

Effect of ketamine, an NMDA-receptor antagonist, on gastric myoelectric activity in experimental pigs

Účinek ketaminu, antagonisty NMDA-receptoru, na žaludeční myoelektrickou aktivitu experimentálních prasat

J. Bureš^{1,2,3}, J. Květiná¹, V. Radochová⁴, M. Zavoral^{2,3}, Š. Suchánek^{2,3}, S. Rejchrt⁵, M. Vališ⁶, V. Knoblochová¹, J. Žďárová Karasová^{1,7}, O. Soukup¹, D. Kohoutová^{1,8}

¹Biomedical Research Centre, University Hospital Hradec Králové

²Institute of Gastrointestinal Oncology, Military University Hospital Praha

³Department of Medicine, Charles University, First Faculty of Medicine, Praha and Military University Hospital Praha

⁴Animal Laboratory, University of Defence, Faculty of Military Health Sciences, Hradec Králové

⁵2nd Department of Internal Medicine – Gastroenterology, Charles University, Faculty of Medicine in Hradec Králové and University Hospital Hradec Králové

⁶Department of Neurology, Charles University, Faculty of Medicine in Hradec Králové and University Hospital Hradec Králové

⁷Department of Toxicology and Military Pharmacy, University of Defence, Faculty of Military Health Sciences, Hradec Králové

⁸The Royal Marsden NHS Foundation Trust, London

Summary: Introduction: Preclinical studies in experimental pigs are carried out mostly under general anaesthesia. Ketamine is commonly used for induction of anaesthesia. However, there are concerns that ketamine, an NMDA-receptor antagonist, may influence gastric motor function. The aim of this study was to investigate porcine gastric myoelectric activity by means of electrogastrography (EGG). **Methods:** Seventeen female animals (mean weight 36.2±3.8 kg) were enrolled. Drugs used for induction of anaesthesia were: Group A (n=5): medetomidine 0.1 mg/kg i.m.; butorphanol 0.3 mg/kg i.m.; midazolam 0.3 mg/kg i.m.; Group B (n=6): azaperon 2.2 mg/kg i.m.; Group C (n=6): ketamine 20 mg/kg i.m.; azaperon 2.2 mg/kg i.m., followed in all groups by i.v. 1% propofol (repeated one-mL boluses, 10–12 mL in total). EGG recording started 15 min. after the induction administration and lasted 30 min. Results were evaluated as the dominant frequency of gastric slow waves (DF) and EGG power (areas of amplitudes). **Results:** In total, 510 one-minute EGG intervals were assessed. DFs were (mean ± standard deviation): 1.4±0.4 (Group A), 1.3±0.3 (Group B) and 0.2±0.1 cycles per min. (Group C). The differences between group C and groups A and B were statistically significant ($p < 0.001$). Median power (IQR) was 0.13 (0.02–0.44; Group A), 0.13 (0.03–0.54; Group B) and 0.30 V² (0.07–1.44; Group C). The difference between groups A and C was of borderline significance ($p = 0.066$; type 2 error beta 0.295). **Conclusions:** Ketamine, administered even in a single intramuscular dose, affected myoelectric function of the porcine stomach. Therefore, it should be avoided in gastrointestinal motility studies in experimental pigs.

Key words: ketamine – NMDA (N-methyl-D-aspartate)-receptor antagonist – electrogastrography – myoelectrical activity – experimental pigs

Souhrn: Úvod: Téměř všechny preklinické studie u experimentálních prasat je třeba provádět v celkové anestezii. Ketamin je běžně používán jako úvod do anestezie. Avšak dosud nezodpovězenou otázkou je, zda ketamin, antagonist NMDA-receptorů, ovlivňuje motorické funkce žaludku. Cílem této práce bylo vyšetřit žaludeční myoelektrickou aktivitu prasete metodou elektrogastrografie (EGG). **Metody:** Do studie bylo zařazeno 17 samic *Sus scrofa f. domestica* (průměrná hmotnost 36,2 ± 3,8 kg). Pro úvod do anestezie byla použita různá léčiva: skupina A (n = 5): medetomidin 0,1 mg/kg i.m.; butorfanol 0,3 mg/kg i.m.; midazolam 0,3 mg/kg i.m.; skupina B (n = 6): azaperon 2,2 mg/kg i.m.; skupina C (n = 6): ketamin 20 mg/kg i.m.; azaperon 2,2 mg/kg i.m. Celková anestezie ve všech skupinách pokračovala podáváním 1% propofolu (opakované 1 ml bolusy, celkem 10–12 ml i.v.). Záznam EGG začal za 15 min. po úvodu do anestezie a trval 30 min. Výsledky byly vyhodnoceny jako dominantní frekvence pomalých žaludečních vln (DF) a plochy pod křivkou (EGG power). **Výsledky:** Celkem bylo vyhodnoceno 510 jednodominutových EGG intervalů (každý dvakrát: DF a power). DF byly (průměr ± směrodatná odchylka): 1,4 ± 0,4 (skupina A), 1,3 ± 0,3 (skupina B) a 0,2 ± 0,1 cykly/min. (skupina C). Rozdíly mezi skupinou C a skupinami A a B byly statisticky významné ($p < 0,001$). Mediány ploch pod křivkou (IQR) byly: 0,13 (0,02–0,44; skupina A); 0,13 (0,03–0,54; skupina B) a 0,30 V² (0,07–1,44; skupina C). Rozdíl mezi skupinami A a C byl na hranici statistické významnosti ($p = 0,066$; chyba 2. typu beta 0,295). **Závěry:** Ketamin, a to i v jedné intramuskulární dávce, ovlivňuje myoelektrické funkce žaludku prasete. Proto by neměl být používán v preklinických studiích gastrointestinální motility experimentálních prasat.

Klíčová slova: ketamin – antagonist receptorů NMDA (N-metyl-D-aspartát) – elektrogastrografie – myoelektrická aktivita žaludku – experimentální prase

Introduction

Gastric motor function is the most complex and most fragile function of the entire gastrointestinal tract [1]. Currently, there is no single gold standard for the diagnostics of gastric dysmotility disorders. It is possible to use gastric emptying scintigraphy, ^{13}C -acetate or ^{13}C -octanoic acid breath tests, electrogastrography, magnetic resonance imaging, antroduodenal manometry, ancillary testing (including barostat, SPECT, and satiety testing), wireless motility capsules, and last but not least EndoFLIP (Endoscopic Functional Lumen Imaging Probe: high-resolution impedance planimetry system) [2–23].

Electrogastrography (EGG) enables non-invasive recording of myoelectric activity of the stomach [24,25]. It is feasible both in humans [26–28] and in the experimental setting, including rats, rabbits, cats, dogs, and pigs [29–39]. Compared to humans, EGG in experimental pigs is the most reliable as the normal range of basic parameters is identical [40]. Previously, we have already presented an experimental porcine EGG in this Journal [41].

Nearly all preclinical porcine experiments must be carried out under general anaesthesia [42–45], and ketamine is commonly used as an induction

of general anaesthesia in veterinary medicine [46–49].

In clinical practice, ketamine has been used since the 1970's for its anaesthetic, analgesic, antidepressant, and anti-inflammatory effect [50,51]. However, ketamine also exerts several side effects in humans, such as dissociative and psychotomimetic effects, memory and cognitive impairment, as well as neurotoxicity, and is associated with a risk of abuse [50]. Ketamine is a phenylcyclohexylamine derivative (Fig. 1) [50].

Its mechanism of action is mainly explained by non-competitive antagonism of the N-methyl-D-aspartic acid (NMDA) receptor. Ketamine also interacts with opioid receptors and the monoamine, cholinergic, purinergic and adrenoceptor systems, as well as having local anaesthetic effects [52].

However, ketamine, as an NMDA-receptor antagonist, might influence gastric myoelectric activity. The aim of this study was to compare the impact of ketamine and ketamine-free induction of general anaesthesia on EGG in experimental pigs.

Methods

Animals

In total, seventeen experimental adult female pigs (*Sus scrofa f. domestica*, hybrids of Czech White and Landrace breeds; 3-month-old; mean weight 36.2 ± 3.8 kg; median 34.5 kg) were enrolled into the study. The animals were purchased from a certified breeder (Štěpánek, Dolní Ředice; SHR MUHO 2050/2008/41). The pigs were housed in an accredited vivarium (Faculty of Military Health Sciences, Hradec Králové). All animals were fed with a standard assorted A1 food (Ryhos, Nový Rychnov) in equal amounts twice a day, and had free access to drinking water.

Design of the study

All experiments were carried out in the morning on overnight fasting animals. Drugs used as an induction of anaesthesia were: Group A (n=5): medetomidine

0.1 mg/kg i.m.; butorphanol 0.3 mg/kg i.m.; midazolam 0.3 mg/kg i.m.; Group B (n=6): azaperon 2.2 mg/kg i.m.; Group C (n=6): ketamine 20 mg/kg i.m.; azaperon 2.2 mg/kg i.m.; followed in all groups by i.v. 1% propofol (repeated one-mL-boluses, 10–12 mL in total). EGG recording started 15 min. after the administration of induction and lasted 30 min. Heart rate monitoring and pulse oximetry were used to secure the experiments.

Electrogastrography

Our original method of porcine surface EGG was already published [53]. We used six active self-adhesive electrodes placed on the upper part of the abdomen, with the 7th basal electrode placed to the left of the middle of the sternum. A special abdominal belt enabled identification of artefacts caused by breathing and body movements. EGG recording was accomplished by means of the EGG Stand (MMS, Enschede, the Netherlands). Recordings were evaluated by MMS software (version 8.19). Running spectral analysis was used for standard evaluation of EGG. Results were conveyed as dominant frequency of gastric slow waves (DF; cycles per min.) and power analysis (areas of amplitudes; V^2).

Statistics

Data was statistically treated by means of descriptive statistics, Fisher test, unpaired t-test, and Mann-Whitney rank sum test using SigmaStat software (Version 3.1, Jandel Corp, Erkrath, Germany). Type 2 error beta was calculated when appropriate.

Ethics

The Project was approved by the Institutional Review Board of the Animal Care Committee of the University of Defence (Protocol Number MO 171673/2019-684800), Faculty of Military Health Sciences, Hradec Králové. The study was conducted in accordance with the policy for experimental and clinical studies [45]. Animals were held and treated in conformity with the European

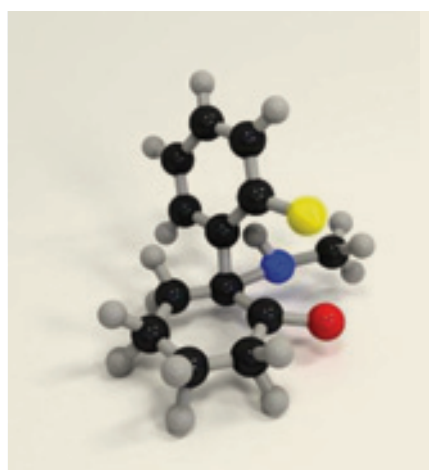


Fig. 1. 3D ketamine molecule structure.

Source: <https://www.turbosquid.com>.
Obr. 1. 3D struktura molekuly ketaminu.
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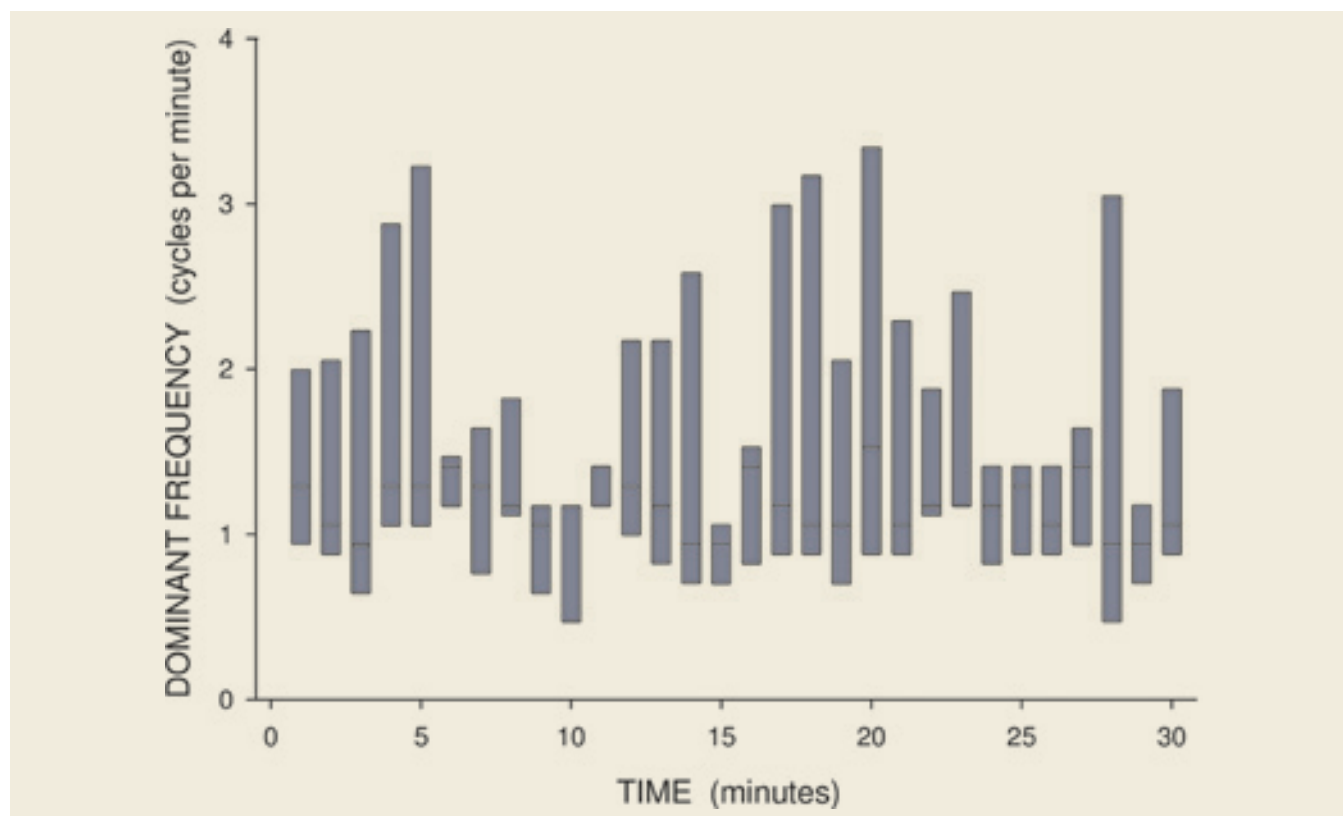


Fig. 2. Dominant frequency in Group A. Median and interquartile range.

Obr. 2. Dominantní frekvence ve skupině A. Medián a interkvartilové rozpětí.

Convention for the Protection of Vertebrate Animals [54].

Results

In total, 510 one-minute EGG intervals were assessed twice (DF and power). A total of 6 outliers (1.2% of all recordings; from various time intervals of different animals in all three groups) were excluded from the final evaluation of the EGG (two in DF and four in power analysis). An outlier is defined as a value outside the interval

$[Q1 - 1.5 \text{ IQR}, Q3 + 1.5 \text{ IQR}]$, where Q1 is lower quartile, Q3 is upper quartile and IQR ($= Q3 - Q1$) is interquartile range. Major results are summarized in Fig. 2–11.

DFs were (mean $\pm$ standard deviation): 1.4 ± 0.4 (Group A), 1.3 ± 0.3 (Group B) and 0.2 ± 0.1 cycles per min. (Group C). The differences between group C and groups A and B were statistically significant ($p < 0.001$). Median power (IQR) was 0.13 (0.02 – 0.44 ; Group A), 0.13 (0.03 – 0.54 ;

Group B) and 0.30 V^2 (0.07 – 1.44 ; Group C). The difference between groups A and C was of borderline significance ($p = 0.066$; type 2 error beta 0.295).

Discussion

Our current study has brought important new insight into the impact of ketamine on porcine gastric myoelectric activity. To the best of our knowledge, this is the first study comparing ketamine and ketamine-free anaesthesia induction in experimental pigs. Surprisingly, ketamine decreased the dominant frequency of gastric slow waves substantially, whereas the impact on EGG power was of borderline significance.

The action of ketamine is mostly dose-dependent [55,56]. In humans, recommended doses for ketamine induction of anaesthesia are 0.5 – 2 mg/kg (i.v.) and 4 – 10 mg/kg (i.m.) [50]. Gastrointestinal side effects are reported rarely (nausea, vomiting, increased salivation) [55–58]. Recommended doses of ketamine for

veterinary purposes vary considerably. They depend on indications (induction or maintenance of anaesthesia) and they also rely on combination with other drugs and different routes of administration (intravenous, intramuscular, subcutaneous, intranasal, peroral, rectal, intraperitoneal). Recommended doses are substantially distinct between different species (e.g. dogs: 0.5 mg/kg ; horses: 2 mg/kg ; cats: 11 mg/kg ; rats: 80 mg/kg ; guinea-pigs: 85 mg/kg) [59]. Recommended doses for ketamine induction of general anaesthesia in experimental pigs are 10 – 27 mg/kg [46,47,59–62].

The impact of ketamine on gastrointestinal motility has been studied in different species with various designs, different doses, and diverse results [63–67]. Schnoor et al. [61] investigated porcine duodenal motility by means of intraluminal impedance measurement. Ketamine (10 mg/kg i.m.) caused significantly prolonged duration of phase I and shortened phase II of MMC (migrating motor

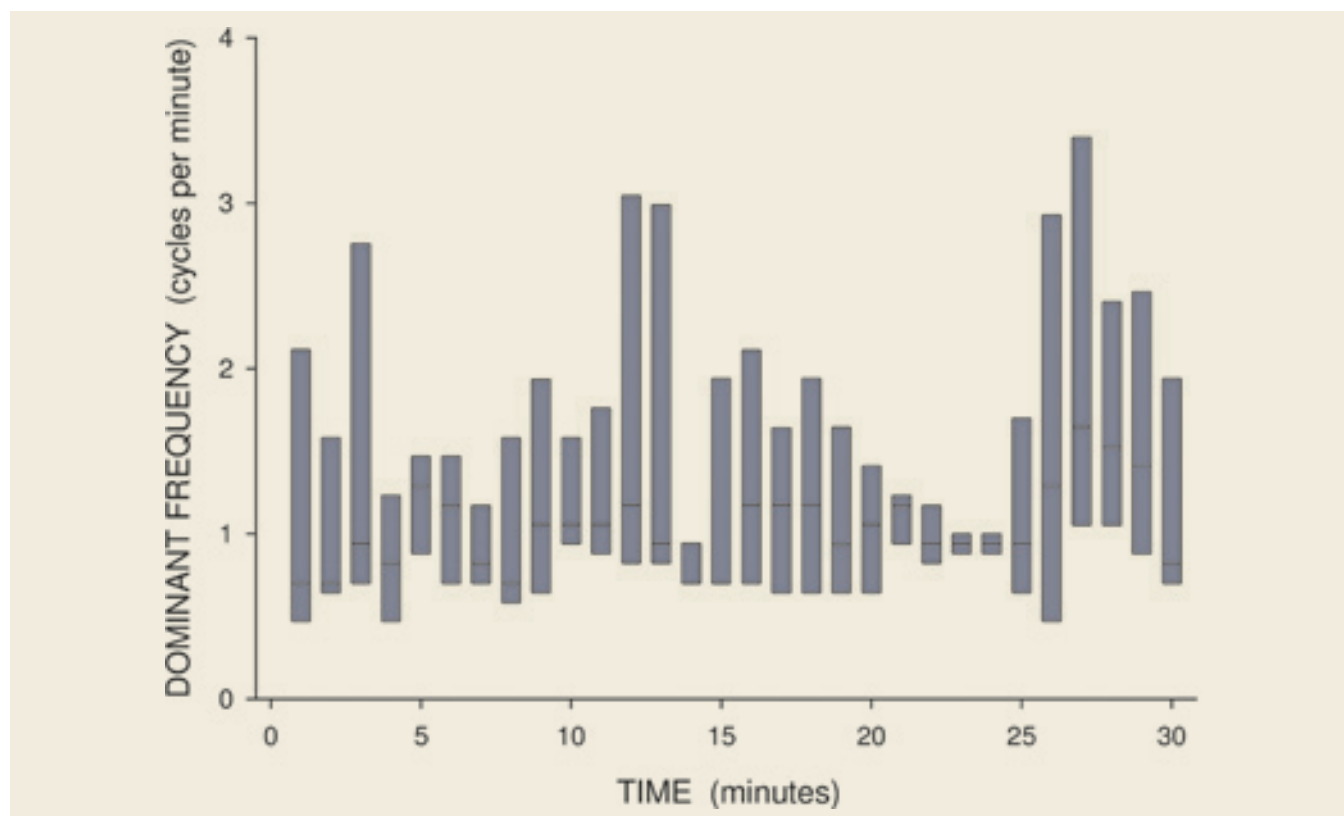


Fig. 3. Dominant frequency in Group B. Median and interquartile range.

Obr. 3. Dominantní frekvence ve skupině B. Medián a interkvartilové rozpětí.

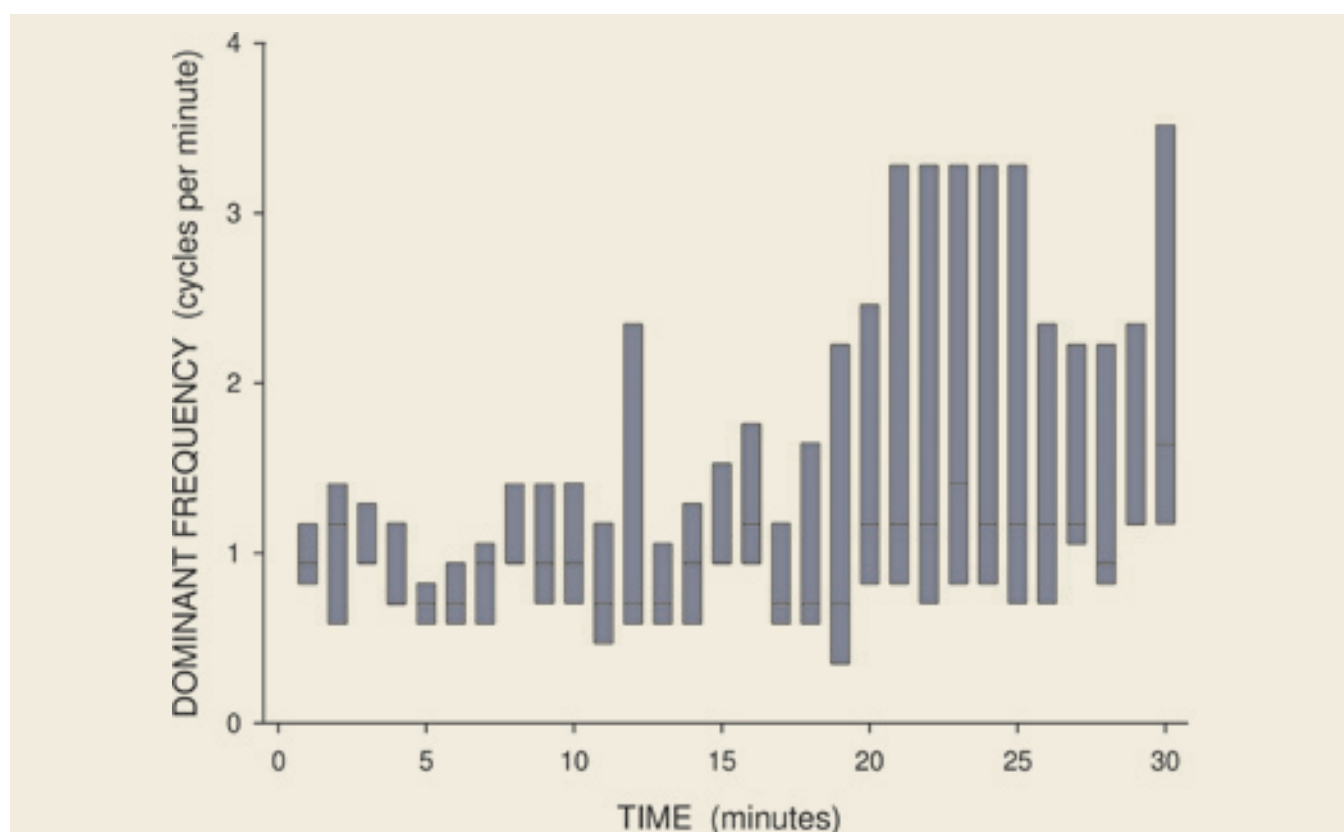


Fig. 4. Dominant frequency in Group C. Median and interquartile range.

Obr. 4. Dominantní frekvence ve skupině C. Medián a interkvartilové rozpětí.

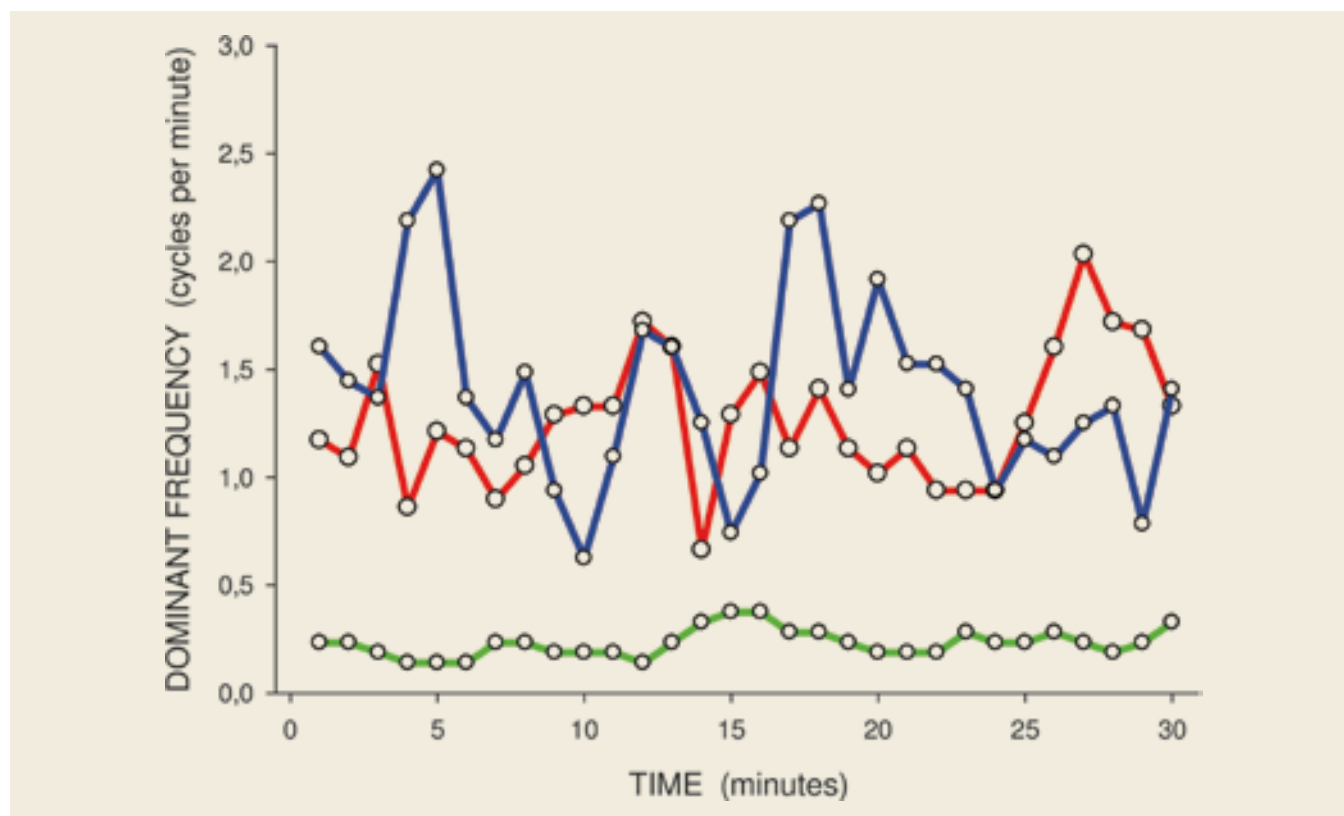


Fig. 5. Electrogastrography. Mean dominant frequency. Group A in blue, Group B in red, Group C in green.

Obr. 5. Elektrogastrografie. Průměrná dominantní frekvence. Skupina A modře, skupina B červeně, skupina C zeleně.

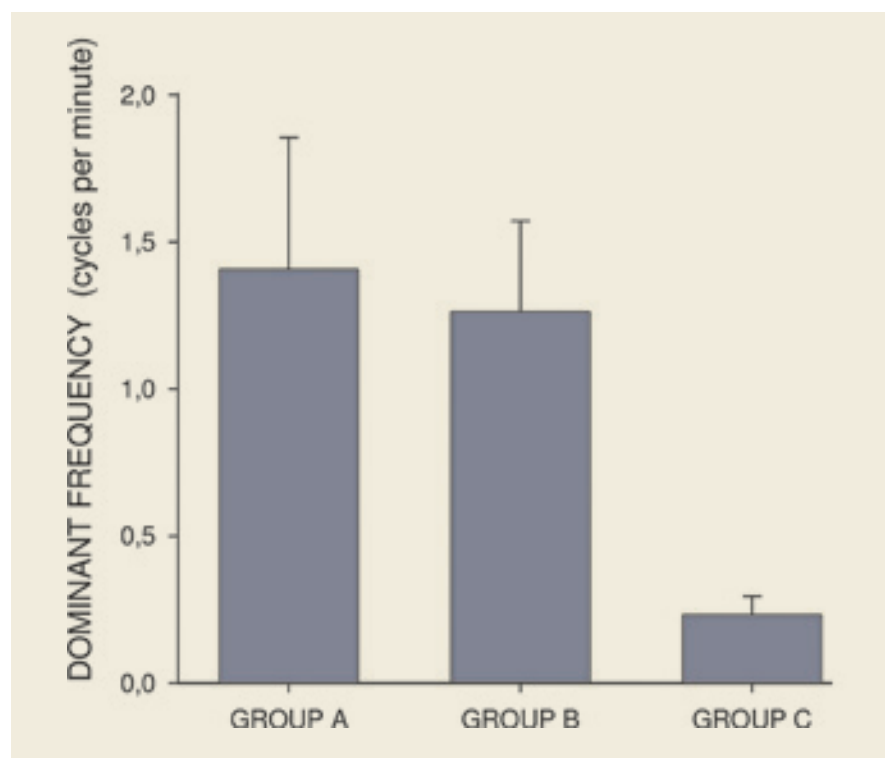


Fig. 6. Dominant frequency (mean + standard deviation). The difference between Group C and Groups A and B was statistically significant ($p < 0.001$).

Obr. 6. Dominantní frekvence (průměr + směrodatná odchylka). Rozdíl mezi skupinou C a skupinami A a B byl statisticky významný ($p < 0,001$).

complex) compared to control animals. The authors concluded that the impact of ketamine, even in a single low dose for induction of anaesthesia, should be taken into account in any gastrointestinal motility studies in experimental pigs [61].

The EGG pattern in experimental pigs reveals a substantial inter- and intra-individual variability [40]. Thus, in preclinical research, each animal represents its own actual control, which allows comparison of its own basal EGG (just prior to the experiment) and the immediately-following EGG study recording. A reliable evaluation has been enabled by the assessment of a greater number (thousands) of one-minute EGG intervals [68,69].

We investigated the impact of memantine on porcine EGG in one of our previous trials [53]. Memantine is also an uncompetitive antagonist of NMDA receptors. A single dose of memantine nearly doubled the DF. Although

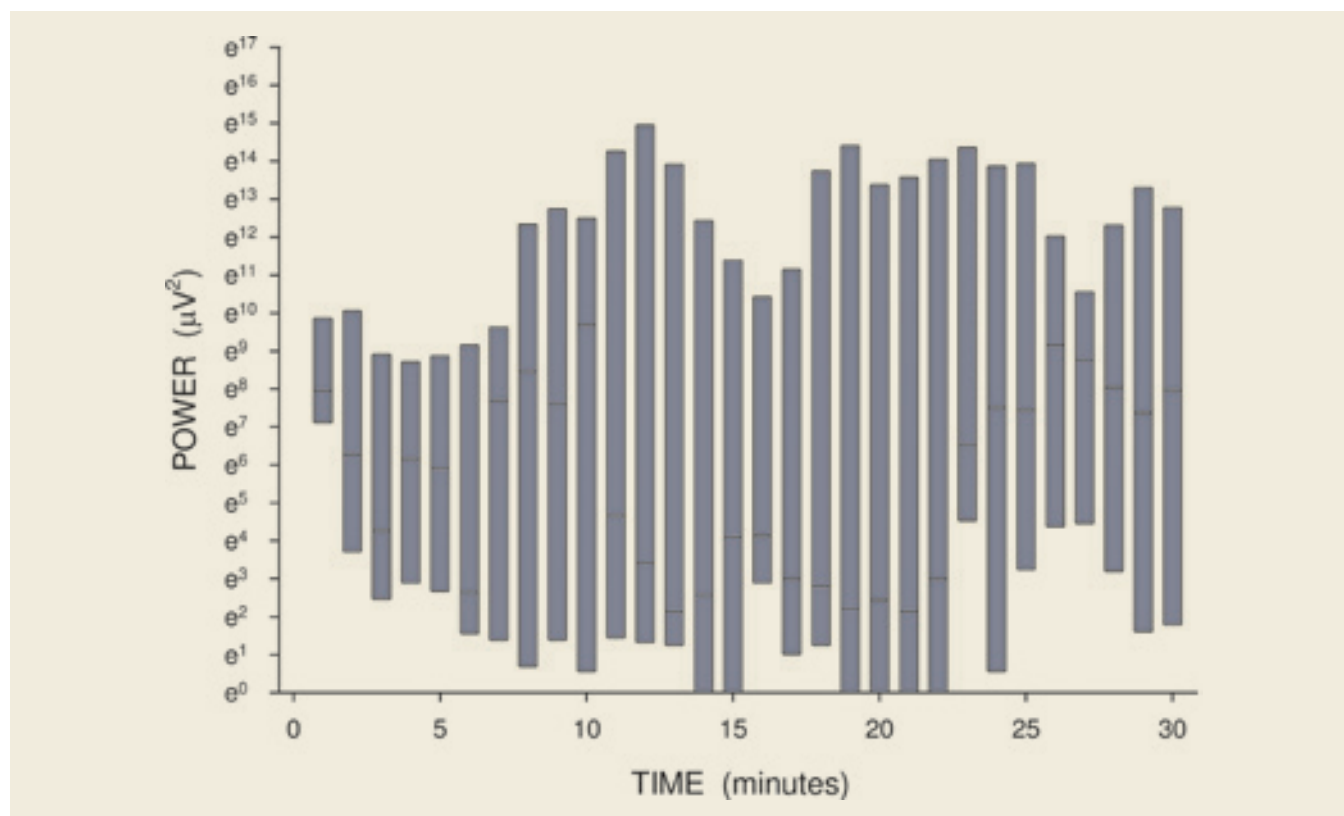


Fig. 7. Power in Group A. Median and interquartile range. Axis Y: natural logarithm scale.

Obr. 7. Plocha pod křivkou (power) ve skupině A. Medián a interkvartilové rozpětí. Osa Y: stupnice v přirozených logaritmech.

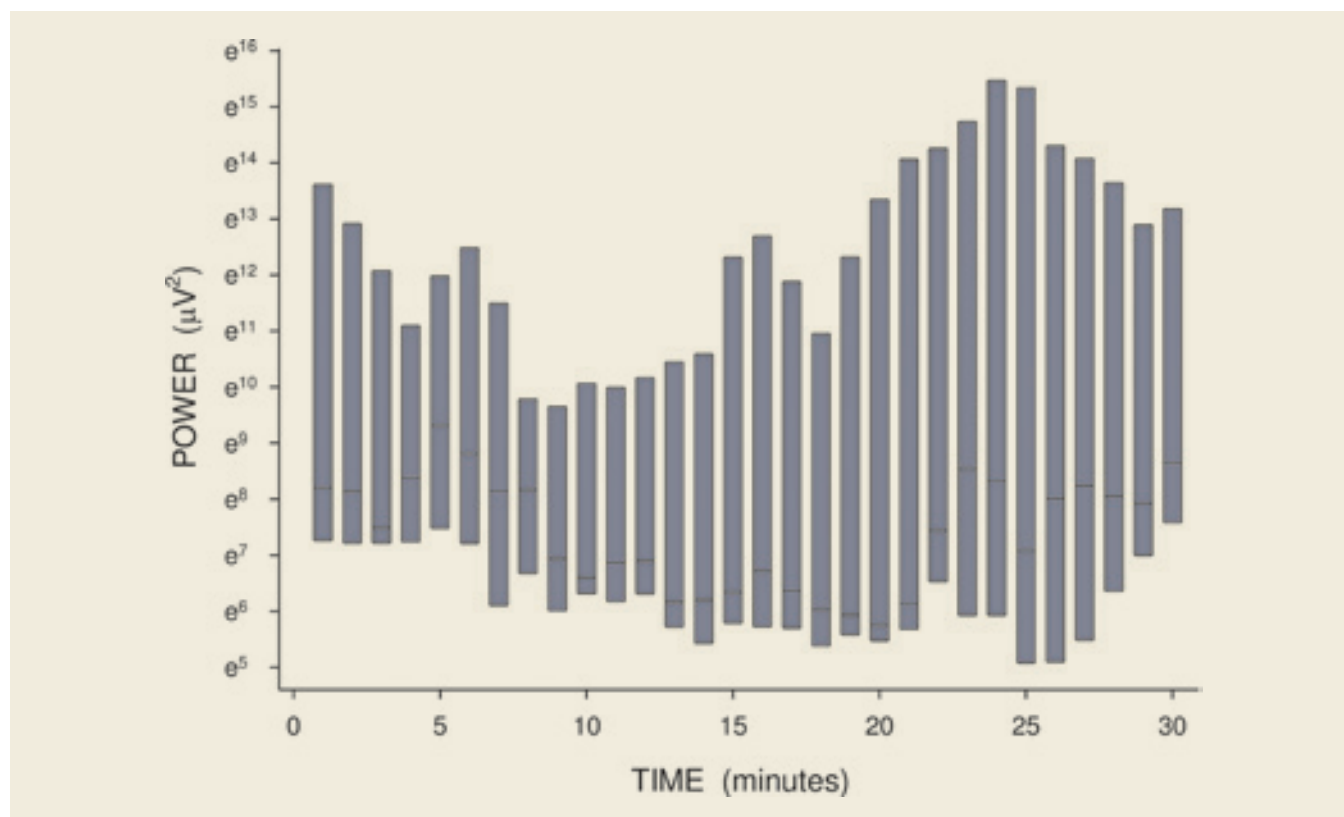


Fig. 8. Power in Group B. Median and interquartile range. Axis Y: natural logarithm scale.

Obr. 8. Plocha pod křivkou (power) ve skupině B. Medián a interkvartilové rozpětí. Osa Y: stupnice v přirozených logaritmech.

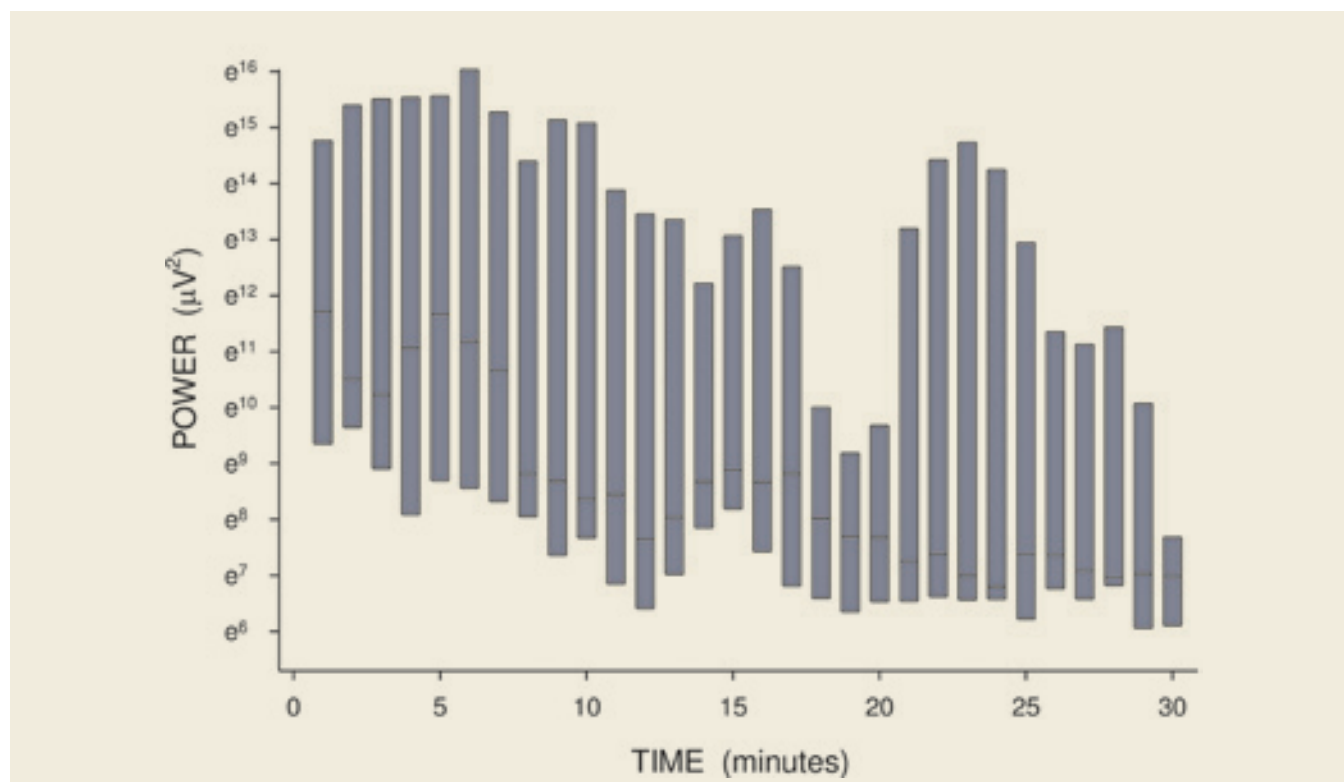


Fig. 9. Power in Group C. Median and interquartile range. Axis Y: natural logarithm scale.

Obr. 9. Plocha pod křivkou (power) ve skupině C. Medián a interkvartilové rozpětí. Osa Y: stupnice v přirozených logaritmech.

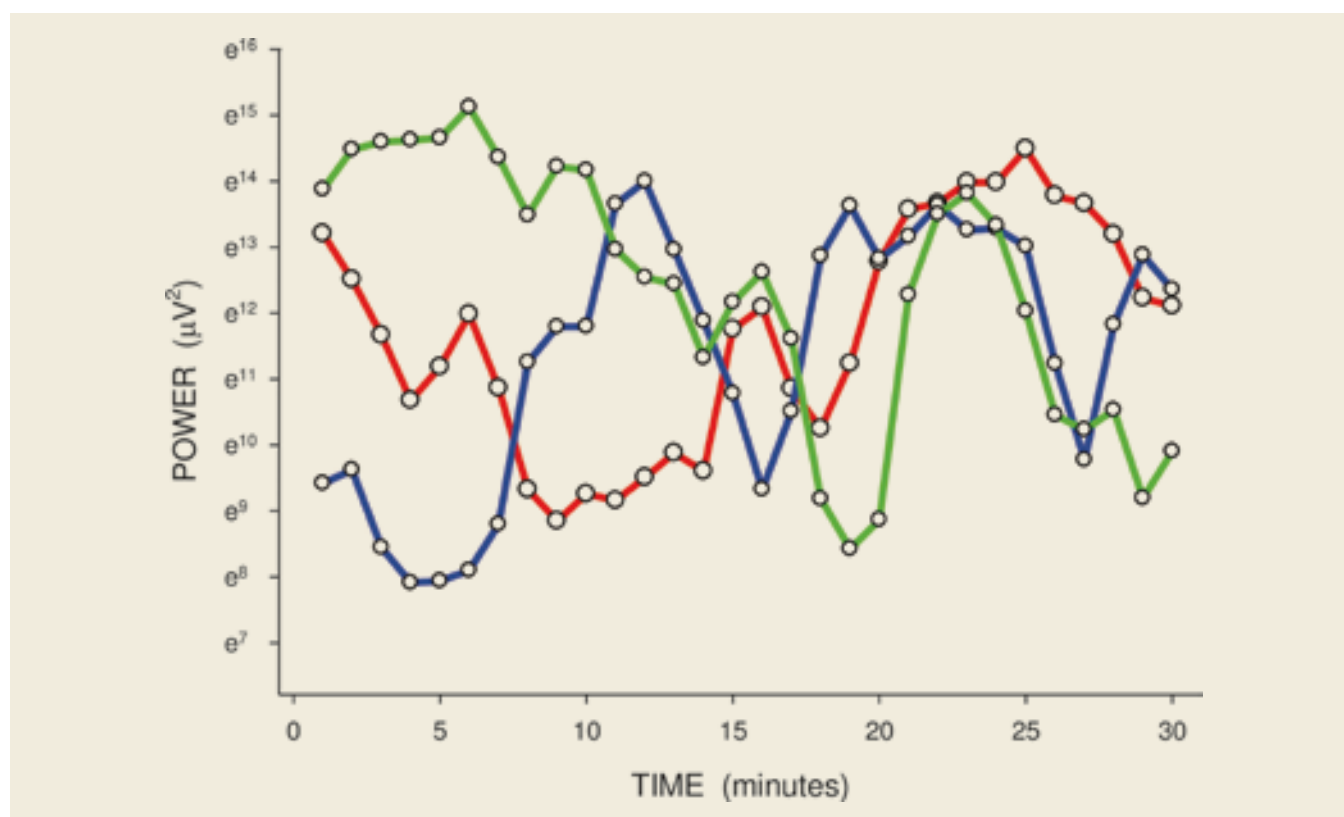


Fig. 10. Electrogastrography. Mean power. Group A in blue, Group B in red, Group C in green. Axis Y: natural logarithm scale.

Obr. 10. Elektrogastrografie. Průměr ploch pod křivkou (power). Skupina A modře, skupina B červeně, skupina C zeleně. Osa Y: stupnice v přirozených logaritmech.

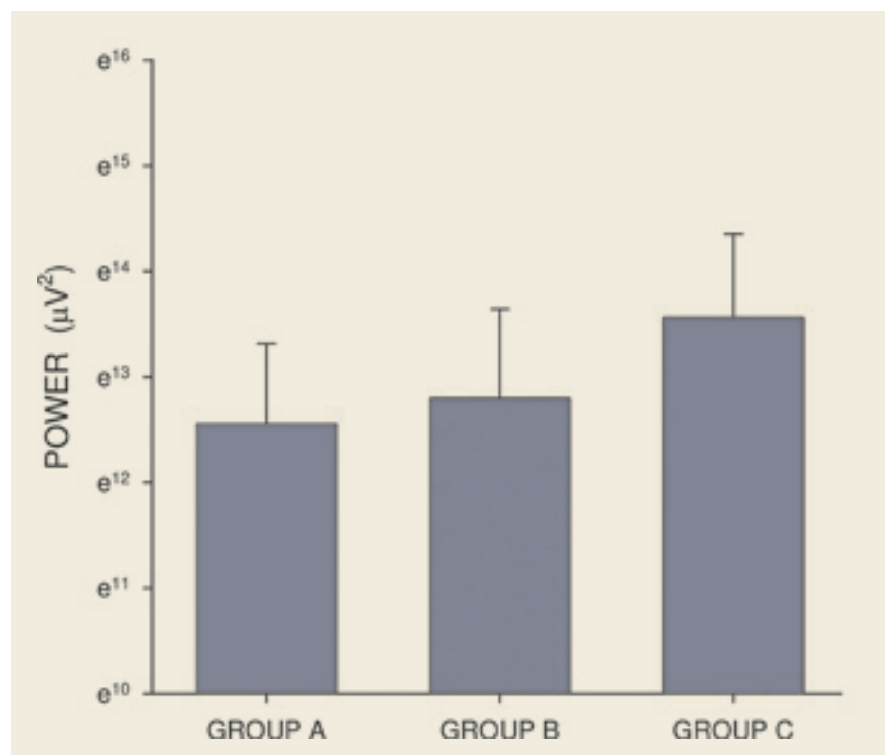


Fig. 11. Power (mean + standard deviation). Axis Y: natural logarithm scale. The difference between groups A and C was of borderline significance ($p=0.066$; type 2 error beta 0.295).

Obr. 11. Plocha pod křivkou (power; průměr + směrodatná odchylka). Osa Y: stupnice v přirozených logaritmech. Rozdíl mezi skupinami A a C byl na hranici statistické významnosti ($p = 0,066$; chyba 2. typu beta 0,295).

repeated administration of memantine caused marked gastric arrhythmia, the basal DF after single and repeated administration were comparable; however, the DF increase was more prominent in the latter. Basal power was significantly higher after repetitively-administered memantine. Severe gastric arrhythmia and long-lasting low power after repeated administration of memantine might explain possible gastric dysmotility side effects in the chronic use of memantine. We used ketamine as an induction of anaesthesia in that study, and hence a possible gastric myoelectric effect of ketamine might have influenced the basal EGG recording. However, the impact of memantine administration remained unaffected by ketamine use [53]. The different EGG effects of the two NMDA-receptor modulators in these two trials can be explained by the distinct mechanism of their action [70–72].

We are aware of possible limits of our current study. We did not design the project as a cross-over trial. We were not able to evaluate intra-individual variability of experimental animals. Last but not least, we did not use higher and/or repeated doses of ketamine.

Conclusions

Ketamine, administered even at a single intramuscular dose, affected myoelectric function of the porcine stomach. Therefore, it should be avoided in gastrointestinal motility studies in experimental pigs.

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ORCID authors

J. Bureš ORCID 0000-0003-0326-117X,
J. Květina ORCID 0000-0002-7115-0247,
V. Radochová ORCID 0000-0002-1477-5451,
M. Zavoral ORCID 0000-0001-7883-7431,
Š. Suchánek ORCID 0000-0003-3659-0252,
S. Rejchrt ORCID 0000-0001-5166-9503,
M. Vališ ORCID 0000-0002-4264-0554,
J. Žďárová Karasová ORCID
0000-0003-0891-9591,
D. Kohoutová ORCID 0000-0001-6937-309X.

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*Prof. Jan Bureš, MD, PhD, FCMA
Institute of Gastrointestinal Oncology
Military University Hospital
U Vojenské nemocnice 1200
169 02 Praha 6
bures.jan@uvn.cz*

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