Impact of intracranial hypertension on the short-term prognosis in dogs undergoing brain tumor surgery

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ABSTRACT. The present study used data from anesthetic records to analyze variables of intracranial pressure (ICP) during brain tumor surgery or in the early postoperative period as prognostic indicators in dogs. Data from 17 dogs which were scheduled to undergo elective craniotomy for brain tumor surgery from 2009 to 2012 were included. Of these, five (29.4%) died during 14 days after the surgery because of respiratory failure following pneumonia (n=2), euthanasia due to difficulty in treatment of status epilepticus (n=1), tumor-bed hematoma (n=1), and unknown reason (n=1). In the 12 surviving dogs, neurological signs were improved or resolved at discharge. All dogs were administered midazolam and droperidol-fentanyl as premedication. General anesthesia was induced using propofol maintained on isoflurane and oxygen. Direct ICP was obtained via a Codman Microsensor strain gauge transducer. ICP hypertension (>13 mmHg) measured after 15 min of recovery from the moment after discontinuation of anesthesia by turning off the vaporizer dial was associated with poor prognosis (odds ratio, 20.00; 95% confidence interval, 1.39−287.60, \(P=0.028\)). This suggests that intracranial pressure influences the postoperative mortality rate in dogs undergoing brain tumor surgery.

KEY WORDS: dog, intracranial pressure monitoring, intracranial tumor, mortality
postoperative prognosis. Therefore, the objective of this study was to analyze ICP monitoring during the brain tumor surgery or in the early postoperative period and the short-term prognosis in dogs.

MATERIALS AND METHODS

The medical records of dogs diagnosed as having a brain tumor by neurological examination and MRI and whose owners had signed informed consents about the brain surgery at the Nihon University from 2009 to 2012 were reviewed. Cases without ICP monitoring or with incorrect recording during the brain surgery, moreover, was excluded.

All dogs were premedicated with an intravenous (IV) administration of midazolam (0.1 mg/kg; Dormicum, Astellas Pharma Inc., Tokyo, Japan) and a droperidol-fentanyl compound agent (0.1 ml/kg; Thalamonal, Daiichi Sankyo Pharma Inc., Tokyo, Japan). Anesthesia was induced by slowly titrating propofol (Mairan, Intervet K.K., Tokyo, Japan) until obtaining the desired effect. As soon as jaw relaxation was achieved, endotracheal intubation was performed and maintained on isoflurane and oxygen. The concentration of isoflurane delivered was adjusted to maintain a light plane of anesthesia. IV lactated Ringer’s solution (10 ml/kg/hr; Fuso Pharmaceutical Industries, Co., Ltd., Osaka, Japan) was immediately administered following the induction of anesthesia through a catheter placed in the cephalic vein. A dorsal pedal artery was cannulated for direct monitoring of the arterial blood pressure with a mercury-calibrated transducer attached to a pressure module and monitor. All dogs were mechanically ventilated via intermittent positive pressure ventilation to an end-tidal CO₂ pressure of 35–40 mmHg and were monitored via side-stream capnography. Core body (rectal) temperature was maintained between 36.5 and 38.0°C with an active air warming system (3M™ Bair Hagger™ System, 3M Japan Ltd., Tokyo, Japan). Pulse oximetry, direct arterial blood pressure, capnography, rectal temperature, heart rate, and lead II ECG were continuously monitored with a multiparameter anesthetic monitoring system (BP-608 Evaluation, FUKUDA COLIN, Co., Ltd., Tokyo, Japan). An elbow connector with a sampling port was placed between the endotracheal tube and Y-piece of the circle anesthetic circuit for measuring the concentrations of end-tidal airway CO₂.

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For the surgical procedure, each dog was positioned in sternal recumbency, with the head elevated via placement in a craniotomy head stand to avoid jugular vein compression. Direct ICP measurements were obtained via a Codman Microsensor strain gauge (CMS) transducer (Johnson & Johnson K. K., Tokyo, Japan) placed in the cerebral hemisphere contralateral to the side of the craniectomy. A longitudinal skin incision was made, and the subcutaneous tissues were dissected to expose the fascia of the temporalis muscle. The fascia and underlying temporalis muscle were incised sharply. A Gelpi retractor was used to retract the cut ends of the temporalis muscle. After dissection of the musculature to expose the site, a small hole (2.5 mm in diameter) was made with a hand-held drill. The dura mater was visualized and incised with a 25-gauge injection needle. The Gelpi retractor was removed to allow for placement of the CMS transducer. The accuracy of all transducers was verified by post hoc calibration within a column of water. The tip of the CMS transducer was advanced approximately 0.5 cm into the brain parenchyma through the puncture in the dura. The wound was closed and the CMS secured by suturing the subcutaneous tissue and skin of scalp. The CMS transducer was not removed until postoperative clinical improvement, that is absence of sustained major neurological deficit such as depressed motor activity, reduced brainstem reflexes, or depressed level of consciousness, then the patients were discharged from the intensive care unit. In dogs who underwent ICP monitoring throughout the procedure, the data analysis included ICP values from first ICP monitor placement to recovery. Before craniectomy, glycerol (0.5 g/kg; Glyceol, Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) and methylprednisolone sodium succinate (10 mg/kg; Solmedrol, Pfizer Japan Inc., Tokyo, Japan) were intravenously titrated for 30 min to reduce brain edema and stabilize the animal.

The ICP measured real-timely and recorded as 5 min value average. And the values of two 15 min interval time points to detect ICP changes as 0 min (from 0 to 5 min) and 15 min (from 15 to 20 min) values after the following events were extracted from anesthetic records: T1 as the moment of CMS transducer insertion, T2 as the moment of craniectomy, T3 as the moment of durotomy, T4 as the period of tumor resection, T5 as the moment after skin closure, and T6 as the moment after discontinuation of anesthesia by turning off the vaporizer dial. The CPP is calculated by subtracting the ICP value from the MAP. Statistical analysis was performed using a software package (JMP ver.14 Japanese Edition, SAS Institute Japan, Ltd., Tokyo, Japan). Data from dogs were divided as poor prognoses (death during the perioperative period; PP group) and good prognoses (GP group). The values for each dependent variable were compared using the Mann-Whitney U test and medians with minimum and maximum values were used to describe nonparametric continuous variables. In addition, changes in each parameter were analyzed using the Kruskal-Wallis one way analysis of variance by ranks test as a baseline for the values after 5 min at T1. Normal ICP has been reported to be <13 mmHg [2]. Using this level as a reference, the mean ICP at 5 and 15 min in both groups was assessed; moreover, odds ratios and 95% confidence intervals for poor prognosis in relation to ICP (>13 mmHg) in dogs undergoing brain tumor resection were analyzed. The level of significance was set at P<0.05.
RESULTS

Perioperative death was defined as death occurring before discharge. Causes of death were determined by a thorough review of individual case histories. Data from 17 dogs with intracranial tumors diagnosed on the basis of histological evaluation were included. The GP group included 12 dogs who recovered with good prognoses, and PP group included five dogs who had worsened postoperative physical status, thereby assessed as having poor prognoses. In the PP group, the causes of death were respiratory failure following suspected pneumonia (n=2), euthanasia due to difficulty in treatment of status epilepticus (n=1), tumor-bed hematoma (n=1), and unknown (n=1). Two dogs had suspected pneumonia based on the results of blood (increased white blood cell counts and C-reactive protein levels) and X-ray (interstitial-alveolar pattern over entire lung fields) examinations, even though these dogs had been administrated a prophylactic antibiotic (IV cefazolin 20 mg/kg, TID) after the extubation as a routine post-operative care procedure. The dogs with pneumonia had been reintubated and ventilated to improve oxygenation and using propofol at a rate of 0.05–0.1 mg/kg/min at 20 hr and 164 hr after the post-operatory extubation. No abnormalities had been found in their mouth and throat at the time. Unfortunately, the two dogs died 4 and 8 days postoperatively due to respiratory failure with both hypoventilation and hypoxemia. The dog, who continued to have frequent seizures before and even after surgery, was euthanized 14 days postoperatively. The dog with tumor-bed hematoma went into cardiopulmonary arrest 2 days postoperatively. Finally, the dog who died from an unknown cause went into cardiopulmonary arrest the day after the operation. In all 12 survivors of the GP group, the neurological signs had improved or resolved at discharge.

The clinical details of all the dogs are shown in Table 1. Weight, sex and age did not considerably differ between the two groups. The results of the univariate analyses of variables during anesthesia are shown in Table 2; no significant differences were observed between the PP and GP groups. Table 3 shows anesthetic ICP monitoring variables during brain tumor resection. The initial MAP was significantly higher in the PP group than in the GP group (P=0.030). The CPPs at 0 and 15 min of T6 were significantly higher in the GP group than 0 min of T1 (P=0.0477 and 0.0404, respectively). Other variables did not significantly differ between the groups, and there were no differences in value between T1–T6 and baseline (after 5 min at T1).

Table 1. Clinical details and description of the lesions in dogs

| Group          | Breed          | Gender | Age (year) | Body weight (kg) | Lesion location | Lesion type         |
|----------------|----------------|--------|------------|------------------|----------------|---------------------|
| Good prognoses (GP) |                |        |            |                  |                |                     |
| 1              | Weimaraner     | Female | 12         | 21.3             | Frontal lobe   | Meningioma         |
| 2              | French bulldog | Female | 5          | 8.0              | Temporal lobe  | Astrocytoma         |
| 3              | Yorkshire terrier | Male   | 8          | 3.0              | Temporal lobe  | Oligodendroglia    |
| 4              | Mix breed dog  | Female | 12         | 4.3              | Frontal lobe   | Meningioma         |
| 5              | Wersh corgi    | Female | 5          | 13.4             | Frontal lobe   | Histiocytic sarcoma|
| 6              | Miniature shnauber | Male    | 7          | 7.0              | Frontal lobe   | Meningioma         |
| 7              | Welsh corgi    | Male    | 10         | 12.0             | Temporal lobe  | Histiocytic sarcoma|
| 8              | Yorkshire terrier | Male    | 11         | 4.9              | Occipital lobe | Astrocytoma         |
| 9              | Shetland sheepdog | Female | 10         | 12.0             | Frontal lobe   | Meningioma         |
| 10             | Welsh corgi    | Male    | 9          | 12.1             | Frontal lobe   | Histiocytic sarcoma|
| 11             | Boston terrier | Male    | 11         | 6.4              | Temporal lobe  | Oligodendroglia    |
| 12             | French bulldog | Male    | 7          | 17.4             | Parietal lobe  | Astrocytoma         |
| Median (range) | 10 (5–12)      | 10.0   | (3.0–21.3) |                  |                |                     |
| Poor prognoses (PP) |                |        |            |                  |                |                     |
| 1              | Welsh corgi    | Female | 11         | 10.0             | Frontal lobe   | Meningioma         |
| 2              | Miniature duchshund | Male   | 12         | 6.4              | Frontal lobe   | Meningioma         |
| 3              | Miniature duchshund | Female | 9          | 5.5              | Occipital lobe | Meningioma         |
| 4              | French bulldog | Male    | 8          | 13.3             | Frontal lobe   | Astrocytoma         |
| 5              | Pomeranian     | Female | 8          | 8.0              | Frontal lobe   | Meningioma         |
| Median (range) | 9 (8–12)       | 8.0    | (5.5–13.3) |                  |                |                     |

Table 2. Anesthetic variables in dogs undergoing tumor resection

| Variables                  | GP (n=12)        | PP (n=5)        | P value |
|----------------------------|------------------|-----------------|---------|
| Duration of surgery (min)  | 618 (367–725)    | 621 (500–688)   | 0.86    |
| Duration of anesthesia (min) | 826 (577–1,455) | 1,000 (871–1,161) | 0.23 |
| Propofol (mg/kg)           | 3.5 (1.8–5.0)    | 5.0 (2.7–5.0)   | 0.32    |
| Remifentanil (µg/kg/min)   | 0.4 (0.3–0.6)    | 0.3 (0.3–0.6)   | 0.39    |
| Dopamine (µg/kg/min)       | 5.0 (1.9–5.0)    | 2.1 (0.4–5.0)   | 0.31    |
| Dobutamine (µg/kg/min)     | 3.7 (0.8–5.0)    | 5.0 (1.2–5.0)   | 0.44    |

Data is shown as median (range). GP, good prognoses; PP, poor prognoses.
Table 3. Anesthetic monitoring variables in dogs undergoing tumor resection

|        | T1          | T2          | T3          |
|--------|-------------|-------------|-------------|
|        | 0 min       | 15 min      | 0 min       | 15 min      | 0 min       | 15 min      |
| HR     |             |             |             |             |             |             |
| PP     | 77 (57–152) | 87 (60–150) | 73 (52–150) | 75 (49–151) | 77 (50–147) | 77 (53–125) |
| SAP    | 103 (58–170) | 111 (60–164) | 118 (66–171) | 118 (72–187) | 132 (79–176) | 114 (80–180) |
| DAP    | 55 (22–124) | 55 (21–87)  | 60 (20–73)  | 60 (23–74)  | 61 (25–74)  | 57 (25–74)  |
| MAP    | 68 (34–131) | 67 (34–105) | 72 (35–95)  | 76 (40–98)  | 78 (42–92)  | 71 (43–96)  |
| (mmHg) |             |             |             |             |             |             |
| HR     |             |             |             |             |             |             |
| PP     | 139 (92–149) | 148 (72–154) | 120 (66–134) | 124 (77–141) | 120 (51–137) | 116 (85–136) |
| SAP    | 103 (58–170) | 111 (60–164) | 118 (66–171) | 118 (72–187) | 132 (79–176) | 114 (80–180) |
| DAP    | 55 (22–124) | 55 (21–87)  | 60 (20–73)  | 60 (23–74)  | 61 (25–74)  | 57 (25–74)  |
| MAP    | 68 (34–131) | 67 (34–105) | 72 (35–95)  | 76 (40–98)  | 78 (42–92)  | 71 (43–96)  |
| (mmHg) |             |             |             |             |             |             |
| HR     |             |             |             |             |             |             |
| PP     | 139 (92–149) | 148 (72–154) | 120 (66–134) | 124 (77–141) | 120 (51–137) | 116 (85–136) |
| SAP    | 103 (58–170) | 111 (60–164) | 118 (66–171) | 118 (72–187) | 132 (79–176) | 114 (80–180) |
| DAP    | 55 (22–124) | 55 (21–87)  | 60 (20–73)  | 60 (23–74)  | 61 (25–74)  | 57 (25–74)  |
| MAP    | 68 (34–131) | 67 (34–105) | 72 (35–95)  | 76 (40–98)  | 78 (42–92)  | 71 (43–96)  |
| (mmHg) |             |             |             |             |             |             |

Table 4 shows the risk and odds ratios between ICP and prognosis in the dogs. ICP in both the groups tended to decrease during the operation, but there were no differences between T1–T6 and baseline. ICP hypertension (>13 mmHg) measured after 15 min of recovery was associated with poor prognosis (odds ratio, 20.00; 95% confidence interval, 1.39–287.60; P = 0.028). The median term for CMS transmitter insertion were 4 days (1–11 days) and 6 days (5–13 days) in dogs of the PP and GP groups, respectively (P = 0.3442). The median postoperative maximum ICP values were 25 mmHg (15.0–50.0 mmHg) and 15.5 mmHg (4.0–50.0 mmHg) in dogs of the PP and GP group, respectively (P = 0.1855). The median time postoperative maximum ICP times were 10.5 hr (1.0–106.0 hr) and 26.0 hr (4.0–56.0 hr) in dogs of the PP and GP groups, respectively (P = 0.2051). The dog with
expected tumor-bed hematoma on computed tomography showed an increase in ICP to 50 mmHg for 10 hr postoperatively. In the two dogs with suspected pneumonia, ICP increases to 22 mmHg for 15 hr and to 25 mmHg for 27 hr postoperatively was observed, respectively. The dog with suspected status epileptics displayed an increase in ICP to 34 mmHg for 14 hr; and the other dog with unknown death cause showed an increase in ICP to 59 mmHg for 9 hr postoperatively.

DISCUSSION

To the best of our knowledge, this is the first study to analyze the association between the ICP variation during the brain tumor surgery or in the early postoperative period and the short-term prognosis in dogs after intracranial tumor resection. The present study aimed to identify clinical variables, including intraoperative ICP, available during surgery or in the early postoperative period that may affect the prognosis. ICP monitoring is a standard procedure in human medicine but has only recently been investigated in dogs. Previous studies have reported the utility of fiber optic ICP monitoring in dogs [3–5]. This device can establish changes in ICP under anesthesia and during brain surgery in dogs. However, the use of the fiber optic system may be limited due to its high cost in veterinary medicine; nevertheless, other systems are available [19]. In addition, implantation of any monitoring device into the brain parenchyma may be associated with many complications, such as infection, cortical damage resulting in seizures, and intracerebral hemorrhage. In this study, one dog, who had to be euthanized, presented a continued status epilepticus postoperatively, but displayed no changes in neurological signs such as in the length or numbers of seizures per a day. However, the possibility of such complications associated with implantation of the CMS device into the brain parenchyma cannot be denied in this study.

ICP is an important variable that directly affects brain function. Normally, according to the Monro-Kellie doctrine, three tissues within the skull (brain parenchyma, CSF, and blood) exist in an equilibrium that maintains ICP within the normal range. An increase in the volume of any of these intracranial components must be compensated by a reciprocal and equal decrease in the volume of one or both other components; otherwise, ICP increases. Progressive increase in ICP is detrimental to normal brain function, and if compartmentalized, results in brain herniation [13]. Herniation is often life-threatening, even when appropriately treated. Therefore, ICP monitoring in certain pathological states is clinically important to determine the increase in ICP and for treatment decision-making. The adequate interval for monitoring of ICP, however, has not been examined for anomaly detection in dogs. In human medicine, it has been reported the frequency of perturbations in ICP detected by the 15-min values were no different from those detected by the end-hour values [21]. Then, we employed and analyzed two time points of 0 min and 15 min values after each event in this study whereas ICP was continuously monitored. This interval could be one of limitations of this study because there are chances to miss out on peak and transient points of cranial hypertension. As a result, there were no differences in values among T1–T5 in ICP values existed in dogs with poor prognoses. However, the CPP value at T1 in the PP group was slightly lower than in the GP group (not significant), but a higher initial MAP at T1 in the PP group than in the GP group is exited. It might have been related to preoperative neurological deterioration, so that level of anesthesia was lighter in the PP group. Therefore, the majority of dogs with cranial hypertension may be still keeping their cerebral autoregulation. In addition, a CPP of at least 50 mm Hg is required to maintain CBF in human patients [12]; however, the clinical normal range of CPP values has not been established for dogs.

In this study, a significant increase in ICP was observed just 15 min after the beginning of the recovery phase in dogs of the PP group. In addition, ahead of that ICP increase, the CPP had increased at the time point of 0 min T6. Surgical removal of overlying skull and incision of the dura mater can decrease ICP [4]. Cerebral autoregulation is preserved with clinically useful concentrations of isoflurane [15]. Transient ICP increases, however, are observed sometimes during surgical manipulations. Therefore, we speculated that some dogs in with a poor prognosis may progress to cerebral dysfunction during or after brain surgery. The delay in ICP increase after a CPP increase may reflect the initial CBF increase after closing head and stopping general anesthesia before the brain volume increment that leads to a higher ICP. A dog with suspected tumor-bed hematoma had ICP increased to 50 mmHg for 10 hr postoperatively. Two dogs with suspected pneumonia had increased ICPs to 22 mmHg for 15 hr and to 25 mmHg for 27 hr.
postoperatively before they started on artificial ventilation. Thus, ICP monitoring even after surgery, anesthesia, and extubation may improve their outcomes by detecting abnormal brain conditions.

Early treatment may be able to improve the outcomes of dogs experiencing postoperative ICP hypertension. In cases of brain tumor surgery, the forceful and prolonged retraction, as well as the need for draining vein coagulation, may contribute to postoperative brain edema development. By monitoring ICP postoperatively, elevations may be detected at an early stage and may be treated using hyperosmolar therapy or re-operation using salvage decompressive craniectomy [4, 8].

In the present study, pneumonia was identified as a cause of poor prognosis after surgery because no dogs in the GP group had pneumonia. A transient increase in ICP during surgery may worsen neurological dysfunction (e.g., pharyngeal and laryngeal paralysis) postoperatively. In humans, ARDS development in a general surgical population is rare and is associated with low median drive pressure, FiO₂, crystalloid volume, and with transfusion requirements [6]. We did not analyze these four factors. However, in veterinary patients, aspiration pneumonia is common, representing 67% of the non-neurological postoperative complications [10]. In addition, mechanical ventilation can result in serious lung injury after four hours in dogs [22]. In veterinary patients, ventilator-induced lung injury after long-term mechanical ventilation may be considered as a case of pneumonia whereas it is not a matching criterion for ventilator-associated pneumonia (VAP) in humans. The VAP in human is defined as pneumonia that occurs 48–72 hr or more after endotracheal intubation, and is characterized by the presence of a new or progressive infiltrate, signs of systemic infection (fever, altered white blood cell count), changes in sputum characteristics, and detection of a causative agent [1].

The results of the present study showed that ICP monitoring during brain tumor surgery may be useful for estimating the early postoperative period prognosis in dogs. A limitation of this study was the relatively small number of animals, which may have influenced the ability to detect significant associations between mortality and prognostic factors. To fully confirm the usefulness and safety of this technique, a larger number of animals need to be investigated.

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