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A Prospective Randomized Clinical Trial of Vincristine versus Human Intravenous Immunoglobulin for Acute Adjunctive Management of Presumptive Primary Immune-Mediated Thrombocytopenia in Dogs

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Background: Dogs with immune-mediated thrombocytopenia (ITP) are at risk of hemorrhage when platelet count is <50,000/μL. Treatment with vincristine (VINC) or human intravenous immunoglobulin (hIVIG) decreases platelet recovery time compared with treatment with corticosteroids alone.

Objectives: To compare the effect of hIVIG versus VINC on platelet recovery in dogs with ITP.

Methods: Prospective, randomized study. Twenty dogs with idiopathic ITP (platelet count <16,000/μL) were enrolled. All dogs were treated with corticosteroids. Dogs were randomly assigned to receive a single dose of hIVIG (0.5 g/kg) or VINC (0.02 mg/kg). Outcome measures were platelet recovery time, duration of hospitalization, and survival to discharge.

Results: There was no significant difference in age, sex, weight, or initial platelet count between dogs treated with hIVIG (n = 10) and dogs treated with VINC (n = 10). Median platelet recovery time for both groups was 2.5 days (P = .51). Median hospitalization time for all dogs that survived to discharge was 4 days and not different between groups (P = .29). Seven of 10 dogs in the hIVIG group and 10 of 10 in the VINC group survived to discharge. Survival analysis did not identify any significant difference between the groups at discharge, 6 months, and 1 year after entry into the study. No adverse effects were reported in either group.

Conclusions and Clinical Importance: Vincristine should be the first-line adjunctive treatment for the acute management of canine ITP because of lower cost and ease of administration compared with human intravenous immunoglobulin (hIVIG).

Key words: Vincristine; Human intravenous immunoglobulin; Platelet recovery time; Thrombocytopenia; Vincristine.

Immune-mediated thrombocytopenia (ITP) is a condition in which antibodies are formed against platelets, leading to their phagocytosis and destruction by macrophages.[1] Immune-mediated thrombocytopenia is considered idiopathic or primary when no underlying cause for thrombocytopenia can be identified and is considered secondary when an underlying etiology is established.[2] Because antiplatelet antibody assays are not widely available and have less than ideal sensitivity and specificity, a clinical diagnosis of presumptive primary ITP is made on the basis of exclusion of other identifiable causes of thrombocytopenia and response to treatment.[3–5]

Clinical signs of ITP typically are those characteristic of a primary hemostatic disorder (eg, petechiae, ecchymosis, epistaxis, and gastrointestinal bleeding). Spontaneous hemorrhage usually does not occur until the platelet count decreases to <30,000–50,000 platelets/μL[4,6] although there is poor correlation between the absolute platelet count and likelihood of serious hemorrhage.[3] Treatment with immunosuppressive doses of glucocorticoids is the initial treatment of choice. To minimize the risk of serious hemorrhage, it is ideal for treatment to increase the platelet count to >30–50,000 platelets/μL as rapidly as possible. Most patients exhibit platelet count recovery within 1–15 days after initiating treatment with glucocorticoids,[3,4] but adjunctive treatment with VINC and hIVIG have been demonstrated to shorten platelet recovery time.[7,8]

In a prospective study assessing platelet recovery time in dogs with severe ITP treated with prednisone alone versus prednisone and VINC, administration of VINC and prednisone together was associated with a more rapid increase in platelet numbers and shortened duration of hospitalization in dogs with ITP, compared with use of prednisone.[7] In a prospective study assessing the adjunctive effects of hIVIG versus placebo in dogs with ITP, dogs treated with hIVIG and prednisone had a reduction in platelet recovery time and length of hospitalization compared with those treated with prednisone and placebo.[8] Efficacy of other drugs for adjunctive treatment of acute ITP has not been studied and there are no published studies

Abbreviations:

ITP	immune-mediated thrombocytopenia
hIVIG	human intravenous immunoglobulin
pRBCs	packed red blood cells
RBC	red blood cell
CBC	complete blood count
VINC	vincristine

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comparing the efficacy of VINC versus hIVIG. This is an important consideration because treatment with hIVIG is much more expensive and administration is more time consuming and challenging than treatment with VINC. The aim of this study was to compare platelet recovery time, duration of hospitalization, transfusion requirements, adverse effects, and long-term outcome in dogs with severe ITP treated with glucocorticoids and either VINC or hIVIG as adjunctive treatment. We hypothesized that there would be no difference between the 2 treatments.

Materials and Methods

Study Population

Client-owned dogs that were presented to Purdue University Veterinary Teaching Hospital (PUVTH) and University of Georgia Veterinary Teaching Hospital (UGVTH) between April 2007 and December 2011 with a diagnosis of severe primary ITP were enrolled in the study. The study was approved by the Purdue University Animal Care and Use Committee and the University of Georgia Veterinary Clinical Research Committee.

Inclusion Criteria

Dogs were included in the study if they had a presumptive diagnosis of primary ITP based on the diagnostic investigation outlined below, if their owners gave informed consent, and if the platelet count was $\leq$16,000/μL upon enrollment. This platelet count cut-off was chosen to be within the range of platelet counts used in previous studies investigating adjunctive therapy for ITP (15–20,000/μL).[7,8]

Exclusion Criteria

Patients with secondary causes of immune-mediated thrombocytopenia, megakaryocytic aplasia, and those with other underlying illness, relapsing ITP or concurrent immune-mediated hemolytic anemia were excluded from the study. Dogs also were excluded if they had been treated with glucocorticoids for more than 48 hours before presentation, had received any additional immunosuppressive therapy before presentation, or had been vaccinated in the 4 weeks before diagnosis or treated with any drug that could have caused secondary ITP.

Diagnostic Investigation

A diagnosis of presumptive primary ITP was made after exclusion of secondary ITP by a diagnostic evaluation that included a complete history, physical examination, CBC, platelet count, serum biochemistry profile, urinalysis, vector-borne disease serology (*Ehrlichia canis, Anaplasma phagocytophilum, Rickettsia rickettsii, Babesia canis, Anaplasma platys, Borrelia burgdorferi*), coagulation profile (prothrombin time [PT], activated partial thromboplastin time [aPTT]), and diagnostic imaging (thoracic radiographs, abdominal radiographs, abdominal ultrasonography or some combination of these). Evaluation of bone marrow cytology or histology or both was performed in all but 1 dog. Bone marrow samples were collected from the proximal humerus. Platelet counts were determined using EDTA-anticoagulated blood and automated cell counters. Platelet counts were performed in the clinical pathology laboratory at PUVTH or UGVTH by laboratory personnel unaware of the treatment group of individual dogs. Platelet counts <30,000/μL were confirmed by manually counting platelets using a hemocytometer. Complete necropsy was performed for the majority of the dogs that did not survive for the 12-month follow-up period.

Study Design

The study was a prospective, randomized, clinical trial. Attending clinicians and intensive care personnel were aware of the treatment received by each patient, but clinical pathology technicians and clinical pathologists who performed manual platelet counts were blinded to the treatment groups. Randomization into the 2 treatment groups was determined using a random number generator. The assigned treatment group was written on individual cards placed within sealed envelopes, which were only opened after patient enrollment. For dogs that did not have an increase in platelet count 7 days after treatment with the assigned treatment, a rescue protocol was instituted which consisted of the alternative study drug (hIVIG or VINC) and azathioprine at a dosage of 2 mg/kg PO q24 h.

Concomitant Treatments

All dogs were treated with glucocorticoids regardless of treatment group. The majority of dogs were treated with prednisone (1.5–2 mg/kg) PO q12 h. Dexamethasone was administered at a dosage of 0.2–0.3 mg/kg SC or IV q24 h in dogs that were vomiting and therefore could not tolerate glucocorticoids PO. Treatment with glucocorticoids was initiated immediately after confirmation of severe thrombocytopenia and completion of diagnostic testing to rule out an obvious underlying cause. Because infectious disease titers were not immediately available, doxycycline (10 mg/kg/d) was administered to dogs in both groups until the results of serologic testing were confirmed to be negative. Treatment with immunosuppressive agents other than the study drugs (ie, hIVIG or VINC) was not permitted unless no improvement was noted after 7 days of therapy with glucocorticoids and the study drug. Supportive care including fresh whole blood or stored packed red blood cell (pRBCs) transfusions and crystalloid fluids were provided as needed at the discretion of the attending clinician. One transfusion was defined as 10 mL/kg pRBCs or 20 mL/kg fresh whole blood.

Test Treatments

Treatment with either hIVIG[a] or VINC[b] was initiated as soon as a clinical diagnosis of presumptive ITP was made, usually within 24 hours of the initial presentation. A single dose of hIVIG (0.5 g/kg) was administered as a continuous IV infusion over 6–12 hours. A single dose of VINC (0.02 mg/kg) was administered as an IV bolus. The IV catheter was flushed with 0.9% saline solution before and after infusion to ensure proper catheter placement and to prevent any extravasation of VINC.

Study Endpoints

The primary endpoints of the study were time required to achieve a platelet count of $\geq$40,000/μL, duration of hospitalization, and survival to discharge. Secondary endpoints were cost of hospital treatment from enrollment to discharge, transfusion requirements, 6 month survival, and long-term (1 year) survival. Although hIVIG and VINC were provided at no cost to the client, the cost of hospital treatment was calculated based on what the cost would have been if the study had not paid the cost of the treatments.

Response Monitoring

All dogs were monitored in the intensive care unit (ICU) for the duration of hospitalization. Patients were assessed for clinical evidence of bleeding and for changes in PCV and platelet count. Daily CBCs were performed with blood samples collected after hIVIG or VINC administration until the platelet count was $\geq$40,000/μL. A response was defined as an increase in platelet count to $\geq$40,000/μL. All dogs were monitored for adverse effects of the drugs administered and any adverse effects were recorded. Patients were discharged from the hospital once the platelet count was $\geq$40,000/μL. After hospital discharge, dogs were followed for 12 months by either recheck evaluations at the hospital or telephone consultation with the referring veterinarians, owners or both. Duration of immunosuppressive therapy and documentation of disease relapse was recorded for each patient.

Statistical Analysis

Daily platelet counts and number of blood transfusions were recorded for each patient. Signalment, initial selected hematological and biochemical data, days to platelet count $\geq$40,000/μL, duration of hospital stay (days), and transfusion requirements were compared between treatment groups by the Student's *t*-test. Survival to discharge, 6 month survival, and 1 year survival were compared by the Fisher's exact test. A value of $P < .05$ was considered statistically significant.

Results

Study Population

Twenty-five dogs were enrolled in the study, but 5 dogs later were excluded because of a final diagnosis of megakaryocytic aplasia in 1 dog, positive infectious disease serology (*Rickettsia rickettsii, Babesia canis*) in 2 dogs, and study protocol violations (recent vaccination and antibiotic administration) in 2 dogs. Of the 20 dogs that completed the study, 18 were enrolled at PUVTH and 2 were enrolled at UGVTH. Ten dogs were randomly assigned to the hIVIG group and 10 dogs were randomly assigned to the VINC group.

Most dogs in the study population were of mixed breeding (n = 7). Pure breeds represented included Shih Tzu (n = 2), Bichon Frise (n = 2), and one each of the following: Golden Retriever, Dalmatian, English Bulldog, Australian Shepherd, Chihuahua, Pug, Italian Greyhound, Toy Poodle, and Boxer. There were no statistical differences in age, sex, weight, initial platelet count, blood urea nitrogen, or other clinicopathologic data between the groups (Table 1).

Presenting complaints included petechiae or ecchymoses (n = 8), melena (n = 6), oral bleeding (n = 6), lethargy (n = 4), cutaneous bleeding (n = 3), decreased appetite (n = 3), epistaxis (n = 2), hematemesis (n = 2), hematochezia (n = 2), hematuria (n = 1), vomiting (n = 1), diarrhea (n = 1), coughing (n = 1), and acute blindness because of hyphema (n = 1). Information regarding duration of clinical signs before presentation was only available for 16 patients. In 1 dog, thrombocytopenia was documented on routine laboratory screening before development of clinical signs. The remaining 15 dogs exhibited clinical signs a median of 2 days before presentation (range, 1–7 days). The median rectal temperature at presentation was 101.9°F (38.8°C; range, 99.6–104.6°F [37.6–40.3°C]. Five of the 20 dogs were febrile with a temperature >102.5°F (>39.2°C). The median heart rate at presentation was 120 beats/min (range, 72–162 beats/min). The median respiratory rate was 40 breaths/min (range, 14–150 breaths/min). The physical examination findings in each group of dogs are summarized in Table 2. On presentation, the median platelet count was 1,000/μL (range, 0–16,000/μL; reference range, 200,000–900,000/μL [PUVTH], 235,000–694,000/μL [UGVTH]) and the median hematocrit was 33.7% (range, 12.7–52.3%; reference range 37–55% [PUVTH], 36.6–59.6% [UGVTH]). Eleven dogs were anemic on admission (hIVIG group = 7, VINC group = 4), but there was no significant difference in hematocrit between the 2 groups ($P = .55$). Serology for *Ehrlichia canis, Borrelia burgdorferi,* and *Rickettsia rickettsii* was negative in all 20 dogs; serology for *Anaplasma phagocytophilum* was negative in the 15 dogs tested, and serology for *Anaplasma platys* was negative in the 14 dogs tested. Nineteen of the 20 dogs had negative serology for *Babesia canis*. The 1 dog that was serologically positive for *Babesia canis*, however, was negative for *Babesia canis* on PCR. Diagnostic imaging did not identify evidence of clinically relevant underlying disease in any dog.

Bone marrow sampling was performed in 19 dogs at presentation to exclude megakaryocytic aplasia or other underlying bone marrow dysfunction. Bone marrow samples were not collected in 1 dog because the dog responded to treatment before sampling could be performed. Bone marrow aspirates were collected for

Table 1. Signalment and initial hematologic data in 20 dogs with presumed primary thrombocytopenia treated with glucocorticoids and either vincristine or human intravenous immunoglobulin.

Parameter	hIVIG n = 10	VINC n = 10	*P*-Value
Age (years) (median and range)	6 (4–11)	6 (3–10)	.97
Sex	6 FS; 4 MN	7 FS; 3 MN	1.00
Weight (kgs) (median and range)	21.6 (12.2–34.1)	15.6 (4.2–41)	.55
Hematocrit on admission (%) (median and range)	31.7 (15.4–50)	33 (12.7–52.3)	.55
Neutrophil count on admission ($x10^3/\mu L$) (median and range)	17.3 (8.9–44.5)	16.9 (3.5–27.4)	.82
Neutrophil band count on admission ($x10^3/\mu L$) (median and range)	0.35 (0–2.32)	0.65 (0–2.42)	.59
Platelet count on admission ($x10^3/\mu L$) (median and range)	1.7 (0–16)	0.2 (0–10)	.94
Blood urea nitrogen (median and range)	21.5 (15–41)	20.5 (12–36)	.29

Table 2. Physical examination findings in 20 dogs with presumed primary thrombocytopenia treated with glucocorticoids and either vincristine or human intravenous immunoglobulin.

Physical Examination Abnormality	Number of Dogs hIVIG Group n = 10	Number of Dogs VINC Group n = 10
Petechiae/ecchymoses	9	9
Melena/hematochezia	7	6
Oral bleeding	3	3
Mild/moderate lymphadenomegaly	2	2
Cutaneous bleeding	1	2
Scleral hemorrhage	3	0
Hematemesis	3	0
Systolic cardiac murmur	3	0
Hematuria	2	0
Hematoma associated venipuncture sites	1	1
Hyphema	1	1
Hemoptysis	1	0
Deficits conscious proprioception	0	1
Hypovolemic shock	0	1
Uveitis	1	0

cytological evaluation as the sole method of bone marrow sampling in 11 dogs, a bone marrow core biopsy was collected for histopathologic evaluation as the sole method of bone marrow sampling in 1 dog, and both aspirates and core samples were collected in 7 dogs. Findings included megakaryocytic hyperplasia (n = 16), adequate numbers of megakaryocytes (n = 1), and megakaryocytic hypoplasia (n = 2).

Adverse Drug Reactions

There were no identifiable immediate or delayed adverse drug reactions detected in any patients during hospitalization or follow-up.

Primary Endpoints

The median platelet recovery time for both groups was 2.5 days ($P = .51$) (Table 3). The median hospitalization time for all dogs that survived to discharge was 4 days. The median hospitalization was 5 days in the hIVIG group and 4 days in the VINC group, and was not different between groups ($P = .29$). Seven of 10 (70%) of the dogs in the hIVIG group survived to discharge and 10 of 10 (100%) of the VINC group survived to discharge. There was no statistical difference in survival to discharge between the 2 groups ($P = .21$).

Secondary Endpoints

The mean cost of treatment was significantly higher in the hIVIG group ($4,108) than the VINC group ($2,426) ($P = <.001$). Seven of 10 dogs (70%) in the hIVIG group received transfusions during hospitalization, whereas 6 of 10 dogs (60%) in the VINC group received transfusions. Six dogs received fresh whole blood, 3 dogs received pRBCs, and 4 dogs received both fresh whole blood and pRBCs. In most cases, fresh whole blood was administered to provide temporary platelet activity. The median number of transfusions for all ITP dogs was 1 transfusion; the median number of transfusions for the hIVIG group was 1.5 transfusions; the median number of transfusions for the VINC group was 1 transfusion. The transfusion requirements were not significantly different between the groups ($P = 1.00$). The rescue protocol was used in 2 dogs that were in the hIVIG group. Both dogs survived to discharge. One is still alive and the other died within 6 months of entering the study.

Table 3. Platelet recovery time, duration of hospitalization, transfusion requirements, and survival to discharge in dogs with presumed primary thrombocytopenia treated with glucocorticoids and either vincristine or human intravenous immunoglobulin.

Parameter	hIVIG n = 10	VINC n = 10	*P*-Value
Hospitalization (days) (median and range)	5 (1.5–10)	4 (3–5)	.29
Platelet recovery time (days) (median and range)	2.5 (0[a]–10)	2.5 (1–4)	.51
Survival to discharge	7/10	10/10	.21
Transfusions required	7/10	6/10	1.00
Cost of treatment ($) (median and range)	4108 (3270–5344)	2426 (909–3270)	<.001

[a]A recovery time of 0 was assigned to dogs that survived less than 1 day so a 2nd platelet count was not measured.

One dog was lost to follow-up and censored from survival data. Six months after entry into the study, 10 of the remaining 19 dogs died; 7 of 9 from the hIVIG group and 3 of 10 from the VINC group ($P = .17$). One year after entry into the study, 11 of the dogs had died; 7 of 9 from the hIVIG group and 4 of 10 from the VINC group ($P = .07$).

Necropsy was performed in 8 of the 11 dogs that died during the 12 months of follow-up. Findings included infectious canine hepatitis, severe gastrointestinal ulceration, cellulitis, disseminated intravascular coagulation, severe hemorrhage, extramedullary hematopoiesis, and vacuolar hepatocellular degeneration. Necropsy results did not show evidence of underlying disease that could have caused secondary ITP in any of the dogs.

Discussion

The results of this prospective clinical trial showed that there was no difference on platelet recovery time or duration of hospitalization for dogs with severe ITP

treated with glucocorticoids and either hIVIG or VINC as adjunctive therapy. The median platelet recovery time of 2.5 days for both groups in this study was similar to the recovery times reported in the treatment arms of both previous prospective studies evaluating VINC and hIVIG for treatment of presumptive ITP.[7,8] In a study evaluating hIVIG treatment of dogs with ITP, the median recovery time for dogs treated with hIVIG was 3.5 days[8] and in a study evaluating VINC as an adjunctive treatment for ITP, the median recovery time for dogs treated with VINC was 4.5 days.[7] The recovery times for both groups in this study were shorter than the glucocorticoid only arms of these previous prospective clinical trials, which were 7.5 days and 6.5 days for hIVIG and VINC, respectively. The median duration of hospitalization of 4 days for the dogs in this study also was similar to that reported in the previous studies of hIVIG (4 days) and VINC (5 days).[7,8]

Vincristine is a vinca alkaloid that has been used in dogs with ITP to rapidly increase the platelet count. Vincristine binds to tubulin in the mitotic spindle, thereby inhibiting cell division. The precise mechanism by which VINC causes an increase in the platelet count in dogs with ITP is unknown, but acceleration of thrombopoiesis and decreased phagocytosis of opsonized platelets by impairment of phagocytic function have been proposed.[2]

Human intravenous immunoglobulin is extracted from pooled human plasma collected from 10,000 to 60,000 donors. The product contains several million antibody specificities.[9] Intravenous immunoglobulin was first demonstrated to have efficacy in treatment of ITP in children in the 1980s and it continues to be included in the treatment protocol for people with acute and chronic ITP.[9] Human immunoglobulin binds to Fc receptors on canine mononuclear cells and this is the main proposed mechanism by which it inhibits destruction of platelets in dogs with ITP.[10] The similarity of the response of dogs with ITP to both hIVIG and VINC is consistent with a common mechanism such as decreased phagocytosis of opsonized platelets.

Adverse effects of VINC include phlebitis if extravasation occurs, and myelosuppression, although this does not typically occur when used at the lower dosage recommended for treatment of ITP. An in vitro study suggested that VINC may interfere with platelet function[11] although clinical bleeding because of platelet dysfunction has not been reported in canine ITP patients treated with VINC once the platelet count increases above 30,000–50,000/μL, suggesting that any platelet dysfunction is not clinically relevant. Adverse effects of hIVIG include anaphylaxis, fever, and predisposition to thromboembolic events,[12] but adverse events are rarely reported clinically.[13] No adverse effects were identified after administration of either drug in this study. The potential cost of treatment in the hIVIG group was significantly higher than that of the VINC group because of the high cost of hIVIG.

The dogs in this study population were similar to those of other reports of dogs with presumptive ITP with regard to signalment, clinical signs, platelet count, initial clinicopathologic findings, radiographic findings, survival to discharge, and 1 year survival.[4,14] Although dogs treated with hIVIG had a lower survival to discharge and 1 year survival than dogs treated with VINC, the difference was not statistically significant. This was likely because the power to detect a difference between the groups was small. Power calculations showed that there would have needed to be 28 dogs in each group to detect a statistically significant difference in these proportions for survival to discharge (80% power) and 20 dogs in each group to detect a statistically significant difference in these proportions for 1 year survival (80% power). It is interesting that the 2 dogs that required implementation of the rescue protocol were in the hIVIG group.

The primary end points in this study were platelet recovery time, hospitalization time, and survival to discharge. Hospitalization time was strongly correlated with platelet recovery time because dogs typically were hospitalized until the risk of serious hemorrhage was considered to have passed as determined by the platelet count. The rationale for focusing on platelet recovery time is that the risk of serious hemorrhage particularly into organs such as the lung, brain, eye, and spinal cord is considered to be highest in dogs with platelet counts <30,000–50,000/μL. Hemorrhage resulting in neurologic signs, however, is rare in dogs with ITP and there also is only a poor correlation between the absolute platelet count and likelihood of serious hemorrhage in dogs with ITP.[3] Whether a faster platelet recovery time is associated with a better long-term outcome in dogs with ITP has not been documented.

This study has some limitations that need to be considered when interpreting the results. The diagnosis of ITP was based on exclusion of secondary causes rather than documentation of the presence of antibodies directed against platelets. Infectious disease screening was not complete in every dog; not all dogs were tested for antibodies to *Anaplasma platys* and *Anaplasma phagocytophilum*.

Necropsies were not performed in all dogs that died during the 12 months of follow-up, and 1 dog was lost to follow-up after discharge. In addition, the drug dosages used were derived from those used in previous studies and may not be optimal for treatment of dogs with ITP. Lastly, the evidence that a faster platelet recovery time is a surrogate for a better longer term outcome could be questioned. Despite these limitations, this study suggests that in dogs with severe presumptive ITP, there is no difference in outcome when dogs are treated with either hIVIG or VINC as adjunctive therapy with glucocorticoids. Because of lower cost, ready availability and ease of administration, VINC should be used as first line therapy for the initial management of dogs with severe ITP.

Footnotes

[a] Gammagard S/D or Gammagard Liquid, Baxter Healthcare Corporation, Deerfield, IL
[b] Vincristine sulfate injection USP, Hospira, Lake Forest, IL

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