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DRUG DEPOSITION

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Cardioprotective effects of short-term statins administration in diabetic rats

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Introduction: Diabetic patients have a higher incidence of cardiovascular diseases and are more prone to cardiac complications than non-diabetic individuals. The HMG-CoA reductase inhibitors (statins) are used extensively in the treatment of hyperlipidemia.1 Statins have also demonstrated cardiovascular improvement in postoperative outcomes among patients taking them in the perioperative period2 regardless of their cholesterol level. This improvement may be related to the pleiotropic effects of these drugs.3 Although multiple clinical trials have demonstrated the beneficial effects of statin therapy for primary and secondary prevention of cardiovascular disease, the optimal time for administration of these drugs to improve postoperative outcomes is still unclear.
Objectives: To determine the optimal time of administration of statins that cardioprotective effects are obtained during the preoperative period in streptozotocin (STZ)-induced diabetic rats.
Methods: To evaluate the effect of statins on the cardiovascular system, echocardiographic evaluations were performed on STZ- diabetic rats treated with simvastatin (SV, 10 mg/kg/day); pravastatin (PV, 10 mg/kg/day); or atorvastatin (AV, 10 mg/kg/day). Untreated diabetic rats were used as controls. Diabetes was induced in male Sprague-Dawly rats by IP injection of streptozotocin (STZ, 65 mg/kg). Diabetic rats were used at four weeks after diabetes induction, and glucose levels were monitored once a week. Serial transthoracic echocardiographic evaluations were performed in treated and untreated diabetic rats. Cardiac function was evaluated at 24-hour and 1 week after statin administration.
Results: A significant increase in ejection fraction was found after 24-hour administration of statins in the three groups (AV: $57.67 \pm 10.47\%$; PV: $51 \pm 8.44\%$; SV $65 \pm 9.5\%$; N=4) when compared to non-treated diabetic rats ($44 \pm 0.1\%$, N=4). Cardiac output index (ml/min x 100 gBW) (AV: 88.55 ± 29.54; PV: 81.58 ± 29.31; SV: 90.39 ± 18.86; N=4) and stroke volume (mL) (AV: 0.63 ± 0.23; PV: 0.58 ± 0.17; SV: 0.60 ± 0.16; N=4) were also significantly increased compared with non-treated diabetic rats (COI: 52 ± 15.76; Stroke Volume: 0.31 ± 0.03 mL). No significant changes in heart rate were noted in any group. After one week administration of AV and SV, cardiovascular parameters were similar to those observed after 24-hour treatment. However, in the PV group, the beneficial effect was not maintained and ejection fraction and cardiac output index were similar to those in untreated-diabetic rats.
Conclusions: These results showed that cardioprotective effects of statins in diabetic rats are seen as early as 24 hours after administration of the drugs. The later may have positive clinical implications on diabetic patients during perioperative period.

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Comparative Effects of Lipid Emulsion on the Recovery from Levobupivacaine-induced or from Ropivacaine-induced Cardiac Arrest in Rats

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Introduction: The infusion of lipid emulsions is a promising approach to treat local anesthetics-induced cardiac arrest. As the postulated mechanism of action, the so-called "lipid sink" effect, may depend on the lipophilicity of local anesthetics.

Objectives: To test the hypothesis that the lipophilicity of local anesthetics has a marked impact on the efficacy of lipid infusions to treat cardiac arrest induced by these drugs, we compared lipid resuscitation from levobupivacaine (high lipophilicity) and ropivacaine (low lipophilicity)-induced cardiac arrest in awake rats.
Methods: Twelve female SD rats anesthetized with sevoflurane were underwent tracheostomy and cannulated through the right femoral artery and vein. Two hours after discontinuation of sevoflurane inhalation, the rats received one of the two local anesthetics, levobupivacaine 0.25% (n=6), or ropivacaine 0.2% (n=6) at a rate of 2 mg/kg/min. We calculated the cumulative doses of local anesthetics required to induce the first seizure activity and pulse pressure of 0 mmHg. When pulse pressure decreased to zero, infusion of local anesthetics was stopped, and ventilation with 100% oxygen and chest compressions were begun immediately, along with intravenous treatment with 30% lipid emulsion (5 ml/kg bolus plus continuous infusion at 0.5 ml/kg/min). Chest compressions were continued until the native rate-pressure product increased by more than 20% of baseline. Electrocardiogram and arterial blood pressure were monitored continuously. Data were expressed as mean ¬¬± SD. Statistical analysis were using Student-t test with Bonferroni correction, and $P<0.05$ was considered statistically significant.
Results: Baseline (before infusion of local anesthetics) arterial blood gas values, mean arterial blood pressure (MAP) and heart rate (HR) did not differ between groups. There were no significant differences between cumulative doses of levobupivacaine and ropivacaine that produced seizures and no pulse pressure. When pulse pressure decreased to 0 mmHg, MAP and HR did not differ between groups (6.8 ± 1.3 vs 7.6 ± 1.3 mmHg, 47 ± 15 vs 40 ± 25 bpm, respectively). The values of MAP were higher in levobupivacaine group than ropivacaine group at 2, 3, 4, 5 and 10 min after the start of resuscitation. (22 ± 6 vs 11 ± 7, 31 ± 5 vs 16 ± 6, 38 ± 13 vs 16 ± 5, 54 ± 32 vs 16 ± 4, 184 ± 15 vs 77 ± 60 mmHg, respectively) ($P< 0.05$). The HR values were higher in levobupivacaine group than ropivacaine group at 5 min after resuscitation. (302 ± 84 vs 152 ± 75 bpm) ($P< 0.05$).
Conclusions: Though there were no significant differences between cumulative doses of levobupivacaine and ropivacaine that produced seizures and cardiac arrest, lipid therapy was more effective in resuscitation from levobupivacaine-induced than ropivacaine-induced cardiac arrest.

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Residual Concentrations of Propofol in the Blood and Brain after Administration in Rats

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Introduction: Mechanism of postoperative cognitive dysfunction (POCD) is not well understood. Spatial memory is reported to be impaired after administration of inhaled anesthetics but not propofol in rats (1). We have also observed that sevoflurane remained in the brain more than 7 days after inhalation in rats (2).
Objectives: If residual anesthetics account for POCD, propofol would disappear from the brain sooner as compared with sevoflurane. To test this hypothesis, we measured propofol concentrations in the blood and brain after administration in rats.
Methods: After approval by the animal research committee, fifteen SD rats were anesthetized with propofol (10 mg/kg bolus plus continuous infusion at 1 mg/kg/min) for 2 hours. Five minutes, 1 and 2 days (n=5 in each group) after discontinuation of propofol infusion, blood samples were collected and brains were perfused with heparinized saline. We also observed control rats without anesthesia (n=3). The blood (1 mL) was placed into a vial containing saline (1 mL) and boric acid buffer solution (0.5 mL, pH=9). Mixture of chloroform and ethyl acetate (extraction solution, 0.5 mL), containing 10 ppm of thymol (an internal standard substance) was added. The blood-solvent mixture was poured into the Ultrafree-CL filter devices and was centrifuged. A 1 μL sample of the extraction solution containing propofol and thymol was injected into the gas chromatograph-mass spectrometry (GCMS-QP2010 Plus, Shimadzu, Kyoto, Japan). The sampled brain was placed into a vial containing the mixture of 2M KCl and 2M NaOH (1 mL, pH=12.4) and was homogenized. All other protocols were identical to those in blood sample. The minimum detection limit is 0.2 ppm, and the concentrations of propoifol were calculated as μg/g. Data were expressed as median (min, max).
Results: Propofol concentrations in the blood and brain after propofol anesthesia were 8.31 (6.79-9.14) and 10.98 (10.86-15.74) μg/g after 5 minutes, and 0.20 (0.19-0.22) and 0.94 (0.91-1.05) μg/g after 1 day, respectively. Propofol was not detected in both blood and brain 2 days after anesthesia as well as in the control rats. Propofol concentrations in the blood and brain 1 day after anesthesia were 2.4 and 8.6% of those of 5 min after anesthesia, respectively. The brain concentrations of propofol 5 min and 1 day after anesthesia were approximately 1.3 and 4.7 times of the corresponding blood concentrations, respectively.
Conclusions: Propofol disappeared in both blood and brain 2 days after propofol anesthesia. Our results indicate that subanesthetic concentration of anesthetics could be one of the causes of POCD.

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Effects of intra-operative sedation with low-doses of s-ketamine on depression: randomized double-blind controlled trial

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Introduction: The available antidepressants block neuronal reuptake of catecholamines, serotonin or both. They take weeks to produce full clinical effects, which suggest that the NMDA system may be involved in the pathophysiology of depression [1]. Ketamine, a non competitive antagonist acting at NMDA receptors, is reported to have a rapid onset of anti-depressive effects [2,3,4].
Objective: To investigate the effect of intra-operative sedation of S-ketamine on indices of depression. **Method**: 80 patients aged 60 to 83 years of age, selected for surgery under epidural anesthesia, were classified as depressed (D) or non-depressed (ND), according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria, and randomized into two sub-groups D1, D2 and ND1, ND2. The sub-groups D1 and ND1 received S-ketamine and midazolam, while the groups D2 and ND2, received only midazolam. Sedation was titrated to achieve grade 3-4 of the Ramsay Sedation Scale. Depression was assessed using the Hamilton Depression Rating (HDR) Scale of 21 items, applied preoperatively and postoperatively.
Results: The mean HDR score decreased from the preoperative value of 18.8 Â ± 6,3 to 12.7 Â ± 4.5 on the second postoperative day in depressed patients who received S-ketamine+midazolam (P Ë“ 0,0001). There were no significant differences between the non depressed groups.
Discussion: Racemic ketamine have clinical effects similar to the classic antidepressants, but with a quicker onset and a lasting effect [2,3,4]. We demonstrated that S-ketamine can improve depressed patients the same way. The modest doses of S-ketamine and the epidural anesthesia may have accounted for the absence of hypertension in all groups. No arrhythmias were found. The use of midazolam lowered the incidence of psychotomimetic effects [5], decreased the cardiovascular stimulating effects of ketamine on the systemic and pulmonary circulation [6,7] and allowed intra-operative sedation. Patients who suffer from depression appear to appreciate pain with greater acuity [8]. Actually, depressed patients felt more pain in the postoperative period than the non-depressed ones. Postoperative analgesic effects of S-ketamine are still under discussion [9,10], but they could potentially have improved depression. However depressed patients (D1) had a significant amelioration in the severity of their depression despite no significant differences in pain scores, from D2 group. Therefore we exclude the putative analgesic effects of S-ketamine as a cause for the improved postoperative depressed state of these patients.
Conclusions: Intra-operative sedation with low doses of S-ketamine has a beneficial effect on depressed patients.

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Comparison between sedative effects of propofol-fentanyl versus propofol-midazolam combinations in microlaryngeal surgeries

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Background and objectives: Considering the growing trend of laryngeal surgeries and the need to protect the airway during and after surgery, among several therapeutic regimens to induce sedation, two regimens of propofol-fentanyl and propofol-midazolam were compared in microlaryngeal surgeries.
Methods: Forty ASA I-II class patients undergoing microlaryngeal surgeries and referring routinely for postoperative visits were randomly recruited into two groups. In all the patients, 0.5 mg/kg of propofol was used as bolus and then after 50 mcg/kg/min of the drug was infused intravenously. One group 0.03 mg/kg bolus of midazolam and in the other group, 2 mcg/kg bolus of fentanyl was administered in combination with propofol. Ramsay system was used in order to evaluate the effect of the two drugs in inducing sedation. The need for additional dose, blood pressure, heart rate, arterial blood oxygen saturation, and also recovery time and

adverse effects such as nausea/vomiting and recalling intraoperative memories, were assessed.

Results: The patients in the two groups were not statistically different regarding number of patients, age, sex, preoperative vital signs, the need for additional doses of propofol, systolic blood pressure and mean systolic blood pressure during laryngoscopy. However, mean systolic blood pressure 1 minute after removal of laryngoscope returned faster to the baseline in midazolam group ($P<0.01$). Mean heart rate returned sooner to the baseline in fentanyl group following removal of stimulation. Besides, heart rate showed a more reduction following administration of fentanyl ($P<0.02$). Mean arterial blood oxygen saturation during laryngoscopy significantly decreased more in fentanyl group ($P<0.05$). The time it took to achieve a full consciousness was shorter in midazolam group ($P<0.01$). Nausea/vomiting was significantly more prevalent in fentanyl group while the patients in midazolam group apparently experienced amnesia more ($P<0.01$).

Conclusion: Inducing laryngeal block and local anesthesia using propofol-midazolam regimen is not only associated with a more rapid recovery and less recalling of unpleasant memories, but also better prevents from reduction of arterial oxygen saturation during laryngoscopy compared with propofol-fentanyl regimen.

Keywords: Sedation; Microlaryngeal surgery; Propofol; Midazolam; Fentanyl