

Effects of Propofol and Remifentanyl Combination Anesthesia on Intraocular Pressure and Hemodynamic Parameters in Dogs

Tae-Sun Lim, Sung-Ho Yun, Ji-Hee Park, Young-Sam Kwon and Kwang-Ho Jang¹

Department of Surgery, College of Veterinary Medicine, Kyungpook National University, Daegu 702-701, Korea

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Abstract : The objective of this study was to determine the effect of propofol and remifentanyl combination on hemodynamics and intraocular pressure (IOP), and to compare with those of isoflurane in beagle dogs. Fourteen clinically healthy beagle dogs were divided randomly into 2 groups and each group was consisted with 7 dogs. Anesthetic agents were propofol (0.2 mg/kg/min) plus remifentanyl (0.5 µg/kg/min, 1% solution in standard saline) in one group (group PRP) and 3% isoflurane in the other group (group ISF). Anesthesia was maintained for 90 min in the both groups. IOP, blood pressure, heart rate and blood gas values (pH, PaCO₂, PaO₂, SaO₂, tCO₂, HCO₃⁻) were recorded at 5, 10, 15, 30, 45, 60, 75 and 90 min in the both groups. IOP values in both eyes were significantly decreased in group PRP compared with those in group ISF. but there were no significant differences between two eyes in each group. Systolic, diastolic and mean blood pressures were significantly decreased in group PRP within the normal range. There were no differences between groups in all blood gas parameters. In this study, propofol and remifentanyl combination could provide stable IOP and blood pressure compared with isoflurane.

Key words : IOP, blood pressure, remifentanyl, propofol, dog.

Introduction

Variable ophthalmic surgeries can be processed with simple local anesthesia in human, even at complicate procedure like phacoemulsification (21,40,41), but general anesthesia is practically essential for restraint in veterinary medicine. Because anesthetic agents may alter the intraocular pressure (IOP) during anesthesia, one of the most important things to be regarded during anesthesia for ophthalmic surgery is to provide adequate control of IOP. Because, patients could have potential glaucoma or other ophthalmic problems, normal or mildly decreased IOP should be maintained during non-ophthalmic surgery as well as ophthalmic surgery (31,35).

The high IOP during anesthesia could make the patient with glaucoma worse, compromise postoperative visual function and impair the intraoperative conditions. It may also cause an expulsion of intraocular contents with transient or permanent damage to the eye. Eventually, raise of IOP worsen the prognosis after surgery. Open eye surgeries, such as removal of foreign body, penetrating keratoplasty, cataract extraction, and iridectomy need especial concern about changes of IOP. Therefore, clinicians should choose the anesthetic regime that could minimize the variations in IOP and, especially, prevent high IOP or IOP spike (19,30).

IOP is altered mainly by aqueous humor production and outflow, and other factors including changes in the choroidal

blood volume, central venous pressure and extraocular muscle tone (15,20,32). Many previous studies tempted to examine the relation of IOP between anesthetic agents. Although precise mechanisms are unclear, most of anesthetic agents reduce IOP by increasing of the aqueous humor outflow, relaxing extraocular muscle tone and depressing diencephalic function, except ketamine (3,12,17). Isoflurane, same as other inhalants, is known to decrease IOP by suppressing formation of aqueous humour and promoting outflow (31).

Propofol is generally used as inducing and maintaining anesthesia in veterinary medicine because it provides smooth induction, rapid onset, fast clearance, short duration of action and rapid recovery (14,34,37). Because propofol has minimal analgesic effect, it has been concurrently administrated with proper analgesic agent, such as alfentanil or remifentanyl (5,33).

Remifentanyl is a potent µ-opioid receptor agonist and phenylpiperidine opioid that has ultra-short acting properties. It has been known that propofol and remifentanyl have synergistic effect to each other (6,23,27,39). Remifentanyl is distinguished with other opioids by the extraordinary metabolism. Alfentanil, fentanyl and sufentanyl metabolized by liver and excreted by kidney. However, remifentanyl metabolized by ester hydrolysis which is wide spread in the body, and it makes remifentanyl independent on hepatic and renal functions (5,11,38,39).

Remifentanyl could reduce IOP and prevent hemodynamic stress response associated with laryngoscopy and intubation, even in patients who coughed or moved in response to intu-

¹Corresponding author.
E-mail : khojang@knu.ac.kr

bation in human (16). Similarly with remifentanyl, a previous study suggested that propofol makes IOP decrease by increasing trabecular outflow and decreasing production of aqueous humor from the ciliary body in human (30), while no alterations were reported by Batista *et al.* (4).

Coughing, nausea and vomiting could make IOP steeply increase by influencing in intrathoracic and intraabdominal pressure. As propofol has antiemetic effects, incidence of post-operative nausea and vomiting (PONV) is lower than inhalant anesthetic agents. Opioids could increase the frequency of PONV, but combination of propofol and remifentanyl has minimal PONV because remifentanyl is an ultra-short acting opioid (10,28).

Propofol and remifentanyl combination could induce mild hypotensive anesthesia. Deliberate hypotension is reported to be useful to provide stable blood pressure, to minimize hemorrhage during operation and to improve operating conditions for the surgeon (8,9). In the dog with patent ductus arteriosus, the combination of propofol and remifentanyl was used for stable hemodynamics, excellent intraoperative condition and smooth recovery (26).

Recently, some veterinary reports suggested that inhalant agent, such as desflurane and sevoflurane, could increase IOP mildly within normal range, contrasted to previous studies (1,2). Furthermore, there was no published study about the correlation between IOP and anesthesia with combination of propofol and remifentanyl in veterinary medicine.

The objective of this study was to determine the effect of propofol and remifentanyl combination on IOP and hemodynamic parameters in beagle dogs and to compare with that of isoflurane.

Materials and Methods

Animals

The protocol was approved by the Kyungpook National University Animal Ethics Committee (KNU 2012- 46). Fourteen clinically healthy beagle dogs were used and divided randomly into 2 groups (group PRP and group ISF). The age of dogs was 2.4 ± 0.3 years, body weight was 8.4 ± 1.7 kg and body condition scores were between 4~5.

All dogs used in this study were normal in ophthalmic examinations consisted of Schirmer tear test, fluorescein staining examination, applanation tonometry and indirect ophthalmoscopy test. Blood cell count and chemistry examination were also performed to select clinically healthy dogs.

Procedures

Dogs fasted for at least 12 hr before anesthesia. One day before experiment, an arterial catheter (Pediatric jugular catheterization set[®], Arrow international, Inc., USA) was inserted into the right femoral artery under anesthesia with propofol (Provive 1%[®], Claris Lifesciences Ltd., India) and isoflurane (Ifran[®], Hana Pharm. Co. Ltd., Korea). Anesthesia was induced with a bolus of 5 mg/kg propofol given slowly over 1 min

and maintained with 1.9% isoflurane. The incision site was locally anesthetized with subcutaneously injection of 2% lidocaine. A catheter tip was inserted into the femoral artery about 5 cm forwarded to the aorta, and the catheter, through a tunnel under the subcutis, was exited on the median sacral crest. It filled with saline diluted heparin (50 IU/ml) to prevent occlusion of the arterial catheter. The arterial catheter was flushed with saline diluted heparin two times a day. It was used for measuring arterial blood pressure and heart rate, and collection of arterial blood samples.

At least 1 hr before each experiment, the dogs were placed in experimental room for enough acclimation. The arterial catheter was connected to a polygraph (Model 7P1, Grass Instrument Co., USA). After measuring of baseline values in setting position, a 22 gauge intravenous catheter was inserted in the cephalic vein.

Each parameter was measured at 5, 10, 15, 30, 45, 60, 75, and 90 min. Ten min before induction, acepromazine (Sedaject[®], Samu median, Korea, 0.05 mg/kg, IV) was injected for premedication in group PRP. All dogs were injected with atracurium (0.1 mg/kg) concurrently at the beginning of induction for facilitating IOP measurement. Propofol (5 mg/kg) was administered intravenously for 1 min for the induction of anesthesia in both groups.

In group PRP, propofol (0.2 mg/kg/min) and remifentanyl (UltivaTM[®], GlaxoSmithKline, Italy, 0.5 µg/kg/min, 1% solution in standard saline) was intravenously infused by using two syringe pumps just after induction.

In group ISF, isoflurane was initially given by 3% and, when anesthetic state was stable, it reduced by 1.9%. Same volume of normal saline as that of propofol and remifentanyl in group PRP was constantly injected.

During anesthesia, in both groups, intermittent positive ventilation with 100% oxygen (15 to 20 ml/kg/min) was applied to maintain SpO₂ and end-tidal CO₂ to 95~100% and 35~45 mmHg, respectively. The inspiratory pressure of ventilator did not exceed 15 mmHg, and inspiration/expiration ratio was 1:2.

Dogs were positioned in right lateral recumbency. Proparacaine hydrochloride (Alcain[®], Alcon-Couvreur, Belgium) were applied to the cornea 1min before measuring IOP with applanation tonometry. Temperature of the dog was maintained in normal range from 37.5°C to 39.0°C by using circulating warm water blanket.

Evaluation parameters

IOP

IOP was measured with an applanation tonometer (Tonopen[®]XL, Medtronic Solan, USA) at the central cornea. The tonometer was calibrated before each measurement and mean IOP was automatically calculated by the tonometer.

Hemodynamic measurement

Heart rate and systolic/diastolic arterial pressure were measured with the polygraph. Heart rate values were recorded at a

speed of 25 mm/sec and were calculated from the mean of 10 seconds. Systolic arterial blood pressure (SAP) and diastolic arterial blood pressure (DAP) were recorded at a speed of 50 mm/min and calculated from the mean of 1 min records. Mean arterial blood pressure (MAP) was calculated based on systolic and diastolic pressure.

Blood gas parameters

pH, PaCO₂, PaO₂, SaO₂, tCO₂ and HCO₃⁻ were measured with an portable blood gas analyzer (i-STAT[®] Analyzer MN300, i-STAT Co. Ltd, USA) and test cartridges (i-STAT[®] G3+ cartridge, Abbott Point of Care Inc., USA). The analysis was carried out immediately after blood sampling. The arterial blood sample was collected by 0.3 ml through the arterial catheter and catheter was flushed with 0.3 ml heparinized saline after each blood sampling.

Statistical analyses

Values were presented as mean ± standard deviation. Statistical analyses were performed with IBM SPSS Statistics Version 19 (IBM SPSS Inc, Chicago, IL, USA). The differences between groups were statistically analyzed by repeated measure analysis of variance (ANOVA). Paired *t*-test was performed to analyze differences between baseline and other values within groups. Statistical differences were compared between group PRP and ISF at each periods using the independent *t*-test.

Results

IOP

In IOP, there was significant difference between groups (F[1,12] = 66.51, *p* < 0.001). The results are shown in Fig. 1

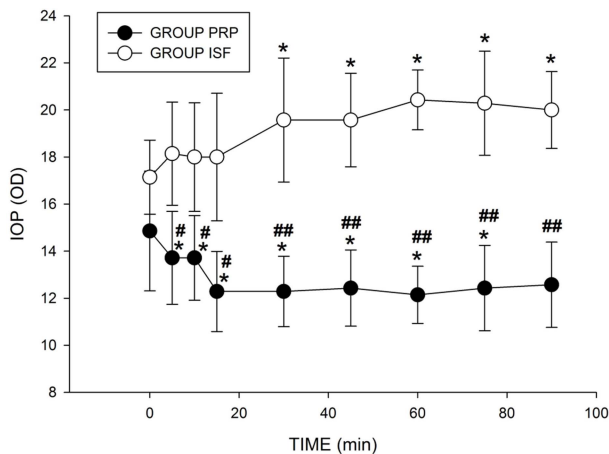


Fig 1. IOP of right eyes in dogs anesthetized with isoflurane or propofol and remifentanyl combination. Group PRP: Group anesthetized with propofol and remifentanyl combination; Group ISF: Group anesthetized with isoflurane. Data are expressed as mean ± SD. *, significantly different from baseline (*p* < 0.05). #, ##, ###; significantly different between groups (*p* < 0.05, *p* < 0.001, respectively).

and 2. The values of IOP in the right eye between group PRP and group ISF were significantly different at independent *t*-test throughout anesthesia (*p* < 0.05).

Right eye's (OD [oculus dexter]) IOP of group PRP were decreased compared to baseline at 10 to 75 min, and that of group ISF were increased at 30 to 90 min (Fig 1). Left eye's (OS [Oculus Sinister]) IOP showed significant difference between group PRP and ISF (F[1,12] = 108.19, *p* < 0.001). Significant differences also appeared between groups in entire anesthetic state. Significant differences were found between

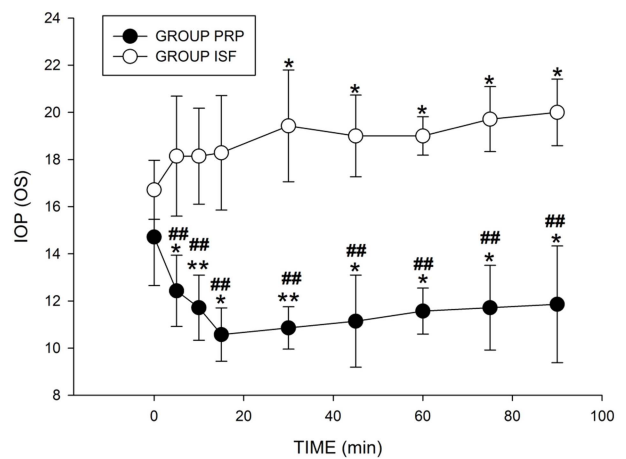


Fig 2. IOP of left eyes in dogs anesthetized with isoflurane or propofol and remifentanyl combination. Group PRP: Group anesthetized with propofol and remifentanyl combination; Group ISF: Group anesthetized with isoflurane. Data are expressed as mean ± SD. *, **, significantly different from baseline (*p* < 0.05, *p* < 0.001, respectively). #, ##, ###; significantly different between groups (*p* < 0.05, *p* < 0.001, respectively).

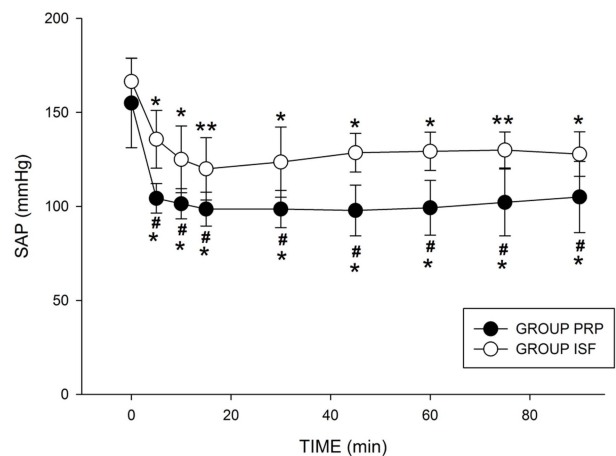


Fig 3. Systolic arterial blood pressure in dogs anesthetized with isoflurane or propofol and remifentanyl combination. Group PRP: Group anesthetized with propofol and remifentanyl combination; Group ISF: Group anesthetized with isoflurane. Data are expressed as mean ± SD. *, **, significantly different from baseline (*p* < 0.05, *p* < 0.001, respectively). #, significantly different between groups (*p* < 0.05).

baseline and other measuring time in group PRP and ISF at 5 to 90 min and 30 to 90 min, respectively (Fig 2).

The mean IOP values of OS were lower than those of OD, but there were no significant statistical differences.

Hemodynamic parameters

In systolic arterial blood pressure, there was significant difference between groups ($F[1,12] = 20.49, p = 0.001$).

Comparing with group ISF, significant decreases in group PRP were observed ($p < 0.05$) and, comparing with baseline,

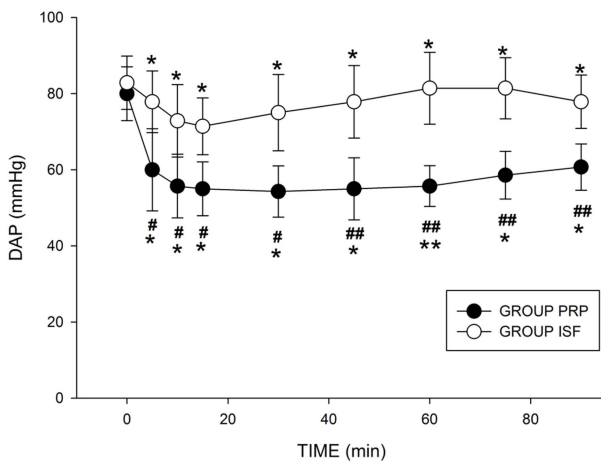


Fig 4. Diastolic arterial blood pressure in dogs anesthetized with isoflurane or propofol and remifentanyl combination. Group PRP: Group anesthetized with propofol and remifentanyl combination; Group ISF: Group anesthetized with isoflurane. Data are expressed as mean \pm SD. *,**, significantly different from baseline ($p < 0.05, p < 0.001$, respectively). #,##, significantly different between groups ($p < 0.05, p < 0.001$, respectively).

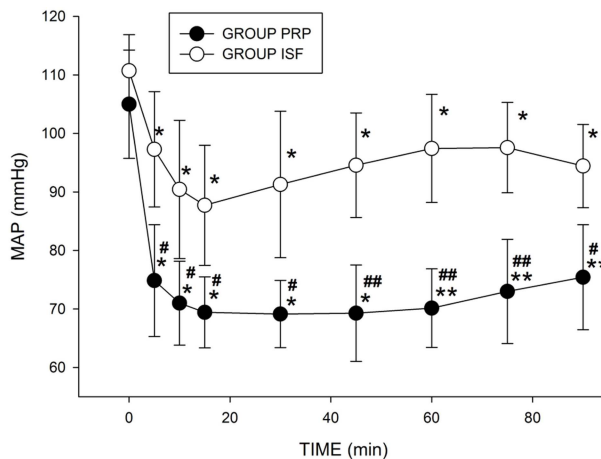


Fig 5. Mean arterial blood pressure in dogs anesthetized with isoflurane or propofol and remifentanyl combination. Group PRP: Group anesthetized with propofol and remifentanyl combination; Group ISF: Group anesthetized with isoflurane. Data are expressed as mean \pm SD. *,**, significantly different from baseline ($p < 0.05, p < 0.001$, respectively). #,##, significantly different between groups ($p < 0.05, p < 0.001$, respectively).

SAP was decreased after anesthesia in both groups ($p < 0.05$, Fig 3).

According to repeated measure analysis, DAP values in group PRP showed significantly decrease compared with group ISF ($F[1,12] = 38.84, p < 0.001$, Fig 4). In comparison with group ISF, Independent *t*-test revealed that there were significant decreases in group PRP ($p < 0.05$). Statistically meaningful decreases within groups were also observed ($p < 0.05$).

MAP were significantly decreased in group PRP compared with group ISF ($F[1,12] = 45.57, p < 0.001$). All values were decrease in both groups after anesthesia ($p < 0.05$). In all groups, independent *t*-test showed significant decrease in all time point besides at baseline (Fig 5).

Heart rates were significantly decreased in group PRP compared with group ISF ($F[1,12] = 47.88, p < 0.001$). In group ISF, the values of heart rates were increased during entire anesthesia compared with baseline. In group PRP, significantly decreased heart rates were observed after 30 min (Fig 6).

Blood gas analyses

pH

There was no significant difference between groups. Mean pH during anesthesia was 7.395 and 7.366 in group PRP and group ISF, respectively. During anesthesia, ranges of pH were 7.321 to 7.475 in group PRP and 7.283 to 7.422 in group ISF (Fig 7).

PaCO₂

In anesthetic period, mean values of PaCO₂ were 39.9 in group PRP and 41.9 in group ISF. No significant difference was observed between groups. PaCO₂ did not over 50 mmHg in all measuring times (Fig 8).

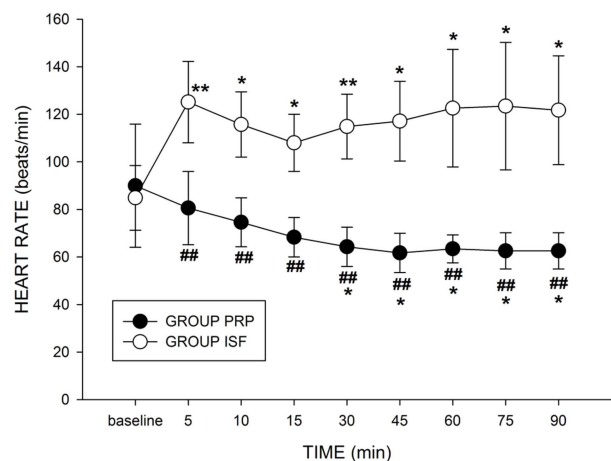


Fig 6. Heart rates in dogs anesthetized with isoflurane or propofol and remifentanyl combination. Group PRP: Group anesthetized with propofol and remifentanyl combination; Group ISF: Group anesthetized with isoflurane. Data are expressed as mean \pm SD. *,**, significantly different from baseline ($p < 0.05, p < 0.001$, respectively). ##, significantly different between groups ($p < 0.001$).

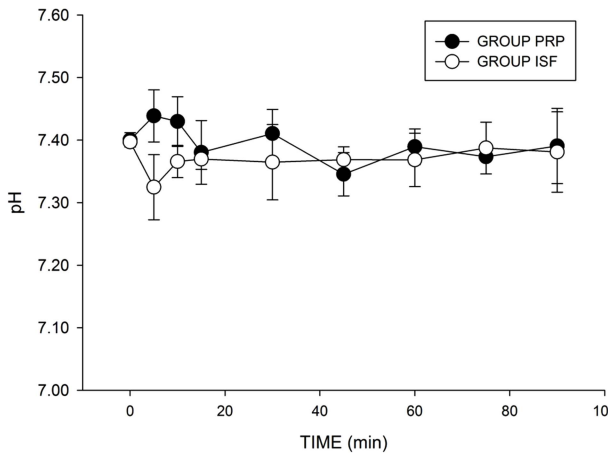


Fig 7. Blood pH in dogs anesthetized with isoflurane or propofol and remifentanyl combination. Group PRP: Group anesthetized with propofol and remifentanyl combination; Group ISF: Group anesthetized with isoflurane. Data are expressed as mean ± SD.

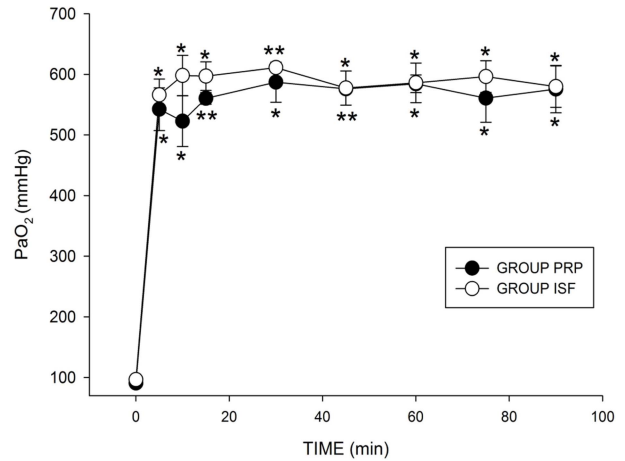


Fig 9. PaO₂ in dogs anesthetized with isoflurane or propofol and remifentanyl combination. Group PRP: Group anesthetized with propofol and remifentanyl combination; Group ISF: Group anesthetized with isoflurane. Data are expressed as mean ± SD. *, **, significantly different from baseline ($p < 0.05$, $p < 0.001$, respectively).

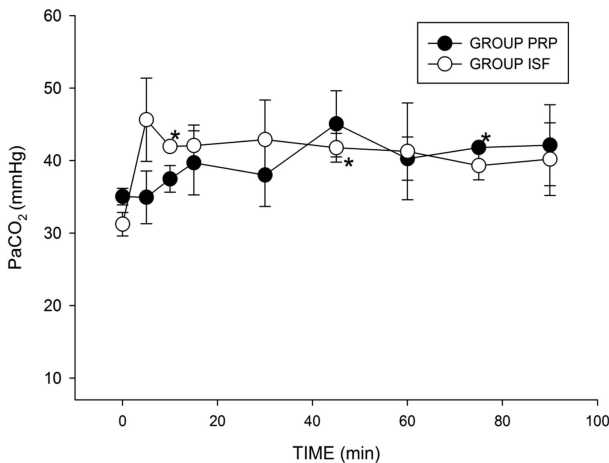


Fig 8. PaCO₂ in dogs anesthetized with isoflurane or propofol and remifentanyl combination. Group PRP: Group anesthetized with propofol and remifentanyl combination; Group ISF: Group anesthetized with isoflurane. Data are expressed as mean ± SD. *, significantly different from baseline ($p < 0.05$).

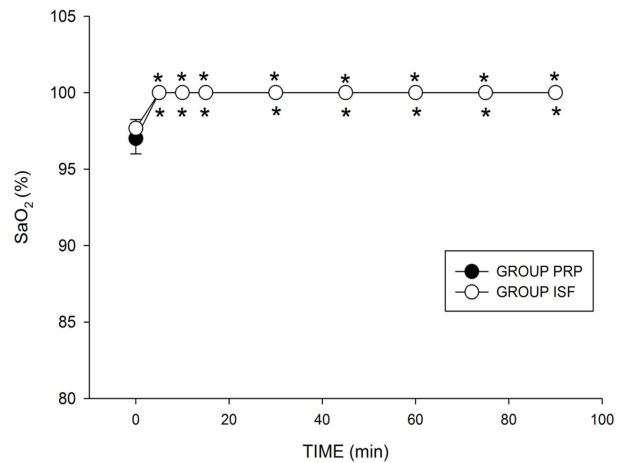


Fig 10. SaO₂ in dogs anesthetized with isoflurane or propofol and remifentanyl combination. Group PRP: Group anesthetized with propofol and remifentanyl combination; Group ISF: Group anesthetized with isoflurane. Data are expressed as mean ± SD. *, significantly different from baseline ($p < 0.05$).

PaO₂

Mean PaO₂ during anesthesia was 564 and 589 in group PRP and group ISF, respectively. The range PaO₂ was 477 to 613 and 542 to 636 in group PRP and group ISF, respectively. There was no significant difference between groups (Fig 9).

SaO₂

There was no significant difference between groups. After anesthesia, SaO₂ in all measuring time in both groups were maintained as 100% (Fig 10).

tCO₂

No significant difference was observed between groups (Fig 11). During anesthesia, mean values of tCO₂ were 25.3

and 25.1 in group PRP and ISF, respectively.

HCO₃⁻

Mean values of HCO₃⁻ during anesthesia were 25.3 in group PRP and 25.1 in group ISF. No significant difference was observed between groups (Fig 12).

Discussion

Propofol solely provide unsatisfactory analgesia, therefore, it requires combination of proper analgesic drug and, until now, remifentanyl seems to be the most adequate agent. However, because hypoventilation is inevitable side effect of

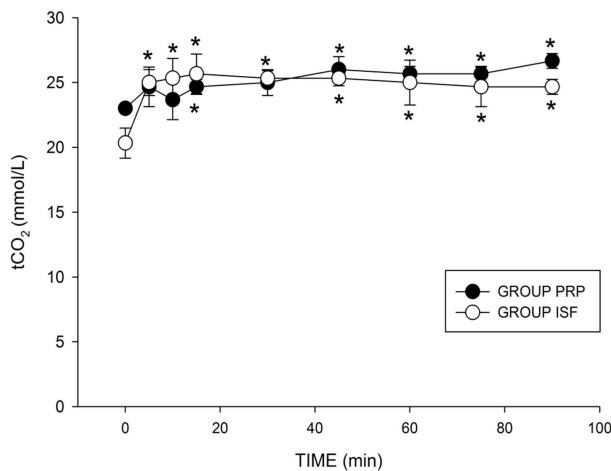


Fig 11. tCO₂ in dogs anesthetized with isoflurane or propofol and remifentanyl combination. Group PRP: Group anesthetized with propofol and remifentanyl combination; Group ISF: Group anesthetized with isoflurane. Data are expressed as mean ± SD. *, significantly different from baseline ($p < 0.05$).

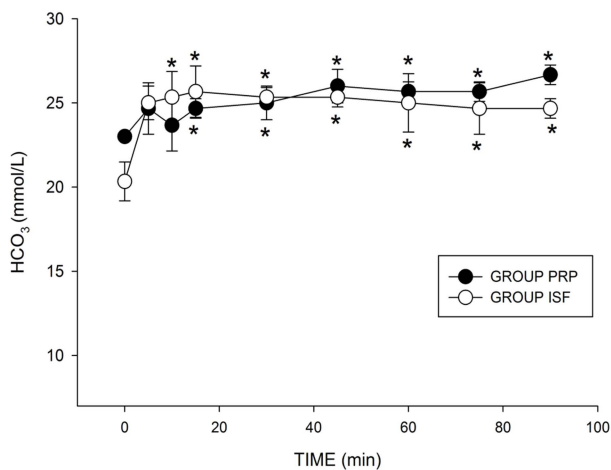


Fig 12. HCO₃⁻ in dogs anesthetized with isoflurane or propofol and remifentanyl combination. Group PRP: Group anesthetized with propofol and remifentanyl combination; Group ISF: Group anesthetized with isoflurane. Data are expressed as mean ± SD. *, significantly different from baseline ($p < 0.05$).

this regime, intermittent positive pressure ventilation is essential in total intravenous anesthesia with propofol and remifentanyl (24). Because increased CO₂ tension could prevent decreasing IOP effect of propofol, the control of CO₂ tension was considered to be necessary (4).

During anesthesia, blood pressure of group PRP was lower than that of group ISF in entire anesthetized period but blood pressures were stable in both groups within normal range.

It was known that mild hypotensive anesthesia rarely caused the side effect, such as postoperative vision loss, and most studies showed no decrease cerebral blood flow while hypotensive anesthesia. Although the use of deliberative hypotensive anesthesia needs cautions, it is known as safe,

typically (25,29).

In this study, blood pressures were mildly decreased within the normal range, but proper titrations of each agent could make deliberative hypotensive anesthesia and it could be utilized in handling of blood rich tissue, such as the choroidal plexus, retina and iris.

In blood gas analyses, there were no significant differences between groups in all measured parameters such as pH, PaCO₂, PaO₂, SaO₂, tCO₂ and HCO₃⁻. PaCO₂ were maintained below 50 mmHg in both group. During anesthesia, SaO₂ were maintained as 100% and PaO₂ were over 450 in both groups.

Dogs were positioned in right lateral recumbency and, although mean values were a little higher in right eyes, there were no statistically differences between the right and left eyes.

The acepromazine, propofol and remifentanyl concentrations used in this study were based on a previous published literature (13), but atracurium was premedicated to facilitate IOP measurement and mechanical ventilation. It is reported that atracurium could remain eye position centrally by relaxing surround muscles, and the effect of atracurium on cardiovascular system and IOP were minimal during anesthesia (22).

In this experiment, isoflurane induced the increase of IOP after 30 min in both eyes. Although the results in this study contradict some previous studies describing the reduction of IOP by volatile agent, increase of IOP was also suggested in dogs anesthetized with sevoflurane and desflurane (1,2). IOP, in spite of increase, was maintained within the normal range throughout total anesthetic period.

According to the literatures, propofol has some contradictory effects in dogs. Propofol decreased IOP during general anesthetic state (7) but induction with propofol could induce moderate and transient increase IOP (18,19). In addition, endotracheal tube insertion causes steep increase of IOP by the hemodynamic response and coughing in human. But remifentanyl and atracurium is expected to alleviate or prevent increase of IOP (16,36).

It is well known that the combination of propofol and remifentanyl effectively reduces IOP in human (32) but, because some anesthetic agents have different effects between human and dogs, obvious correlations of IOP with propofol in dogs should be defined.

In the situation that mild increase in IOP might be deleterious to the eyes, combination of propofol and remifentanyl could be concerned as an alternative anesthetic method.

In this study, combination of propofol and remifentanyl could provide stable and effectively reduced IOP and blood pressure compared with isoflurane.

Acknowledgement

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개에서 Propofol/Remifentanyl 병용마취 후 안압 및 혈액학 변화

임태선 · 윤성호 · 박지희 · 권영삼 · 장광호¹

경북대학교 수의과대학

요 약 : 본 실험에서는 propofol과 remifentanyl 병용 마취법 사용 시 안압 및 혈액학적 변화를 측정하고 isoflurane 마취 결과와 비교하였다. 건강한 14마리의 비글견을 7마리씩 2군 (PRP군, ISF군)으로 나누었으며 PRP군은 마취 도입 10분 전에 acepromazine (0.05 mg/kg, IV)으로 전마취제 투여하고 atracurium 0.1 mg/kg 투여 후, propofol (5 mg/kg, IV)으로 마취 유도하였다. 마취 유지에는 propofol (0.2 mg/kg/min)과 remifentanyl (0.5 µg/kg/min)을 사용하였다. ISF군에서는 propofol (5~7 mg/kg, IV)로 마취를 유도하고, isoflurane 흡입마취법으로 마취를 유지하였다. 초기 isoflurane 농도를 3%으로 유지하다가 마취가 안정된 후 1.9%로 낮추어 유지 하였다. 모든 군에서 간헐적인 100% 양압 호흡을 사용해 CO₂는 38에서 45 mmHg사이를 유지하고 SpO₂는 95에서 100사이를 유지하였다. 총 마취 시간은 90분이었으며 안압, 혈압, 심박수를 각각 5, 10, 15, 30, 45, 60, 75, 90에 측정을 하였다. 실험 결과 propofol과 remifentanyl 병용 마취법이 isoflurane 흡입마취법 보다 안정적으로 안압과 혈압을 낮출 수 있었다.

주요어 : IOP, blood pressure, remifentanyl, propofol, 개