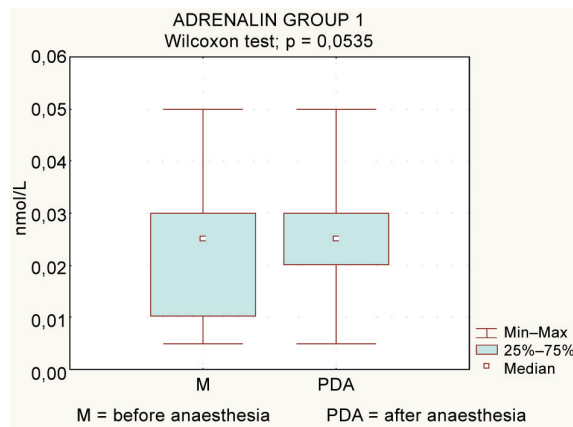


Figure 1. There was no statistically significant difference of adrenalin in plasma between the group of patients before administering anaesthesia and after epidural anaesthesia had been administered.

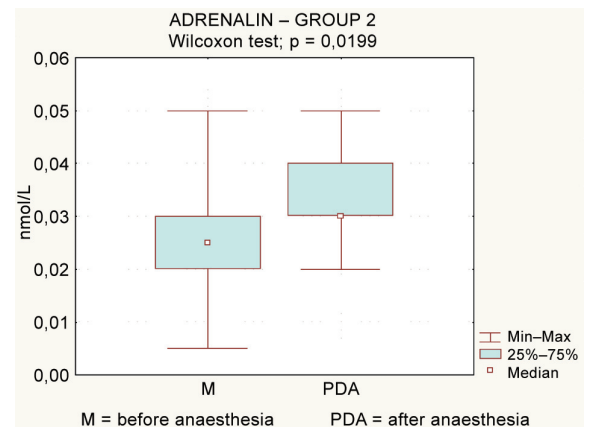


Figure 2. In Group 2, which was given 0.5% bupivacaine and 1 mL (25 mg) of S-(+)-ketamine into the epidural space, adrenalin showed no significant changes compared to when no injections were given into the epidural space. Adrenalin remained within referent values.

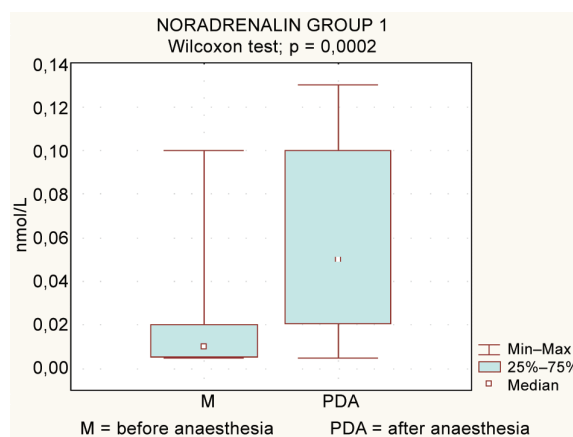


Figure 3. Noradrenalin showed statistically significant differences in Group 1 (bupivacaine 0.5%) when measured during epidural anaesthesia compared to one when measured without epidural anaesthesia, however, it remained within referent values.

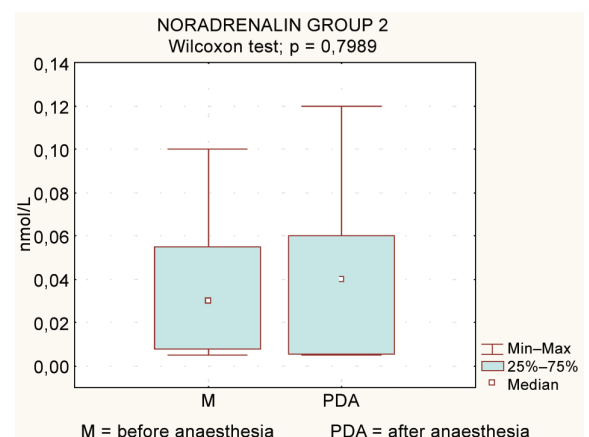


Figure 4. Noradrenalin showed no statistically significant differences in Group 2 (bupivacaine 0.5% + 25 mg S-(+)-ketamine) when measured during epidural anaesthesia. It remained within referent values.

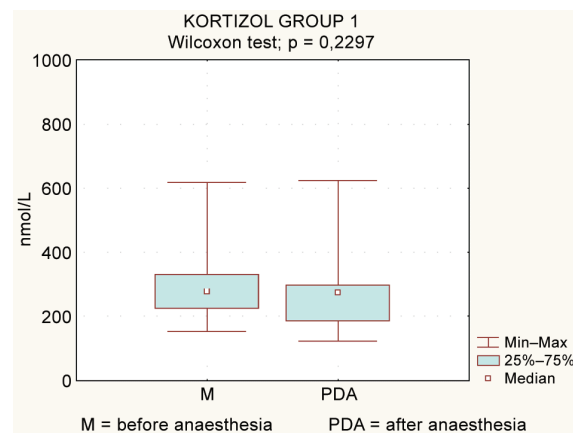


Figure 5. There were no statistically significant changes of cortisol in Group 1, which was given 0.5% bupivacaine into the epidural space. Cortisol remained within referent values.

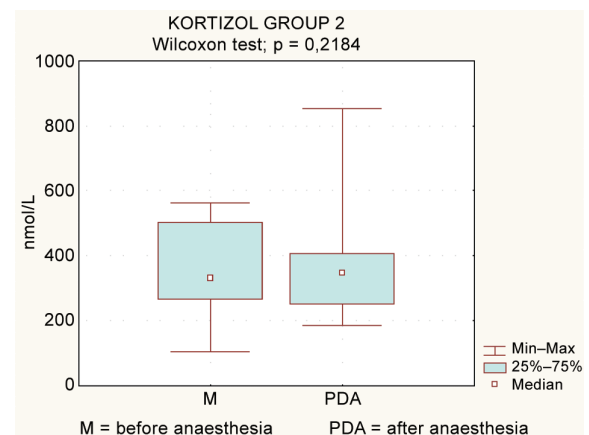


Figure 6. There were no statistically significant changes of cortisol in Group 2, which was given 0.5% bupivacaine and 25 mg S-(+)-ketamine into the epidural space. Cortisol remained within referent values.

Plasma concentrations of catecholamines and cortisol remained within referent values before and after administering epidural anaesthesia (Figures 1–6). Adding low analgesic bolus doses of S-(+)-ketamine, substance that acts like a sympathomimetic and local anaesthetic, has no effect on concentrations of catecholamines and cortisol.

CONCLUSION

Performing epidural nervous block before skin incision, using local anaesthetic, and S-(+)-ketamine, leaves concentrations of stress hormones in plasma within referent values. Adding a low dose of S-(+)-ketamine into the epidural space in combination with 0.5% bupivacaine does not have an effect on the concentration of stress hormones in plasma.

REFERENCES

1. LITZ R 2003 Einfluss des Anästhesieverfahrens auf die postoperative Stressantwort. Deutscher Anästhesiecongress 2003. *Anaesthesist* 52:11
2. ADAMS H A, WERNER C 1997 Von Racemat zum Eutomer (S) Ketamin. *Der Anaesthesist* 46: 1026–1042
3. ADAMS H A, BAUER R, GEBHARD B, MENKE W, BALTES-GÖTZ 1994 TIVA mit S-(+) Ketmain in der orthopädischen Alterschirurgie Endokrine StreBreaktion, Kreislauf- und Aufwacherhalten. *Anaesthesist* 43 (2): 92–100
4. AGNEW W S, LEVINSON S R, BRABSON J S, RAFTERY M A 1978 Purification of the tetrodotoxin-binding component associated with the voltage-sensitive sodium channel from *Electrophorus electricus* electroplax membranes. *Proc Natl Acad Sci USA* 75: 2606–2010
5. ADAMS H A 1997 Endokrine Reaktionen nach S(+) Ketamin. *Der Anaesthesist* 46: 30–37
6. AVOLIO A P, DENG F Q, LI W Q *et al.* 1985 Effects of aging on arterial distensibility in populations with and low prevalence of hypertension: comparison between urban and rural communities in China. *Circulation* 71: 202–210
7. GRAF B M, MARTIN E, BOSNJAK ZJ, STOWE 1997 De. Stereospecific effect of bupivacaine isomers on atrioventricular conduction in the isolated perfused quinea pg heart. *Anesthesiology* 86: 410–419
8. ZIELMANN N, KAZAMAIER S, SSHNULLI S, WEYLAND A 1997 S (+) Ketamin und Kreislauf. *Der Anaesthesist* 46: 43–46
9. TOGAL T, DEMIRBILEK S, GOROGLU A, YAPICI E, ERSOY 2004 O. Effect of S (+) ketmaine added to bupivacaine for spinal anaesthesia for prostate surgery in elderly patients. *Eur J Anaesthesiol* 21(3): 193–7
10. EULER 1972 Pathophysiological aspect of catecholamine production. *Clin Chem* 18: 1445–1448
11. LITZ R, BLEYL J U, FRANK M, ALBRECHT 1999 D M. Kombinierte Anästhesieverfahren *Der Anaesthesist* 48: 359–72
12. DAHL J B, ROSENBERG J, KEHLET H 1992 Effect of thoracic epidural etidocain 1,5% on somatosensory evoked potentials cortisol and glucose during cholecystectomy. *Acta Anaesthesiol Scand* 36(4): 378–82
13. TIMM C L, LINSTEDT U, WEISS T, ZENZ M, MAIER C 2008 Sympathomimetische Effekte auch bei nidrige Dosierung von Esketamin. *Der Anaesthesist* 57: 338–346
14. MIHALJEVIĆ S, ŠAKIĆ K, STAMBOLIA V, MAJEROVIĆ M, MIHALJEVIĆ LJ, GALIĆ J 2007 Haemodynamic effects of epidural anaesthesia with 0,5% bupivacaine and S-(+) Ketamine. *Period biol* 109: 331–334
15. DICK A 2005 Kombinationsanästhesie verindert die Stressantwort auf chirurgischen Reiz-Untersuchungen von hämodynamischen und hormonellen Regulationvorgängen im vergleich zur balancierten Allgemeinenanästhesie. Dissertation medizinischen Fakultät der Charite-Universitätsmedizin, Berlin.