

Variable change in renal function by hypertonic saline

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Received: September 16, 2013 Revised: December 9, 2013

Accepted: January 13, 2014

Published online: May 4, 2014

Abstract

AIM: To investigate the effects of hypertonic saline in the neurocritical care population.

METHODS: We retrospectively reviewed our hospital's use of hypertonic saline (HS) since March of 2005, and prospectively since October 2010. Comparisons were made between admission diagnoses, creatinine change (Cr), and HS formulation (3% NaCl, 3% NaCl/sodium acetate mix, and 23.4% NaCl) to patients receiving normal saline or lactated ringers. The patients ($n = 1329$) of the retrospective portion were identified. The data presented represents the first 230 patients with data.

RESULTS: Significant differences in Acute Physiology and Chronic Health Evaluation II scores and Glasgow

Coma Scale scores occurred between different saline formulations. No significant correlation of Cl^- or Na^+ with Cr, nor with saline types, occurred. When dichotomized by diagnosis, significant correlations appear. Traumatic brain injury (TBI) patients demonstrated moderate correlation between Na^+ and Cr of 0.45. Stroke patients demonstrated weak correlations between Na^+ and Cr, and Cl^- and Cr (0.19 for both). Patients receiving HS and not diagnosed with intracerebral hemorrhage, stroke, subarachnoid hemorrhage, or TBI demonstrated a weak but significant correlation between Cl^- and Cr at 0.29.

CONCLUSION: Cr directly correlates with Na^+ or Cl^- in stroke, Na^+ in TBI, and Cl^- in other populations. Prospective comparison of HS and renal function is needed.

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Key words: Hypertonic saline solution; Sodium chloride; Acute kidney injury; Cerebral edema; Critical care

Core tip: This work adds to the literature that changes in Na^+ and Cl^- in the neurocritical care population correlate to adverse changes in renal function. It is critical for the neurointensivist to remain cognizant of this when choosing whether or not to use hypertonic saline, and what to monitor when doing so. Unlike previous work, this data suggests some diseases may have more or less a change in renal function from Na^+ or Cl^- . This argues for further study of how the formulations of these fluids may change outcome in the neurocritically ill.

Corry JJ, Varelas P, Abdelhak T, Morris S, Hawley M, Hawkins A, Jankowski M. Variable change in renal function by hypertonic saline. *World J Crit Care Med* 2014; 3(2): 61-67 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v3/i2/61.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v3.i2.61>

INTRODUCTION

A nearly ubiquitous problem in the neurocritical care population is cerebral edema (CE). Cerebral edema has been implicated in delayed neurological deterioration, and worse outcome, through the elevation of intracerebral pressure (ICP)^[1]. The role of CE in outcome is contentious, with evidence suggesting that the extent of CE may, and may not, correlate with outcome^[2-6]. Animal models of CE demonstrate increased water content of edematous tissue correlates with inflammation and neuronal death^[7]. Potentially, reduction of this edema may reduce the degree of neuronal death, potentially improving outcome and decreasing hospital length-of-stay.

The medical management of CE is not without problems. Mannitol use is common, but is complicated by deleterious effects on renal function, fluctuations in intravascular volume, and pH. Over time, mannitol's slow elimination from the cerebrospinal fluid may require progressively higher doses to control ICP and rebound CE^[8,9]. Increasingly, hypertonic saline (HS) is being used to abate cerebral edema. Used in bolus or a continuous infusion fashion, HS has been shown to be safe and effective in reducing ICP in patients with traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), and stroke^[10,11]. HS shifts fluid from endothelium and surrounding tissues into the vascular compartment, normalizing the endothelial volume, increasing capillary diameter, and reducing resistance to flow^[12]. Edema can be reduced in this manner. Further, hypertonic fluids produce smooth muscle vasodilation improving regional blood flow^[12]. HS is relatively inexpensive. The early use of HS may reduce secondary cell injury caused by cerebral edema^[13]. These characteristics make HS an ideal therapeutic option in conditions such as SAH, intracerebral hemorrhage (ICH), stroke, and TBI.

However, the use of HS has not demonstrated any survival or outcome benefit despite reductions in ICP^[12,14]. Further, HS may be associated with increased risk-of blood-stream infections, and possibly increased risk-of nosocomial and urinary tract infections^[14]. A growing body of evidence suggests a possible link between HS use, renal dysfunction, and mortality^[15-17]. We hypothesize the use of HS correlates to adverse changes in renal function.

MATERIALS AND METHODS

Study setting

The Henry Ford Neurocritical Care Unit (NCCU) is a 16 bed unit with a yearly census over 1000 patients. The Henry Ford Neurocritical Database records data on stroke, TBI, ICH, SAH, SE, and spinal cord injury patient populations admitted to the NCCU. The data has been prospectively collected since October of 2010, with data added retrospectively from March of 2005 (when the first neurointensivist joined the staff) until October 2010. Between March 2005 and October 2010, 1329 patients of the retrospective cohort meet the inclusion criteria. The

data presented represents the first 230 patients with data.

Study design

With institutional review board approval, we mined the Henry Ford Neurocritical Database to identify all patients from March of 2005 to October 2010 with the aforementioned diagnosis who received HS. These patients were cross matched with the institution's pharmacy database to ascertain which saline formulation patients in the retrospective cohort received. In this retrospective sample, if patients were identified who received HS, and were not in the NCCU database, their data was retrospectively collected. Data was collected from admission until NCCU discharge, death, or post admission day (PAD) 13. Variables sought included: (1) IVF formulation: Normal saline (NS), ringer's lactate (LR), HS (3% NaCl, 3% NaCl:Na acetate, 23.4%); (2) physiologic: Mean arterial pressure; serum sodium, creatinine, chloride, HCO₃, BUN, creatinine; admission weight; (3) clinical: Admission Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, admission Glasgow coma scale in all patients, Hunt and Hess grade in SAH patients, NIH stroke scale in stroke patients, presence of external ventricular drain, and duration of ICU stay. APACHE II scores were retrospectively calculated on all patients in the retrospective cohort; and (4) demographics: Age; sex; race; presence of hypertension, diabetes, pre-existing renal insufficiency and etiology of renal insufficiency, history of coronary artery disease or congestive heart failure. Patients received various formulations of HS at the discretion of the attending NCCU staff. Correlations to renal function, as measured by Cr, to the formulation of saline used, and to changes in serum sodium and chloride levels were made. Patients receiving only LR or NS served as a comparison group.

Statistical analysis

Intervariable associations were calculated between using Pearson's correlation coefficients. The *P* values for these correlation coefficients were computed using clustering methods that take into account the multiple measures from the same patient. This was done with the entire sample as well as within each saline type and within each diagnosis type.

RESULTS

Who received HS solutions?

Table 1 summarizes the baseline characteristics of this cohort. There were no significant differences in diagnosis between groups. There were significant differences in the APACHE II scores and Glasgow Coma Scale (GCS) scores between the different formulations of HS. Significant differences emerged in admission Na⁺, A-a gradient, APACHE II score, and GCS. In pairwise comparisons, patients receiving HS demonstrated higher APACHE II scores and lower GCSv scores. 3% patients uniformly scored lower on GCS components compared to LR/NS patients, and lower in the GCSm and GCSe

Table 1 Baseline characteristics by saline type

Variable	23.40% (n = 22)	3% (n = 13)	NS/LR (n = 194)	P value
Diagnosis				0.078
ICH	15 (68)	7 (54)	67 (35)	
Other	3 (14)	3 (23)	47 (24)	
SAH	4 (18)	2 (15)	43 (22)	
Stroke	0 (0)	0 (0)	28 (14)	
TBI	0 (0)	1 (8)	9 (5)	
Age (yr)	61.9 ± 15.6	59.2 ± 19.6	56.8 ± 16.2	0.356
HCT (mmHg)	38.2 ± 6.9	38.1 ± 6.2	38.1 ± 7.0	0.999
WBC (10 ⁹ /L)	12.5 ± 6.2	11.6 ± 5.2	11.4 ± 9.1	0.865
Temperature (°C)	37.3 ± 0.9	37.2 ± 0.7	36.8 ± 2.5	0.514
HR	81.3 ± 20.3	86.5 ± 19.1	82.6 ± 16.7	0.668
RR	18.1 ± 4.6	17.5 ± 7.3	18.6 ± 4.4	0.633
MAP	98.3 ± 18.2	100.8 ± 33.2	106.5 ± 24.8	0.267
Na	141.5 ± 6.4	8.2 ± 5.3	139.0 ± 4.1	0.037
K	3.9 ± 0.6	3.7 ± 0.5	4.0 ± 2.0	0.888
Glasgow coma Scale (verbal)	2.6 ± 1.7	2.3 ± 1.5	3.4 ± 1.7	0.010
1	10 (45)	6 (46)	53 (27)	
2	1 (5)	2 (15)	10 (5)	
3	2 (9)	1 (8)	15 (8)	
4	5 (23)	3 (23)	29 (15)	
5	4 (18)	1 (8)	87 (45)	
Glasgow Coma Scale (motor)	5.0 ± 1.5	3.9 ± 1.8	5.3 ± 1.3	0.002
1	1 (5)	1 (8)	5 (3)	
2	1 (5)	3 (23)	4 (2)	
3	2 (9)	2 (15)	16 (8)	
4	2 (9)	1 (8)	13 (7)	
5	4 (18)	2 (15)	27 (14)	
6	12 (55)	4 (31)	129 (66)	
Glasgow coma Scale (eyes)	2.9 ± 1.3	2.0 ± 1.0	3.3 ± 1.1	< 0.001
1	5 (23)	5 (38)	28 (14)	
2	4 (18)	4 (31)	15 (8)	
3	2 (9)	3 (23)	31 (16)	
4	11 (50)	1 (8)	120 (62)	
A aGrad ¹	6.1 ± 195.3	173.7 ± 141.2	125.3 ± 154.9	0.024
pH ²	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	0.306
PCO ₂ ³	27.0 ± 1.7	27.0 ± 3.0	26.0 ± 3.3	0.756
PaO ₂	209.2 ± 114.6	189.5 ± 136.8	150.8 ± 115.1	0.053
Baseline Cr	1.3 ± 1.4	0.9 ± 0.3	1.4 ± 1.8	0.655
APACHE II	14.9 ± 7.6	17.5 ± 5.2	10.7 ± 6.5	< 0.001

¹23.4%, n = 19; 3%, n = 12; normal saline/ringer's lactate (NS/LR), n = 177;
²23.4%, n = 19; 3%, n = 10; NS/LR, n = 111; ³23.4%, n = 3; 3%, n = 3; NS/LR, n = 83. ICH: Intracerebral hemorrhage; TBI: Traumatic brain injury; SAH: Subarachnoid hemorrhage; HCT: Hematocrit; MAP: Mean arterial pressure; APACHE II: Admission acute physiology and chronic health evaluation II scores.

compared to 23.4% patients (Table 2). This would suggest patients receiving HS, particularly 3% solutions, had a greater illness burden at admission.

What are the effects of HS on renal function?

Table 3 summarizes the effects of HS on renal function in this cohort. No significant correlation occurred with Na⁺ or Cl⁻ with Cr when grouped according to saline type. The correlation between Na⁺ and Cr within each of the saline types does not differ much from the overall correlation, except for within the 3% saline group. The correlation for the 3% saline group is 0.256 but this was not statistically significantly different from zero (P = 0.26).

Table 2 Pairwise comparisons for those that were significant

Dependent	23.4% vs 3%	23.4% vs NS/LR	3% vs NS/LR
Na ⁺	0.035	0.016	0.503
A aGrad	0.370	0.009	0.306
Apache II	0.261	0.005	< 0.001
GCS v	0.579	0.034	0.019
GCS m	0.027	0.294	< 0.001
GCS E	0.028	0.123	< 0.001

NS/LR: Normal saline/ringer's lactate; APACHE II: Admission acute physiology and chronic health evaluation II scores; GCS: Glasgow coma scale.

Table 3 Correlations between Cl⁻, Na⁺ and Cr

Population	Na ⁺ and Cr			Cl ⁻ and Cr		
	n	Corr	P value	n	Corr	P value
Overall	230	0.025	0.63	229	0.074	0.16
Saline type						
23.40%	22	0.037	0.58	22	0.042	0.65
3%	13	0.256	0.26	13	0.181	0.43
NS/LR	194	0.026	0.65	194	0.097	0.09
Diagnosis type						
ICH	89	0.145	0.10	89	0.058	0.55
Other	53	0.096	0.09	53	0.287	< 0.001
SAH	50	0.125	0.08	50	0.085	0.28
Stroke	28	0.187	< 0.001	28	0.185	0.001
TBI	10	0.447	0.048	10	0.361	0.1

NS/LR: Normal saline/ringer's lactate; ICH: Intracerebral hemorrhage; TBI: Traumatic brain injury; SAH: Subarachnoid hemorrhage.

The same holds true for the correlation between Cl⁻ and Cr, it is greater in the 3% saline group but still not statistically significantly different from zero (r = 0.18, P = 0.43). When the correlations were dichotomized by the diagnosis, significant findings appear.

The strongest correlations were found in TBI, patients given HS and not diagnosed with TBI, stroke, SAH, or ICH (other), and stroke. With respect to TBI, a moderate correlation was found between rise in Cr and Na⁺. For stroke, weak correlations between rise in Cr and both increases in Na⁺ and Cl⁻ occurred. Patients in this "other" category demonstrated a significant, yet weak, correlation between increases in Cl⁻ and Cr.

DISCUSSION

Even small increases in creatinine the first two days following admission are predictive of mortality^[16,18]. Thus, therapies precipitating kidney injury are concerning. Presentation or development of diminished renal function is a predictor of poor outcome and mortality in stroke, ICH and SAH^[19-25]. In the case of ICH, this has been associated with hemorrhage volume and GCS^[21,22,26]. Similarly, development of renal dysfunction during hospitalization has been linked to increased mortality and is associated with lower GCS and higher APACHE III score in TBI^[27,28].

Frequently neurointensivists are asked to control cerebral edema *via* the use of mannitol and HS. Superi-

ority of one agent remains a matter of debate. Not yet recruiting at the time of this manuscript, investigators at Massachusetts General Hospital are investigating if induced, sustained hyponatremia to a goal of 150-160 mmol/L following traumatic brain injury will decrease the rate of cerebral edema formation and improve patient outcomes^[29]. One study, sponsored by Indiana University, currently enrolling is looking at 20% mannitol *vs* 3% saline for the treatment of intracranial hypertension^[30].

Mannitol appears to reduce ICP through reducing brain water content^[31]. However, its use may result in kidney injury and rebound edema^[8,9]. Increasingly HS saline is being used in various formulations either as a preventative or acute therapy^[12,32]. HS appears to have a number of beneficial effects. In TBI, the use of 23.4% NaCl results in ICP reductions and elevations in cerebral perfusion pressure with commensurate elevations in brain tissue oxygenation^[33,34]. These reductions in ICP are most notable in patients with the greatest elevations in ICP. Further, in cerebral hemorrhages ≥ 30 mL, the early use of HS to target a serum sodium between 145-155 mmol/L demonstrates both absolute and relative reductions of cerebral edema when compared to normonatremic patients^[32].

These effects appear to be the result of a combination of actions including reduction in brain water content *via* osmotic forces, reductions in peripheral vascular resistance, and arteriolar vasodilatation with improvement in capillary blood flow^[12,13,35]. Further, animal models treated with HS have demonstrated reduced aquaporin 4 expression on astrocytes with attenuation of brain water content^[13]. In addition, increasing evidence demonstrates HS possesses immune-modulating properties *via* reduction in cytokine production and neutrophil activation^[36,37]. Finally, animal models have demonstrated reductions in neuronal apoptosis.

Despite the ample experimental evidence, the clinical use of HS has not demonstrated any survival or outcome benefit and is not without risk^[12,14]. Hyponatremia is associated with insulin resistance, reduced hepatic gluconeogenesis and lactate clearance, delirium, rhabdomyolysis, and reduced cardiac function^[38,39]. Not surprisingly, ICU acquired elevations or reductions in serum sodium, dysnatremia, are common in neurosurgical and trauma patients, and associated with kidney injury^[40]. Further, when compared to normonatremic patients, dysnatremia is associated with increased disease severity, longer length-of-stay, and mortality^[40-42].

Our group inquired whether the formulation of saline used affected renal function in the neurocritical care population. The question of IVF formulation affecting patient outcome has been debated for some time. Evidence is increasingly suggesting formulation of saline and/or rapid change in serum sodium or chloride may adversely affect renal function^[15-17]. A study in healthy subjects has demonstrated greater natriuresis and sooner time to first post-bolus micturition in those receiving LR *vs* NS^[43]. Huang *et al*^[16] reported the use of HS in burn patients produced significant increases renal, pulmonary,

and cardiac failure compared to LR use. Patients receiving HS had less urine output. Further, the development of renal failure was heralded by a greater initial rise and slower subsequent fall in serum sodium levels during the first week of admission. Although this study was in burn patients, its findings are provocative. More recently, a study evaluating the effects of a Cl⁻ restrictive *vs* Cl⁻ liberal usage in critical ill patients demonstrated more acute kidney injury and greater use of renal-replacement therapy in the Cl⁻ liberal group^[44]. Though the populations of these studies differ from the neurocritical care population, this suggests the formulation of saline may have an effect on renal function.

With respect to our initial question, does saline type affect renal function; we found no such correlation in our sample. We found patients receiving HS have higher disease severity as assessed by lower GCS and higher APACHE II scores. Not surprisingly, we found sicker patients more frequently received HS in this sample. This correlation has been previously reported^[15]. This makes intuitive sense, with evidence suggesting early use of HS may limit the development of CE^[32]. Similar to the findings of Aiyagari *et al*^[15], Froelich *et al*^[17] reported adverse changes in renal function with serum Na⁺ > 155 mmol/L. This was not associated with the use or formulation of HS, a finding noted in our study too.

Unexpectedly, when we dichotomized by diagnosis, we found weak to moderate correlations between admitting disease and changes in Cr associated with hyperchloremia or hyponatremia. This was most noted in TBI, stroke, and non-vascular NCCU diagnosis; trends were also noted in ICH and SAH too. The explanation for this association is uncertain. Previous studies demonstrate correlations to Na⁺ increase and renal dysfunction^[15,17]. Although patients receiving a continuous HS infusion, when compared to a cohort receiving NS, do not have a higher risk of renal dysfunction, a significant correlation between severe hyponatremia and renal dysfunction does exist^[17]. This could however reflect a more severe underlying brain injury rather than effect of HS.

Both clinical and experimental literature provides insight as to how Na⁺ and Cl⁻ could adversely affect renal function. HS solutions initially cause renal vasodilatation and increased renal blood flow^[45]. It is theorized hyponatremia may produce renal injury *via* intravascular dehydration and vasoconstriction^[46]. Canine models undergoing rapid renal artery sodium elevations demonstrate reduced renal blood flow and glomerular filtration rate with inhibition of rennin secretion^[47]. Clinical studies have demonstrated hyponatremia is associated with elevations in creatinine in approximately 10% of patients^[15]. This noted increase parallels elevations in sodium and APACHE II scores, and is inversely related to admission GCS scores. However, save for sodium values > 160 mEq/L hyponatremia is not independently associated with mortality^[15,17].

While direct proof linking saline-induced hyperchloremia to nephrotoxicity is not available, a strong cir-

cumstantial case can be made^[48]. NS, with 154 mmol/L of chlorine can result in hyperchloremia and an acidosis^[43,49]. Elevation in chloride can reduce renal blood flow and decreases the excretion of sodium^[43,45]. Hyperchloremia appears to cause a renal vasoconstriction specific to renal vasculature and independent of the renal nerve^[45]. This reduction in renal blood flow could precipitate renal ischemia and reducing glomerular filtration rate^[45,50]. At the macula densa, Cl⁻ activates tubuloglomerular feedback by precipitating afferent arteriolar vasoconstriction and decreased glomerular filtration rate^[51]. Further, animal models suggest Cl⁻ increases thromboxane synthesis resulting in renal vasoconstriction and reduced renal blood flow^[52].

This single center, retrospective study has a number of limitations. First is the choice of serum creatinine as a biomarker of renal function. Though regularly used to infer kidney health and glomerular filtration, it is at best a crude measure of these. Often creatinine may be insensitive to early, deleterious changes in renal function. Next, given the time and cost of collecting retrospective data, this data represents an interim analysis to see if continued collection of these variables was warranted. As such, its small size and single center nature limit its applicability. Other centers with different demographics or practices may have different outcomes from what is represented here. The retrospective design and single center location limits what questions can be asked, data obtained, and the number of patients available. Regarding the disease specific correlations, a number of deficiencies exist. Regarding TBI, this study did not collect data on vasopressor use, blood pressure targets, or volume received, all variables noted to augment renal blood flow^[53]. Intense sympathetic stimulation alters prostaglandin-mediated vasodilation, resulting in reduced glomerular filtration^[54]. Data on antecedent medication use was not collected. Could prior use of medications such as angiotensin converting enzyme inhibitors, in the setting of rapid changes in serum Na⁺ and Cl⁻, result in diminished renal blood flow? Finally, after dichotomizing by diagnosis, differences in baseline physiologic variables was not assessed. Perhaps these correlations occurred in patients who were inherently more ill when viewed from the perspective of admitting diagnosis. Despite these limitations, this data is provocative in suggesting the admitting disease may affect the physiologic response to a therapy.

This study adds to the literature demonstrating the use of HS is not inherently injurious to renal physiology. Further, we too note the correlation of injury severity to HS use. Finally, our data suggests when viewed from the perspective of admitting diagnosis, HS use may correlate to the development of kidney injury. However, the nature of this correlation needs further exploration. Variables to investigate include rate change of Na⁺ and Cl⁻; HS administration times over the course of disease; role of premorbid medications; and regional differences in population makeup. Wide variability exists in the treatment of cerebral edema among intensivists^[55]. With no clear “right answer” to the question of cerebral edema,

more investigation is needed regarding the risks/benefits of the treatments available and the patients who would be best suited for particular therapies. Prospective comparisons of HS formulation and renal function are needed to further assess if formulation affects outcome and cost. Prospective studies are warranted to better define this association and its effect on outcome.

COMMENTS

Background

The treatment and management of cerebral edema is among the duties of a neurointensivist. When and how to treat cerebral edema remain contentious. Further, a neurointensivist must remain cognizant of how their neurocentric therapies may affect the rest of the patient's body.

Research frontiers

Intravenous fluids and hypertonic saline are ubiquitous in the critical care and neurocritical care setting. Data has previously demonstrated “not all fluids are created equal.” Understanding how the formulation of intravenous fluids may affect outcome is critical to providing effective critical care. Discovery of deleterious correlations may help generate prospective, hypothesis driven, studies on patient or disease specific intravenous fluids aimed at improving outcome.

Innovations and breakthroughs

Prior work has demonstrated that the formulation of hypertonic saline (HS) may not affect renal function. However, the relative change of Na⁺, and presence in particular of hypernatremia, may correlate with development of kidney injury and worse outcomes. Much of this work was in a mixed critical care or mixed neurocritical care population. This study assessed if not only Na⁺, but if Cl⁻, HS formulation, and disease state played a role. The data here presented suggests potential rolls of Cl⁻ and disease state to adverse renal function. These findings need to be confirmed by larger, prospective trials. Potentially, such findings could form the basis for developing patient or disease specific intravenous fluids aimed at reducing cerebral edema and mitigating adverse renal effects. Further, if borne out in future studies, better understanding of what interactions occur between intravenous fluids, disease state, and comorbidities may allow for development of new therapeutic options in neurocritical care.

Applications

Data presented here, and in the context of literature to date, may suggest to the bedside clinician to be judicious with the prescription of HS to patients with cerebral edema, to closely monitor renal function, and use Cl⁻ limiting formulations of HS.

Terminology

Cerebral edema is the process whereby injured brain develops increase free water by cytotoxic or vasogenic means. Typically, these two pathologies combine in a temporal fashion. Much of the overall change of brain volume is related to this, a concern in the rigid volume provided within the skull. Potentially, cerebral edema may exacerbate inflammation. Hypertonic saline, or HS, are intravenous fluids of higher osmolality aimed at increasing serum sodium. This has a multitude of effects including: (1) reducing brain free water and edema; (2) reducing aquaporin production and thus water entry into cells preventing/limiting the development of cerebral edema; (3) improving red blood cells malleability and ability to travel through injured tissue; and (4) potential mitigating effects on inflammation. Creatinine, Cr, is a biomarker of kidney health. Though crude, this is a readily available biomarker that can guide the clinicians management of a patient.

Peer review

This analysis provides some provocative findings that need a larger study to confirm. Further, it summarizes much of the literature on this topic to date.

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