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Sequential changes in urine production, glomerular filtration rate, and electrolyte excretion after mannitol administration

Gilad Segev[1] | Cheryl Stafford[2] | John Kirby[2] | Larry D. Cowgill[2]

[1]School of Veterinary Medicine, The Hebrew University of Jerusalem, Rehovot, Israel

[2]Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, California

Correspondence
Gilad Segev, School of Veterinary Medicine, The Hebrew University of Jerusalem, P.O. Box 12, Rehovot, 76100, Israel.
Email: gilad.segev@mail.huji.ac.il

Abstract

Introduction: Acute kidney injury (AKI) leading to severe uremia is associated with high morbidity and mortality. Mannitol is an osmotic diuretic, widely used in the management of AKI, both as a bolus injection and as a constant rate infusion (CRI).

Objectives: To determine the plasma concentration of mannitol after a bolus injection and CRI at the recommended dosages, and to assess the effect of mannitol on renal function variables including urine production, glomerular filtration rate (GFR), and solute excretion.

Methods: Prospective cross-over design study, using 6 healthy dogs. Each dog underwent 3 protocols with at least a 7-day washout period between protocols. The first protocol included bolus injection of mannitol, the second protocol included bolus injection followed by CRI of mannitol and the third protocol (control) included injection of 5% dextrose in water (D5W). Urine production, GFR, and fractional excretion (FE) of solutes were measured for 10 hours.

Results: For all protocols, urine production significantly ($P < .001$) increased after bolus injection, but no significant difference in urine production or GFR was observed among the treatment groups. Mannitol injection increased the FE of sodium and urea nitrogen, but these effects were short-lived.

Conclusions: Mannitol has minimal effect on urine production and GFR but does increase FE of urea nitrogen and sodium, immediately after bolus injection. Constant rate infusion at a conventional dosage of 1 mg/kg/min cannot maintain these effects in dogs with normal renal function, because mannitol concentration decreases rapidly.

KEYWORDS

acute kidney injury, chronic kidney disease, diuretics, dog

1 | INTRODUCTION

Acute kidney injury (AKI) leading to severe uremia is associated with high morbidity and mortality.[1–3] Medical management includes elimination of known causes of renal injury, if identified, and supportive treatment to control the clinicopathologic consequences of uremia.[4] One of the most consistent risk factors for mortality in AKI patients is anuria. Thus, monitoring and intervention should be applied to promote urine production and avoid transition to an anuric state.[1,3] This is achieved by judicious fluid administration and use of diuretics.[4] The most common diuretics in use in veterinary medicine include loop (eg, furosemide) and osmotic (eg, mannitol) diuretics.[4] The use of

Abbreviations: AKI, acute kidney injury; CRI, constant rate infusion; FE, fractional excretion; GFR, glomerular filtration rate.

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dopamine is controversial, and it no longer is used routinely in human patients.[5] Recently, fenoldopam has been evaluated in human and veterinary patients with conflicting results.[6–8]

Mannitol is an osmotic diuretic, widely used in the management of AKI, both as a bolus injection and as a constant rate infusion (CRI).[4] Potential beneficial effects of its use include increases in glomerular filtration rate (GFR), renal blood flow, and tubular flow.[9,10] Mannitol also is a free radical scavenger and may facilitate elimination of selected uremic toxins by interfering with their reabsorption from the renal tubules to the peritubular capillaries.

Despite the wide use of mannitol in the clinical setting, the effect of therapeutic dosages on electrolyte concentrations, urine production, and renal function variables (eg, GFR, fractional excretion [FE] of solutes) have rarely been reported in the veterinary literature. Previous studies investigating the effects of mannitol on the structure and function of the kidney did not mimic the clinical settings and therapeutic dosages in which this osmotic diuretic is used.[11–13] These studies did determine, however, that mannitol might be associated with adverse effects in both human patients and dogs.[13,14] Consequently, current therapeutic dosages are mostly opinion based, the effects of therapeutic dosages on renal function variables are not well established, and mannitol still is widely used despite potential adverse effects.[4]

In the clinical setting, both bolus injection and CRI of mannitol are used, the latter of which is used to maintain high mannitol concentrations. Although the pharmacokinetics of mannitol previously was studied in dogs after bolus injection,[12] plasma concentrations of mannitol after CRI were not described. Thus, it currently is unknown if the recommended CRI dosage can maintain effective plasma concentrations of mannitol. As a result, the currently recommended CRI dosage also is not supported by evidence, but rather is opinion based. Furthermore, the recommended dosage (bolus or CRI) does not take into consideration renal function, and, therefore, the plasma concentrations of mannitol may vary substantially among patients with different GFR, because the kidney is the only route of mannitol elimination.[12]

Our aims were to determine plasma concentrations of mannitol after a bolus injection of 0.5 g/kg and a CRI infusion of 1 mg/kg/min and to assess the effect of mannitol on renal function variables including urine production, GFR, and solute excretion.

2 | MATERIALS AND METHODS

2.1 | Study design

Our study followed a prospective cross-over design. Six staff-owned dogs were considered healthy, based on medical history, physical examination findings and normal CBC, serum biochemistry, urinalysis, and urine culture results. The study was approved by the Institutional Animal Use and Care Committee. Each dog underwent 3 protocols with at least 7 days of washout period between protocols. Based on the pharmacokinetics of mannitol, normal GFR, and the amount of fluids provided during the protocol, we determined that homeostasis would be restored within 24 hours after completion of the protocol. The protocol was selected by drawing slips from an envelope for each dog. For each protocol, dogs were fasted for 12 hours before the study day, but water was provided ad libitum. On the study day, each dog had urinary and IV (peripheral and sampling) catheters placed. For all 3 protocols, baseline endogenous creatinine clearance (ie, baseline GFR), blood urea nitrogen, and electrolyte concentrations as well as urine production were measured twice, each time by 30-minute urine collections. In all 3 protocols, GFR was measured by urinary clearance of creatinine.

Protocol A (bolus injection) included an IV mannitol injection (0.5 g/kg, diluted 1:3 in 5% dextrose in water [D5W] over 2 minutes). Protocol B (CRI) included a mannitol injection at the same dosage followed by a mannitol CRI (1 mg/kg/min, diluted 1:3 in D5W). Protocol C (control) included a bolus injection of D5W at the same volume and rate (6 mL/kg over 2 min) similar to Protocols A and B. All dogs received D5W after the bolus injection at a rate of 2.5 mL/kg/h (including the mannitol CRI in protocol B) to assure that all dogs in all protocols received the same amount of fluids. For all protocols, blood samples were collected in heparinized tubes at 30 seconds and 1, 2.5, 5, 15, 30, 60, 90, 120, 240, 480, and 600 minutes (total of 36 mL/dog/protocol) post-injection. Plasma was separated immediately and stored (−80°C), pending analysis using a wet chemistry analyzer calibrated for canine blood. Analyses included plasma mannitol (as described below), creatinine, urea nitrogen, phosphorus, sodium, chloride, and potassium concentrations. Urine was collected hourly after bolus injection for the first 6 hours followed by final urine collection 10 hours after bolus injection. At the end of each urine collection, the bladder was emptied by aspiration followed by a series of 3 infusions of 10 mL of air to ensure complete bladder empting. Samples were stored (−80°C) pending analysis that included mannitol, creatinine, BUN, and electrolyte concentrations. Urine production was measured at each urine collection using an analytic scale. At times of blood collection, blood pressure was measured using an oscillometric device.

2.2 | Mannitol assay

Plasma mannitol concentration was determined by an enzymatic photometric end point assay utilizing mannitol 2-dehydrogenase (MDH) from Leuconostoc mesenteroides and NAD^+ as previously described.[12,15] Briefly, a 6-point standard curve (0.0-3.0 mmol/L of D-mannitol in 4% bovine serum albumin) was generated in addition to samples to be determined for mannitol concentration. Standards and plasma samples were deproteinized with 10% (wt/vol) cold trichloroacetic acid and incubated at room temperature for 10 minutes followed by centrifugation at 16000*g* for 6 minutes. Forty microliters supernatant were incubated (37°C for 1 hour) with 30 μL of 30 mmol/L NAD^+ (in 1 mol/L Tris-HCl pH 8.5 at 37°C) and 160 mU of MDH (in distilled H_2O). At the end of the incubation period, 1 mL of 10 mmol/L Tris-HCl, pH 8.5 was added to each tube and mixed. Absorption of each solution was read at 340 nm wavelength on a spectrophotometer. Blanks were measured at incubations identical to the standards and samples.

2.3 | Statistical analysis

Normality was assessed using the Shapiro-Wilk test. Sample size was calculated (power, 80%; alpha, 5%) based on the assumption that

urine production would be doubled after mannitol administration and GFR would increase by at least 1 mL/min/kg. Baseline continuous variables (eg, GFR, urine production, FE of solutes) were compared among the study groups using 1-way analysis of variance (ANOVA). Continuous variables were compared among protocols using repeated-measures ANOVA. When changes over time were significant, paired Student *t* tests were calculated to compare these variables between baseline (average of 2 urine collections before bolus injection) and each of the subsequent urine collections within each protocol. When differences among groups or interactions were significant, 1-way ANOVA was used to compare variables of the same urine collection among the study groups and, when significant, a Student *t* test with Bonferroni correction was used to compare these variables among individual protocols.

Analysis was performed using NCSS software (LLC, Kaysville, Utah). $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Baseline variables

Six healthy dogs were enrolled (3 castrated males and 3 spayed females). Five were mixed breed dogs and 1 was a Rottweiler. Mean ± SD age was 5.3 ± 2.3, mean ± SD body weight was 29.3 ± 11.9. All dogs were assessed to be hydrated at the beginning of the study.

3.2 | Mannitol concentration

Mean mannitol concentration 1 minute after bolus injection was 270 ± 65.0 mg/dL and decreased to 172 ± 24.3 mg/dL after 15 minutes (Figure 1). Administration of mannitol at a CRI of 1 mg/kg/min maintained a serum mannitol concentration of approximately 40-50 mg/dL at 180-600 minutes after injection (Figure 1).

3.3 | Urine production

Mean urine production at baseline was 0.9 ± 0.7 mL/kg/min, 0.9 ± 0.4 mL/kg/min, and 1.1 ± 0.5 mL/kg/min for protocols A, B, and C, respectively. No statistically significant difference in baseline urine production was observed among the 3 protocols (Figure 2). For all protocols, a significant increase in urine production was identified over time, but neither significant difference among study groups nor interaction was identified. Urine production significantly ($P < .001$) increased in protocols A, B, and C at the first urine collection (60 minutes after bolus injection) to 5.3 ± 1.3 mL/kg/min, 6.1 ± 1.4 mL/kg/min, 5.2 ± 2.2 mL/kg/min, respectively, but no significant differences were observed among the treatment groups at this time point. Urine production also was not significantly different among the groups throughout the study period (Figure 1).

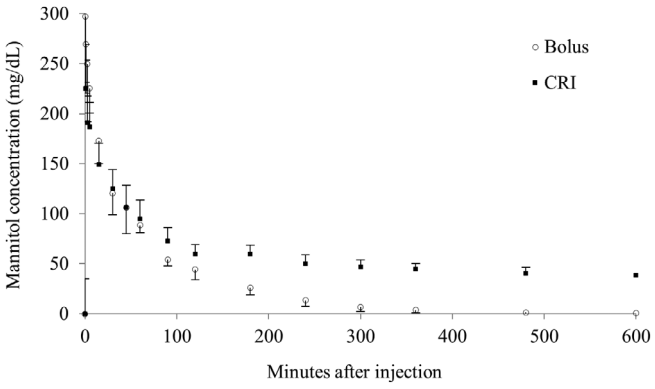

FIGURE 1 Changes in mannitol concentration (mean and SD) after bolus injection of 0.5 mg/kg (open circles) and after bolus injection of 0.5 mg/kg followed by a constant rate infusion of mannitol at 1 mg/kg/min

3.4 | Glomerular filtration rate

Mean GFR at baseline was 2.1 ± 0.4 mL/min/kg, 2.0 ± 0.3 mL/min/kg, and 2.3 ± 0.5 mL/min/kg for protocols A, B, and C, respectively. No statistically significant difference in GFR was observed among protocols at baseline. Glomerular filtration rate significantly increased in protocols A, B, and C at the 60 minutes urine collection to 2.3 ± 0.5 mL/min/kg, 2.1 ± 0.2 mL/min/kg, and 2.6 ± 0.5 mL/min/kg, respectively, but no statistically significant differences were observed among the treatment groups.

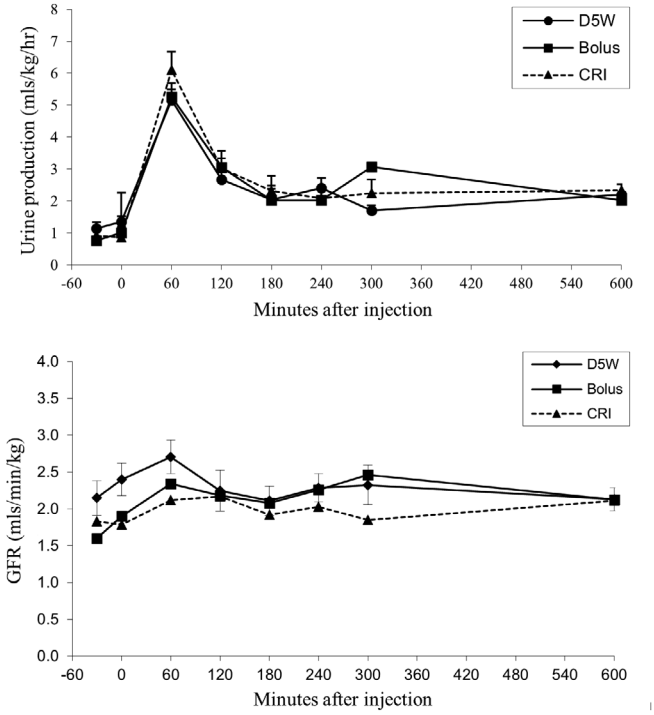

FIGURE 2 Sequential changes in urine production (upper panel) and glomerular filtration rate (GFR; lower panel) in the 6 dogs after bolus injection of mannitol (bolus group), bolus injection of mannitol followed by constant rate infusion (CRI group) and bolus injection of D5W (D5W group). There was a rapid increase in urine production as measured 60 minutes after bolus injection; however, no significant differences were observed among groups, both for urine production and for GFR

3.5 | Fractional excretion of solutes

No significant differences were found among the study groups at baseline for fractional excretion (FE) of any of the solutes. A significant ($P < .001$) interaction was found for FE of sodium and BUN (Figure 3). Mean FE of sodium significantly increased after bolus injection of mannitol from 0.002 ± 0.002 at baseline to 0.01 ± 0.002 1 hour after bolus administration (Figure 2, $P = .007$) in protocol A and from 0.002 ± 0.001 at baseline to 0.01 ± 0.005 1 hour after bolus administration ($P = .002$) in protocol B. Fractional excretion of sodium returned to baseline in the subsequent 120 minutes of urine collection in protocol A and in the 180-minute urine collections in protocol B. No significant difference between FE of sodium at baseline and after bolus injection was observed in protocol C (0.004 ± 0.002 and 0.004 ± 0.003, respectively, $P = .86$) as well as from the baseline to subsequent urine collections within this protocol.

A similar pattern was found for FE of urea. A significant increase in FE of urea was observed after mannitol injection in both protocols A and B (Figure 3). Fractional excretion of urea increased in protocol A from 0.4 ± 0.16 at baseline to 0.68 ± 0.16 1 hour after bolus administration ($P < .001$) and from 0.34 ± 0.09 at baseline to 0.63 ± 0.11 1 hour after bolus administration ($P < .001$) in protocol B (Figure 3). Fractional excretion of urea also increased significantly at the 1 hour urine collection compared with baseline in protocol C (0.35 ± 0.11 to 0.49 ± 0.11, respectively, $P = .01$), but FE of urea was significantly ($P = .05$) lower at this time point compared to the other protocols. Fractional excretion of urea remained higher compared to baseline both after bolus administration alone and after bolus administration followed by CRI until 3 hours post-bolus administration, but no statistically significant differences were observed in FE of urea among the 3 protocols at any of the other time points.

Fractional excretion of potassium and phosphorous were not significantly different at baseline among the groups and throughout the study period, but in all groups, a significant decrease in FE of potassium was observed over time.

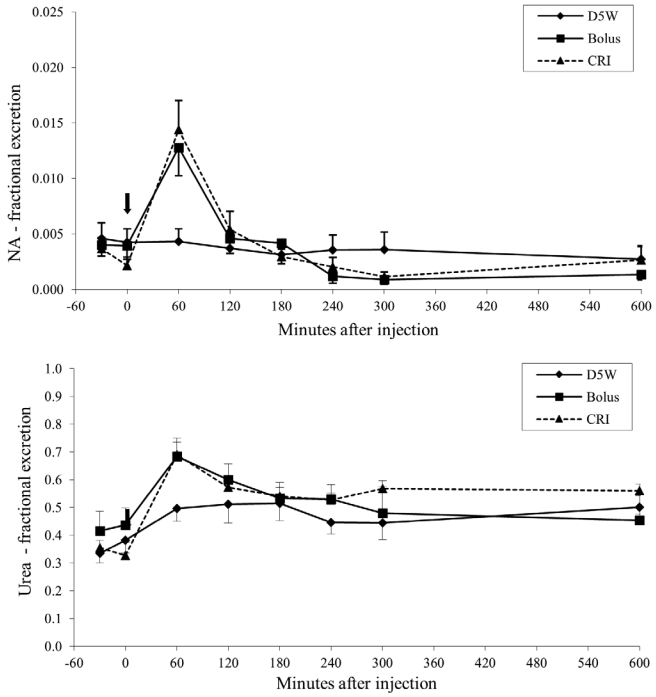

FIGURE 3 Sequential changes in FE of sodium (upper panel) and FE of urea (lower panel) in the 6 dogs undergoing bolus injection of mannitol (bolus group), bolus injection of mannitol followed by constant rate infusion (CRI group) and bolus injection of D5W (D5W group). Note the increase in FE of sodium (upper panel) and urea (lower panel) after bolus injection of mannitol at 0.5 g/kg, but these effects were not maintained with CRI of mannitol at 1 mg/kg/min

4 | DISCUSSION

We demonstrated that mannitol administration has only a small and short-lived effect on urine production and GFR but does increase FE of urea and sodium, immediately after bolus administration. Constant rate infusion of mannitol at a conventional dosage of 1 mg/kg/min cannot maintain these effects because mannitol concentration decreases rapidly, despite CRI.

Mannitol is widely used in veterinary medicine as an osmotic diuretic as well as to increase serum osmolality in the management of brain edema.[16,17] In our study, maximal mannitol concentration documented after bolus administration was approximately 300 mg/dL, and the concentration decreased rapidly, most likely because of redistribution in the extracellular fluid and elimination. Thus, the increase in plasma osmolality that can be achieved after a mannitol bolus of 0.5 g/kg is relatively modest, and the effect is very short-lived. Therefore, when osmolality is to be increased as part of the management of increased intracranial pressure, higher and more frequent doses should be considered. Nonetheless, caution should be used because very high doses of mannitol have been implicated in renal damage.[13]

Mannitol has several theoretical beneficial effects in patients with AKI. It often is used in oliguric animals to promote urine production, increase GFR and tubular flow, and relieve intraluminal tubular obstruction resulting from casts and debris.[4] Additional beneficial effects include decreased cellular swelling, often associated with acute tubular necrosis, scavenging of free radicals, induction of prostaglandin production, thus promoting vasodilation, and induction of atrial natriuretic peptide release.[4,10] Mannitol also may decrease the influx of calcium into mitochondria in injured tubular cells, preventing progression to lethal damage.[4,10] Despite its wide use, to date, no randomized clinical trials support its use in veterinary patients with AKI.[9]

Our study suggests that some of the attributed effects of mannitol might not be of clinical relevance. For example, urine production significantly increased after mannitol administration, but the increase was not different from that achieved after an equivalent volume of D5W, suggesting that the diuretic effect resulted mostly from administration of fluids rather than from mannitol itself. Furthermore, urine production was not different at any time point during the 10-hour follow-up period among the study groups, including the CRI group. These results suggest that mannitol cannot be regarded as a potent diuretic in otherwise healthy animals with normal renal function.

Glomerular filtration rate is maintained at a relatively constant rate as a result of various autoregulatory mechanisms.[18] Glomerular filtration rate is determined by the filtration coefficient and the net filtration force, which includes the hydrostatic pressure within the glomerular capillaries (the main force promoting filtration), oncotic pressure within the glomerular capillaries, and the hydrostatic and oncotic pressures within Bowman's capsule.[18] Of these, mannitol administration potentially alters only the oncotic pressure within the glomerular capillaries, thereby potentially increasing GFR. In our study, mannitol administration was not associated with an increase in GFR. A mild and short-lived increase in GFR was identified in all study groups after mannitol or D5W administration, but the differences among the groups were not statistically significant. It is possible that the rapid bolus injection of fluids temporarily increased systemic blood pressure, and therefore, to some extent, intra-glomerular pressure (despite the autoregulatory mechanism that maintains constant renal blood flow at wide ranges of systemic blood pressure),[18] or temporarily decreased oncotic pressure within the glomerular capillaries as a result of a dilutional effect. However, none of these changes can be attributed to mannitol itself because no GFR differences were found among the study groups. With the exception of the urine collection performed 60 minutes after the bolus administration of mannitol or D5W, no significant difference in GFR was observed between the baseline and any of the subsequent measurements during the 10 hours. It can be concluded that mannitol administration at 0.5 g/kg does not alter GFR in otherwise healthy dogs, even if followed by a conventional CRI dosage (ie, 1 mg/kg/min).

The 2 major effects identified after mannitol administration were the increase in FE of sodium and urea. The FE of sodium increased approximately 10-fold immediately after bolus administration, but the effect was not maintained. In fact, sodium FE was lower in both the bolus and in the CRI groups, compared to the control group, from 2 hours after bolus administration. This finding might result from a decrease in plasma sodium concentration, which could have triggered activation of the renin-angiotensin-aldosterone system, resulting in increased sodium reabsorption along the renal tubules, thereby decreasing FE of sodium. Solute diuresis might be beneficial in the management of AKI patients because it decreases sodium reabsorption and therefore energy demands. Sodium FE, however, increases in dogs with AKI even when mannitol is not administered and to substantially higher levels.[8,19]

The FE of urea also increased significantly after bolus administration, most likely because of decreased urea reabsorption in the renal tubules. This effect also was documented after administration of D5W, but the effect was less pronounced compared to mannitol administration. These results suggest that high serum mannitol concentration might facilitate elimination of nitrogen waste products and thus decrease the magnitude of uremia in hospitalized AKI patients. The effect was short lived, however, indicating that plasma mannitol concentration might need to be higher to facilitate the elimination of nitrogen waste products. Administration of mannitol at a CRI of 1 mg/kg/min did not maintain the increase in urea FE after bolus administration. Apart from changes in sodium and urea FE, mannitol administration did not have any effect on any of the other solutes measured. Thus, mannitol should not be used in an attempt to promote potassium or phosphorus excretion.

Our study was performed in healthy dogs with normal GFR. Because the kidneys are the major route of mannitol elimination, dogs with decreased renal function are expected to maintain higher plasma mannitol concentrations compared to normal dogs in proportion to their decrease in GFR. Thus, the effects documented in our study might be more pronounced and long-lasting at the same dosage, when administered to dogs with decreased renal function. This possibility also should be considered when mannitol is administered repeatedly in dogs with AKI in an attempt to promote urine production, because frequently repeated mannitol administration in the face of markedly decreased GFR will result in high plasma mannitol concentration, resulting in electrolyte derangements and potentially further aggravating renal function.[13] The pharmacokinetics of mannitol administration should be studied further in animals with variable degrees of decreased renal function.

Our study had limitations. First, it included only 6 dogs, which limited the statistical comparisons. Therefore, the absence of effects documented in our study should not be regarded as a clear evidence of their absence. Second, only 1 dosage of mannitol and 1 dosage of CRI were studied, whereas recommended dosages in the veterinary literature vary. Third, dogs had normal renal function, and conclusions regarding these effects in animals with decreased GFR are limited.

In conclusion, conventional dosages of mannitol (bolus and CRI) had limited effects on renal function variables including urine production and FE of electrolytes in normal dogs.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The study was approved by the IACUC of the Hebrew University of Jerusalem. This study used staff owned healthy dogs.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Gilad Segev https://orcid.org/0000-0003-4714-3159

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