Can Pupillary Reflex Dilatation predict the response to skin incision?

Rational

There is currently no reliable monitoring assessing the intensity of analgesia for every patient before applying a noxious stimulus. As pupil diameter is known to increase in parallel with noxious stimulations, Pupillary Reflex Dilatation (PRD), wich is the percentage of dilatation of the pupil in response to a calibrated tetanic stimulation, may be used to predict response to surgical stimulations. The aim of this study was to evaluate the place of the PRD to predict the response to skin incision in non paralyzed patients.

Patients and methods

This prospective and observational study was approved by the local ethics committee. Patients scheduled to undergo breast or skin surgery under general anaesthesia without neuromuscular blockade (sevoflurane or propofol and remifentanil in Target Controlled Infusion) with a laryngeal mask where included. The PRD after a tetanos of 60mA during 5 seconds applied to cubital nerve was measured just before skin incision. Its correlation with the occurrence, within 10 minutes after incision, of a movement, an increase of systolic arterial blood pressure (SAP) ≥20%, a laryngospasm, an increase of airway pressure ≥20%, or a reaction of any type (movement, hemodynamic, laryngeal, or need for increase of target concentrations) was studied by comparing responders to non responders using a Mann & Whitney test. The results are expressed as median and [interquartile].

Results

Forty one patients, ASA status 1 or 2, were included. The PRD before skin incision was significantly higher in patients who then moved (41% [34 – 46] *vs.* 12% [7 – 20], p = 0.008), increased SAP (15% [11 – 29] *vs.* 9% [5 – 19], p = 0.05), increased airway pressure (18% [14 – 40] *vs.* 10% [6 – 20°], p = 0.02) or a reaction of any type (18% [12 – 30) *vs.* 7% [5 – 17], p = 0.004), but did not differ significantly in patients who had a laryngospasm (30% [23 – 38] *vs.* 12% [7 – 21], p = 0.09). The receiver-operating characteristic curves were built. The AUC was 0.9 for the movement, 0.8 for laryngospasm, 0.7 for SAP increase and 0.8 for all responses. The threshold value corresponding to the highest ratio between sensitivity and sensibility was ~ 15%. The PRD was a better predictive factor than target remifentanil concentration which was significantly correlated only to the hemodynamic response.

Discussion

The PRD seems to be a relevant monitoring to predict the response to skin incision. It may then be useful to guide opioids titration according to the needs of each patient. However, the number of patients was low and the results need to be validated by a larger study. Moreover, the performances described here depend of the intensity of the calibrated tetanos and of the noxious stimulation (here, the skin incision), and results for other settings or in other surgical contexts remain to be studied.

Summary

In this study, the place of the PRD to predict the response to skin incision in patient under general ansthesia, is evaluated. It seems to be a relevant monitoring, better than Cet remi, to predict the movement, hemodynamic or laryngeal response.

Performance evaluation of improvements in a rapid propofol concentration analyser

The authors evaluated a new referencing approach implemented in the Pelorus 1000, a research analyserthat uses solid phase extraction and colorimetry to rapidly quantify the concentration of the intravenous anesthetic propofol in whole blood samples. Previous characterization of the instrument demonstrated a small systematic bias in operation, resulting in a Limit of Quantification of 0.75 ug/ml [1]. The colorimetric analysis approach has been refined to normalize absorbance before and after development of the characteristic indophenol complex [2]. The performance of the modified analyzer was characterized with respect to linearity, precision in control solutions and whole blood and limit of quantification and compared to the HPLC based reference method. The Pelorus 1000 was also evaluated for cross interference by substances that could be expected to potentially interfere with the solid phase extraction step or the analyte detection principles of the system.

Methods

All testing was carried out using the Pelorus 1000 device (Sphere Medical Ltd, Cambridge, UK, http://www.spheremedical.com) in a laboratory setting according to the manufacturer's operating instructions. The reference method used was a high performance liquid chromatography (HPLC) assay based on the method described by Cussonneau [3]. It uses a Luna C18(2) HPLC column (3µm 150 x 4.6mm) from Phenomenex. The results were analysed using Excel and an Excel add-in Analyse-It program. Whole blood testing was carried out using freshly drawn human blood from healthy volunteers. Propofol spiked samples were used to obtain the concentration range for the linearity, precision and the limit of quantification. Written informed consent was obtained from donors who were all enrolled in Sphere Medical's blood donation program, a waived program for the performance evaluation of instrumentation that has been reviewed and approved by the company's independent directors.

Results

The assay was found to be linear with a R^2 of 0.994 in the range of 0-20 µg propofol /ml. The Limit of Quantification (LOQ) was calculated as the lowest concentration at which the bias or imprecision is no more than 20% of the target value. The LOQ of the assay is 0.25 µg /ml. Total imprecision reported in SD (CV%) in control solutions containing propofol in solvent using three different instruments was 0.28 (5.39%) at 5.27 µg /ml and 0.47 (4.34%) at 10.82 µg /ml. Within run imprecision in whole blood from healthy blood donors was 0.06 (8.00%) at 0.75 µg /ml, 0.03 (0.99%) at 3.03 µg /ml, 0.09 (1.44%) at 6.21 µg propofol/ml and 0.29 (2.00%) at 14.46 µg /ml. The only cross interference found was for the bilirubin conjugated where the system was over reading 1.14 µg propofol /ml for the concentration of bilirubin tested of 342 µM with respect to the HPLC reference (A dose response study suggests that a total error of +/-0.5µg/ml is met at a concentration of 137µM). Also a 50% hematocrit level was found to cause a small bias of 0.06 µg propofol/ml over reading with respect to the HPLC reference. In comparison to the reference method, the overall bias of the Pelorus 1500 system over the range of 0-12 µg propofol/ml is estimated to be 0.048 µg/ml (95% confidence interval -0.57 to 0.66 µg/ml). This comparison was performed using three different instruments.

Discussion

The modified Pelorus 1000 analyser has been demonstrated to have an analytical performance for the measurement of propofol concentrations in whole blood samples comparable to that previously reported [2]. The modified Pelorus 1000 analyser fulfils the requirements for measurement of propofol levels in whole blood samples with precision and accuracy suitable for investigating propofol pharmacokinetics. A significant improvement is the reduction on the limit of quantification to 0.25 ug/ml, which in principle allows quantitative measurement of drug concentrations in light sedation during research.

References

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Background & Aim: shivering is one of the most common and important complications after surgery and anesthesia in the recovery room. It increases oxygen consumption, systemic blood pressure and heart rate as well as cardiac arrhythmias. Due to the various drugs which is used in general anesthesia and necessity of choosing effective intravenous and inhaled drugs to reduce their potential effects, so this study was done to compare the effects of propofol and isoflurane on postoperative shivering.

Materials and methods: This is a randomized, Inclinical trial, double-blind 70 patients 18 to 65 years in two groups of 35 patients for rhinoplasty surgery were randomly assigned to receive propofol or isoflurane. Occurrence and severity of postoperative shivering in the two groups were compared and from zero to four was classified. Data analysis was done using SPSS software. Independent sample t-Test and Chi-Square test were used for data analysis. A $p < 0.05$ was considered significant.

Results: There was no significant difference between the two groups regarding to age, sex and the duration of anesthesia. The prevalence and intensity of shivering in recipients of isoflurane group was significantly less than propofol group.

Conclusion: To reduce postoperative shivering in adult patients undergoing rhinoplasty surgery using isoflurane is better than propofol.

Keywords: propofol, isoflurane ,postopoerative shivering, rhinoplasty surgery

The effects of pre-anesthetic single-dose dexmedetomidine on attenuation of stress response to endotracheal intubation

Objectives

This randomized and double-blinded study aimed to investigate the effects of pre-anesthetic single-dose dexmedetomidine on attenuation of stress response to endotracheal intubation in patients with general anesthesia.

Methods

Sixty ASA I～II patients aged 20-51 years scheduled for gynecologic laparoscopy procedure with general anesthesia were randomly divided into two groups. The final enrollment was 53 patients. 28 patients involved into group D (study group) received intravenous infusion of dexmedetomidine 0.6μg/kg diluted with normal saline over 15 min before induction. 25 patients involved into group C (control group) received the same volume of normal saline infusion. Anesthesia was induced with propofol (Target-controlled infusion, plasma concentration 3μg/ml),fentanyl (3μg/kg) and rocuronium (0.6mg/kg). Endotracheal intubation was performed when plasma concentration of propofol reached to 3μg/ml. Hemodynamic parameters including heart rate (HR) and mean arterial pressure (MAP) at baseline, before induction (right after finishing infusion of dexmedetomidine or normal saline), and right after tracheal intubation were documented. Plasma concentrations of norepinephrine and epinephrine at baseline and after intubation were measured by high performance liquid chromatography.

Results:

In group D, hemodynamic parameters kept stable during induction, while in group C both MAP and HR significantly increased after intubation compared with baseline and before induction ($P<0.05$). There was no significant difference of plasma concentrations of norepinephrine and epinephrine between baseline and after intubation in group D ($P>0.05$). Plasma concentrations of norepinephrine and epinephrine increased significantly after endotracheal intubation in group C ($P<0.05$). Although plasma concentrations of norepinephrine and epinephrine between two groups were similar at baseline ($P>0.05$), both of them were statistically higher after intubation in group C than those of in group D ($P<0.05$).

Conclusions:

A single dose of dexmedetomidine given before induction of general anesthesia significantly decreased the stress hormone response to endotracheal intubation, kept hemodynamics more stable, and contributed to perioperative safety.

Key words:

dexmedetomidine; endotracheal intubation; stress response; hemodynamics;

Table1 Hemodynamic Parameters (means±SD)

Group	n	Baseline		Before Inducation		After Intubation	
		MAP (mmHg)	HR (Beats/min)	MAP (mmHg)	HR (Beats/min)	MAP (mmHg)	HR (Beats/min)
DEX	28	78.1±8.6	93.3±14.6	79.4±12.2	75.5±8.8	84.3±14.6	81±9.0
Control	25	80±6.8	84.2±13.9	73.6±9.5	79.3±11.0	89.9±13.9*	91.6±15.0*

* $P<0.05$, compared with baseline and before induction

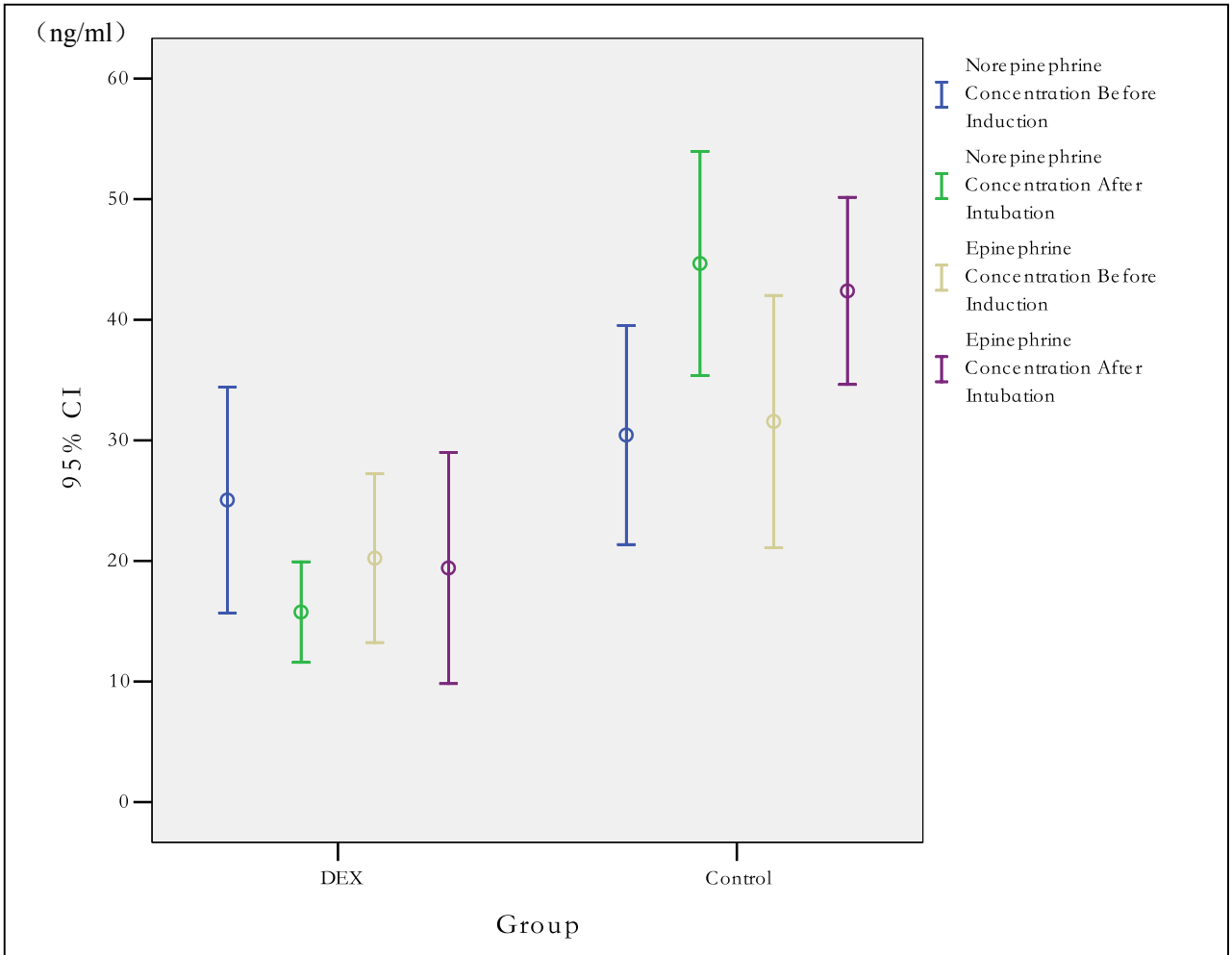


Fig1. Plasma Concentrations of norepinephrine and epinephrine

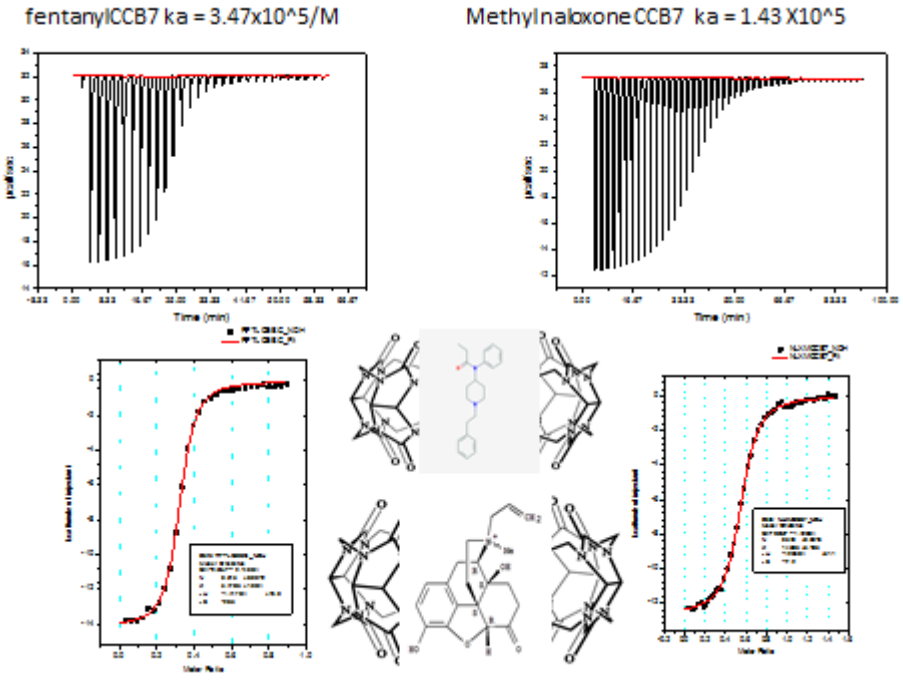
A Slow Releasing Molecular Fentanyl Flask

Introduction: Intrathecal narcotics revolutionized pain relief during labor by providing analgesia without motor block. Can fentanyl analgesia be prolonged by storage in a slow release formulation suitable for subarachnoid delivery?

Methods: Cucurbiturils(CBs), barrel -shaped macrocycles possessing a hydrophobic cavity that is surrounded by electrostatically negative ureidyl carbonyl portals, have high affinity for diamines ,tertiary ,and quaternary amines. The binding constants of cucurbituril to fentanyl and methynaloxone were determined using a micro calorimeter to solve the equation $lnK = (T\Delta s - \Delta H)/rT$.

Results: CBs bind narcotics with affinity constants in the range of 10^5/M (figure). This would allow a steady dissociation of fentanyl from its cucurbituril-macrocycle complex. This differs from very tight sugammadex binding of rocuronium which occurs at a Ka = 10^7/M. The order of binding to CB: diamine fentanyl>quaternary amine methylnaloxone, >naloxone. The latter two narcotic antagonists were used because a quaternary form of morphine is not available.

Discussion: Currently a slow release form of fentanyl is available as a matrix impregnated transdemal patch. Morphine, sequestered in liposomes, can be administered into the epidural space. Cucurbiturils can function as a sustained slow release intrathecal fentanyl delivery system .



Title: Real-Time Monitoring of Exhaled Propofol Reflects Changes in Propofol Effect Without Hysteresis (ASA 2012 abstract A052)

Background: Propofol is exhaled during anesthesia and can be measured in breath in real time.1 After i.v. administration propofol equilibrates between blood and lung and between blood and brain as its effect-site. If these equilibration coefficients are similar, changes in exhaled propofol might closely match effect site changes in the brain. As a result, a graph plotting brain effects against exhaled propofol concentrations would show no hysteresis, and exhaled propofol concentrations (Cexp) could be used as a clinical surrogate for propofol effect and propofol concentrations in the brain. Therefore, we examined human volunteers to determine the hysteresis between Cexp and propofol effect during propofol anesthesia.

Methods: Following IRB approval 20 volunteers (ASA I, age 29.3±8.0 yrs, BMI 25.4±4.3) underwent propofol anesthesia. The study protocol consisted of 4 consecutive phases with increasing and decreasing propofol blood concentrations. Phase I: Rapid propofol infusion of 0.4 mg/kg/min (0-10 min); phase II (10 - 30 min): no infusion; phase III (30 - 90 min): four escalating infusion rates (for 15 min each) to achieve targeted plasma concentrations of 2, 3, 4 and 5 mg/ml; phase IV (90 min until wake-up): no infusion, recovery. Cexp was determined continuously by ion molecule reaction mass spectrometry (V&F, Absam, Austria). The Bispectral Index (BIS, Covidien, Boulder, CO) was measured as a surrogate for the cerebral propofol effect. Twenty-one arterial blood samples per volunteer were collected and propofol plasma concentrations modelled using NONMEM® (ICON, Ellicot City, MD). Individually predicted plasma concentrations and measured Cexp were plotted vs. BIS and evaluated graphically.

Figure 1: Dose-response curve for propofol of one sample study person

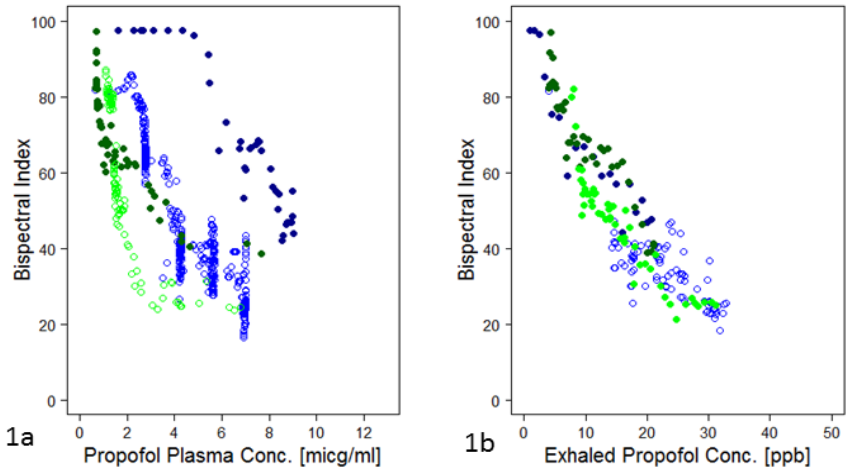
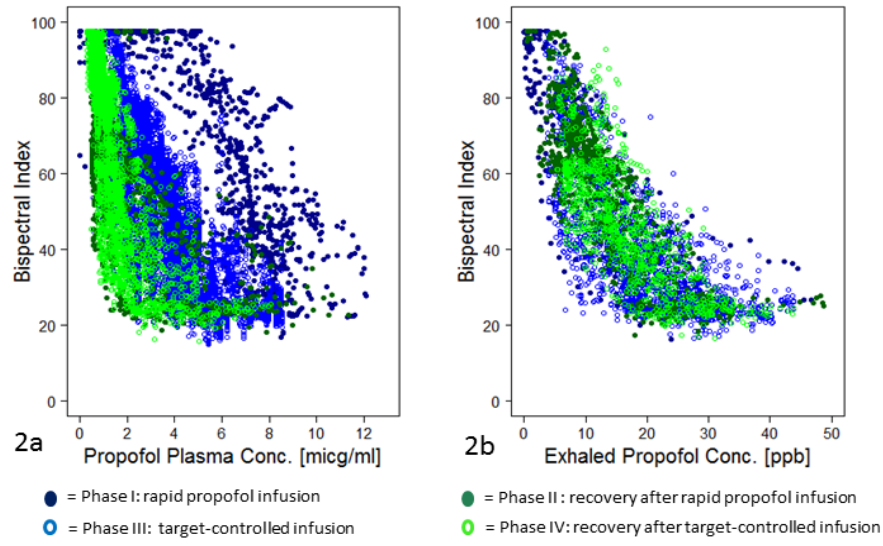


Figure 2: Dose-response curve for propofol of all 20 study persons



Results: When individually predicted propofol plasma concentrations were plotted against BIS a hysteresis loop for plasma propofol and BIS could be observed. However, this hysteresis was not present for Cexp. During increasing and decreasing plasma propofol concentrations similar breath concentration were associated with the very same effect. Figures 1a and 1b show data from one sample individual, figures 2a and 2b show data from all study persons. Dark blue (phase I) and light blue circles (phase III) reflect measurements during propofol infusion, dark green (phase II) and light green circles (phase IV) measurements during the recovery periods without propofol infusion.

Conclusion: The lack of hysteresis between exhaled propofol concentrations and propofol effect suggests that exhaled propofol concentrations and propofol effect follow changes in propofol plasma concentrations within a similar time frame. This supports the clinical utility of propofol breath monitoring. Ongoing work will compare propofol effect site concentrations and breath concentrations by means of population PKPD modeling.

Reference: 1) Anesthesiology 2007; 106:665-74.

Abstract

Background: Propofol (2, 6-diisopropylphenol) has been known to have neuroprotective effects. Excitatory amino acid transporter 4 (EAAT4) is a glutamate transporter predominantly expressed in the cerebellar Purkinje cells, which is vulnerable to ischemic injury. Thus, we hypothesized that propofol reverses reduced EAAT4 activity which was induced by oxidative stress and investigated the effects of propofol on EAAT4 under oxidative stress induced by *tert*-butyl hydroperoside (*t*-BHP).

Methods: EAAT4 was expressed in *Xenopus* oocytes by injection of its mRNA. By using two-electrode voltage clamping, membrane currents were recorded before, during, and after application of L-aspartate (3 μM) in the presence or absence of *t*-BHP and propofol.

Results: L-aspartate induced an inward current in EAAT4 expressing oocytes. Exposure of these oocytes to t-BHP (1–20 mM) for 10 min dose-dependently decreased EAAT4 activity. (1 ± 0.01 μC for control; 0.88 ± 0.05 μC for 1 mM; 0.83 ± 0.03 μC for 2mM; 0.65 ± 0.04 μC for 3 mM; 0.51 ± 0.07 μC for 5 mM; 0.45 ± 0.03 f μC for 10 mM and 0.24 ± 0.06 μC for 20 mM). IC_{50} for t-BTH was 6.05 mM and further study was performed with 10 mM t-BTH. Propofol (3–10 μM) dose-dependently reversed this t-BHP-attenuated EAAT4 activity.

Conclusions: Oxidative stress by t-BHP decreased EAAT4 activity and 3-10 μM propofol restored oxidative stress-reduced EAAT4 activity.

Key Words: excitatory amino acid transporter 4, glutamate transporter, propofol, *tert*-butyl hydroperoside, *Xenopus* oocytes.

The inhibition of cerebral ABC-type efflux transport by cyclosporine does not alter the intracranial signal of C11-marked morphine in a PET–imaging study in human volunteers.

Several findings indicate a role for ABC-type (ATP-binding cassette) drug efflux transport proteins in influencing the variability of clinical opioid effects. This phenomenon is attributed to variations in expression and activity of efflux transport proteins at the blood-brain-barrier, which are known to transport opioids in humans. Intracranial PET signals of drug-transport substrates such as verapamil have been shown to vary due to cyclosporine (CsA)-mediated transport inhibition in humans.

The present study therefore investigated the influence of CsA, a known efflux transport inhibitor, on morphine disposition 6 healthy human volunteers, who received 0.5 mg/kg/h CsA over two hours, with an injection of 10-20 mCi of of [^{11}C]morphine over 10 seconds after the first hour, followed by a PET scan of the head and arterial blood draws over one hour, in a self-controlled crossover study with and without CsA.

Radioactivity counts in the arterial and venous systems as well as the samples from the arterial line followed an expected sudden increase and subsequent decline in all scans. However, there was very little activity in cerebral capillary regions, which was unchanged after the addition of CsA. Given the quality control as well as metabolite measurements, there was very little cerebral uptake of radioactive drug into the brain, regardless of ABC-transport inhibition.

We conclude that the PET-visible amount of morphine readily bound to intracerebral receptors is very small, even if an intervention known to increase central morphine effects is conducted. This phenomenon cannot be readily explained by morphine serum levels and warrants further investigation.

Summary:

ABC-type (ATP-binding cassette) efflux transporters may influence clinical opioid effects. PET imaging of cerebral [^{11}C]morphine uptake did not show variations due to cyclosporine (CsA)-mediated transport inhibition in humans.

The study was funded by grants from the Foundation for Anesthesia Education and Research and the Barnes-Jewish Hospital Foundation to KM, from NIH R01-DA14211 and K24-DA00417 to EDK, and RR024992 to Washington University.

Nitrous Oxide Anesthesia and Perioperative Myocardial Infarction

The VINO Randomized Controlled Trial

Abstract

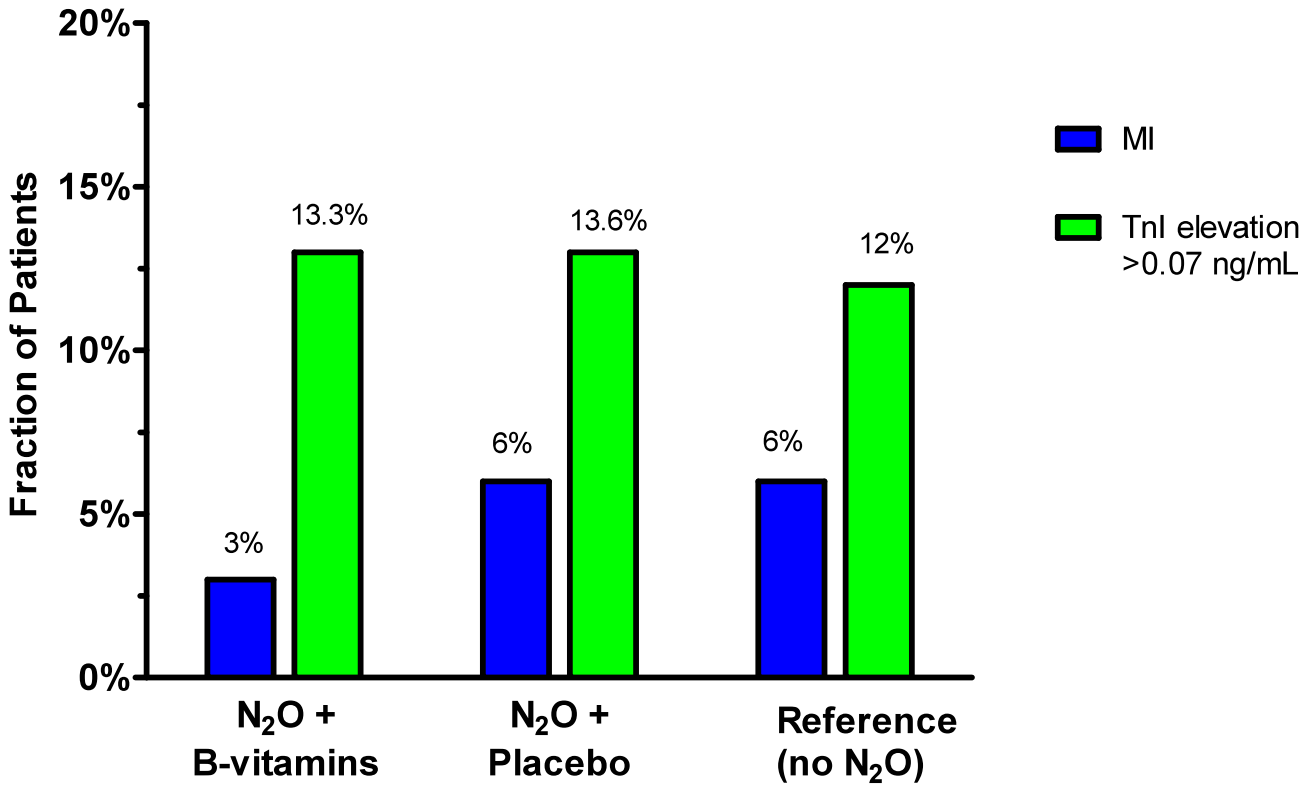
Background — Nitrous oxide anesthesia has been associated with an increased risk for perioperative myocardial ischemia and infarction, but the evidence is conflicting. Acute increase in plasma homocysteine, which is more pronounced in among patients homozygous for the *MTHFR* C677T or A1298C allele, has been suggested as the causal mechanism.

Methods — In a double-blind randomized controlled trial, 625 adult patients with cardiac risk factors undergoing nitrous oxide anesthesia for noncardiac surgery were randomly assigned to receive intravenous B-vitamins before and after surgery (250 patients) to reduce homocysteine concentrations or to placebo (250 patients). A reference group without nitrous oxide was concurrently enrolled (125 patients). Serial cardiac biomarkers and 12-lead electrocardiograms were obtained. Primary endpoint was the incidence of cardiac troponin I elevation within the first 72 hours after surgery. In addition, a novel high-sensitivity troponin T assay was used to measure the change between preoperative and peak postoperative level.

Results — Patients who received B-vitamins and nitrous oxide had a smaller increase in plasma homocysteine (2.7 ± 4.4 μmol/L) than patients who received nitrous oxide/placebo (4.1 ± 5.8 μmol/L, $p<0.001$); patients who did not receive nitrous oxide had no increase. No significant differences in the incidence of cardiac troponin elevation or myocardial infarction were observed among the study arms: 13.3% and 2.8% in the nitrous oxide/B-vitamin group, 13.6% and 6.0% in the nitrous oxide/placebo group, and 12.0% and 6.4% in the reference group ($p=0.91$ for troponin elevation; Figure 1). The median increase in high-sensitivity troponin T was similar in all groups: +3.1 ng/L, +2.8 ng/L, +3.9 ng/L for the nitrous oxide/B-vitamin, nitrous oxide/placebo and reference group, respectively ($p> 0.17$). The *MTHFR* genotype had no effect on homocysteine increase or cardiovascular outcomes.

Conclusions — Nitrous oxide anesthesia, *MTHFR* genotype and subsequent hyperhomocysteinemia are not associated with perioperative troponin elevation and myocardial infarction. B-vitamins are efficacious in blunting nitrous oxide-induced homocysteine increase but have no effect on cardiac outcomes.

Figure 1. Incidence of primary outcome events



Blue: incidence of myocardial infarction; green: incidence of cardiac troponin elevation (defined as a postoperative troponin I increase > 99th percentile [0.07 ng/mL].

Activation of the CB_2 receptor system reverses amyloid-induced memory deficiency

Abstract

Cannabinoid type 2 (CB_2) agonists are neuroprotective and appear to play modulatory roles in neurodegenerative processes in Alzheimer's disease. We have studied the effect of 1-((3-benzyl-3-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl) piperidine (MDA7)—a novel, blood brain barrier-permeant, and highly selective CB_2 agonist that lacks psychoactivity—on ameliorating the neuroinflammatory process, synaptic dysfunction, and cognitive impairment induced by bilateral microinjection of amyloid-beta ($A\beta_{1–40}$) fibrils into the hippocampal CA1 area of rats. In rats injected with $A\beta_{1–40}$ fibrils, compared to the administration of intraperitoneal (i.p.) saline for 14 days, treatment with 15 mg/kg of MDA7 i.p. daily for 14 days (i) ameliorated the expression of CD11b (microglia marker; Fig. 1A) and GFAP (astrocyte marker; Fig. 1B), (ii) decreased the secretion of IL-1β (Fig. 1C), (iii) decreased the upsurge of CB_2 receptors (Fig. 1D), (iv) promoted Aβ clearance (Fig. 1E), and (v) restored synaptic plasticity (Fig. 1F), cognition and memory (Fig. 1G). The effects of MDA7 were abrogated by prior administration of a CB_2 antagonist AM630. The administration of AM630 alone did not result in any beneficial effect on Aβ-related pathology. Our findings suggest that MDA7 is an innovative therapeutic approach for the treatment of Alzheimer's disease.

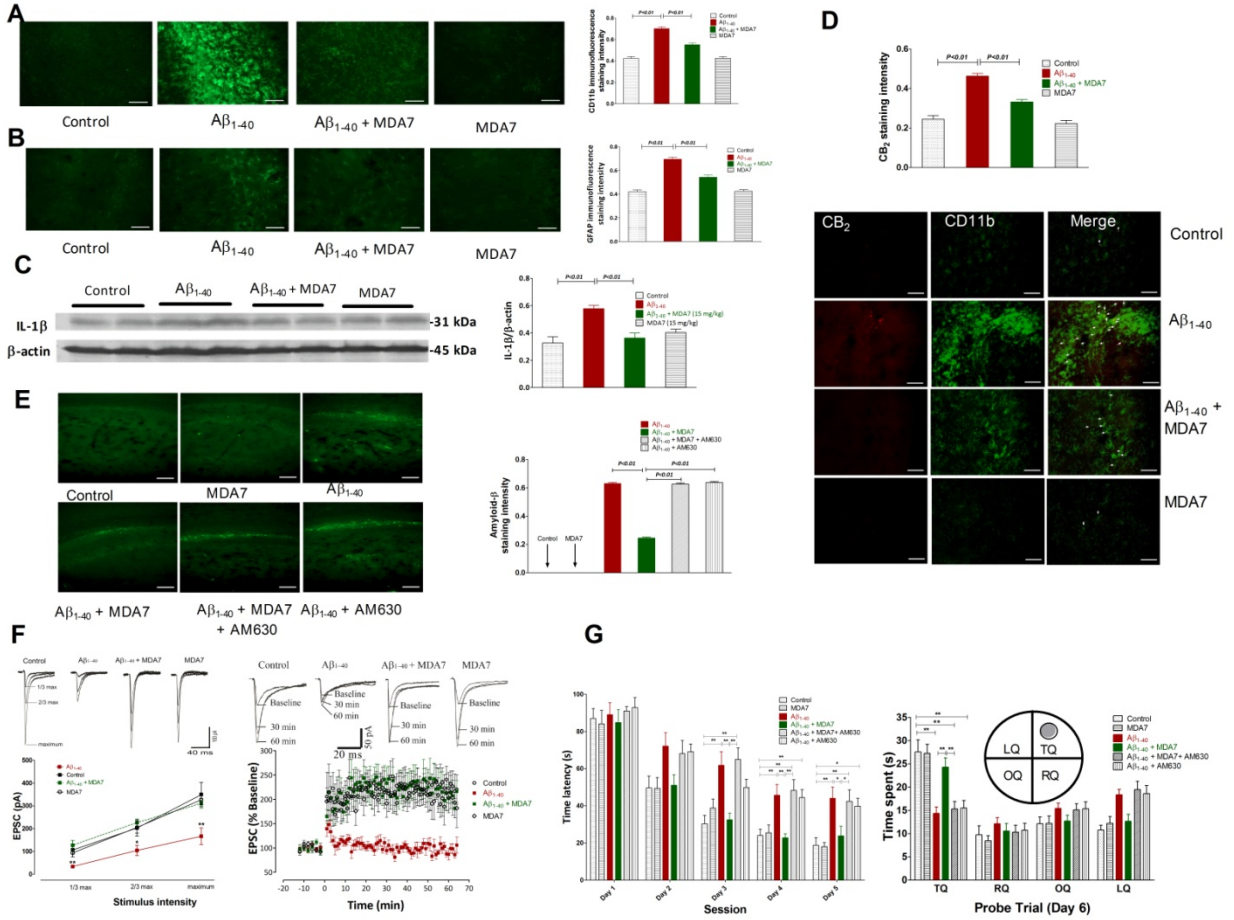


Fig. 1. *Administration of MDA7 clears β-amyloid and reverses deficits in Alzheimer's disease rat model. Statistical significance was determined by one-way ANOVA followed by Student-Newman-Keuls multiple range test. Data are shown as mean ± SEM (n = 8-10 per group). Scale bar = 40 µm. *P<0.05, **P<0.01.*

TITLE

A Novel, Non-invasive Method to Assess Clinical Sedation States: extending the MOAA/S score with truly noxious stimulation to identify general anesthesia.

INTRODUCTION

To test the hypothesis that general anesthesia is not a singular threshold but is a continuum of central nervous system depression that is dependent on the degree of nociceptive stimulation, this study was designed to develop a new, non-invasive method to assess clinical sedation states.

METHODS

Twenty healthy (ASA I and II) adult male and female subjects were exposed to a steady state effect site concentration of fentanyl (0.8 ng/ml) and increasing levels of propofol using target controlled infusion technology. Propofol was initiated at a target of 0.5 μg/ml and was increased by 0.25 μg/ml. At each target, the subject's responsiveness was assessed using MOAA/S (5 awake and alert, 0 general anesthesia determined by non-responsiveness to trapezius squeeze-TS), followed by TES (transcutaneous electrical stimulation). The propofol target was increased until the subject was unresponsive to 50 mA of electrical stimulation. The concentration-effect relationships were analyzed using logistic regression techniques.

RESULTS

The pre-TES MOAA/S scores associated with each propofol level are shown in Figure 1. The concentration-effect relationships and potencies are plotted in Figure 2. Substantially higher propofol concentrations were required to produce unresponsiveness to TES compared to TS.

CONCLUSIONS

A continuum can be seen in subjects transitioning from minimal sedation to non-responsive to TES at 50mA. TS does not readily distinguish between deep sedation and general anesthesia. Adding TES to the MOAA/S method increased the dynamic range of the assessments to include truly noxious stimulation, thereby enabling the identification of states more consistent with general anesthesia.

Figure 1

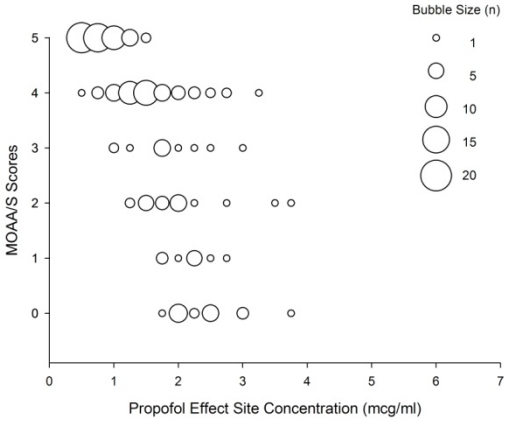
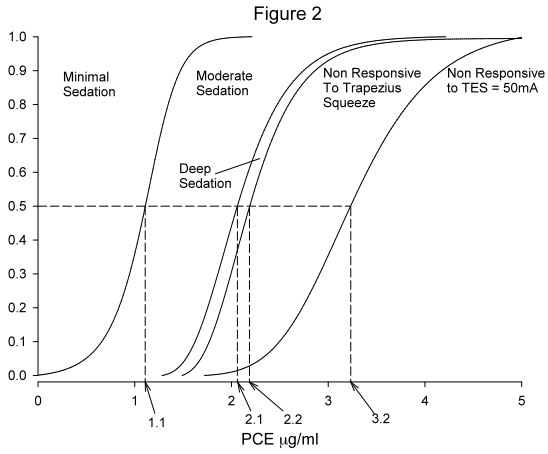


Figure 2



Research on the Clinical Efficacy of Colloid combined with Methoxamine Preload in the prevention of hypotension after the Induction of General Anesthesia

Abstract：

Objective： To assess the Clinical Efficacy of Colloid combined with Methoxamine Preload in the prevention of hypotension after the Induction of General Anesthesia.

Methods: 200 ASA Ⅰ-Ⅱ non-cardiac surgery patients aged 18-65 were involved in this investigation. They were randomly divided into 2 groups: group Methoxamine (A) and group control (B). Each patient received HES 130/0.4 Injection （6ml/kg）before induction of anesthesia. In group A, patients received Methoxamine, whereas in group B, patients received the same amount of physiological saline. Monitor and record systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR) and BIS value before induction,immediately after induction and 1,2,3,4,5,6,7,8,9,10mins after induction respectively. Compare the Hemodynamic stability and the incidence of hypotension, hypertension and bradycardia during the induction period of the two groups.

Results: The changes of SBP/DBP/MAP of group A are more stable than those of group B during the period of induction（$P<0.05$）, but the HR of group A 3mins after the induction has a larger decline than group B（$P<0.05$）. The incidence of hypotension of group A and group B is 13% and 61% respectively, with the remarkable difference in statistical significance（$P<0.05$）.There were no statistical significance between the two groups regarding their incidence of hypertension and bradycardia（$P>0.05$）.

Conclusions: Colloid preload combined with methoxamine preload can prevent the hypotension after the induction of general anesthesia and make the hemodynamic changes more stable.

Key words: induction of General Anesthesia, Colloid, methoxamine, hypotension

Propofol Inhibits LPS-Induced BV-2 Microglia Cells Activation via Inhibition of TLR4: Possible Involvement of GSK-3β

BACKGROUND: Microglia is as an immune cell in CNS and to be able to produce many inflammatory mediators in response to stressors ,so that play a critical role in the neuroinflammatory processes. Inflammation is a crossover in the pathogenesis of the chronic neurodegenerative diseases, such as Alzheimer's Disease, Parkinson's disease. Toll-like receptors (TLRs), especially TLR4 in the microglia is a important signaling pathway for inflammation response. Lipopolysaccharide (LPS) can activate microglia, which via toll-like receptor 4 (TLR4), and stimulate the expression of inflammatory cytokines. Also, glycogen synthase kinase-3β (GSK-3β) can modulate the inflammatory responses and tilt the balance in favor of pro-versus anti-inflammatory cytokines. Propofol, a well-known anesthetic, has been reported to inhibit LPS-induced inflammation response,such as in macrophagocyte. The aim of our study was to investigate the effect of propofol on LPS-induced inflammation in BV-2 microglia cells, which has been widely used in vitro experiments, and explore whether this effect is related to TLR4 and GSK-3β.

METHODS: Cells were randomly divided into four groups by using random number table: C group(Control group), LPS group, Propofol group and LPS+ Propofol group. The concentration of LPS and propofol were 1μg/mL and 30μM, respectively. Cell viability was measured using 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) assay. Interleukin (IL)-1β and tumors necrosis factor-α (TNF-α) released in culture medium were examined by enzyme-linked immunosorbent assay (ELISA). TLR4 mRNA expression was analyzed by reverse-transcription (RT) and real-time polymerase chain reaction (PCR). Protein expression of TLR4, p-GSK-3β and total GSK-3β were analyzed by western blotting. Statistical analysis was performed with GraphPad Prism statistical procedures. One-way analysis of variance was used followed by Dennett's t multiple comparison test. A P-value <0.05 was considered statistically significant.

RESULTS: Compared with group C, the production of IL-1β, TNF-α, TLR4 and phosphorylation of GSK-3β in the LPS group were significantly increased (P<0.05). Meantime, content of IL-1β, TNF-α and TLR4 expression were significantly decreased, whereas phosphorylation of GSK-3β increased in LPS+Propofol group compared with LPS group(See:Table 1/Figure 1). No significant differences were detected in the content of above targets between group C and group Propofol (P>0.05).

CONCLUSIONS: Our results demonstrate that 30 μM propofol pretreatment reduces the release of inflammatory cytokines induced by LPS in BV-2 microglia cells. Propofol not only increase phosphorylation of GSK-3β,but also inhibits TLR4 expression. It suggests thatTLR4 and GSK-3β may be the important cellular mediators involved in the anti-inflammation effects of propofol on LPS-induced neuroinflammation in microglia.

KEYWORDS: Glycogen synthase kinase 3 beta; Inflammation; Lipopolysaccharide; Propofol; Toll-like receptor

Figure 1:

Table 1. The expression level of IL-1β and TNF-α in BV-2 microglia cells. [n=8， M(P25~P75)， pg/mL]

target	C	LPS	propofol	LPS+propofol
IL-1β	200(151~368.5)	1600(1314~2210)*	230(152~397.5)	708(536~828)*#
TNF-α	215(148~300.5)	1180(946~1202)*	310(176.5~317.5)	500(319.5~554)*#

Statistically significant from C group (P<0.05). #Statistically significant from LPS group (#P< 0.05).

Figure 2

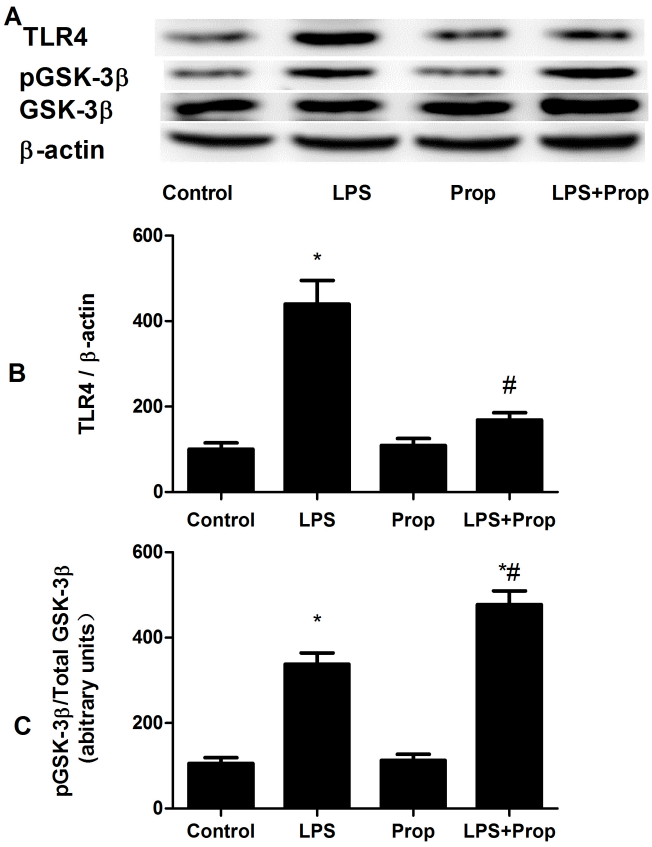


Figure 1. Effects of propofol (Prop) on TLR4 and p-GSK-3β protein expression induced by LPS in BV-2 microglia cells.*Statistically significant from C group (*P<0.05). #Statistically significant from LPS group (#P< 0.05).

Relationships Between the Preoperative HbA1c Levels and the Changes of MAP, HR and Blood Glucose During the Induction With Tracheal Intubation in the Geriatrics

BACKGROUND: As a criteria for screening and diagnosing diabetes mellitus (DM), Glycated hemoglobin (HbA1c) has been increasingly concerned. Geriatrics usually accompany with cardiovascular disease (CVDs) and DM. HbA1c was an independent risk predictor for the outcome of CVDs and/or DM[1]. The severe cardiovascular reaction following tracheal intubation has threatened geriatrics' safety. So we investigated the relationship between the different preoperative HbA1c levels and changes of mean arterial pressure (MAP), heart rate (HR) and blood glucose (Glu) during intubation in geriatrics.

METHODS: 112 geriatrics scheduled for noncardiac surgery were induced with midazolam 0.05mg/kg, propofol 1.5mg/kg, fentanyl 3μg/kg, vecuronium 0.15mg/kg. After 3 mins, tracheal intubation was done though oral way. MAP and HR were recorded before induction (T_0),just before intubation (T_1),at intubation (T_2),1,2,3,5,8 and 10 mins after intubation (T_{3-8}). Blood samples were taken at T_0 to test HbA1c. Glu was measured at T_0,T_1,T_6 and T_8. In view of stratified analysis, cases were divided into 4 groups: group A(HbA1c<5.7%,24 cases), group B (5.7%≤HbA1c≤6.4%,34 cases), group C(6.5% ≤HbA1c<7%,27 cases), group D(7%≤HbA1c≤8%,27 cases). Comparison within groups was done by single factor analysis of variance, comparison among groups by ANCOVA; The relationship of variable was analyzed by the liner correlation analysis(R as correlation coefficient), 0.5<R≤0.8 as significant correlation ,0.8<R≤1 as highly significant correlation .

RESULTS: Compared with group A or B, MAP decreased markedly at T_{1-8} in group C or D(P<0.05). Compared with group C , MAP decreased markedly at T_1,T_{6-8} in group D(P<0.05). HR had no significant difference between group A and B at T_0, while HR of group C and D was more higher than that of group A and B (P<0.05). Compared with T_0, HR decreased markedly at T_1,T_{6-8} in group C and at T1-3,T_{5-8} in group D (P<0.05). Compared with group A or B,HR decreased markedly at T_{1-2},T_{6-8} in group D(P<0.05). Compared with group C,HR decreased markedly at T_{6-8} in group D(P<0.05). The T_Δ (the difference value of MAP between T_0 and T_8 points) of all elder patients was significant correlation with preoperative HbA1c levels(R = 0.637); The H_Δ(the difference valve of HR between T_0 and T_8 points) was significant correlation with preoperative HbA1c levels(R = 0.502). The levels of Glu were gradually increased at T_{0-1},T_6,T_8 respectively in the four groups. There were significant difference among four groups(P<0.05).But after induction, except the Glu levels at T_6 was significantly lower than that at T_0 in group B (P < 0.05), there were no significant difference in each group(P>0.05). Levels of Glu of 112 patients at different times are highly significant correlated with preoperative HbA1c levels (R=0.871, 0.845, 0.847, 0.859, respectively).

CONCLUSION: Changes of MAP, HR and Glu levels during the induction with tracheal intubation were significant correlated with preoperative HbA1c levels. MAP and HR of geriatrics with higher preoperative HbA1c level dropped more obviously after tracheal intubation.

KEY WORDS: Geriatrics; Glycosylated hemoglobin; Tracheal intubation; Mean arterial pressure; Heart rate; Blood glucose

Ref:1.Colayco DC, Niu F, McCombs JS, et al. Glycosylated hemoglobin and cardiovascular outcomes in type 2 diabetes A Nested Case-Control Study. Diabetes Care, 2011;34 (1):77-83.

Figure 1:

Table 1: Patients Charateristics

Groups	Cases	Sex(male/female)	Weight(Kg)	Age (year)	Intubation time (s)
A	24	12/12	60.21±8.17	68.25±4.95	54±3
B	34	25/9	61.56±9.67	66.18±4.81	55±5
C	27	16/11	63.93±10.64	68.26±4.78	54±4
D	27	18/9	63.04±9.59	67.11±3.83	55±3

Table 2: Changes of MAP during anesthesia induction (mmHg , $\bar{x}\pm s$)

	Group A	Group B	Group C	Group D
T_0	98±6	95±8	94±9	98±8
T_1	66±7*	64±9*	53±6*▲●	47±6*▲●★
T_2	89±14 *	90±20	67±11*▲●	66±7*▲●
T_3	103±13*	94±16▲	80±14*▲●	83±12 *▲●
T_4	95±11	91±16	78±13*▲●	79±7*▲●
T_5	83±10 *	81±13*	69±13 *▲●	68±7*▲●
T_6	74±8*	74±10*	63±7*▲●	55±6*▲●★
T_7	70±6*	69±7*	59±7*▲●	51±7*▲●★
T_8	70±6*	66±7*	57±5*▲●	48±6*▲●★

Compared with T_0 ●P < 0.05 ; Compared with A ▲P < 0.05 ; Compared with B ◆P < 0.05 ; Compared with C ★P < 0.05 ;

Table 3: Changes of HR during anesthesia induction (bpm, $\bar{x}\pm s$)

	Group A	Group B	Group C	Group D
T_0	72±8	73±11	80±10▲●	80±10▲●
T_1	64±8*	64±12*	64±10*●	61±10*▲●
T_2	81±12	80±14	78±14	74±7*▲●
T_3	91±11*	85±13*▲	87±13▲	89±9*
T_4	85±12*	78±13▲	87±15	84±9
T_5	79±11	72±11▲	74±11▲	73±6*▲
T_6	70±8	68±9	69±12*	64±6*▲●★
T_7	65±7*	65±8	64±9*	59±6*▲●★
T_8	62±6*	63±8*	61±8*●	57±7*▲●★

Compared with T_0 ●P < 0.05 ; Compared with A ▲P < 0.05 ; Compared with B ◆P < 0.05 ; Compared with C ★P < 0.05 ;

Table 4: Changes of blood glucose during anesthesia induction(mmol/L , $\bar{x}\pm s$)

	Group A	Group B	Group C	Group D
T_0	5.10±0.51	6.06±0.62▲	6.89±0.91▲●	8.73±1.38▲●★
T_1	4.82±0.62	5.79±0.64▲	6.45±0.88▲●	8.34±1.30▲●★
T_2	4.86±0.54	5.70±0.72*▲	6.62±0.94▲●	8.40±1.29▲●★
T_3	5.14±0.57	5.92±0.65▲	7.03±0.93▲●	8.87±1.32▲●★

Compared with T_0 ●P < 0.05 ; Compared with A ▲P < 0.05 ; Compared with B ◆P < 0.05 ; Compared with C ★P < 0.05 ;

Bispectral index-guided dexmedetomidine and midazolam infusion during epidural anesthesia: which provide better patient or surgeon satisfaction?

BACKGROUND: This study aimed to evaluate the patient and surgeon satisfaction with dexmedetomidine or midazolam while titrating the sedation level with the bispectral index (BIS) during epidural anesthesia.

METHODS: The double blind study enrolled eighty consenting ASA class I-II patients who were electively undergoing epidural anesthesia. A random infusion of 4 ug ml(-1) Dexmedetomidine (Group D) or 0.2 mg ml(-1) midazolam (Group M) was administered after mounting a BIS monitor. Infusion rate was adjusted according to the target BIS level (85± 5) .The day after operation, patient satisfaction was evaluated using Iowa Satisfaction with Anesthesia Scale and surgeon satisfaction was evaluated using visual analogue.

RESULTS: The Iowa Satisfaction with Anesthesia Scale results showed that patients were significantly more satisfied in dexmedetomidine group versus midazolam group (2.2 vs 1.6, $P<0.05$). The visual analogue showed no significant differences favoring between dexmedetomidine group and midazolam group (3.6 vs 4.0, $P>0.05$).

CONCLUSIONS: Dexmedetomidine infusion provide better patient satisfaction than midazolam during epidural anesthesia. There were no significant differences in surgeon satisfaction between dexmedetomidine and midazolam.

Co-relation of HIV & Tuberculosis in terms of clinical and radiological presentation with CD4 counts in Rajasthan

Introduction: In India, estimated 40% of population is infected with tuberculosis as against 1% with HIV infection. HIV co-infection is strongest known risk factor for the development of tuberculosis disease. The fact is that tuberculosis kills more adults in the most productive age group in India than any other infectious diseases. Unlike other opportunistic infections that occur at CD-4 cell counts <200/cumm, active tuberculosis occurs throughout the course of HIV disease. As HIV related immunosuppression increases, the clinical pattern of TB changes with increasing number of smear negative and extrapulmonary tuberculosis cases. Thus clinical radiological presentation depends upon the degree of immunosuppressant.

Objectives: to know the prevalence & spectrum of clinical radiological presentation of tuberculosis in HIV positive patients and find out correlation with CD4 cell counts.

Methodology: The present study was carried out at Government Medical Colleges in Rajasthan, included indoor 153 HIV positive patients during Sep.2009 to Sep.2010. Written consent was taken with proper counseling. HIV sero-status was done in all the patients as per NACO guidelines. Routine blood tests, sputum examination for AFB & Culture, chest X-ray, USG, tuberculin test with 5 TU, were performed. FNAC, Biopsy, fluid Cytology, Biochemistry were used to diagnose EPTB and CD 4 counts were performed.

Results: Out of 153, 138 patients were diagnosed to have HIV-TB co-infection, amount that 78.99% males and 21,01% were females, Pulmonary lesions were present in 82.61% patients; Extra-pulmonary alone in 17.39% and 53.62% have both pulmonary & Extra-pulmonary tuberculosis. 42.98 (49) had sputum smear positive for AFB whereas 57.07% were smear negative. Overall 50/138 (36.23%) had lymph node TB, followed by pleural (22.46%) & abdominal tuberculosis (19.57%).

The most common presenting symptoms was cough (82.61%), followed by fever (68.12%), loss of appetite & shortness breathlessness (52.17% & 42.75%) respectively. 79.73% of pulmonary & Extra-pulmonary patients had CD4 cell counts <200/cumm.

Conclusion: Most of the HIV-TB co-infected patients were belong to productive age group of 21 to 40 yrs and were sexually active. Driving was most common occupation (28%) & females were housewives. This study highlights the higher prevalence of HIV & TB in patients who lack basic education and awareness. Patients with low CD4 counts (<200/cumm) had more incidence of Extra-pulmonary & pulmonary tuberculosis with atypical radiological presentation.

Introduction:
Can an anesthesiologist predict how a patient will react after anesthetic administration? How variable can the patient reactions be? Past research on pharmacokinetic and pharmacodynamic models predict the dose-response relationship. Through computer simulations on we aim to show the variability, consistency, and distinguishability of the dose-response relationship.

Methods:
1000 PK/PD parameter sets were created using the model reported distributions. The sample dosing scheme; propofol infusion of 100 mcg/kg/min, remifentanil infusion of 0.2 mcg/kg/min, two fentanyl boluses of 2 mcg/kg, and propofol bolus of 2 mcg/kg. The infusions were administered for 90 minutes, the first fentanyl bolus was administered at t=0 minutes, the propofol bolus was administered at t=3 minutes, and the second fentanyl bolus was administered at t=75 minutes. PD models were assumed clinical surrogacy for predictors of consciousness, laryngoscopy, pain, and ventilatory depression.

Results:
The PK/PD variability at induction was small while during emergence the variability was large. We have created a movie illustrating the variability which can be viewed online at https://www.dropbox.com/sh/lrzosr7qt6norj9/rCQ2WQL7ys#/. Prediction consistencies at induction were high but dipped during emergence. Overall the ability to change post-anesthetic responsiveness, pain, and intolerable ventilatory depression for remifentanil was poor while propofol and fentanyl were moderate.

Discussion:
Through PK/PD simulation we found there is considerable variability and low consistency within the dynamic range while outside the dynamic range there is small variability and high consistency. This may indicate that to ensure no response amidst inter-patient variability anesthesiologist typically overdose patients.

High serum cortisol level is associated with early postoperative cognitive dysfunction after coronary artery bypass graft surgery

Abstract

Background: The pathophysiology of postoperative cognitive dysfunction (POCD) remains poorly understood. It had been found that high serum cortisol level was associated with increased risk of postoperative delirium and that delirium was closed related to the occurrence of POCD. The purpose of this study is to investigate the relationship between serum cortisol level and early POCD in patients undergoing coronary artery bypass graft (CABG) surgery.

Methods: One hundred and sixty-eight adult patients who underwent elective CABG surgery were consecutively enrolled. Delirium was assessed using Confusion Assessment Method for the Intensive Care Unit during the first seven postoperative days. A neuropsychological test battery that included 7 tests with 9 subscales was administered one day before surgery and one week after surgery. POCD was defined using the same definition that was used in the ISPOCD1 study. Blood samples were obtained on the first postoperative day for measurement of serum cortisol concentration. Multivariate Logistic regression analyses were performed to identify predictors of POCD.

Results: Cognitive dysfunction occurred in 40.5% (68 of 168) of patients one week after surgery. High serum cortisol level was significantly associated with the occurrence of early POCD (odds ratio 2.352, 95% confidence interval 1.047 to 5.286, P = 0.038). Other independent predictors of early POCD included use of penehyclidine as premedication and prolonged duration of postoperative coma or delirium.

Conclusions: POCD was a common complication early after CABG surgery. High serum cortisol level on the first day after surgery was significantly associated with increased risk of early POCD.

High serum interleukin-6 level is associated with increased risk of postoperative delirium in elderly patients: a prospective cohort study

Abstract

Objective: To investigate the relationship between serum interleukin-6 (IL-6) concentration and the occurrence of postoperative delirium (POD) in elderly patients (≥ 60 years) after orthopedic and open-abdominal surgery.

Methods: A total of 338 patients were enrolled. Patients were evaluated with Mini-Mental State Examination (MMSE) on the preoperative visit. Blood samples were obtained before anesthesia and in the first day after surgery for measurement of serum IL-6 concentrations. Occurrence delirium was assessed using Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), and the intensity of pain was evaluated with visual analogue score (VAS), twice daily during the first three postoperative days. Multivariate logistic regression analysis was performed to identify predictors of POD.

Results: POD occurred in 14.8% (50 of 338) of patients. High serum IL-6 level was significantly associated with the occurrence of POD (OR 1.468，95% CI 1.127-1.913，P = 0.004). Other independent predictors of POD included advanced age (OR 1.103, 95% CI 1.046-1.163, P < 0.001) and elevated total VAS pain score (OR 1.100, 95% CI 1.056-1.145, P < 0.001). While higher preoperative MMSE score was associated with decreased risk of POD (OR 0.867, 95% CI 0.758-0.992, P = 0.038). Patients who developed postoperative delirium had prolonged duration of postoperative hospital stay [14(12-20) vs. 12(8-15) days, P = 0.001)].

Conclusions: POD was a frequent complication in elderly patients after orthopedic and open-abdominal surgery. High serum IL-6 concentration was significantly associated with increased risk of POD. Patients with delirium had a longer postoperative hospital stay.

Title:The response of bispectral index to laryngoscopy, comparison between healthy hemispheres during pseudo-steady state propofol and remifentanil anesthesia.

Introduction:
We observed whether clinically relevant asymmetric responses occur on bilateral BIS measurements after laryngoscopy in healthy adults during propofol and remifentanil anesthesia. We hypothesized that high or low dose of remifentanil may affect the interhemispheric difference.

Methods and materials:
After ethics committee approval and patients informed consent, 40 cervical and lumbar hernia patients were included. We measured bilateral BIS(VISTA-XP4 with BIS-quarto™ sensor)(Covidien, Dublin, Ireland). Effect-site titration of remifentanil(Ce_{REMI}) (Minto Model) and propofol(Ce_{PROP}) (Schnider model) was administered. All data was captured by RUGLOOPII(Demed, Temse, Belgium). Ce_{REMI} was started in high(5ng/ml) or low(3ng/ml) dose until steady state. Ce_{PROP} was started at 2µg/ml and increased stepwise(0.5µg/ml/step) until loss of consciousness(LOC), defined as a transition from level 3 to 2 on the Modified Observers Assessment of Alertness and Sedation scale. After an equilibration delay, laryngoscopy was performed and a blinded BIS response was measured for 3 minutes. Interhemispheric differences in BIS larger than 10% are clinically relevant.

Results:
No demographic differences were present between high and low Ce_{REMI} groups, except for age(Table 1). Time to LOC and BIS at LOC was not statistically different between groups(Table 2). Ce_{PROP} at laryngoscopy was 3.4+/-0.7 and 3.7+/-0.9(Mean +/-SD) for respectively the low and high CeREMI group. Regardless of CeREMI, we could not observe interhemispheric BIS responses larger than 10%.

Table 1:

Demographics	Age (years+/-SD)	Weight (kg+/-SD)	Height (cm+/-SD)	Time to LOC (sec+/-SD)
3CeREMI group	50 +/- 11 *	74 +/- 16	170 +/- 9	598 +/- 124
5CeREMI group	43 +/- 9 *	77 +/- 14	173 +/- 10	609 +/- 170

*** p<0.05**

Table 2:

	BIS at LOC	Median BIS one minute before laryngoscopy (baseline)	Median BIS one minute after laryngoscopy	Delta BIS = BIS response
Left hemisphere				
3 CeREMI group	68 +/- 10	57 +/- 9	59 +/- 10	2 +/- 5
5 CeREMI group	73 +/- 8	57 +/- 9	56 +/- 9	-1 +/- 5
Right hemisphere				
3 CeREMI group	69 +/- 9	56 +/- 10	60 +/- 10	3 +/-6
5 CeREMI group	73 +/- 10	57 +/- 10	56 +/- 9	-1 +/-5

Conclusion:
Bilateral BIS measurements may only provide clinical relevant information in diseased brains, as the normal population does not seem to suffer from large interhemispheric differences in BIS behavior.

Objective Cancer-induced bone pain (CIBP) is a major clinical problem for which current treatments lack full efficacy. One of the major reasons is increased osteoclastogenesis activity within cancer bone microenvironment. Calpain inhibitor, a previously demonstrated osteoclastogenesis regulator, was applied both in murine RAW264.7 cells in vitro and in rat CIBP model in vivo to determine whether it could suppress CIBP.

Methods In vitro, Calpain inhibitor Calpastatin Peptide (50nM) was applied in Receptor Activator of NFκB Ligand (RANKL, 50ng/ml)-induced murine RAW264.7 cells for 6 days to investigate its inhibitory effect on osteoclastogenesis activity, through Tartrate-resistant acid phosphatase (TRAP) stain and pit formation assay. In the in vivo study in rat CIBP model using Walker 256 cell line injected into the tibia, the efficacy of Calpain inhibitor III (MDL28170, 1mg/kg) on pain-related behavior test on post-tumor day (PTD) 2, 5, 8, 11, 14, as well as on TRAP stain of the tumor bone on PTD14 were examined.

Results Calpastatin Peptide significantly inhibited TRAP positive cell count ($p<0.05$) and pit formation area ($p<0.05$) in murine RAW264.7 cells in vitro, compared with RANKL induction alone group. Moreover, the behavioral study showed that Calpain inhibitor III can effectively attenuate the operative side pain measured by mechanical withdrawal threshold (MWT) on PTD 5,8,11 in rat CIBP model in vivo ($p<0.05$), but not normalize to the baseline degree ($p<0.05$). Interestingly, the same attenuation effect was seen on the contralateral side of the operation ($p<0.05$). TRAP staining of the tumor injected bone indicated that such analgesic effect was accomplished through inhibition of TRAP positive multinucleated osteoclast cell count ($p<0.05$).

Conclusions Calpain inhibitor can effectively reduce CIBP originated from both ipsilateral and contralateral side of tumor injection in rat model through inhibition of RANKL-induced osteoclastogenesis both in vitro and in vivo. Calpain inhibitor could be a novel therapeutic target to treat CIBP and might involve in neuropathic pain mechanism. Future study is needed to clarify its role in treatment of CIBP.

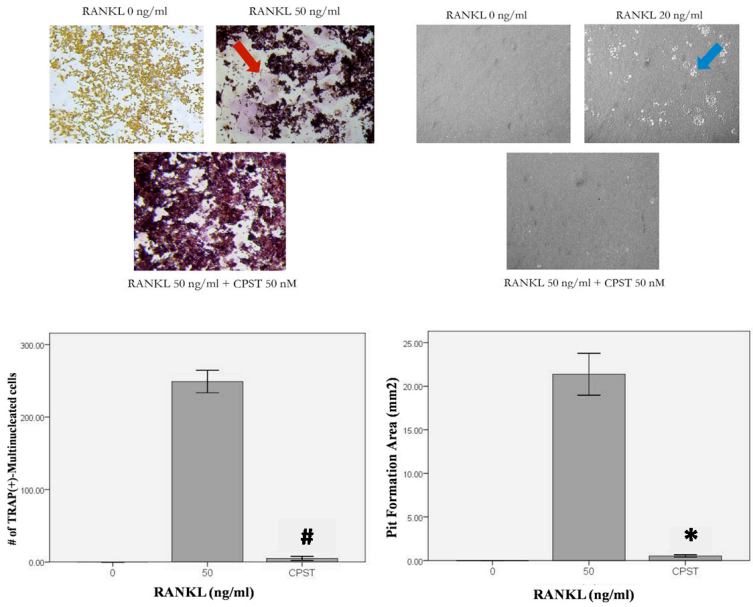


Fig 1 Calpain inhibitor suppresses RANKL-induced osteoclastogenesis in RAW264.7 cells. CPST=Calpastatin. Red arrow indicates TRAP(+) multinucleated cells, blue arrow indicates pit formation. #, * $P<0.05$ for CPST inhibition vs. RANKL induction only in both TRAP(+) cell count and pit formation area.

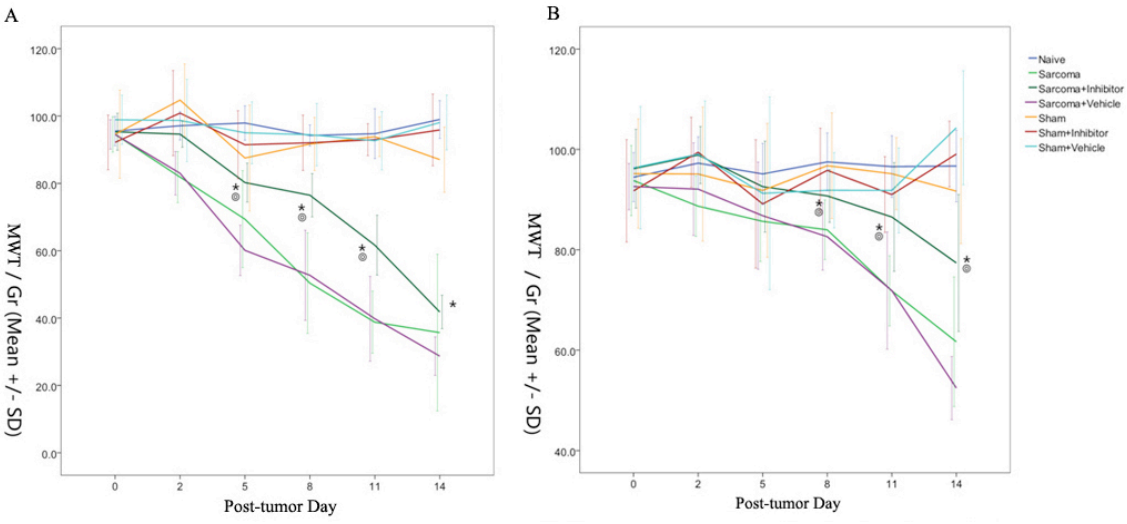


Fig 2 Mechanical Withdrawal Threshold (MWT) of operative side (A) and non-operative side (B) limbs of each group. *, P<0.05 for Sarcoma+Inhibitor vs. Naïve; ◎ , P<0.05 for Sarcoma+Inhibitor vs. Sarcoma+Vehicle.

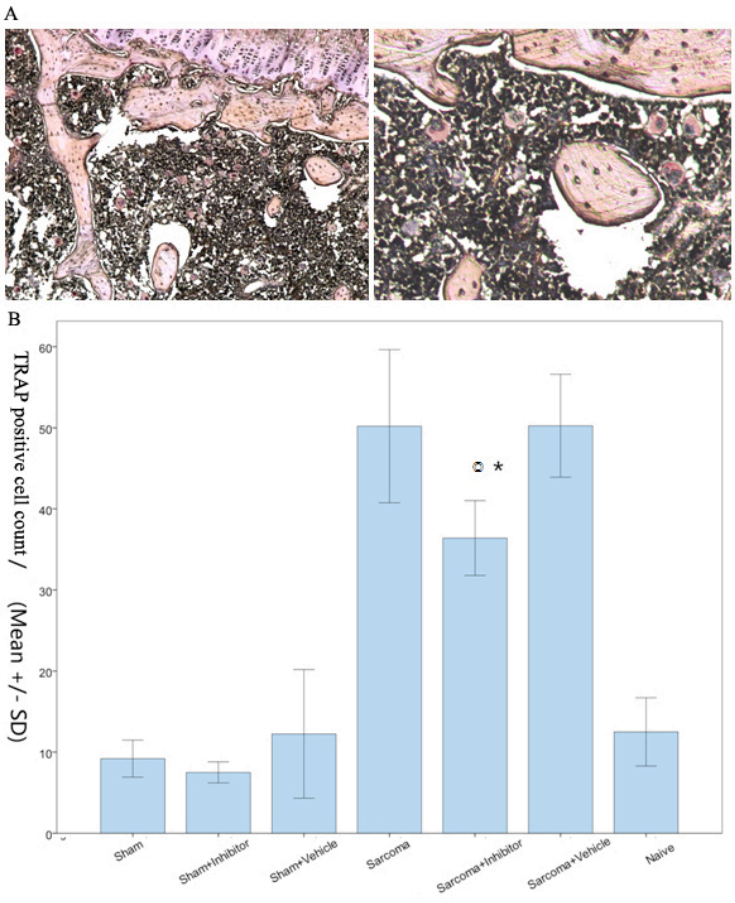
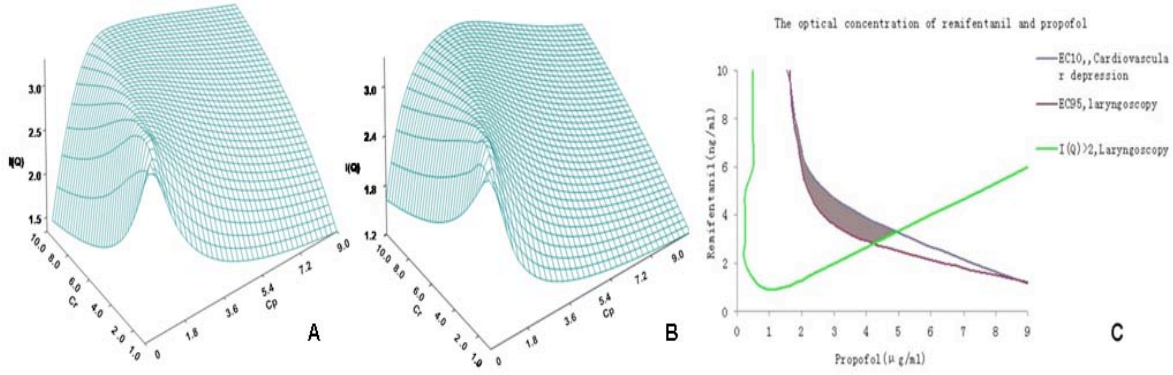


Fig 3 A, TRAP stain of matured osteoclasts in tumor bone site (left 10×10, right 10×20). Arrow indicates matured multinucleated osteoclasts. B, TRAP positive cell count in tumor injected tibia bone of each group. *, P<0.05 for Sarcoma+Inhibitor vs. Naïve; ◎ , P<0.05 for Sarcoma+Inhibitor vs. Sarcoma+Vehicle.

Background: Response surface model (RSM) is a new method to study the pharmacodynamic interactions among anesthetics. The objective of the study was to apply RSM to characterize the interactions between remifentanil and propofol.
Methods: The study was an open-label, randomized, prospective study using parallel slices design. 70 patients with ASA Ⅰ or II, aged 18-65 yr, received target-controlled infusion of remifentanil (0-10ng/ml) and propofol (0-9μg/ml) at various target concentration pairs. After reaching pseudo–steady state drug levels, the response to laryngoscopy and cardiovascular side effects were observed for each target concentration pair. The pharmacodynamic interactions were analyzed by RSM. The response surfaces of laryngoscopy and cardiovascular side effects were combined to identify target concentration range of remifentanil and propofol that provided a high probability of nonresponsiveness to larygoscopy and a low probability of cardiovascular side effects.
Results: Figure A and fugure B showed the relations between remifentanil-propofol concentration and the interaction index (I(Q)) for response to laryngoscopy and cardiovascular side effects, respectively. I(Q) described the pharmacodynamic interactions qualitatively and quantitatively, which indicated strongly synergy between remifentanil and propofol ($P< 0.001$). The dark area in Figure C showed the optical combinations that blunt laryngoscopy without cardiovascular side effects.
Conclusion: RSM can analyze the pharmacodynamic interactions qualitatively and quantitatively. RSM reveals the tremendous synergy between remifentanil (0-10ng/ml) and propofol(0-9μg/ml) in blunting responses to laryngoscopy and cardiovascular side effects.
Supported by the Foundation of the National Natural Science Funds of China (Grant No. 30801423).



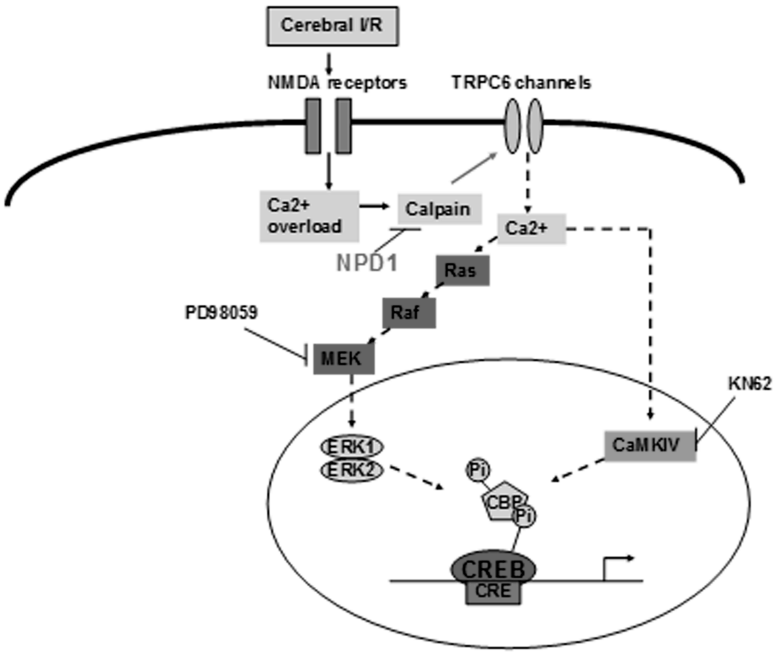
ABSTRACT

Background and objective: Neuroprotectin D1 (NPD1) could serve as an endogenous neuroprotective role in brain ischemia injury, yet the underlying mechanism is poorly understood. We aim to investigate whether intracerebroventricular (ICV) injection of NPD1 is neuroprotective against transient focal cerebral ischemia. We also sought to verify the neuroprotective mechanisms of NPD1.

Experimental approaches: Rats subjected to 2 h ischemia followed by reperfusion were treated with NPD1 at 2 h after reperfusion. PD98059 or KN62 was administrated 20 minutes prior to the operation. Western blot analysis was performed to detect the protein levels of calpain-specific aII-spectrin breakdown products of 145kDa (SBDP145), TRPC6 and phosphorylation of cAMP/Ca^{2+}-response element binding protein (p-CREB) at 12, 24 and 48 h after reperfusion. The immunoreactivity of p-CREB and TRPC6 were measured by Quantum Dots-based Immunofluorescence analysis. Infarct volume and neurologic scoring were evaluated at 48 h after reperfusion.

Results: NPD1, when applied at 2 h after reperfusion, significantly reduced infarct volumes and increased neurologic scores at 48 h after reperfusion accompanied by elevated TRPC6 and p-CREB activity and decreased SBDP145 activity. When mitogenactivated protein kinase kinase (MEK) or calcium/calmodulin-dependent protein kinase (CaMKIV) activity was specifically inhibited, the neuroprotective effect of NPD1 was attenuated and correlated with decreased CREB activity.

Conclusions: Our results clearly showed that ICV injection of NPD12 h after reperfusion improves the neurological status of MCAO rats through the inhibition of calpain-mediated TRPC6 proteolysis and the subsequent activation of CREB via the Ras/MEK/ERK and CaM/CaMKIV pathways.



Electrophysiological effects of etomidate on neurons of primary sensory cortex in rat

Introduction: The primary somatosensory cortex（S1）is the senior nerve center of the specific projection system , one of the key brain structures for central processing of somatic noxious information to produce pain perception. At present, most investigation in the mechanism of general anesthesia is focused on thalamus and hippocampus, which refers to consciousness and memory. But the local effects of anesthetics on the specific projection system are barely reported. Our previous *in vivo* studies have demonstrated that the spontaneous activity in S1 was weakened under propofol anesthesia (propofol inhibits the spontaneous activity of S1). However, no *in vivo* information is available for the properties of electrophysiology of pyramidal neurons in S1. We therefore studied the electrophysiological actions of etomidate (Et) on pyramidal neurons in S1 area slices of juvenile rats.

Aim: Using whole cell patch-clamp techniques, we investigated the effects of Et on sodium channels, potassium channels and action potential (AP) of pyramidal neurons in S1.

Methods: After the preparation and maintenance of the slices as well as electrophysiological and pharmacological techniques are used, Near steady-state, voltage-current relationships were obtained by applying ramp commands during voltage-clamp condition (and AP were obtained during current-clamp condition). According to the different kinds of ion channels, the slices were divided into the sodium channels group, the potassium channels group and the AP group. Each group contains control group and the experiment group. The control group was perfused with normal ACSF; the experiment group was perfused with ACSF containing

different concentrations of Et. Then by applying various protocols, we investigated if the Et could dose-dependently affect the activation process, the deactivation process and the de-inactivation process of the sodium channels; the activation process of the potassium channels; and the electronic portrait of single AP.

Results:

1. Action potentials: When perfused with increasing concentrations of Et, the threshold potential of neurons was ascended, action potential amplitude was decreased, duration of threshold potential to peak potential was widened, and slope of depolarization was slowed(Fig.1).

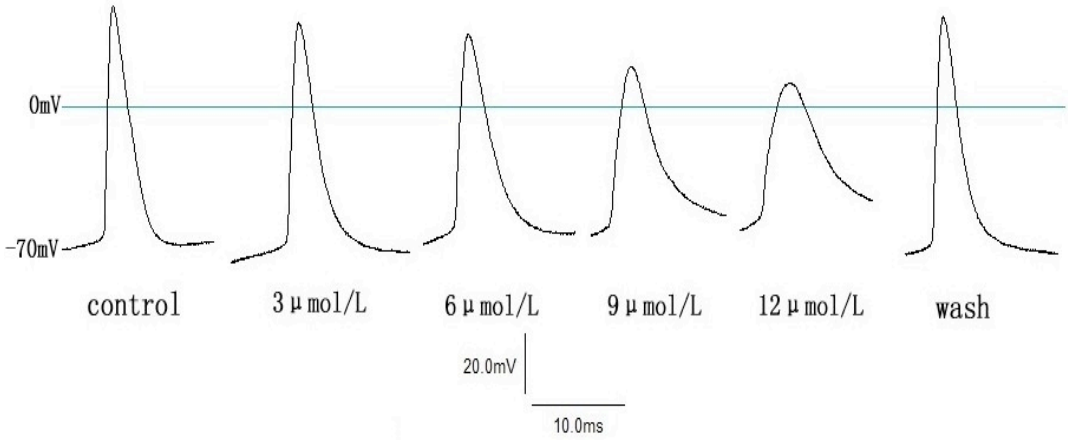


Fig.1 Et could dose-dependently change the electronic portrait of single APTable.1

2. The sodium currents on pyramidal neurons in S1 was remarkably decreased under different concentrations of Et; however, different concentrations of Et did not affect the activation property of sodium current on pyramidal neurons in S1; Et could dose-dependently hyperpolarize the steady-state inactivation curve of sodium currents on pyramidal neurons in S1; and prolong the time course of the recovery from inactivation.

3. The transient outward potassium currents on pyramidal neurons in S1 was dose-dependently reduced by Et; furthermore, Et could dose-dependently depolarize the steady-state activation curve of

transient outward potassium currents on pyramidal neurons in S1; however, Et dose-dependently activated the delayed rectification potassium channels without affecting the activation property of delayed rectification potassium current.

Conclusions:

We demonstrated for the first time that etomidate dose-dependently suppressed the excitability of neurons through blocking neural sodium channels and potassium channels, which may contribute to the mechanisms of Et-induced general anesthesia.

Preliminary research of neuroprotective effects of recombinant human erythropoietin in pediatric open-heart surgery

Backgroud

Erythropoietin(EPO) has been widely used in different clinical conditions. Recent studies have demonstrated that EPO may play a role in the development of the brain and subsequently in the maintenance of cerebral homeostasis. Evidences have established that EPO offers promise as a treatment for brain injury. The purpose of this study was to evaluate the neuroprotective effects of EPO on children scheduled for open-heart surgery.

Materials and methods

45 children scheduled for VSD and/or ASD repairment were randomly divided into control group and two study groups(n=15). The patients in study groups received single dose of recombinant human erythropoietin(rHuEPO) 50IU/kg(EPO1) or 100IU/kg(EPO2) intravenously before anesthesia induction, respectively. Cerebral oxygenation was monitored continuously and non-invasively using near-infrared spectrometry(NIRS) during surgery. Blood samples were taken intravenously before anesthesia induction(t_1), 1h(t_2) and 20h(t_3) after CPB. Serum concentrations of neuron specific enolase(NSE) and S100 protein were detected.

Results

Intracranial oxygenation status at different time point showed significant difference within each group(P<0.01). But there wasn't significant difference among three groups(P>0.05). After pretreatment with rHuEPO 50IU/kg, all of the parameters provided by NIRS showed ameliorated tendency but with no statistical significance. Among those, ScO_2 representing for the balance of oxygen supply and consumption decreased less compared with that of control group. ΔHHb representing for oxygen extraction changed to a relatively less extent than control group. ΔO_2Hb representing for cerebral arterial blood flow recovered relatively faster after ischemia and ΔcHb representing for cerebral blood volume decreased relatively slower. Increasing the dosage of rHuEPO didn't bring further improvement of these parameters. Serum concentrations of NSE and S100 protein at different time point had significant differences within each group and among three groups(P<0.01). The serum

concentrations of these two neurobiochemical markers increased significantly at 1h after CPB compared with basic level and remained higher at 20h after CPB in control group, while in EPO1 group the serum concentrations increased significantly at 1h after CPB and recovered to basic level at 20h after CPB. Giving high dosage(100 IU/kg) didn't show any further improvement.

Conclusions

rHuEPO could ameliorate neurobiochemical markers of children undergoing open-heart surgery. The results of cerebral oxygenation could also be improved to some extent. rHuEPO might play a role of neuroprotection in CNS ischemic-hypoxic injury.

Reference

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2. Juul S. Erythropoietin in the central nervous system, and its use to prevent hypoxic-ischemic brain damage. *Acta Paediatr Suppl.* 2002;(438):36-42.

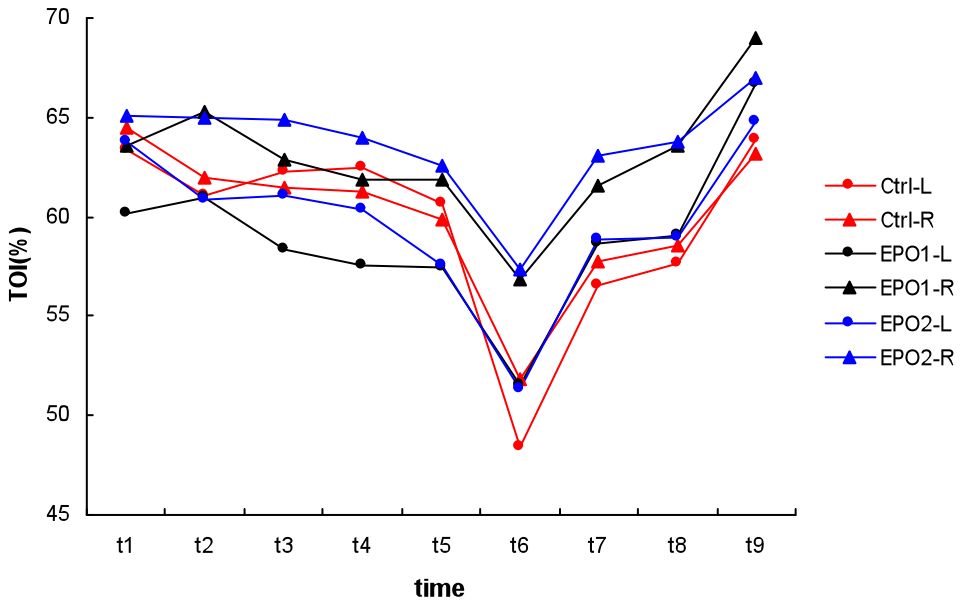

Fig. 1 Changes in bilateral TOI（%）

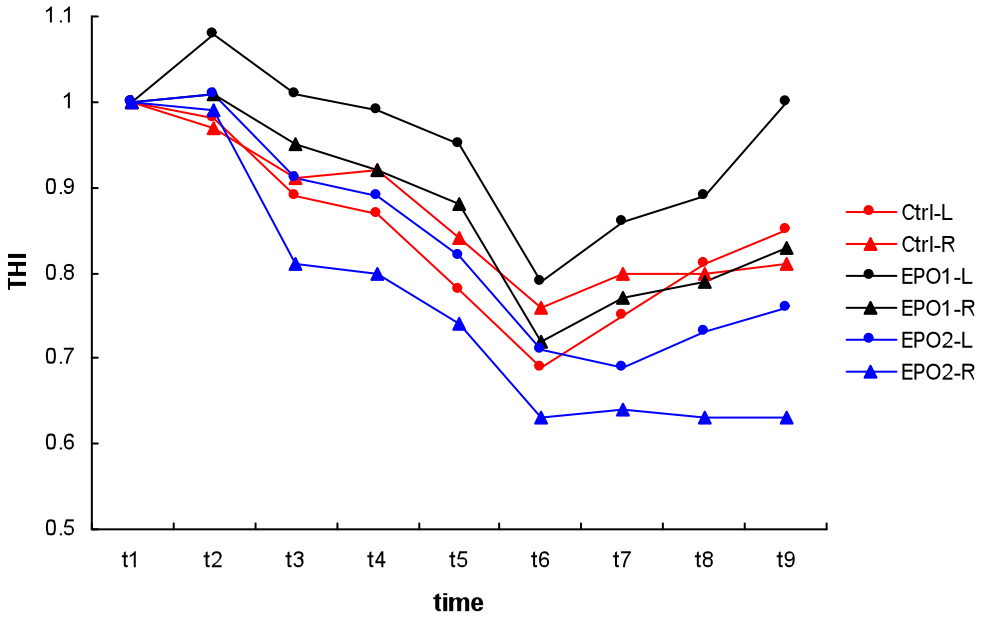

Fig. 2 Changes in bilateral THI

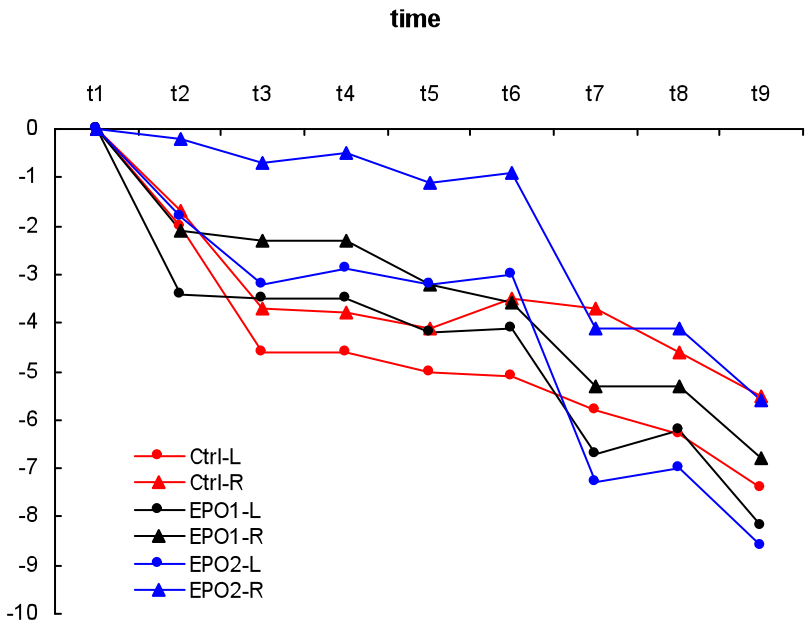

Fig. 3 Changes in bilateral ΔHHb

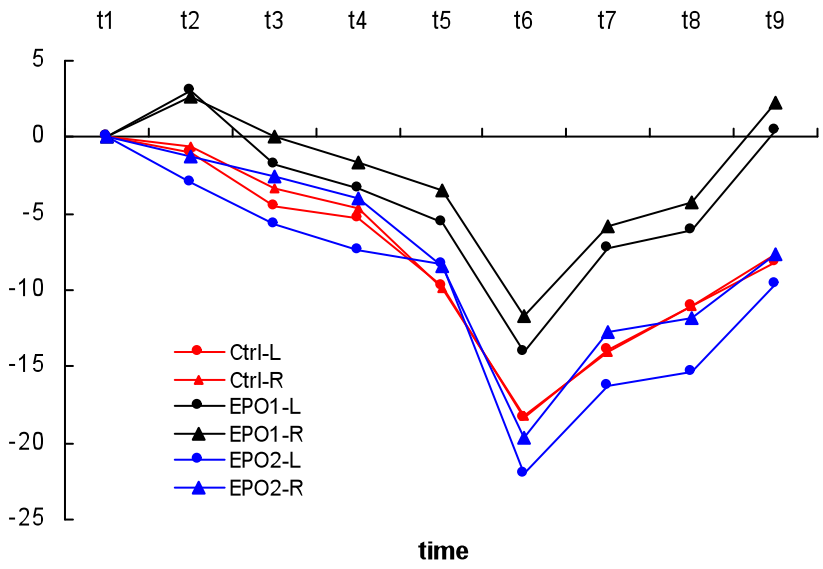

Fig. 4 Changes in bilateral ΔO_2Hb

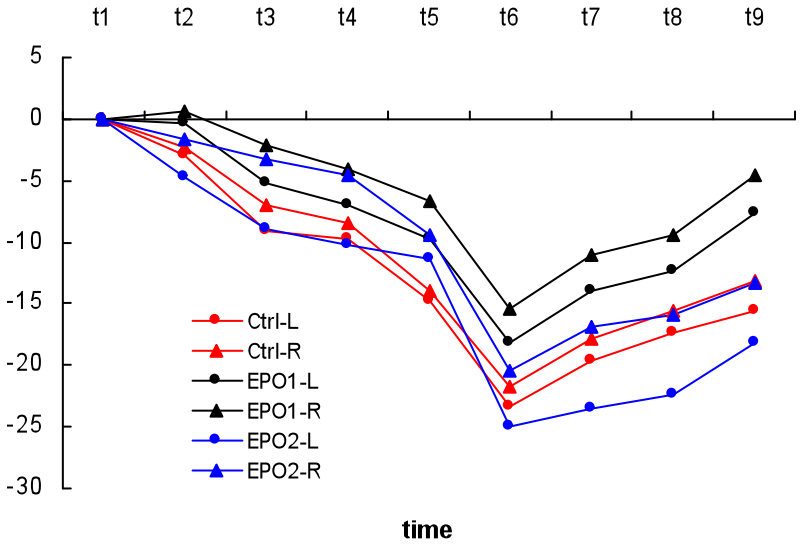

Fig. 5 Changes in bilateral ΔcHb

Table 1. Changes in NSE and S100 protein (μg/L) ($\bar{x}$ ±s)

		NSE			S100		
	n	t_1	t_2	t_3	t_1	t_2	t_3
Ctrl group	15	6.5±2.0	35.3±14.5**	23.4±7.3**	0.55±0.11	1.20±0.43**	0.85±0.47
EPO1	15	5.4±1.6	27.7±7.4**	9.8±5.3$^{\Delta\Delta\#\#}$	0.62±0.07	0.91±0.11**$^{\#\#}$	0.70±0.12$^{\Delta\Delta}$
EPO2	15	6.3±2.3	29.7±10.9**	17.4±12.8	0.62±0.13	1.09±0.33**	0.74±0.17$^{\Delta\Delta}$

**P<0.01, compared with t_1; $^{\Delta\Delta}P$<0.01, compared with t_2; $^{\#\#}P$<0.01, compared with control group

Objective To investigate the effect of parecoxib on postoperative hyperalgesia induced by remifentanil-based anesthesia.

Methods One hundreds ASA Ⅰ or Ⅱ patients, aged 21-64yr, weighing 50~80 kg, undergoing elective laparoscopic operation, were randomly divided into 5 groups (n=20 each): parecoxib group(group P), small-dose remifentanil group (group S), large-dose remifentanil group (group L), small-dose remifentanil + parecoxib group (group SP) and large-dose remifentanil + parecoxib group (group LP). Parecoxib 40 mg was injected intravenously at 30 min before anesthesia in Group P, SP and LP. Anesthesia was induced with midazolam 0.05 mg/kg, etomidate 0.2 mg/kg, cisatracurium 0.15 mg/kg and remifentanil 1 μg/kg (fentanyl 4μg/kg in group P). The patients was tracheal intubated and mechanically ventilated. $P_{ET}CO_2$ was maintained at 35-45 mm Hg. Anesthesia was maintained with infusion of remifentanil at 0.05μg·kg^{-1}·min^{-1}(in group S and SP) or at 0.3μg·kg^{-1}·min^{-1} (in group L and LP) combined with inhalation of sevoflurane and infusion of cisatracurium at 0.12mg·kg^{-1}·h^{-1} . At 30 min after operation, numeric rating scale (NRS) was used to assess the degree of pain at rest and during activity. Tramadol 1.5 mg/kg was injected intravenously after opration if needed. NRS scores were maintained ≤5. The use of tramadol and adverse effects during 24h after operation were recorded.

Results Compared with group P, NRS scores at rest and during activity were significantly increased at 30 min after operation in group S and L, the incidence of shivering and the number of patients who needed tramadol were significantly increased in group L, and no change was found in NRS scores at rest and during activity at 30 min after surgery, the incidence of adverse effects and the number of patients who needed tramadol in group SP and LP. Compared with group S, NRS scores at rest and during activity at 30 min after operation, the incidence of shivering and the number of patients who needed tramadol were significantly increased in group L, NRS scores at rest and during

activity at 30 min after surgery were significantly decreased and no change was found in the incidence of adverse effects and the number of patients who needed tramadol in group SP. Compared with group L, NRS scores at rest and during activity at 30 min after operation, the incidence of shvering and the number of patients who needed tramadol were significantly decreased in group LP.

Conclusion intravenous injection of parecoxb 40 mg at 30 min before anesthesia can attenuate postoperative hyperalgesia induced by remifentanil-based anesthesia.