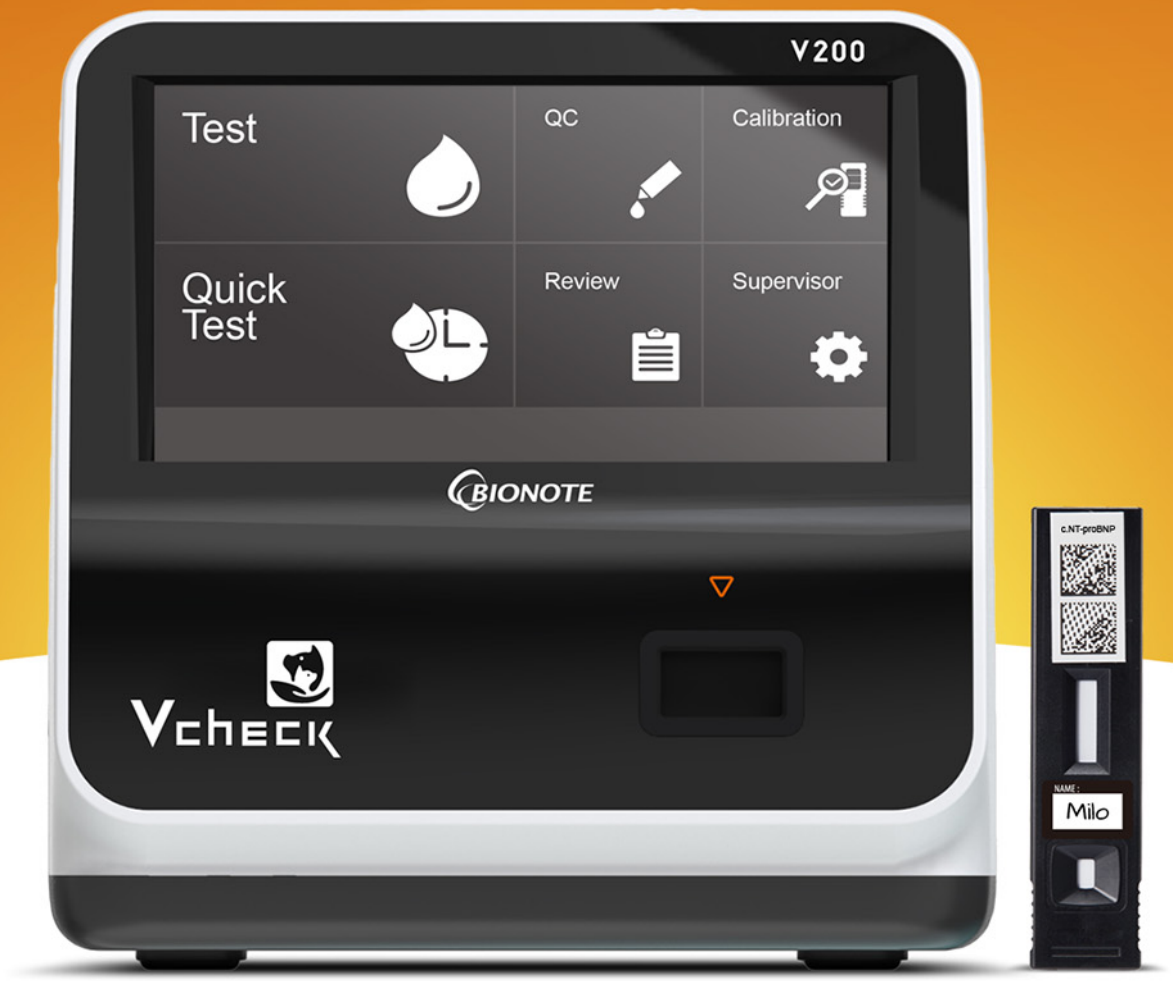

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Original Study

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Retrospective cohort study on the incidence of acute kidney injury and death following hydroxyethyl starch (HES 10% 250/0.5/5:1) administration in dogs (2007–2010)

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Abstract

Objective – To determine the incidence of in-hospital adverse outcomes including acute kidney injury (AKI) and death in a population of dogs admitted to the intensive care unit (ICU) receiving 10% hydroxyethyl starch (HES) [250/0.5/5:1] compared with the general ICU population, while controlling for illness severity.
Design – Cohort study conducted between January 2007 and March 2010.
Setting – Veterinary teaching hospital.
Animals – Consecutive sample of dogs receiving HES ($n = 180$) were compared with a randomly selected sample of dogs ($n = 242$) admitted to the ICU over the same period.
Interventions – None
Measurements and Main Results – AKI was defined as an at least 2-fold increase in baseline creatinine concentration or new onset of oliguria/anuria persisting for ≥12 hours. The primary outcome was a composite of in-hospital death or AKI. Unadjusted and adjusted analysis controlling for illness severity using the acute patient physiologic and laboratory evaluation ($APPLE_{fast}$) score and other confounders was performed. HES was administered either as incremental boluses (median dose 8.2 mL/kg/day, interquartile range [IQR] 5.0–11.3 mL/kg/day) or as a continuous rate infusion (CRI; median dose 26mL/kg/day, IQR 24.0–48 mL/kg/day). In unadjusted analysis, HES administration was associated with increased risk of mortality (odds ratio [OR] = 2.33, 95% confidence interval [CI] = 1.51–3.58, $P < 0.001$) or AKI (OR = 3.87, 95% CI = 1.21–12.37, $P = 0.02$). In an adjusted analysis after controlling for illness severity, admission type, and concurrent administration of blood products, HES administration remained an independent risk factor for the composite adverse outcome (OR = 1.98, 95% CI = 1.22–3.22, $P = 0.005$), with a number needed to harm (NNH) = 6 (95% CI = 4–23).
Conclusions – HES therapy is associated with increased risk of an adverse outcome including death or AKI in dogs. A randomized controlled trial investigating the safety of HES therapy in canine patients is warranted.

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Keywords: colloids, fluid therapy, complications, AKI, canine

Abbreviations

AKI	acute kidney injury
$APPLE_{fast}$	acute patient physiologic and laboratory evaluation
CI	confidence interval
CRI	continuous rate infusion
HES	hydroxyethyl starch
ICU	intensive care unit
IQR	interquartile range
OR	odds ratio

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The authors declare no conflict of interests.

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Introduction

Hydroxyethyl starches (HESs) are artificial colloid fluid solutions administered intravenously to provide volume expansion and oncotic support. Clinical use is widespread in small animal veterinary medicine; however, species-specific clinical data are relatively sparse.[1] The information available reports that HES

is effective at increasing systolic blood pressure and oncotic pressure[2–5] but also that HES use causes changes in coagulation function with decreased platelet function and reductions in coagulation factor VIII and von Willebrand factor activities.[6–8] No published studies have evaluated the effects of HES on canine kidney function outside of the laboratory setting. To date, no clinical studies on veterinary patients have investigated the incidence of adverse effects resulting from HES use or whether use of HES improves patient survival.

The adverse effects of HES in the human patient population are well documented, and include volume overload, coagulopathy, acute kidney injury (AKI), proinflammatory effects, and allergic reactions.[9] Due to increasing evidence of the association between HES use and AKI and bleeding complications, the Federal Drug Administration has mandated the inclusion of a new boxed warning in the package insert of HES products in the United States regarding the use of HES in critically ill human patients.[1] The Surviving Sepsis Campaign Committee including the pediatric subcommittee has changed the latest version of the guidelines to recommend against HES use in septic patients.[10] The European Medicines Agency's Pharmacovigilance Risk Assessment Committee initially recommended that marketing authorizations for HES be suspended due to an unfavorable risk:benefit ratio, and has since recommended that HES products should only be used to treat hypovolemia caused by acute blood loss and that it should be discontinued after 24 hours.[11] These recommendations follow a number of large randomized controlled trials and meta-analyses that have identified increased need for renal replacement therapy and increased mortality risk in critically ill human patients receiving HES. The controversies surrounding HES use have been well summarized in a recent review article in this journal.[11] In the absence of species and population specific data, it has been unclear how veterinarians should react to these recommendations.

The primary objective of this study was to evaluate whether HES use was associated with an increased risk of adverse outcomes including nonsurvival and AKI in a population of canine intensive care unit (ICU) patients. In view of the fact that HES may be administered to a more severely ill subset of the overall ICU population, the study was designed to include collection of a severity of illness measure facilitating an adjusted analysis. The hypothesis was that HES administration was not associated with increased risk of AKI and mortality.

Materials and Methods

This retrospective cohort study was conducted on canine patients admitted to the ICU between January 2007 and March 2010 in a veterinary teaching hospital setting. The HES group included all dogs that had received HES therapy and for which outcome information and admission acute patient physiologic and laboratory evaluation ($APPLE_{fast}$) score were available. The non-HES group consisted of a randomly selected sample of dogs admitted to the ICU over the same period that had not received HES therapy and for which outcome and $APPLE_{fast}$ score data were available. The HES used during the study period was 10% HES 250/0.5/5:1.[a] HES administration was at the discretion of the primary clinician. Due to the observational nature of the study, client consent was waived by the Institutional Animal Care and Use Committee.

Data collection

Data collection was performed in 2010, enrolling patients admitted between 2007 and 2010. Recorded data included $APPLE_{fast}$ score (calculated on information obtained within 24 hours of admission), HES dose, and method of administration (continuous rate infusion [CRI] or bolus), whether new onset AKI (defined as $\geq 2\times$ increase in admission creatinine concentration or development of oliguria/anuria of <0.5 mL/kg/h for ≥ 12 h) occurred over the hospital stay,[12] and survival status at discharge. Additional information was collected on patient signalment, primary diagnosis, and comorbidities including the identification of sepsis, the nature of the admission (medical vs. surgical, surgical elective vs. emergent vs. trauma), the total financial cost of the visit, the concurrent use of crystalloid fluid therapy and blood products, and whether a new onset requirement for supplemental oxygen support occurred over the hospital stay (defined as new requirement for oxygen support not required at admission, and prompted by increased respiratory rate/effort in conjunction with SpO_2 <95% on room air). Sepsis was defined as the presence (probable or documented) of infection together with $\geq 2/4$ of the systemic inflammatory response syndrome criteria.[9,13]

Statistical methods

Data were analyzed using commercial statistical software.[b] Descriptive statistics were computed for all study variables. Nonparametric tests of comparison were used for variables evaluated as not normally distributed. Difference testing was performed between the groups using the 2-tailed *t*-test, Mann–Whitney *U*-test, chi-square test, and Fisher exact test as appropriate. Continuous data are presented as mean ± standard deviation where normal or median and interquartile range (IQR) where not normal and categorical data as number (%) unless otherwise indicated. All comparisons were

Table 1: Characteristics of HES administration ($n = 180$)

	Bolus group ($n = 49$)	CRI group ($n = 131$)
Bolus/CRI (%)	27	73
Cumulative dose*	8.2 (5.0–11.3)	23.4 (11.1–49.0)
Hourly dose**	5.0 (2.5–8.2)	1.1 (1.0–2.0)

*Median and interquartile range in milliliter per kilogram.
**Median and interquartile range in milliliter per kilogram per hour.
HES, hydroxyethyl starch; CRI, continuous rate infusion.

two-tailed and $P < 0.05$ was considered to be statistically significant. We performed a multivariable logistic regression analysis with a composite outcome consisting of in-hospital nonsurvival or new onset AKI as the dependent factor. Age, sex, admission type (medical, surgical elective, surgical emergent, trauma), $APPLE_{fast}$ score, cumulative crystalloid fluid administration, HES administration, blood product administration, admission serum albumin concentration, history of trauma, and fulfillment of the sepsis criteria on admission[9,13] were considered as independent variables. Covariates were selected and entered into the model if they attained a $P < 0.2$ on a univariate basis. Collinearity between variables was tested prior to modeling by computing the correlation of estimates, with an $R^2 > 0.7$ considered significant. Interactions between covariates were excluded prior to modeling. Variables were considered to be acting as confounders based on biological plausibility and if removal caused a >20% change in the odds ratios (ORs) of the remaining variables. The Hosmer-Lemeshow goodness-of-fit test was performed and ORs (95% confidence interval [CI] were computed.

Results

Characteristics of the study groups

There were 180 dogs in the HES group and 242 dogs in the non-HES group. The doses and methods of administration of HES for the HES group are shown in Table 1.

The population characteristics of the study groups are shown in Table 2. The HES group had greater severity of illness ($P < 0.001$), longer duration of ICU stay ($P < 0.001$), and lower admission albumin ($P < 0.001$). A larger proportion of the HES group were surgical admissions ($P = 0.003$), had a history of trauma ($P = 0.053$), or were assessed to have a sepsis diagnosis over the course of the admission ($P < 0.001$).

The fluid administration characteristics of the 2 groups are shown in Table 3. Due to the longer median duration of ICU stay, the HES group received a greater cumulative administration of crystalloid ($P < 0.001$); however, there was no difference in median hourly crystalloid fluid administration rates between the 2 groups ($P = 0.110$). The HES group was more likely to receive blood product therapy ($P = 0.002$).

Table 2: Characteristics of the study groups (mean ± standard deviation or median and interquartile range (IQR)

	HES group ($n = 180$)	Non-HES group ($n = 242$)	*P* value
Age (years)	7.0 (4.0–9.0)	7.5 (4.0–10.0)	0.253
Male (%)	54	53	0.768
Bodyweight (kg)	24.5 (9.2–36)	24.4 (8.9–34.6)	0.512
Admission APPLE score	22.6 ± 7.4	18.9 ± 6.0	<0.001
Duration of ICU stay (h)	81 (40–134)	46 (24–74)	<0.001
Admission albumin (g/L)	25 (19–33)	33 (29–36)	<0.001
Surgical admissions (%)	33	20	0.003
Trauma (%)	12	6	0.053
Sepsis (%)	21	6	<0.001

HES, hydroxyethyl starch; ICU, intensive care unit; APPLE, acute patient physiologic and laboratory evaluation.

Table 3: Fluid administration characteristics of study groups (median and IQR or *n* [%])

	HES group ($n = 180$)	Non-HES group ($n = 242$)	*P* value
Cumulative dose crystalloid (mL/kg)	176.3 (88.2–331.1)	89.6 (47.9–169.3)	<0.001
Hourly dose crystalloid (mL/kg/h)	2.4 (1.6–3.5)	2.2 (1.3–3.2)	0.110
Red blood cell transfusion	43 (24%)	29 (12%)	0.002
Fresh frozen plasma transfusion	50 (28%)	10 (4%)	<0.001

HES, hydroxyethyl starch.

Morbidity and mortality

The overall mortality incidence was 28%, $n = 120$. Of these patients, 18 died as a result of naturally occurring cardiorespiratory arrest, and the remainder by euthanasia. Of the euthanized animals, the primary reason for euthanasia was recorded in 80 animals as due to the severity of illness, in 20 animals as due to a terminal diagnosis being identified, and in 2 animals as due to financial constraints. The overall AKI incidence was 3.6%, $n = 15$. Of the animals that experienced AKI, 8 died or were euthanized, and 7 survived to discharge. The morbidity and mortality characteristics of the HES and non-HES groups are shown in Table 4. The incidence of nonsurvival to discharge and AKI was greater in the HES compared with the non-HES group ($P < 0.001$). In univariable analysis, without adjusting for the previously noted disparities between the HES and non-HES groups, HES administration was associated with increased risk of mortality

Table 4: Morbidity and mortality characteristics of study groups

	HES group ($n = 180$)	Non-HES group ($n = 242$)	*P* value
Nonsurvival (*n*, %)	69, 38%	51, 21%	<0.001
Renal injury (*n*, %)	11, 6%	4, 2%	0.017
Respiratory failure (*n*, %)	32, 18%	31, 13%	0.169
Total cost (USD)	4,175 (2,759–6,257)	1,969 (1,286–3,590)	<0.001

HES, hydroxyethyl starch.

(OR = 2.33, 95% CI = 1.51–3.58, $P < 0.001$) and AKI (OR = 3.87, 95% CI = 1.21–12.37, $P = 0.02$). The odds of not surviving to discharge were 2.33 times higher in the HES group than in the non-HES group. The odds of suffering AKI, as previously defined, were 3.87 times higher in the HES group than in the non-HES group. The overall odds of experiencing an adverse outcome including death or AKI were 2.61 times higher in the HES group (OR = 2.61, 95% CI = 1.70–4.00, $P < 0.001$). Proportionally more patients in the HES group than in the non-HES group experienced new onset requirement for supplemental oxygen therapy (18% vs. 13%) but this difference did not reach statistical significance (OR = 1.47, 95% CI = 0.86–2.52, $P = 0.17$).

Multivariable adjustment for confounders

This association between HES administration and adverse outcome was retained in multivariable analysis (OR = 1.98, 95% CI = 1.22–3.22, $P = 0.005$) after controlling for the confounding effects of illness severity, emergency surgical admission classification, and administration of blood products. This OR is equivalent to a number needed to harm of 6 (95% CI = 4–23). The area under the receiver operator characteristic curve of the final model was 0.72, indicating good discrimination. The Hosmer-Lemeshow characteristic was 3.33, $P = 0.91$, indicating good calibration of the final model. The other variables assessed in the model were dropped either due to lack of significance or lack of an effect modification on the remaining variables. The ORs of the variables in the final model with a composite outcome consisting of in-hospital death or AKI as the dependent variable are shown in Table 5. The model was rerun after excluding all patients that underwent euthanasia for financial reasons or due to diagnosis of a terminal disease process with poor long-term prognosis ($n = 22$). Starch administration remained an independent predictor of poor outcome (OR = 2.15, 95% CI = 1.29–3.60, $P = 0.004$). In post hoc analysis, the individual associations between HES administration and AKI and HES administration and death were assessed in a multivariable context. These results are shown in Table 6.

Table 5: Odds ratios of variables in final model

Variable	Odds ratio	95% CI	*P* value
HES administration	1.98	1.22–3.22	0.005
APPLE score	1.07	1.03–1.11	<0.001
Blood product administration	1.93	1.16–3.25	0.01
Emergency surgical admission	0.28	0.15–0.52	<0.001

HES, hydroxyethyl starch; APPLE, acute patient physiologic and laboratory evaluation; CI, confidence interval.

Table 6: Odds ratios of hydroxyethyl starch administration in the final model assessed against both composite and separate outcomes of acute kidney injury (AKI) and death

Outcome	Odds ratio	95% CI	*P* value
Composite	1.98	1.22–3.22	0.005
AKI	4.87	1.37–17.35	0.015
Death	1.69	1.03–2.76	0.04

CI, confidence interval.

The presence of a dose-response relationship between HES administration and in-hospital adverse outcomes was also assessed. In a population restricted to dogs that received HES ($n = 180$), higher doses per kilogram bodyweight per hour of HES independent of method of administration were associated with an increasing risk of in-hospital death or AKI with an OR = 12.15 (95% CI = 3.93–37.51, $P < 0.001$, $n = 180$) for each milliliter per kilogram per hour increase in dose.

Discussion

To our knowledge, this is the first study to examine the potential adverse effects of HES administration in canine ICU patients. The main findings of this study were as follows: (1) HES administration showed an independent association with increased risk of in-hospital adverse outcomes including death and AKI, after attempting to control for the differences in illness severity, blood product administration, and emergency surgical admission classification between the HES and non-HES groups and (2) A dose-response relationship was present, with higher doses per kilogram per hour of HES associated with increasing risk compared with lower doses.

The impetus for the study came from reports associating the use of HES with higher risk of mortality, longer ICU stays, coagulopathies, and AKI in adult and pediatric human patients. These reports represent the results of meta-analyses of multiple randomized controlled trials conducted in human medicine, and appear to be consistent across all HES products. Adverse effects have been most consistently identified in septic patients.[9,11,14–16]

The mechanism of HES-induced AKI is incompletely understood, but appears to be due to the accumulation of lysosomes in the proximal tubule resulting from the pinocytosis of the colloid particles, which results in tubular cell swelling and interstitial inflammation. The oncotic force of the colloid also acts to decrease renal filtration pressure. These lesions have been well documented in canine kidneys in the laboratory setting, and HES has been shown to persist within macrophages and parenchymal cells in the canine kidney up to 18 days after administration.[17,18] Additional adverse effects of HES include tissue accumulation in the liver, bone marrow, endothelial cells, and tissue resident macrophages. Lyosomal accumulation and macrophage dysfunction occur as a result of the inability of cells to readily metabolize HES, with documented persistence in some organs for >8 years.[18,19] Greater HES storage has been shown to occur at higher doses. Cellular accumulation and dysfunction have been suggested as the mechanism underlying the link between HES administration and increased mortality risk.[18] A dose-response relationship has been documented, with higher mortality risk at higher doses of HES. This relationship was also identified in this study.

The study design has two features that merit discussion. A composite outcome was used as the primary outcome of interest both to improve the power of the study by increasing the overall event rate, and because we felt that both components of the composite were clinically relevant.[20] It was also anticipated that illness severity would act as a confounder in any observational study evaluating the relationship between HES administration and adverse outcome; more severely ill patients may be both more likely to receive HES as well as more likely to die. The study was designed to allow analytic adjustment for this issue using the $APPLE_{fast}$ score. This is an illness severity score that operates independent of primary diagnosis, and was developed at this center. Since development, the score has been externally validated by multiple centers to demonstrate excellent predictive value.[21–23] The score includes albumin as a component of calculation, which may have accounted for the between group differences in albumin baseline failing to act as an independent predictor or confounder in the final adjusted model.

This study has a number of limitations. First, the study design was observational in nature, limiting conclusions to reporting association rather than causation. In addition, there were multiple differences identified between the HES and non-HES groups at baseline. Second, although we attempted to control for the effect of baseline differences and confounders in the analysis, the multivariable approach is intrinsically limited by the variables included in the analysis. If a major confounder is not included, the effect of the key variable of interest, in this case HES administration, may be biased. Third, the data were collected retrospectively and follow-up was limited to the point of discharge from hospital. This may have resulted in underreporting of long-term consequences of HES administration. Fourth, despite multiple reports of the effects of HES on coagulation in dogs, no attempt was made to document coagulopathies as an adverse outcome. No dogs in the study were reported as having overt clinical bleeding, and there were limited coagulation testing data available for the dogs enrolled. Finally, the study was underpowered to assess for specific HES effects within subgroups, for example septic dogs or dogs receiving only bolus HES therapy.

The findings of this study were both surprising and concerning, as the clinical impression of HES in veterinary medicine based on the anecdotal and experiential evidence available to date has been one of safe volume expansion.[1] An association was found between HES use and adverse outcomes. After adjusting for the treatment group differences, the number needed to harm was calculated as 6. This suggests that if 6 patients are treated with HES, one will experience an adverse outcome associated with HES use. This is one of the first attempts to formally evaluate HES safety in the veterinary context, and in our opinion the findings merit reevaluation of the appropriate role of HES in veterinary emergency and critical care. There may be significant differences in safety profiles both between moderate and low molecular weight HES, and also between using HES as short-term bolus therapy limited to the initial stabilization versus using repeated dosing over several days or as a CRI.

Administration of HES as a CRI is unique to veterinary medicine. The majority of the dogs in this study (73%) received HES by CRI. By maintaining a high plasma concentration over a prolonged period with renal elimination limited to the smaller sized biproducts of amylase degradation, in our opinion CRI administration may favor increased tissue uptake of the larger molecular weight components of the polydisperse HES solution with accompanying negative effects on organ and immune function. The authors are unaware of any research data evaluating HES CRIs to support this theory.

We are also uncertain how applicable our findings are to dogs receiving forms of HES other than 10% 250/0.5. There are many formulations available, and the ICU in which this study was conducted has since transitioned to HES 6% 130/0.4. We cannot provide informed comment on potential adverse effects of HES distinct to the one studied here, which was higher in molecular weight and molecular substitution than tetrastarch (HES 130/0.4.), as well as being relatively hyperoncotic. However, it is worth noting that so far human critical care has failed to identify a "safe" HES formulation.[16]

In conclusion, further research in this area, specifically a randomized controlled trial with stratification on method of HES administration and assessment of both short- and long-term outcomes following HES use is required to robustly answer the questions regarding HES safety. The findings of this study should be considered preliminary due to the limitations discussed above, but provide early evidence that HES administration may not be as safe in this species as previously assumed.

Footnotes

[a] Pentaspan, Bristol-Myers Squibb, Montreal, QU, Canada.
[b] Stata 13.0, Stata Corp, College Station, TX.

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