The Journal of Veterinary Medical Science

FULL PAPER

Surgery

Effects of thoracolumbar epidural anesthesia with lidocaine on the systemic hemodynamics and hepatic blood flow in propofol anesthetized dogs

Toshie ISERI[1)]*, Masaya NAKAMORI[2)] and Yuka FUJIMOTO[3)]

[1)]Department of Clinical Veterinary Science, Joint Faculty of Veterinary Medicine, Yamaguchi University, 1677-1 Yoshida, Yamaguchi-shi, Yamaguchi 753-8515, Japan
[2)]Otokuni Animal Hospital, 26 Shimokaiinji, Nagaokakyo-shi, Kyoto 617-0845, Japan
[3)]Department of Advanced Clinical Medicine, Graduate School of Life and Environmental Sciences, Osaka Prefecture University, 1-58 Rinku-Oraikita, Izumisano-shi, Osaka 598-8531, Japan

ABSTRACT. General anesthesia reduces hepatic blood flow (HBF) from circulatory depression. Total intravenous anesthesia (TIVA) is associated with decreased circulatory depression compared to inhalation anesthesia, and epidural anesthesia using local anesthetics increases blood flow by blocking the sympathetic nerves and expanding blood vessels. We investigated the effects of thoracolumbar epidural anesthesia with TIVA on HBF in dogs. Six Beagle dogs had epidural catheters placed between T13 and L1 and were anesthetized with propofol and vecuronium. Physiological saline (control) or 2% lidocaine (0.2 ml/kg, followed by 0.2 ml/kg/hr) was administered at 1–2 weeks intervals. Heart rate (HR), cardiac index (CI), mean arterial pressure (MAP), and systemic vascular resistance index (SVRI) were recorded at 10-min intervals from before epidural injections (T0) to 110 min. Indocyanine green test was used to measure HBF during the awake state and until 90 min after epidural injections. HR and CI did not differ between treatments. MAP and SVRI after lidocaine were significantly lower than those of controls, and the lowest MAP value was 65 ± 11 mmHg at T10. Compared to T0, after lidocaine treatment, HBF was significantly higher at T30, T60 and T90 ($P<0.05$); while, after control treatment, no significant change was evident at any time point. Despite a decrease in MAP by this technique, HBF was either maintained at pre-anesthetic levels or increased in comparison to controls, probably due to vasodilation of the hepatic artery induced by the selective blockade sympathetic ganglia.

KEY WORDS: dog, epidural anesthesia, hepatic blood flow, lidocaine, local analgesia

J. Vet. Med. Sci.
83(12): 1877–1884, 2021
doi: 10.1292/jvms.20-0611

Received: 19 October 2020
Accepted: 3 October 2021
Advanced Epub:
14 October 2021

The liver is a vital organ that metabolizes and synthesizes, detoxifies toxins, and produces bile. Hepatic blood flow tends to decrease during circulatory suppression by general anesthesia, intraoperative traction, or retraction of abdominal organs, which increases the risk of liver damage and delays the drug metabolism [34]. To minimize further hepatic damage, techniques and drugs that support liver function, including vital organ blood flow and oxygen delivery, should be used for patients with hepatic disease [36]. Therefore, anesthesia that maintains the normal hepatic blood flow is essential for protecting the intraoperative hepatic functions [25]. Local anesthesia is recommended for patients with liver disease due to its potent analgesic effect with low drug doses [25].

Epidural anesthesia reversibly blocks the sensory nerves through the administration of an analgesic agent into the epidural space. Local anesthesia blocks not only the sensory nerves but also the sympathetic neurotransmission, leading to vasodilation in the blocked region, thereby increasing the blood flow [28]. To perform a nerve block of the spinal segment that dominates the liver in dogs, a block of the first lumbar vertebrae (L1) from the twelfth thoracic vertebrae (T12) is necessary [30]. Increased hepatic blood flow is expected when epidural anesthesia is performed at the thoracolumbar vertebrae.

Hepatic blood flow is affected by the circulation's general dynamics. General anesthesia and epidural anesthesia may inhibit the circulatory dynamics and possibly cancel the effect of increased blood flow to the organs when the sympathetic nerves are inhibited by epidural anesthesia [28]. To maintain the systemic arterial blood pressure (BP), we decided to use total intravenous anesthesia (TIVA), which has a relatively mild circulatory inhibitory effect compared to inhaled anesthetics [13, 14]. As the systemic lidocaine concentration increases, the BP decreases [15]. Therefore, it is necessary to measure the lidocaine concentration as well

*Correspondence to: Iseri, T.: iseri@yamaguchi-u.ac.jp

to ensure that circulatory suppression is not due to the elevated blood lidocaine concentrations.

The present study aimed to investigate the effects of thoracolumbar epidural anesthesia with lidocaine on the systemic hemodynamics and hepatic blood flow in dogs anesthetized with propofol/vecuronium.

MATERIALS AND METHODS

Animals

The present study was approved by the Institutional Review Board on Animal Research and Ethics of the Graduate School of Life and Environmental Sciences, Osaka Prefecture University (No. 21-88). Six healthy dogs (female Beagles; bodyweight, 11.0 ± 0.6 kg; age, 1.6 ± 0.3 years) were included in this study. This was a randomized crossover study, and two experiments were conducted on each dog. The subjects were assigned to a treatment option that received an epidural administration of either physiological saline (control treatment [treatment C]; n=6) or lidocaine (lidocaine treatment [treatment L]; n=6). The interval between the experiments for each dog was one to two weeks. Furthermore, physical, neurological, and blood (complete blood cell count and biochemical studies) examinations were conducted for all dogs before the experiment, confirming that no abnormalities were present. In addition, physical and neurological examinations were conducted one day and one month after the experiment. The dogs were then returned to the research colony.

Methods of anesthesia administration

After oxygenation, endotracheal intubation was performed by the slow administration of intravenous propofol (6 mg/kg; MSD Animal Health K.K., Tokyo, Japan) using a 22-gauge catheter (Surflow, TERUMO Co., Ltd., Tokyo, Japan) placed in the left cephalic vein. After intubation, respiratory management was performed with intermittent positive pressure ventilation using a ventilator (100% oxygen inhalation; PRO-45Va, ACOMA Medical Industry Co., Ltd., Tokyo, Japan). Respiratory rate (f_R) and tidal volume were adjusted appropriately to maintain the end-tidal carbon dioxide tension ($EtCO_2$) at 35–40 mmHg and the peripheral oxygen saturation (SpO_2) at ≥96%. $EtCO_2$, SpO_2, and f_R were measured using a multifunctional monitor (BP-608V, FUKUDA COLIN Co., Ltd., Tokyo, Japan); the monitor was calibrated by a qualified service provider. General anesthesia was maintained with continuous intravenous administration of propofol and vecuronium (Muscurate Intravenous, Fuji Pharma Co., Ltd., Tokyo, Japan). Propofol was continuously administered at a rate of 0.4 mg/kg/min [21]. A bispectral index (BIS) monitor (Vista A-3000, NIHON KOHDEN Co., Tokyo, Japan) was used to confirm if sufficient sedation was being maintained in the experimental dog. Electrodes for BIS measurements were modified from those used by Campagnol *et al*. [5]. In brief, spiral needle electrodes (OA209-025 and OA209-028, Unique Medical Co., Ltd., Osaka, Japan) were used, with the first electrode placed at the midpoint of the left and right frontal zygomatic processes, the second electrode placed at the right dorsal side of the frontal zygomatic process, the third electrode placed at the right temporal bone at the base of the ear, and the fourth electrode placed at the caudal dorsal side of the right external eye angle; the BIS values calculated from the obtained electroencephalograms were recorded. Vecuronium was continuously administered at an initial rate of 0.4 mg/kg/hr [20], which was subsequently titrated to achieve the desired level of muscle relaxation determined using the train-of-four (TOF) ratio and count (TOF-watch SX, NIHON KOHDEN Co.) [20]. Muscle relaxation monitoring was assessed by percutaneously applying four continuous 2 Hz TOF stimuli to the ulnar nerve via electrodes (Vitrode F, NIHON KOHDEN Co.) that were affixed to the skin on the lateral aspect of the right forelimb and measuring the contraction of the paw with an accelerometer. In the present experiment, after the TOF ratio reached 0, the vecuronium administration rate was appropriately titrated to maintain the muscle relaxation state at a TOF count of 1 [20].

Rectal temperature (RT) was measured using a multifunctional monitor (BP-608V, FUKUDA COLIN) and maintained at 37–38°C using a warm water mat (T/PUMP, GAYMAR, Orchard Park, NY USA) and forced-air warming device (Patient warming system PWU-5050, Arizant Healthcare Inc., Eden Prairie, MN USA). Ringer's lactate solution (SOLULACT, TERUMO Co., Ltd.) was infused during the experiment at 5 ml/kg/hr. After all measurements were completed, the epidural injection and continuous intravenous infusion of propofol and vecuronium were stopped, and the dogs were awakened from anesthesia after confirming complete recovery from muscle relaxation using the muscle relaxation monitor.

Placement of the epidural catheter

With the dog in the left lateral recumbent position, the thoracolumbar vertebral area was clipped and sterilized, and 0.1 ml/kg of 2% lidocaine hydrochloride (Xylocaine 2% for Intravenous Injection, Aspen Japan K.K., Tokyo, Japan) was subsequently administered around the ligament flava from the L2 to L4 spinous process to induce desensitization. Five min later, under X-ray fluoroscopy (ARCADIS Varic, Siemens Healthcare K.K., Tokyo, Japan), a 19-gauge Tuohy needle (Hakko Co., Ltd., Medical Device Division, Chikuma, Japan) was percutaneously inserted into the epidural space between the L2 and L3 under aseptic conditions. The position of the epidural needle tip was confirmed using the loss of resistance method with physiological saline. An epidural catheter (0.6 × 700 mm, Hakko Co., Ltd., Medical Device Division) was inserted through the epidural needle. After inserting the epidural catheter, 2 ml/head of the contrast medium (OMNIPAQUE 300 injection, GE Healthcare Japan Co., Ltd., Tokyo, Japan) and X-ray fluoroscopy were used to confirm if the catheter tip was located in the epidural space of L1 from T13. After preparations were completed, lidocaine was administered to the epidural space more than 60 min after epidurography.

Measurement of hemodynamic variables

A 24-gauge catheter (Surflow, TERUMO Co., Ltd.) was inserted into the dorsal pedal artery and connected to a BP transducer

(DX-300, NIHON KOHDEN Co.), a multifunctional monitor (BP-608V, FUKUDA COLIN) with a flush of heparinized saline (5 unit/ml), to measure the mean, systolic, and diastolic arterial pressures (MAP, SAP, and DAP, respectively). Heart rate (HR) and heart rhythm by lead II electrocardiography were also measured using the multifunctional monitor (BP-608V, FUKUDA COLIN). The pressure transducer was calibrated using the atmospheric pressure at the height of the right atrium.

A 6-Fr sheath (Radifocus introducer II H, TERUMO Co., Ltd.) introducer was inserted into the right jugular vein using the Seldinger technique, and a 5-Fr Swan-Ganz catheter (Swan-Ganz thermodilution catheters, Edwards Lifesciences Co., Irvine, CA, USA) was inserted through this sheath with the distal end of the catheter placed in the pulmonary artery. This was confirmed using X-ray fluoroscopy. The Swan-Ganz catheter was connected to a BP transducer (DX-300, NIHON KOHDEN Co.) closed infusion supply system (CO-set+, Edwards Lifesciences Co.) and a monitor (BSM-9510, NIHON KOHDEN Co.).

Mean pulmonary artery pressure (MPAP) was measured using a Swan-Ganz catheter from the catheter distal port, and the right atrial pressure (nearly identical to central venous pressure [CVP]) was measured from the proximal port, 15 cm from the distal end of the catheter. Both ports were connected to their respective pressure transducers. The balloon at the Swan-Ganz catheter tip was inflated with approximately 0.4 ml of air to wedge the pulmonary artery. The port at the distal end measured the MPAP and pulmonary artery occlusion pressure (PAOP) as an indicator of the left atrial pressure. Additionally, 3 ml of physiological saline cooled to 0–4°C was administered from the catheter's proximal port. Cardiac output (CO) was measured using the thermodilution method, and the mean value of three measurements performed at each measured time point was recorded. From these measured values, the systemic and pulmonary vascular resistance index (SVRI and PVRI, respectively) and the cardiac output index (CI) were calculated using the following formulas:

(1) SVRI (dynes•second/cm^5/m^2)=(MAP−right atrial pressure) × 79.92/CI;

(2) PVRI (dynes•second/cm^5/m^2)=(pulmonary arterial pressure−pulmonary artery occlusion pressure) × 79.92/CI;

(3) CI (l/min/m^2)=CO/body surface area; *1 mmHg=1,332.8 dynes/cm^2; 1 mmHg/(l/min)=(1,332.8 dynes/cm^2)/(16.66 cm^3/sec)=79.92 dynes•sec•cm^5.

The time at which the catheter placement and preparation of the hemodynamic measurement was completed, was set as the pre-epidural administration time (T0). Following the measurement of the T0 values, physiological saline was administered under treatment C and 2% lidocaine hydrochloride under treatment L via the epidural catheter over 1 min at a dose of 0.2 ml/kg; it was subsequently continuously administered at a dose of 0.2 ml/kg/hr using a syringe pump. Measurement and calculation of circulatory dynamics were carried out every 10 min after epidural administration for 110 min.

Measurement of hepatic blood flow

The indocyanine green test was used to estimate the changes in the hepatic blood flow [29]. The indocyanine green plasma clearance rate describes the volume of blood that is cleared from the dye over a defined time interval [10] and reportedly reflects the effective liver blood flow rate [26]. Although the indocyanine green plasma clearance rate in dogs is reported to be lower than that in humans, it has been examined in both healthy dogs and dogs with experimentally induced hepatic dysfunction [10].

Venous blood was collected using a 22-gauge catheter (Surflow, TERUMO Co., Ltd.) from the right cephalic vein before indocyanine green (Diagnogreen for injection, DAIICHI SANKYO CO., Ltd., Tokyo, Japan) was administered at 0.5 mg/kg through the left cephalic vein. Thereafter, 1.5 ml of venous blood was collected from the right cephalic vein at 5, 10, and 15 min after the dye administration. The plasma obtained by centrifugation at 1,600 *g* for 10 min was diluted threefold with physiological saline; the absorbance was measured at a wavelength of 805 nm using a microspectrophotometer (DU730, Beckman Coulter, Inc., Brea, CA, USA). The half-life of the administered indocyanine green was calculated from the measured values before administration and at 5, 10, and 15 min after administration. The plasma clearance rate of indocyanine green, indicative of effective hepatic blood flow rate, was calculated using the following formula:

Indocyanine green plasma clearance rate=0.693 (constant)/$t_{1/2}$,

where $t_{1/2}$ is the indocyanine green half-life time.

Indocyanine green was administered before (T0) and at 30 (T30), 60 (T60), and 90 (T90) min after the epidural administration, and the plasma clearance rate was calculated for each time point. Similarly, the indocyanine green plasma clearance rate was calculated for each dog that was not under anesthesia as reference data. This was used as the measurement value of the awake state (T_{awake}). T_{awake} was measured in awake dogs, at intervals of 9–28 days from each experiment, similar to that for treatment C and L.

Measurement of serum lidocaine concentration

At T0, T30, T60, and T90, 5 ml of venous blood was collected via catheter from the right cephalic vein into a serum tube with a clot activator. Serum obtained by centrifugation at 1,600 *g* for 10 min was stored frozen at −30°C until measurement. High-pressure liquid chromatography (HPLC) was used to measure the concentration of lidocaine in the blood based on the method described by Kang *et al*. [16].

Statistical analysis

Data were presented as median (range). While cardiovascular data were measured every 10 min, the statistical evaluation was performed using hemodynamic variables data taken every 30 min: at T0, T30, T60 and T90. The measured values of HR, MAP, SAP, DAP, CI, SVRI, and PVRI at T0 were set as the baseline (100%). Wilcoxon rank sum test was used to assess differences between treatments C and L at each measured time point. The Steel method was used to examine the changes in T0 of the indocyanine green test, and in the serum lidocaine concentrations. Statistical analyses were performed using EZR (Saitama Medical

Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as $P<0.05$.

RESULTS

Anesthesia management and presence of neurological abnormalities

The range of the median BIS values at each measured time point was 56.0 to 59.5 with treatment C and 56.5 to 63.0 with treatment L. No significant differences were observed between the two treatments (Table 1). The rate of vecuronium administration was decreased gradually after its initiation as the TOF ratio was adjusted to maintain a ratio of 1. After 90 min, the vecuronium rate was nearly constant; the mean rate at 90 min was 0.21 ± 0.03 mg/kg/hr for treatment C and 0.20 ± 0.04 mg/kg/hr for treatment L.

Physical and neurological examinations one day and one month after the experiment revealed no abnormalities in the dogs.

Table 1. Bispectral index (BIS) and hemodynamic variables were recorded in six mechanically ventilated Beagle dogs anesthetized with propofol and vecuronium that were treated with physiological saline (treatment C) or 2% lidocaine (treatment L, 0.2 ml/kg over 1 min, followed by 0.2 ml/kg/hr) administered into the thoracolumbar epidural space through an epidural catheter

	Treatment	T0	T30	T60	T90
BIS	C	56 (53–62)	57.5 (55–61)	59 (51–65)	59.5 (54–63)
	L	63 (53–66)	56.5 (49–65)	56 (52–62)	56.5 (50–61)
HR (bpm)	C	91 (59–96)	85 (66–111)	86.5 (60–106)	85 (62–103)
(%)		100.0	103.7	101.7	99.9
	L	76 (63–90)	73.5 (59–99)	76.5 (54–113)	76 (64–99)
		100.0	100.0	104.8	101.6
MAP (mmHg)	C	80.5 (60–92)	87.5 (72–97)	88.5 (61–94)	86 (63–90)
(%)		100.0	107.4	101.5	103.1
	L	72 (66–86)	63 (56–81)**	66 (56–82)*	65.5 (58–80)*
		100.0	88.1*	90.7*	91.8*
SAP (mmHg)	C	118.5 (96–144)	124 (104–148)	123 (103–144)	117.5 (107–141)
(%)		100.0	105.6	104.9	100.3
	L	107.5 (89–137)	102 (87–132)	102.5 (78–143)	105.5 (79–136)
		100.0	96.1**	94.4*	95.6
DAP (mmHg)	C	61 (55–70)	65.5 (48–77)	66.5 (50–72)	66 (52–72)
(%)		100.0	107.2	100.5	99.8
	L	59 (48–70)	49.5 (42–65)	50.5 (41–68)	51 (43–63)
		100.0	88.7*	87.0*	88.9*
CI ($l/min/m^2$)	C	3.4 (2.7–4.2)	3.5 (2.9–4.4)	3.4 (2.7–4.6)	3.3 (2.5–4.0)
(%)		100.0	102.9	100.7	95.3
	L	3.2 (3.1–4.1)	3.1 (2.9–4.0)	3.4 (2.8–4.2)	3.3 (2.7–4.1)
		100.0	93.8	98.9	100.8
SVRI ($dynes•sec/cm^5/m^2$)	C	2,036.4 (1144.6–2330.6)	2,116.2 (1322.1–2417.4)	2,134.3 (1070.4–2747.9)	2,167.2 (1,250.4–2778.7)
(%)		100.0	102.6	105.2	108.6
	L	1,805.2 (1,301.8–2,205.5)	1,624.2 (1,111.5–2,145.3)	1,594.1 (1,071.4–2,164.0)	1,708.2 (1,130.4–2,266.3)
		100.0	94.8	92.0	90.5*
PVRI ($dynes•sec/cm^5/m^2$)	C	164.2 (70.4–207.7)	129.8 (65.0–266.4)	126.4 (67.3–308.5)	134.1 (104.5–258.7)
(%)		100.0	91.2	86.8	98.7
	L	113.7 (77.7–233.5)	110.3 (79.4–136.3)	105.6 (53.9–168.6)	103.6 (78.0–172.6)
		100.0	98.2	85.1	93.4
CVP (mmHg)	C	0 (−3–2)	0 (−3–2)	0 (−2–2)	−1 (−3–3)
	L	0 (0–3)	0 (0–2)	0 (0–1)	0 (0–2)
MPAP (mmHg)	C	9.5 (7–13)	10 (5–13)	9 (7–14)	10 (5–12)
	L	8.5 (8–11)	7.5 (7–10)	9 (7–11)	8 (7–11)
PAOP (mmHg)	C	4 (−1–6)	4 (0–7)	4.5 (0–6)	4 (0–6)
	L	4 (0–7)	3.5 (2–5)	5 (2–5)	3.5 (2–5)

Statistical evaluation was performed on data taken before (T0) and at 30, 60, and 90 min (T30–T90) after epidural injections. Data are presented as median (range) and percentage change (%) relative to T0 of each treatment in parentheses. BIS, bispectral index; HR, heart rate; MAP, mean arterial pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; CI, cardiac output index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; CVP, central venous pressure; MPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure. **, *; vs. treatment C at the same time point ($P<0.01$, 0.05).

Hemodynamics

No significant differences were observed between treatments C and L in any of the measurements at T0 (Table 1). For each measured time point, there was a significant decrease in MAP, DAP (T30, T60 and T90) and DAP (T30, T60) for treatment L compared with that for treatment C ($P<0.05$). The lowest mean values of MAP, SAP, and DAP for treatment L were 65.2 ± 10.9 mmHg (T10), 103.2 ± 19.4 mmHg (T20), and 50.8 ± 9.1 mmHg (T40), respectively, which are within the normal limits [37]. Moreover, SVRI decreased significantly more with treatment L compared to treatment C (T90) ($P<0.01$).

Hepatic blood flow

Indocyanine green plasma clearance rates at each measured time point are shown in Table 2. Median (range) indocyanine green plasma clearance rate at T_{awake} was 0.089 (0.080–0.095). Indocyanine green plasma clearance rate for treatment L increased significantly in comparison to treatment C at each measured time point except for T0 ($P<0.01$). Indocyanine green plasma clearance rate for treatment L was significantly higher at T30, T60, and T90 than at T0 ($P<0.05$). However, indocyanine green plasma clearance rate for treatment C did not show any significant change at any time point than at T0.

Serum lidocaine concentration

Serum lidocaine concentrations are shown in Table 3. The values with treatment L were significantly higher than those with treatment C at T30, T60 and T90 ($P<0.05$). However, compared with T0, there was no significant change over time for either treatment.

DISCUSSION

This study demonstrates that when epidural anesthesia is delivered at the thoracolumbar vertebrae in combination with TIVA, the hepatic blood flow rate reduced by TIVA increases significantly compared to treatment without epidural anesthesia. Compared to T_{awake}, which was not measured under anesthesia and was measured on a different day, lidocaine treatment temporarily decreased the hepatic blood flow rate by 70.3% at T0 and then returned to the T_{awake} values (86.8% at T30, 91.9% at T60, and 92.4% at T90); however, control treatment showed no change at any measured time point (69.8% at T30, 69.2% at T60, and 74.3% at T90), once it was reduced at T0 (67.5%). The liver receives dual blood flow, and the portal vein blood flow comprises 75% of the effective hepatic blood flow [9, 17]. In dogs, the hepatic artery is dominated by nerves branching from the coeliac ganglion; this is formed mainly by large visceral nerves that branch out from the spinal ganglion at around T13 [4, 30]. The portal vein is dominated by nerves branching from the anterior mesenteric ganglion, mainly formed by small visceral nerves that emanate from the spinal ganglion of L1 to L4 [4, 30]. In this study, epidurography confirmed that the position of the tip of the epidural catheter was at T13 to L1. It appeared that these segments, dominated by blood vessels to the liver, were blocked. As the hepatic artery pressure is almost similar to the peripheral arterial BP, it is assumed to be susceptible to changes in arterial BP. By contrast, as the portal vein pressure is almost the same as the hepatic sinusoidal pressure, it is thought to be easily influenced by changes in the circulating blood volume [8]. If the circulatory blood volume remains almost constant, the fluctuations in arterial BP have a significant influence on the hepatic blood flow. Therefore, when examining the effect of epidural anesthesia with TIVA on hepatic blood flow, the effect of the three factors (TIVA, epidural anesthesia, and blood lidocaine levels) on arterial BP should be considered.

The first factor was the influence of TIVA on the systemic circulatory dynamics. Neither treatments exhibited bradycardia (heart rate <60/min) or hypotension (MAP <60 mmHg) at T0, i.e., before epidural administration. TIVA appeared to have no

Table 2. Indocyanine green plasma clearance rates in six Beagle dogs during propofol total intravenous anesthesia with saline (treatment C) or 2% lidocaine (treatment L) infused through an epidural catheter between the thirteenth thoracic and first lumbar vertebrae at 0.2 ml/kg/hr

Treatment	T0	T30	T60	T90
C	0.060 (0.051–0.074)	0.062 (0.046–0.064)	0.061 (0.057–0.071)	0.066 (0.053–0.076)
L	0.062 (0.057–0.076)	0.077 (0.071–0.087)*††	0.081 (0.072–0.094)*††	0.082 (0.074–0.093)*†

Measurements were taken before epidural injection (T0), and at 30, 60, and 90 min (T30–T90) after dye injection. Data are presented as median (range). *; vs. T0 ($P<0.05$), ††, †; vs. group C ($P<0.01$, 0.05) at the same time point.

Table 3. Serum lidocaine concentrations (μg/ml) in six Beagle dogs before epidural administration (T0) and during propofol total intravenous anesthesia with saline (treatment C) or 2% lidocaine (treatment L) infused through an epidural catheter between the thirteenth thoracic and first lumbar vertebrae at 0.2 ml/kg/hr

Treatment	T0	T30	T60	T90
C	0.78 (0.12–1.31)	0.46 (0.07–0.86)	0.42 (0.15–0.65)	0.28 (0.10–0.65)
L	0.65 (0.29–1.13)	1.13 (0.40–3.57)*	0.89 (0.26–3.49)*	1.35 (0.17–3.56)*

Measurements were taken before epidural injection (T0) and at 30, 60, and 90 min (T30–T90) after epidural injection. Data are presented as median (range). *; vs. group C ($P<0.05$) at the same time point.

major influence on the systemic circulatory dynamics in this study. Since vecuronium has no histamine-releasing or autonomic nerve blocking actions, it is thought that its influence on the circulatory dynamics is small [33]. However, propofol is known to suppress respiration and lower BP and CO [2, 6]; these reductions may affect hepatic blood flow. Therefore, when the indocyanine green plasma clearance rate at T_{awake}, during which neither treatment received any anesthetics, was compared to that at T0 when anesthesia was established by TIVA, there was a decrease of 67.5% and 74.3% in treatment C and L, respectively. Hepatic blood flow reportedly decreases by 35% to 42% in the first 30 min of anesthesia induction in healthy volunteers [25]. This suggests an influence of TIVA on the hepatic blood flow rate, although there were no clinical problems from TIVA in the current study using healthy dogs. Thus, TIVA itself has a risk of reducing hepatic blood flow by decreasing BP.

The second factor was the effect of epidural anesthesia in the thoracolumbar vertebrae on circulatory dynamics; a significant decrease in BP and SVRI was noted for treatment L compared to treatment C, likely to the blocked sympathetic and sensory nerves. Blood vessels in the blocked region expand and the peripheral vascular resistance decreases, resulting in a decrease in BP. There were no significant changes in the HR or CI between the two treatments. In cases where local anesthetic solutions are administered across the first thoracic vertebra (T1) to the fourth thoracic vertebra (T4) levels, heart rate and cardiac contractility may be decreased when sympathetic outflow from these segments is blocked [23]. In the present experiment, thoracolumbar epidural anesthesia may not have reached T1–T4, the spinal nerve segment innervating the heart [31], suggesting that the sympathetic nerves of the heart were not blocked. There was no change in CVP over time with both treatments, and the circulatory blood volume remained constant. Thus, the thoracolumbar epidural anesthesia decreased BP through vasodilation.

The last factor was the serum lidocaine concentration. For treatment L, the concentration of lidocaine in the blood increased as lidocaine was absorbed from the epidural space into the venous plexus. However, it appeared that the liver gradually degraded the lidocaine and maintained its blood concentration at a constant level. Further, the serum lidocaine concentration in this experiment was lower than that in the previous experiments with dogs administered with 2% lidocaine in the epidural space (2.4 µg/ml at 30 min) [27]. Propofol used in TIVA is degraded by hepatic cytochrome P450 (CYP) 3A4 [12] and lidocaine by CYP 3A4 or 1A2 [22], but propofol is not known to inhibit the lidocaine metabolism [20]. Therefore, thoracolumbar epidural anesthesia may have increased the hepatic blood flow and caused the blood lidocaine to be degraded more rapidly in the liver. Additionally, it has been reported that a lidocaine concentration of 7.2 µg/ml or less in the blood has almost no effect on the circulatory dynamics [34]. The maximum concentration in this experiment (1.6 ± 1.3 µg/ml at 30 min) for treatment L suggests that lidocaine had little effect on the circulatory dynamics.

When epidural anesthesia is administered using local anesthetics, the blood volume increases in the region where the sympathetic nerve is blocked and decreases where it is not blocked [1, 34]. Based on these findings, although both TIVA and thoracolumbar epidural anesthesia suppressed circulation dynamics, the hepatic blood flow reduced by TIVA appeared to have increased due to the dilation of the hepatic artery and portal vein by epidural anesthesia. For treatment L, the hepatic blood flow was restored to the same level as it was before anesthesia, with no abnormal increase.

In previous reports, hepatic blood flow decreased as the arterial BP decreased due to the lumbar or thoracic epidural anesthesia [32], except in pigs [35]. Previous studies on dogs with epidural anesthesia up to T1–T5 reported a 50% reduction in the arterial BP, reduced portal blood flow, and reduced vascular resistance that preserved the hepatic arterial blood flow but led to circulatory insufficiency [11]. The hepatic artery buffer response is a physiological protective mechanism by which the hepatic artery flow increases in order to maintain global liver perfusion in response to the reduction in the portal vein flow [24]. It is difficult to maintain a hepatic blood flow if severe hypotension occurs. The differences observed between the current and previous studies may be due to the mild degree of BP decrease as TIVA was used instead of inhalation anesthesia; the hepatic arterial pressure was maintained without the CI decrease because the cardiac sympathetic nervous system was not blocked.

Regarding the TIVA method used in the present study, BIS in both treatments were within the range of 56 to 63, which is the appropriate depth of anesthesia for surgery [18]. Moreover, the administration rate of vecuronium in this experiment was similar to the previously reported value of 0.22 ± 0.04 mg/kg/hr [20]. Therefore, the TIVA anesthetic method used in the present study was considered stable.

In the present study, the hepatic blood flow was measured by the indocyanine green test and involved no invasive procedures. Surgical trauma, intraoperative traction, or retraction of abdominal organs might reduce the hepatic blood flow [35]. This is a limitation of the present experiment; however, it was considered appropriate as a simple and clear method to study the effect of combined TIVA and epidural anesthesia on the hepatic blood flow. Further study is needed to determine whether the epidural analgesia method used in this study is sufficient for surgery.

As another method, it is possible to advance the epidural catheter to the region between T13 and L1 from the usual insertion site (the lumbosacral spine) in dogs [23]. It is conceivable that since the lumbar enlargement of the spinal cord occurs from L3 to L4, the epidural space narrows [7], and the risk of intravascular catheter ablation, bending, and rupture at extraction increases [3, 19]; if catheter placement in the epidural space is less than 4 cm to 5 cm, the danger is reduced [19]. Therefore, we decided to place the epidural catheter above the usual puncture site. Furthermore, no abnormalities were observed during the neurological examination after the experiment, similar to a previous report [38].

In conclusion, the thoracolumbar epidural blockade induced by lidocaine causes a systemic vasodilatory effect, which causes a moderate decrease in the arterial blood pressure in healthy dogs. Despite a decrease in MAP by this technique, the hepatic blood flow was either maintained at pre-anesthetic levels or increased in comparison to the control treatment, probably due to the vasodilation of the hepatic artery induced by the selective blockade sympathetic ganglia.

POTENTIAL CONFLICTS OF INTEREST. The authors have nothing to disclose.

REFERENCES

1. Arndt, J. O., Höck, A., Stanton-Hicks, M. and Stühmeier, K. D. 1985. Peridural anesthesia and the distribution of blood in supine humans. *Anesthesiology* **63**: 616–623. [Medline] [CrossRef]
2. Aun, C. S. 1999. New i.v. agents. *Br. J. Anaesth.* **83**: 29–41. [Medline] [CrossRef]
3. Boey, S. K. and Carrie, L. E. 1994. Withdrawal forces during removal of lumbar extradural catheters. *Br. J. Anaesth.* **73**: 833–835. [Medline] [CrossRef]
4. Bozkurt, E. U., Kurtul, I., Cevik, A. and Dursun, N. 2003. Origin, course and distribution of the major and minor splanchnic nerves in the dog. *Indian Vet. J.* **80**: 800–803.
5. Campagnol, D., Teixeira Neto, F. J., Monteiro, E. R., Beier, S. L. and Aguiar, A. J. A. 2007. Use of bispectral index to monitor depth of anesthesia in isoflurane-anesthetized dogs. *Am. J. Vet. Res.* **68**: 1300–1307. [Medline] [CrossRef]
6. Cattai, A., Rabozzi, R., Ferasin, H., Isola, M. and Franci, P. 2018. Haemodynamic changes during propofol induction in dogs: new findings and approach of monitoring. *BMC Vet. Res.* **14**: 282. [Medline] [CrossRef]
7. Done, S. H., Goody, P. C., Evans, S. A. and Stickland, N. C. 2009: Chap. 9 The vertebral column. pp. 421–443. In: Color Atlas of Veterinary Anatomy Volume 3 dog and cat, 2nd ed., Mosby,
8. Gelman, S. I. 1976. Disturbances in hepatic blood flow during anesthesia and surgery. *Arch. Surg.* **111**: 881–883. [Medline] [CrossRef]
9. Gelman, S. 1987. General anesthesia and hepatic circulation. *Can. J. Physiol. Pharmacol.* **65**: 1762–1779. [Medline] [CrossRef]
10. Grobelna, A. P., Honkavaara, J., Restitutti, F., Huuskonen, V., Sakka, S. G. and Spillmann, T. 2016. Evaluation of a transcutaneous method to assess canine liver function by indocyanine green plasma disappearance rate in healthy adult Beagle dogs. *Vet. J.* **209**: 169–173. [Medline] [CrossRef]
11. Greitz, T., Andreen, M. and Irestedt, L. 1983. Haemodynamics and oxygen consumption in the dog during high epidural block with special reference to the splanchnic region. *Acta Anaesthesiol. Scand.* **27**: 211–217. [Medline] [CrossRef]
12. Hamaoka, N., Oda, Y., Hase, I., Mizutani, K., Nakamoto, T., Ishizaki, T. and Asada, A. 1999. Propofol decreases the clearance of midazolam by inhibiting CYP3A4: an in vivo and in vitro study. *Clin. Pharmacol. Ther.* **66**: 110–117. [Medline] [CrossRef]
13. Ilkiw, J. E. 1999. Balanced anesthetic techniques in dogs and cats. *Clin. Tech. Small Anim. Pract.* **14**: 27–37. [Medline] [CrossRef]
14. Iizuka, T., Kamata, M., Yanagawa, M. and Nishimura, R. 2013. Incidence of intraoperative hypotension during isoflurane-fentanyl and propofol-fentanyl anaesthesia in dogs. *Vet. J.* **198**: 289–291. [Medline] [CrossRef]
15. Jones, R. S. 2001. Epidural analgesia in the dog and cat. *Vet. J.* **161**: 123–131. [Medline] [CrossRef]
16. Kang, L., Jun, H. W. and McCall, J. W. 1999. HPLC assay of Lidocaine in plasma with solid phase extraction and UV detection. *J. Pharm. Biomed. Anal.* **19**: 737–745. [Medline] [CrossRef]
17. Lautt, W. W. 2007. Regulatory processes interacting to maintain hepatic blood flow constancy: Vascular compliance, hepatic arterial buffer response, hepatorenal reflex, liver regeneration, escape from vasoconstriction. *Hepatol. Res.* **37**: 891–903. [Medline] [CrossRef]
18. Lopes, P. C., Nunes, N., Paula, D. P., Nishimori, C. T. D., Guerrero, P. N. H. and Conceição, E. D. V. 2008. Bispectral index in dogs at three intravenous infusion rates of propofol. *Vet. Anaesth. Analg.* **35**: 228–231. [Medline] [CrossRef]
19. Michalek-Sauberer, A., Oehmke, M. J., Scharbert, G., Neumann, K., Kozek-Langenecker, S. A. and Deusch, E. 2008. Withdrawal forces of lumbar spinal catheters: no dependence on body position. *Br. J. Anaesth.* **100**: 846–849. [Medline] [CrossRef]
20. Nagahama, S., Nishimura, R., Mochizuki, M. and Sasaki, N. 2006. The effects of propofol, isoflurane and sevoflurane on vecuronium infusion rates for surgical muscle relaxation in dogs. *Vet. Anaesth. Analg.* **33**: 169–174. [Medline] [CrossRef]
21. Nakayama, S., Miyabe, M., Kakiuchi, Y., Inomata, S., Osaka, Y., Fukuda, T., Kohda, Y. and Toyooka, H. 2004. Propofol does not inhibit lidocaine metabolism during epidural anesthesia. *Anesth. Analg.* **99**: 1131–1135. [Medline] [CrossRef]
22. Orlando, R., Piccoli, P., De Martin, S., Padrini, R., Floreani, M. and Palatini, P. 2004. Cytochrome P450 1A2 is a major determinant of lidocaine metabolism in vivo: effects of liver function. *Clin. Pharmacol. Ther.* **75**: 80–88. [Medline] [CrossRef]
23. Otero, P. E. and Campoy, L. 2013. Chap. 14. Epidural and spinal anesthesia. pp 227–259. In: Small Animal Regional Anesthesia and Analgesia (Campoy, L. and Read, M. R. eds.), Wiley-Blackwell, Oxford.
24. Pereira, A. J., Jeger, V., Fahrner, R., Djafarzadeh, S., Lensch, M., Takala, J. and Jakob, S. M. 2014. Interference of angiotensin II and enalapril with hepatic blood flow regulation. *Am. J. Physiol. Gastrointest. Liver Physiol.* **307**: G655–G663. [Medline] [CrossRef]
25. Rahimzadeh, P., Safari, S., Faiz, S. H. and Alavian, S. M. 2014. Anesthesia for patients with liver disease. *Hepat. Mon.* **14**: e19881. [Medline] [CrossRef]
26. Sakka, S. G. 2018. Assessment of liver perfusion and function by indocyanine green in the perioperative setting and in critically ill patients. *J. Clin. Monit. Comput.* **32**: 787–796. [Medline] [CrossRef]
27. Sakonju, I., Maeda, K., Karasawa, K., Tadokoro, T., Kakuta, T. and Takase, K. 2011. Plasma concentration and cardiovascular effects of lidocaine during continuous epidural administration in dogs anesthetized with isoflurane. *J. Vet. Med. Sci.* **73**: 393–398. [Medline] [CrossRef]
28. Sayan, H., Aydogan, M. S., Bıcakcıoğlu, M., Toprak, H. I., Isık, B. and Yılmaz, S. 2015. Effects of thoracic epidural anesthesia on liver blood flow and indocyanine green clearance test in living-donor liver transplantation: a prospective, randomized, double-blind study. *Transplant. Proc.* **47**: 1462–1465. [Medline] [CrossRef]
29. Scheingraber, S., Richter, S., Igna, D., Flesch, S., Kopp, B. and Schilling, M. K. 2008. Indocyanine green disappearance rate is the most useful marker for liver resection. *Hepatogastroenterology* **55**: 1394–1399. [Medline]
30. Stromberg, M. W. 1969. Chap. 18 The autonomic nervous system. pp. 1030–1058. In: Anatomy of the Dog, 2nd ed. (Miller, M. E. ed.), WB Saunders, Philadelphia.
31. Torske, K. E. and Dyson, D. H. 2000. Epidural analgesia and anesthesia. *Vet. Clin. North Am. Small Anim. Pract.* **30**: 859–874. [Medline] [CrossRef]
32. Trepenaitis, D., Pundzius, J. and Macas, A. 2010. The influence of thoracic epidural anesthesia on liver hemodynamics in patients under general anesthesia. *Medicina (Kaunas)* **46**: 465–471. [Medline] [CrossRef]
33. Ueda, N., Muteki, T. and Tsuda, H. 1992. What anesthesiologist should know about neuromuscular monitoring today? *J. Anesth.* **6**: 192–206. [Medline] [CrossRef]
34. Valverde, A., Doherty, T. J., Hernández, J. and Davies, W. 2004. Effect of lidocaine on the minimum alveolar concentration of isoflurane in dogs. *Vet. Anaesth. Analg.* **31**: 264–271. [Medline] [CrossRef]

35. Vagts, D. A., Iber, T., Puccini, M., Szabo, B., Haberstroh, J., Villinger, F., Geiger, K. and Nöldge-Schomburg, G. F. E. 2003. The effects of thoracic epidural anesthesia on hepatic perfusion and oxygenation in healthy pigs during general anesthesia and surgical stress. *Anesth. Analg.* **97**: 1824–1832. [Medline] [CrossRef]
36. Weil, A. B. 2010. Anesthesia for patients with renal/hepatic disease. *Top. Companion Anim. Med.* **25**: 87–91. [Medline] [CrossRef]
37. Williamson, J. A. and Leone, S. 2012. Noninvasive arterial blood pressure monitoring. pp. 134–144. In: Advanced Monitoring and Procedures for Small Animal Emergency and Critical Care (Burkitt Creedon, J. M. and Davis, H. eds.), Wiley-Blackwell, Ames.
38. Zhang, D., Nishimura, R., Nagahama, S., Iseri, T., Mochizuki, M., Nakagawa, T. and Sasaki, N. 2011. Comparison of feasibility and safety of epidural catheterization between cranial and caudal lumbar vertebral segments in dogs. *J. Vet. Med. Sci.* **73**: 1573–1577. [Medline] [CrossRef]