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## SCIENTIFIC ARTICLE

# Sympathetic activity of S-(+)-ketamine low doses in the epidural space

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### KEYWORDS

S-(+)-ketamine;  
Epidural space;  
Low doses;  
Sympathetic activity

### Abstract

**Background and objectives:** S-(+)-ketamine is an intravenous anaesthetic and sympathomimetic with properties of local anaesthetic. It has an effect of an analgetic and local anaesthetic when administered epidurally, but there are no data whether low doses of S-(+)-ketamine have sympathomimetic effects. The aim of this study was to determine whether low doses of S-(+)-ketamine, given epidurally together with local anaesthetic, have any effect on sympathetic nervous system, both systemic and below the level of anaesthetic block.

**Methods:** The study was conducted on two groups of patients to whom epidural anaesthesia was administered to. Local anaesthesia (0.5% bupivacaine) was given to one group (control group) while local anaesthesia and S-(+)-ketamine were given to other group. Age, height, weight, systolic, diastolic and mean arterial blood pressure were measured. Non-competitive enzyme immunochemistry method (Cat Combi ELISA) was used to determine the concentrations of catecholamines (adrenaline and noradrenaline). Immunoenzymometric determination with luminescent substrate on a machine called Vitros Eci was used to determine the concentration of cortisol. Pulse transit time was measured using photoplethysmography. Mann–Whitney *U*-test, Wilcoxon test and Friedman ANOVA were the statistical tests. Blood pressure, pulse, adrenaline, noradrenaline and cortisol concentrations were measured in order to estimate systemic sympathetic effects.

**Results:** 40 patients in the control group were given 0.5% bupivacaine and 40 patients in the test group were given 0.5% bupivacaine with S-(+)-ketamine. Value  $p < 0.05$  has been taken as a limit of statistical significance.

**Conclusions:** Low dose of S-(+)-ketamine administered epidurally had no sympathomimetic effects; it did not change blood pressure, pulse, serum hormones or pulse transit time. Low dose of S-(+)-ketamine administered epidurally did not deepen sympathetic block. Adding 25 mg of S-(+)-ketamine to 0.5% bupivacaine does not deprive sympathetic tonus below the level of epidural block at the moment of most expressed sympathetic block and has no effect on sympathetic tonus above the block level.

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**PALAVRAS-CHAVE**

Cetamina S-(+);  
Espaço epidural;  
Doses baixas;  
Atividade simpática

**Atividade simpática de cetamina S-(+) em doses baixas no espaço epidural****Resumo**

*Justificativa e objetivos:* cetamina S-(+) é um anestésico intravenoso e simpaticomimético com propriedades de anestésico local. Tem efeito analgésico e de anestésico local quando administrada por via epidural, mas não há dados que relatem se cetamina S-(+) em doses baixas tem efeitos simpaticomiméticos. O objetivo deste estudo foi determinar se cetamina S-(+) em doses baixas, administrada por via epidural em combinação com anestésico local, tem algum efeito sobre o sistema nervoso simpático, tanto sistêmico quanto abaixo do nível do bloqueio anestésico.

*Métodos:* o estudo foi conduzido com dois grupos de pacientes submetidos à anestesia epidural. Anestesia local (bupivacaína a 0,5) foi administrada a um grupo (controle), enquanto anestesia local em combinação com cetamina S-(+) foi administrada ao outro grupo (teste). Idade, altura, peso, pressão arterial sistólica e diastólica e pressão arterial média foram medidos. O método imunológico de inibição enzimática não competitiva (Cat Combi Elisa) foi usado para determinar as concentrações de catecolaminas (adrenalina e noradrenalina). O ensaio imunoenzimométrico com substrato luminescente em uma máquina chamada Vitros Eci foi usado para determinar a concentração de cortisol. O tempo de transição do pulso foi medido com fotoplethysmografia. Para análise estatística, os testes de Wilcoxon, *U* de Mann-Whitney e Anova de Friedman foram usados. Pressão arterial, pulso e concentrações de adrenalina, noradrenalina e cortisol foram medidos para estimar os efeitos simpáticos sistêmicos.

*Resultados:* receberam bupivacaína a 0,5% 40 pacientes do grupo controle e 40 do grupo teste receberam bupivacaína a 0,5% com cetamina S-(+). Um valor de  $p < 0,05$  foi aceito como o limite de significância estatística.

*Conclusões:* dose baixa de cetamina S-(+) administrada por via epidural não teve efeitos simpaticomiméticos; não alterou a pressão arterial, o pulso, os hormônios séricos ou o tempo de transição de pulso. Dose baixa de cetamina S-(+) administrada por via epidural não aprofundou o bloqueio simpático. A adição de 25 mg de cetamina S-(+) à bupivacaína a 0,5% não deprimiu o tônus simpático abaixo do nível do bloqueio epidural no momento máximo de bloqueio simpático e não tem efeito sobre o tônus simpático acima do nível do bloqueio.

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**Introduction**

Sympathetic activity regulates the blood vessels' tonus and is connected with haemodynamic changes.<sup>1</sup>

Epidural sympathetic block lessens blood vessels' vasoconstriction of lower extremities leading to:

- (a) lessened resistance in arterioles and increased blood flow through them
- (b) increased amount of blood flow due to reduced blood vessels' tonus
- (c) increased blood vessels compliance – change of blood vessels' volume per change of pressure unit – due to combined decrease of vascular tonus.<sup>1,2</sup>

Various drugs that have effect on paravertebral spinal nerves, spinal ganglia, ventral and dorsal spinal roots and spinal cord are given into epidural space. They block sensor and motor fibres below the point at which anaesthetic was applied.<sup>2</sup>

S-(+)-ketamine, given intravenously, causes prominent cardiovascular stimulation – increasing minute volume of the heart, myocardial oxygen consumption, heart rate, mean arterial and pulmonary pressure and central venous pressure.<sup>3-5</sup>

Low doses of S-(+)-ketamine, given intravenously, cause haemodynamic changes within 5 min. Arterial pressure gets increased 10 min after injection and is averagely increased by 23% maximum. Heart rate is averagely maximally increased 15 min after injection. Normalisation occurs after 45 min.

Photoplethysmography is a method that investigates blood volume pulsations by detection and real-time analysis of optic radiation, presenting periodical changes of light transmission through skin which occur due to changes in tissue and arterial volume that are induced by the heart. Indirect method for estimating arterial compliance dependent on sympathetic activity is measuring the pulse transmission time (*Nitzan*).<sup>6</sup> Pulse transit time reflects changes in sympathetic activity below the level of anaesthetic block.<sup>5,7</sup>

Lumbar epidural anaesthesia, administered for operations of lower abdomen and lower extremities, is followed by lessened sympathetic activity in lower abdomen, lower extremities and toes, so that pulse transit time is extended after applying epidural anaesthesia.<sup>8-10</sup>

Endocrine stress response in anaesthesiology and surgery is mediated through:

- Sympathoadrenergic system with adrenaline and noradrenaline

- Neurohypothalamic gland with anti-diuretic hormone (ADH)
- Adenohypothalamic gland – supraadrenal gland axis with adrenocorticotropic hormone (ACTH) and cortisol.<sup>11</sup>

Bolus application of S-(+)-ketamine leads by itself, without surgical stress, to general stimulation of endocrine stress response. Adrenaline and noradrenaline rise, while ACTH rises insignificantly and ADH does not rise at all. "Dissociative anaesthesia", caused by ketamine, represents endogenous psychical stress and contributes to stress response.<sup>4,11,12</sup>

Ketamine inhibits catecholamine re-uptake on sympathetic end-plate, which can explain the increased effects of endo- and exogenous catecholamines (adrenaline and noradrenaline concentration rises). Adrenaline,  $\beta$ -mimetic, affects heart and metabolism, while noradrenaline,  $\alpha$ -mimetic, affects blood vessels and blood stream.<sup>12</sup> Epidural anaesthesia prevents catecholamine secretion from adrenal gland that happens because of stimulation from operation field. Epidural anaesthesia has no effect on secretion of cortisol, probably because afferent vagus paths are not blocked.

## Materials and methods

This study was conducted with approval of ethical committee of Clinical hospital Zagreb and after all patients gave their written informed consent.

### Choosing patients

Research of the sympathetic activity was made on 80 patients aged 18–45 years ASA II who underwent surgical intervention under epidural anaesthesia. Patients were introduced to course and aims of the study and drugs that are going to be used through 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 epidural space and group 2 who received an injection of 0.5% bupivacaine and low dose (25 mg) of S-(+)-ketamine into epidural space.

Excluding criteria were:

1. Contraindications for EDA anaesthesia
2. Accompanying cardiovascular diseases (arteriosclerosis, hypertension, Raynaud syndrome), neuromuscular diseases, diabetes
3. Patients whose prescription therapy were vasoactive drugs
4. Patients younger than 18 years and older than 45 years.
  - 40 patients underwent surgical intervention under epidural anaesthesia with epidural catheter that was set on the level of L3–L4 in lateral lying position
  - 0.5% isobaric bupivacaine, 1 mL per segment, plus 0.1 mL per segment for every 5 cm for patients higher than 150 cm was given into epidural space
  - Control group, consisting of 40 patients, underwent surgical intervention under epidural anaesthesia with catheter set on the level of L3–L4

- 0.3 to 0.75 mL of 0.5% isobaric bupivacaine was given into epidural space per second. 1 mL per segment, plus 0.1 mL per segment for every 5 cm for patients higher than 150 cm.

## Anaesthesia and monitoring

The night before the operation, patients were given 5 mg of diazepam orally, as well as 1 h before the operation.

Every patient took eventually prescribed drugs up to the morning before the operation.

Vein pathway (cannula 16 G) was set on a 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

Indirect measuring of the blood pressure using automatic manometer before and every 5 min after epidural anaesthesia, ECG II lead, pulse oximetry on fingers and temperature.

## Haemodynamic parameters

- heart rate
- systolic blood pressure
- diastolic blood pressure
- mean arterial pressure

## Epidural anaesthesia

Epidural space was punctured and fitted with epidural catheter on the level of L3–L4 using hanging drop technique. After epidural space was identified, 2 mL of 0.9% NaCl were injected and after that, the catheter was set 2–3 cm into the epidural space. Catheter was fixated and the filter was set.

Correct position of catheter is checked using aspiration test – neither blood nor liquor is being aspirated – and test dose – 3 mL of 0.5% bupivacaine – in order to exclude the subarachnoid catheter position.

## Vasoactive hormones

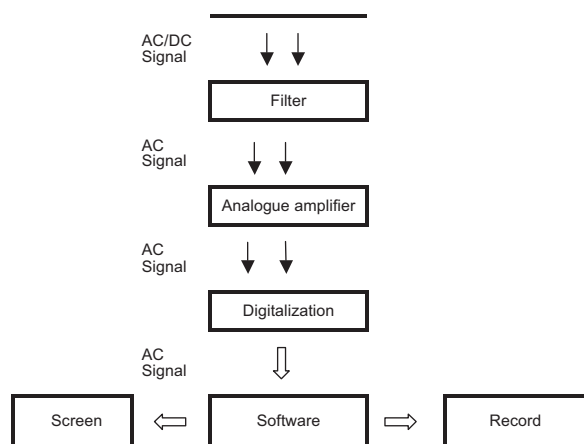
Blood was taken to determine concentrations of adrenaline, noradrenaline and cortisol 30 min before setting vein pathway and again between 17 and 25 min after epidural injection.

Non-competitive enzyme immunochemistry method (Cat Combi ELISA) was used to determine the concentrations of catecholamines (adrenaline and noradrenaline). Sample should contain 1.1 mL of plasma or blood, taken by EDTA.

Referent value of adrenaline in plasma is <0.69 nmol/L, while for noradrenaline it is <3.55 nmol/L.

Immunoenzymometric determination (IEMA) with luminescent substrate on a machine called Vitros Eci was used to determine the concentration of cortisol. Sample contained 0.2 mL of serum. Referent value in the morning is 138–690 nmol/L.

Biopac system configuration for measuring PPG signal



**Figure 1** Biopac system configuration for measuring PPG signal.

### Photoplethysmographic measurement technique (PPG)

PPG measurements were done on the second toe using Biopac system – SS4LA pulse Plethysmograph Transducer which uses infrared light source and photo detector (Emitter/detector wavelength  $860 \pm 900$  nm). Infrared light is modulated to a frequency of 3 kHz. Detector's output is filtered through a narrow tube on to 3 kHz, in order to avoid detecting the light from the background. Demodulated detector's output enables PPG signal, that is filtered through low-passing filter (Cut-off filter, wavelength 800 nm), to reduce high frequency noise (Fig. 1).

### Recording technique

Patient's leg was laid down to surface and fixated. PPG probe was fixated on to second toe in such way that fixation did not alter received signal.

PPG signal was measured 3 min, monitored in order to correct dislocations of a sensor or artefacts and saved as a digital record for further analysis.

First standard ECG lead was gathered and monitored simultaneously with recording PPG signal.

After every examination, PPG curves were shown on the screen and the part that includes 50 PPG pulses with relatively low fluctuations. The first standard ECG lead curve simultaneously was shown.

Recorded data were marked in separate sequences of 180 s and saved in separated files. Software enables repeated display of unprocessed data sequence as continuous signal. There is a possibility of selecting unprocessed data which were used in further analysis. Screen was used to display data. It shows cut of measurement in time. Y axis shows signal power. Cursor can be used to move signal cuts in time in both directions. It is possible to get a review of the whole recorded signal and any time point can be analysed into details.

### Times of measuring PPG signal

1. T1 – 5–10 min before epidural injection
2. T2 – just before administering 500 mL of infusion
3. T3 – 17–25 min after epidural injection

Patient's position: 30% supination towards horizontal, patient lies still on an operation desk.

### Statistical methods

Data are shown in Table 1 with median and belonging range.

Differences between the two patient groups (group 1 vs. group 2) were tested with nonparametric test for independent samples (Mann–Whitney *U*-test).

Differences between two single parameters measurements of the same patients were tested with nonparametric test for dependent samples (Wilcoxon test).

Differences between three or more single parameters measurements of the same patients were tested with nonparametric analysis of variance for dependent samples (Friedman ANOVA).

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

Value  $p < 0.05$  has been taken as a limit of statistical significance.

Statistical processing has been made on a PC using programme called Statistica 6.

### Results

It is obvious that both groups of patients were homogeneous in relation to age, weight and height which enabled better comparison and more accurate results.

Groups contained young people with well developed compensatory mechanisms. There were no statistically significant differences between patients regarding age, body mass and height. Mann–Whitney *U*-test ( $p = 0.7234$ ).

The dose of S(+)-ketamine given into epidural space was 0.326 mg/kg; altogether given volume of S(+)-ketamine given into epidural space respective to homogeneity of groups was 14.5 mL of 0.5% bupivacaine (1.14 mg/kg) and 1 mL (25 mg) of S(+)-ketamine, as regards, 0.326 mg/kg bm (Fig. 2).

The results show that adding S(+)-ketamine to 0.5% bupivacaine into epidural space before the skin incision was performed did not cause any statistically significant changes of systolic blood pressure (Fig. 3).

The results show that adding S(+)-ketamine to 0.5% bupivacaine into epidural space before the skin incision is performed did not cause any statistically significant changes of diastolic blood pressure (Fig. 4).

Heart rate had been measured before the skin incision was performed and before administering epidural anaesthesia, as regards, before 0.5% bupivacaine was administered to the group 1 and before 0.5% bupivacaine plus 25 mg S(+)-ketamine were administered to the group 2. It was measured again after 5, 10, 15 and 20 min after administering (Figs. 5–10).

**Table 1** Age, weight 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)	$p=0.7234$
Weight (kg)	84 (60–102)	81.5 (50–102)	$p=0.2910$
Height (cm)	179 (158–191)	176 (152–188)	$p=0.1545$

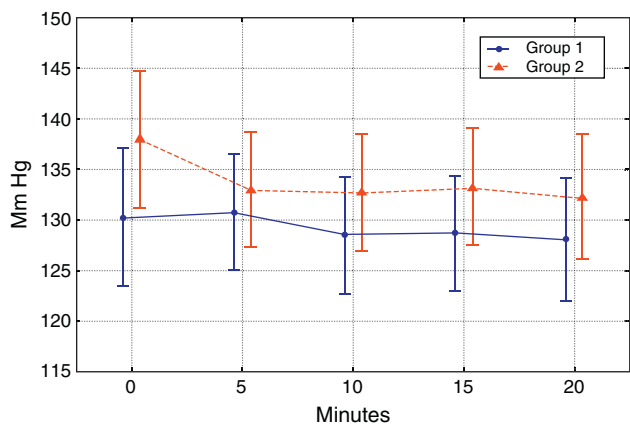
**Pulse transit time**

Pulse transit time presents the time interval between R wave on ECG and first value on PPG signal curve (Tables 2 and 3).

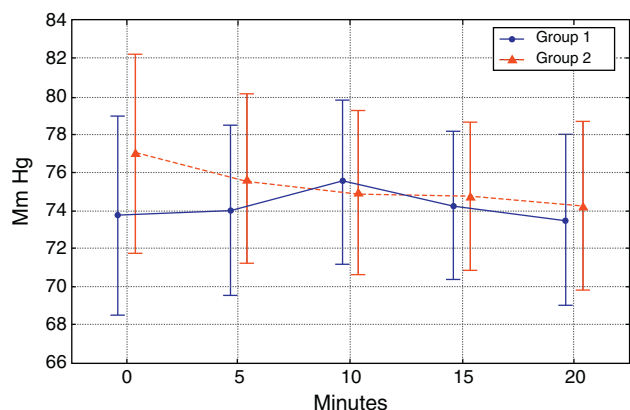
Pulse transit time in both groups did not change significantly after administering crystalloid infusion before anaesthesia ( $p=0.9031$ , Mann-Whitney U-test) (Fig. 11).

Pulse transit time to toe changed significantly in both groups of patients after administering epidural anaes-

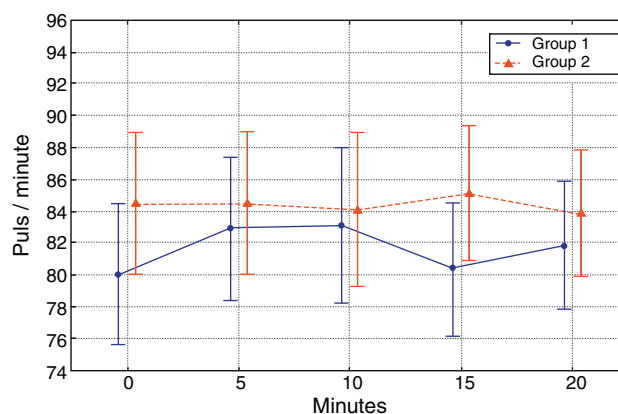
thesia, compared to state before administering epidural anaesthesia (Mann-Whitney test). Group 1:  $p=0.007$ , group 2:  $p=0.0079$ . However, there was no significant difference in specified measurement points between group 1 and group 2 (repeated ANOVA test). There were no significant differences of pulse transit time between groups that were



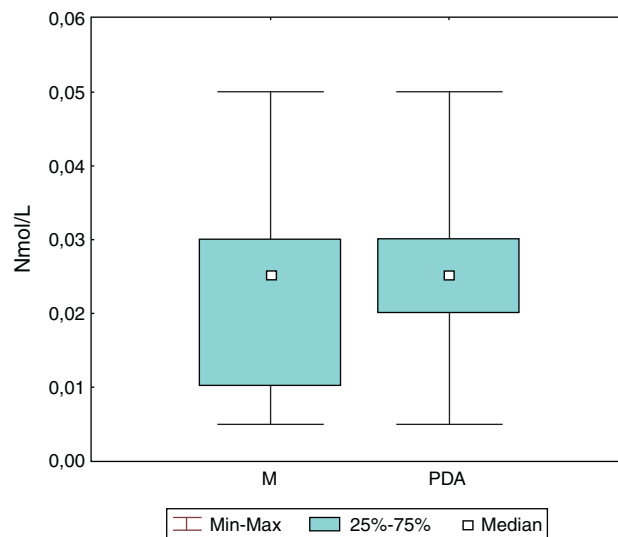
**Figure 2** Systolic pressure. There were no statistically significant differences ( $p=0.22696$ ) of systolic pressure between group 1 and group 2 in specified measure marks (repeated measures ANOVA).



**Figure 3** Diastolic pressure. There were no statistically significant differences ( $p=0.40124$ ) of diastolic blood pressure between the groups of patients in specified measure marks (repeated measures ANOVA).



**Figure 4** Pulse. There were no statistically significant differences ( $p=0.39709$ ) in heart rate between the groups at the same time intervals (repeated measures ANOVA).



**Figure 5** Adrenaline group 1. There were not statistically significant changes ( $p=0.0535$ ) of adrenaline concentrations after administering adrenaline epidurally. Adrenaline remained within referent values (Wilcoxon test). M= before anaesthesia; PDA= after anaesthesia.

**Table 2** Group 1. Pulse transit time.

	Before anaesthesia N = 40 Median (range)	Anaesthesia N = 40 Median (range)	Wilcoxon's pair test
$\Delta T$	0.3000 (0.2350–0.3458)	0.3050 (0.2667–0.3600)	$p = 0.0070$

**Table 3** Group 2. Pulse transit time.

	Before anaesthesia N = 40 Median (range)	Anaesthesia N = 40 Median (range)	Wilcoxon's pair test
$\Delta T$	0.3000 (0.2350–0.3458)	0.3043 (0.2436–0.3795)	$p = 0.0071$

administered epidural anaesthesia, despite the fact that group 2 was administered low doses of S-(+)-ketamine epidurally ( $p = 0.7043$ , Mann-Whitney *U*-test).

## Discussion

Spontaneous changes of heart rate, blood pressure and other cardiovascular system parameters are well known.<sup>13–15</sup> These changes are classified depending on their frequency and each frequency of changes comes from different activity of two autonomic nervous system branches – sympathetic and parasympathic.<sup>16</sup>

Ketamine causes prominent cardiovascular stimulation increasing minute volume of the heart, myocardial oxygen consumption, heart rate, mean arterial and pulmonary pressure and central venous pressure.<sup>13,14,16,17</sup>

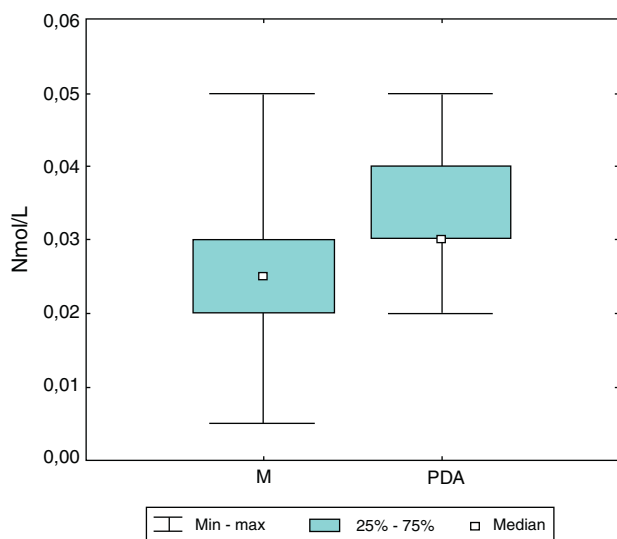
Adding S-(+)-ketamine to bupivacaine intrathecally did not cause significant changes of arterial pressure compared to group which was given only bupivacaine.<sup>12</sup>

Arterial compliance on fingers was increased after sympathetic block.<sup>6–9</sup>

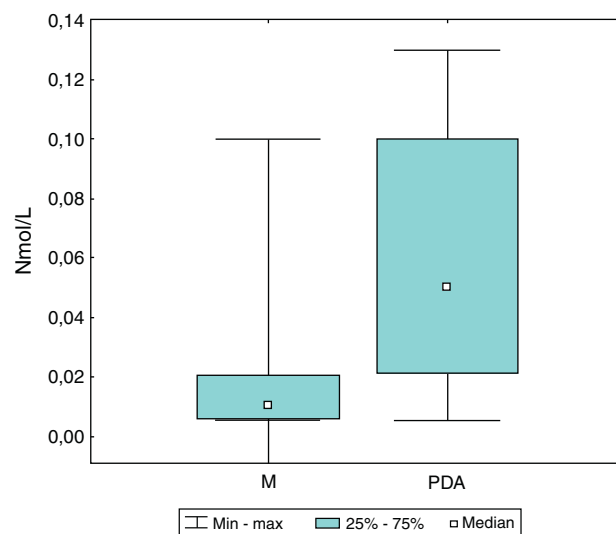
Togal<sup>18</sup> reports that S-(+)-ketamine administered intrathecally to elder patients does not cause negative haemodynamic effects.

Higher sympathetic activity above the place of block results in increased tonus and decreased compliance of cutaneous arteries.<sup>6–9</sup>

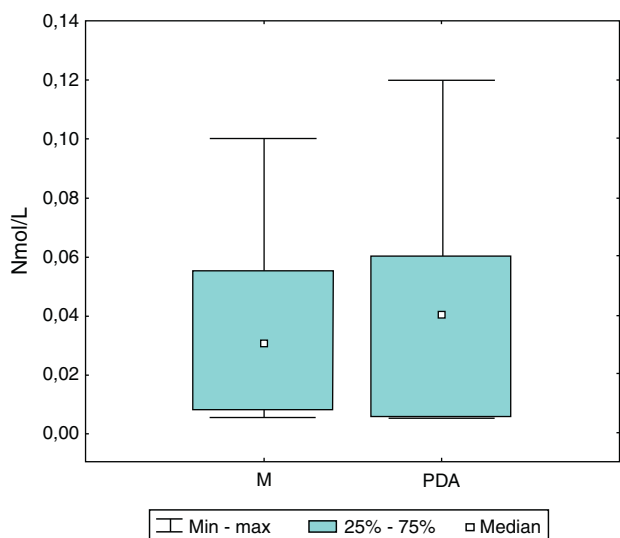
Blood accumulation in lower body parts after applying epidural sympathetic block did not significantly change systolic, diastolic or mean arterial pressure neither in group 1 (epidural space – 0.5% bupivacaine) nor in group 2 (epidural space – 0.5% bupivacaine and S-(+)-ketamine). There was



**Figure 6** Adrenaline group 2. Concentrations of adrenaline remained within referent values ( $p = 0.0199$ , Wilcoxon test). M = before anaesthesia; PDA = after anaesthesia.



**Figure 7** Noradrenaline group 1. Noradrenaline showed statistically significant differences ( $p = 0.0002$ ) in group 1 when measured during epidural anaesthesia compared to one measured without epidural anaesthesia; however, it remained within referent values (Wilcoxon test). M = before anaesthesia; PDA = after anaesthesia.

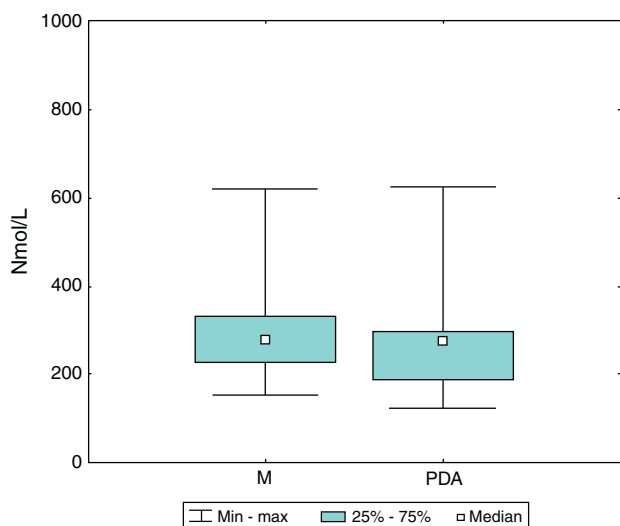


**Figure 8** Noradrenaline group 2. Noradrenaline showed no statistically significant differences ( $p=0.7989$ ) in group 2 when measured during epidural anaesthesia. It remained within referent values (Wilcoxon test). M=before anaesthesia; PDA=after anaesthesia.

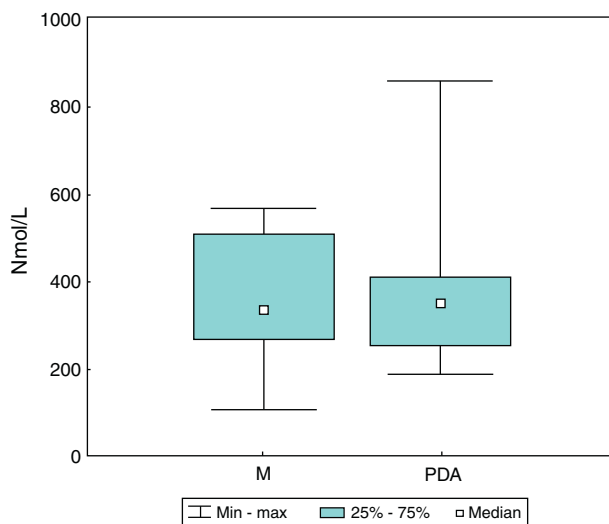
no statistically significant difference between group 1 and 2 in specified measure marks (repeated ANOVA test).

Despite adding S-(+)-ketamine into epidural space, there were no blood pressure and heart rate changes during anaesthesia. Results obtained at patients who were given S-(+)-ketamine epidurally are similar to ones Togonal obtained when bupivacaine and S-(+)-ketamine were given intrathecally. Negative haemodynamic effects of epidurally injected S-(+)-ketamine in group 2 were not caused either by central or neuroaxial activity.

Preoperational fluid compensation is important for patient’s intraoperational haemodynamic stability. Sufficient intravasal volume is inevitable for blood pressure



**Figure 9** Cortisol group 1. There were no statistically significant changes ( $p=0.2297$ ) of cortisol in group 1. Cortisol remained within referent values (Wilcoxon test). M=before anaesthesia; PDA=after anaesthesia.

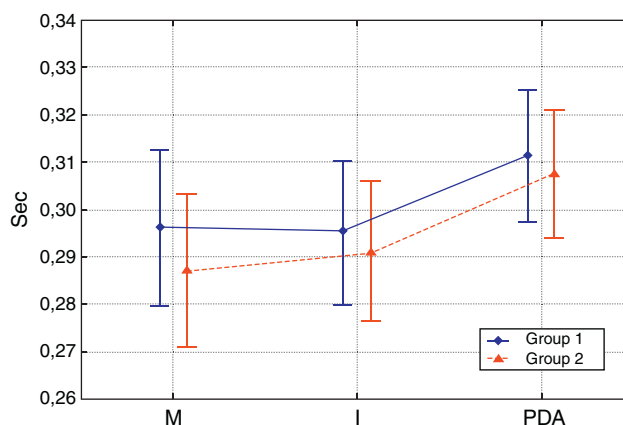


**Figure 10** Cortisol group 2. There were no statistically significant changes ( $p=0.2184$ ) of cortisol in group 2, which was given 0.5% bupivacaine into epidural space. Cortisol remained within referent values (Wilcoxon test). M=before anaesthesia; PDA=after anaesthesia.

stability and adequate tissue perfusion. Only because of not taking food and water from 10pm the day before the operation, there is a preoperative fluid deficit of averagely 1400 mL in adults. Crystal isotonic solutions are distributed into extracellular space – out of 1000 mL of infused crystal solutions, after 1 h only 200–300 mL is still placed intravasally.<sup>19</sup> Intravasal volume is decisive for haemodynamic stability.

Both groups of patients were given 500 mL of crystalloids preoperatively in order to compensate the blood pressure drop caused by blocking sympathetic below the level of sympathetic block.

Because crystalloid infusion had been administered into epidural space before local anaesthetic, the infused crystalloid remained within intravascular space and did not



**Figure 11** Pulse transit time before administering anaesthesia. Pulse transit time between the group 1 and group 2 did not statistically significantly change ( $p=0.4016$ ) before administering anaesthesia (Mann-Whitney U-test). M=before anaesthesia; PDA=after anaesthesia.

redistribute into extracellular space. That caused less drop of blood pressure despite sympathetic block.

Since the patients were young and had well developed compensatory mechanisms, combination of preoperative volume compensation and good compensatory mechanisms contributed to haemodynamic stability in both groups of patient.

Anaesthetic primarily takes effect on nervous system, but is undoubtedly related with effect on endocrine system. Catecholamines adrenaline and noradrenaline and cortisol are important stress hormones which are being excreted as an outcome of different stress stimuli. 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 preoperatively. This can be avoided by talking to the patient and explaining him the planned course of anaesthesia and operation as an adequate premedication.<sup>11</sup>

In our study, an interview was done with the patients and anaesthesia protocol was explained. Patients were introduced to medicaments that will be used during anaesthesia and were given premedication. In addition to that, they gave their written informed consent.

In former studies different local anaesthetics were compared and results have shown that there are differences in their effect on concentrations of catecholamines in plasma.

When S-(+)-ketamine is intrathecally added to bupivacaine, there are no significant changes of arterial pressure compared to when only bupivacaine is administered intrathecally.<sup>18</sup>

Togal's<sup>18</sup> report indicates that combinations of bupivacaine and S-(+)-ketamine, administered intrathecally, give results that match our results. Bupivacaine and low dose of S-(+)-ketamine, administered epidurally, do not cause significant changes of heart rate, systolic, diastolic and mean arterial pressure, which are the reflection of cardiovascular sympathomimetic activity and concentration of stress hormones in plasma.

Dahl et al.<sup>20</sup> proved that setting epidural nervous block before the skin incision, using only local anaesthetic, does not significantly change concentration of stress hormones in plasma.

Our study shows that concentrations of catecholamines and cortisol in plasma remain within referent values before and after administering lumbar epidural anaesthesia using only bupivacaine and administering lumbar epidural anaesthesia using bupivacaine and S-(+)-ketamine. Stress response was absent and concentrations of stress hormones were within referent values in both groups of our patients before and after administering epidural anaesthesia. We have to emphasise that measurements were done before the skin incision, so that surgical stress is excluded.

### Pulse transit time

Babchenko<sup>2</sup> comes to a cognition that lumbar epidural anaesthesia, administered for operations of lower abdomen and lower extremities, is followed by lessened sympathetic activity in lower abdomen, lower extremities and toes, so that pulse transit time is extended after applying epidural anaesthesia.

Elyad<sup>21</sup> points out that pulse transit time changes (pulse delay time) were significantly longer at higher concentrations of local anaesthetic. This parameter depends on dose and can reflect haemodynamic changes induced by sympathetic block with higher reliability than changes of blood pressure and temperature.

Low dose of S-(+)-ketamine, administered epidurally, did not change the pulse transit time.

Sigham points out that pulse transit time changes reflect autonomic response to noxious stimuli and changes of anaesthesia depth independently of heart rate. Pulse transit time at our patients reflects only the effect of lumbar sympathetic block caused by administering 0.5% bupivacaine to group 1 and 0.5% bupivacaine and low dose (25 mg) of S-(+)-ketamine to group 2 ( $p > 0.90138$ ).

In our study, there were no noxious stimuli during pulse transit time measuring, so there was no autonomic nervous system response to them. Therefore, there is no statistically significant difference of pulse transit time between patients anaesthetised with 0.5% bupivacaine and patients anaesthetised with 0.5% bupivacaine and low dose (25 mg) of S-(+)-ketamine ( $p > 0.903108$ ).

Nitzan<sup>6</sup> cites that lessening of pulse transit time relative to patient's age is attributed to direct structural lessening of arterial compliance, not the functional effects of increased blood pressure combined with ageing, while parameters of pulse transit time do not depend on diastolic pressure, despite measurement are done at the end of diastole.

In our study, structural lessening of arterial compliance in respect of patient's age could not affect pulse transit time.

Average age of group 1 was 41 (23–45). Average age of group 2 was 42 (19–45). Therefore, there is no statistically significant difference (Mann–Whitney *U*-test,  $p = 0.7234$ , Table 1) which would affect pulse transit time decrease.

Babchenko<sup>2,6</sup> points out that arterial compliance lessens because of higher sympathetic activity which stretches arterial wall and increases pulse pressure velocity. Our patients were epidurally injected 0.5% bupivacaine which caused lessening arterial compliance, which was visible from prolonged pulse transit time in specified measurement points in both groups of patients (Wilcoxon test, ANOVA in specified measurement points, graph 15). Low dose of S-(+)-ketamine (25 mg) combined with 0.5% bupivacaine did not lead to additional arterial compliance lessening, which can be seen from changes of pulse transit time. Pulse transit time is an indirect scale for arterial compliance. When S-(+)-ketamine is administered intravenously, blood pressure and striking blood volume get increased. However, we did not find those changes on PPG curve when S-(+)-ketamine was administered epidurally in addition to bupivacaine, because pulse transit time was not statistically significantly changed.

Our results have shown that S-(+)-ketamine did not take effect on sympathetic block, so we can conclude that it did not deepen sympathetic block.

### Conclusion

Adding 25 mg of S-(+)-ketamine to 0.5% bupivacaine epidurally does not deprive sympathetic tonus under the level of epidural block at the moment of most expressed



sympathetic block and sympathetic tonus above the level of sympathetic block. In other words, adding low dose of S-(+)-ketamine epidurally in combination with 0.5% bupivacaine does not deprive haemodynamics. There are no changes of pulse, systolic, diastolic and mean arterial pressure when low dose (25 mg) of S-(+)-ketamine is administered epidurally in combination with 0.5% bupivacaine. Setting central nervous block before skin incision, using local anaesthetic, and S-(+)-ketamine, leaves concentrations of stress hormones in plasma within referent values. Adding low dose of S-(+)-ketamine into epidural space in combination with 0.5% bupivacaine does not have effect on concentration of stress hormones in plasma.

There is no change of sympathetic activity under the level of block, neither area, nor pulse transit time on PPG curve if low dose (25 mg) of S-(+)-ketamine is added to 0.5% bupivacaine.

### Conflicts of interest

The authors declare no conflicts of interest.

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