Review Article

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Hypertonic Saline Infusion for Hyponatremia: Limitations of the Adrogué-Madias and Other Formulas

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Abstract

Hypertonic saline infusion is used to correct hyponatremia with severe symptoms. The selection of the volume of infused hypertonic saline (V_{Inf}) should address prevention of overcorrection or undercorrection. Several formulas computing this V_{Inf} have been proposed. The limitations common to these formulas consist of (1) failure to include potential determinants of change in serum sodium concentration ([*Na*]) including exchanges between osmotically active and inactive sodium compartments, changes in hydrogen binding of body water to hydrophilic compounds, and genetic influences and (2) inaccurate estimates of baseline body water entered in any formula and of gains or losses of water, sodium, and potassium during treatment entered in formulas that account for such gains or losses. In addition, computing V_{Inf} from the Adrogué-Madias formula by a calculation assuming a linear relation between V_{Inf} and increase in [*Na*] is a source of errors because the relation between these two variables was proven to be curvilinear. However, these errors were shown to be negligible by a comparison of estimates of V_{Inf} by the Adrogué-Madias formula and by a formula using the same determinants of the change in [*Na*] and the curvilinear relation between this change and V_{Inf}. Regardless of the method used to correct hyponatremia, monitoring [*Na*] and changes in external balances of water, sodium, and potassium during treatment remain imperative.

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Introduction

The methods for correcting dysnatremias are based on the pivotal work of Edelman and coinvestigators. They demonstrated that the determinants of sodium concentration in serum water ($[Na]_{SW}$) consist of total body exchangeable sodium, total body exchangeable potassium (TBK_{Exch}), and total body water (TBW).[1] Formula 1 in Table 1 expresses $[Na]_{SW}$ as a function of these three determinants. This formula, which represents the multiple linear regression developed by Edelman,[1] suggests that the way for changing $[Na]_{SW}$ is by changing the relation between Na_{Exch} plus TBK_{Exch} and TBW. The Rose formula, formula 2 in Table 1, which expresses serum sodium concentration ($[Na]$), not $[Na]_{SW}$, as a function of total body sodium ($TBNa$), total body potassium (TBK), and TBW, represents a simplified version of the Edelman formula.[2] Several studies[3,4] and a review[5] have documented that changing the fraction expressed by the Rose formula by changes in water, sodium, and potassium body contents is necessary for altering $[Na]$.

Hypotonic hyponatremia is associated with adverse outcomes, including deaths.[6–8] Guidelines for treating severe symptomatic hyponatremia advocate hypertonic saline infusion.[9–12] Hypertonic saline infusion risks include overcorrection and undercorrection of $[Na]$, which have severe consequences and must be avoided.[8,13] A vital element of the efforts to prevent correction issues is calculating the volume of the infused hypertonic saline (V_{Inf}) accurately. There are several published formulas for this calculation. The ideal application of a formula computing the required volume of hypertonic saline has two features: (1) the formula must contain all the determinants of the change in $[Na]$ resulting from hypertonic saline infusion and (2) the quantity of each determinant entered in the formula must be accurately computed.

Formulas calculating the required V_{IF} of hypertonic saline for a specific rise in $[Na]$ represent modifications of the Edelman or Rose formulas.[5] The Adrogué-Madias formula[14,15] (formula 3 in Table 1) has been applied extensively. When a potassium salt is also administered, a value of potassium concentration in the infusate, calculated when the potassium salt is administered separately from the saline infusion, is added to the numerator of this formula.[16] This review aims to discuss the limitations of this formula and the other formulas.

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Adrogué-Madias and Related Formulas

According to the Adrogué-Madias formula, the magnitude of increase in [*Na*] after infusion of 1 L of hypertonic saline is determined by the concentration of sodium in the infusate ($[Na]_{Inf}$), the baseline serum sodium concentration ($[Na]_1$), the initial *TBW*, and V_{Inf}. The fundamental difference between this formula and previous methods of computing the required V_{Inf} is the addition of V_{Inf} to the determinants of the change in [*Na*]. This addition is important. Infusion of hypertonic solutions in anuric animals demonstrated that omitting V_{Inf} from the calculations of the osmotic parameters resulting from infusion of the hypertonic solutions led to errors.[17,18] Subsequent similar studies included V_{Inf} in these calculations.[19,20]

The original Adrogué-Madias formula expresses the increase in [*Na*] after infusion of 1 L of hypertonic saline in a closed system, that is, without any gains or losses of sodium, potassium, and water, other than the infused saline. Formula 4 in Table 1 expresses the V_{Inf} required for the desired increase in [*Na*] computed using the calculation of the Adrogué-Madias formula.[21,22] Formula 5 in this Table, which is based on the Rose formula, expresses sodium conservation in a closed system after hypertonic saline infusion.[23] Formulas 6 and 7, which were derived from formula 5, express a direct computation of V_{Inf} [23,24] and the [*Na*] value that results from V_{Inf} ($[Na]_2$). When a potassium salt is also administered, a calculated concentration of potassium in the infusate should also be added to the denominator of formula 6.[23,24] The original purpose of formula 6 was to simplify the calculation of V_{Inf} by reducing the steps required in the Adrogué-Madias formula.[23]

Several other formulas estimating V_{Inf} for the desired rise in [*Na*] have been reported after the Adrogué-Madias formula.[16,21,25,26] Other than the Nguyen-Kurtz formulas,[21] which are based on the Edelman formula, all other estimators are based on the Rose formula. Formulas reported after the Adrogué-Madias formula are more complex and include terms expressing gains and losses of water, sodium, and potassium during treatment other than the infused saline. A review of studies comparing the Adrogué-Madias and other formulas concluded that the accuracy of the formulas studied was reasonable on the average, although the ranges of the differences between predicted and actual $[Na]_2$ values were wide for all formulas; none showed clear superiority.[5]

Limitations of the Adrogué-Madias Formula and Other Formulas

Table 2 presents the reported limitations of the original Adrogué-Madias formula.[5,23,27–49] The first four limitations in Table 2 have been examined in detail elsewhere.[5,7,8,23] In this report, they will be reviewed synoptically.

Changes in the External Balances of Sodium, Potassium, and Water Resulting from Gains or Losses Other than Saline Infusion

As noted, the original Adrogué-Madias formula strictly applies to a closed system. Water, sodium, and potassium losses through the skin, the respiratory system, the gastrointestinal system, and the urinary system during treatment of hyponatremia affect the change in [*Na*].[5,27] Urinary losses tend to vary during saline infusion with degrees depending on the pathophysiology of hyponatremia.[5,7,8] Saline infusion in patients with water diuresis can overcorrect hyponatremia treatment.[28–30]

Concomitant desmopressin and hypertonic saline infusion are strategies to avoid hypotonic urine during hyponatremia treatment.[31] The pathophysiologic mechanism of hyponatremia should guide whether desmopressin is used. Desmopressin should be used whether plasma vasopressin levels are low or are expected to be lowered. Examples include psychogenic polydipsia and correction of hypovolemic hyponatremia.[32] Further studies are needed to evaluate the accuracy of the various formulas during desmopressin therapy.

Exchanges of Sodium between Osmotically Active and Inactive Stores after Hypertonic Saline Infusion

TBNa consists of three sodium stores: (1) an osmotically active compartment, (2) an osmotically inactive and nonexchangeable compartment, and (3) an osmotically inactive compartment that can exchange sodium with the osmotically active store.[5] The skin, cartilage, endothelial layers, and other tissues represent the osmotically inactive/exchangeable compartment. In this compartment, sodium is stored in polyanionic proteoglycans comprising the extracellular matrix.[5,33] A recent study provided evidence supporting the view that the nonosmotic storage of sodium affects the homeostasis of multiple body systems, including the lymphatic system; is not hypertonic; and results in water shifts from the intracellular to the extracellular compartments.[34] Glycosaminoglycans are in the class of proteoglycans involved in osmotically inactive sodium storage.[35]

Clinical studies suggest that sodium is exchanged between the osmotically active and inactive compartments when [*Na*] changes rapidly.[36–38] Experiments involving infusion of hypertonic saline suggest that there is rapid osmotic inactivation of part of the infused sodium.[39–41] In one study performed on human volunteers, the osmotic inactivation apparently developed within the first 4 hours after the end of the infusion.[39] This exchange of sodium between osmotically active and inactive compartments needs further elucidation.[5] Notably, changes in glycosaminoglycan structure influence such exchanges between osmotically active and inactive sodium stores.[42] Several disease states, for example, diabetes mellitus, produce changes in glycosaminoglycan structure.[43]

Changes in Water Binding to Hydrophilic Polymers during Hypertonic Saline Infusion

Water hydrogen binds to hydrophilic compounds in body fluids.[5,44] The concentration of sodium, and other ions, is significantly lower in the water zone bound to the hydrophilic compounds.[45] Neither the size of the part of body water in this exclusion zone nor whether rapid changes in [*Na*] affect the size of the exclusion zone are known.[5] Future studies should address these topics.

Genetic Influences on the Regulation of Serum Sodium Concentration and the Development of Dysnatremias.

Genetic influences are major determinants of the range of [*Na*] and affect the development of dysnatremias.[5,35,46] A loss-of-function polymorphism of the osmoregulatory gene TRPV4 is a source of hyponatremia.[47] Hereditary polyanionic proteoglycan structure deviations alter the

Table 1. Formulas related to the change in serum sodium concentration after hypertonic saline infusion

Formula Number	Formula	References
1	$[Na]_{SW}=1.11\times\frac{TBNa_{Exch}+TBK_{Exch}}{TBW}-25.6$	1
2	$[Na]=\frac{TBNa+TBK}{TBW}$	2
3	$[Na]_2-[Na]_1=\frac{[Na]_{Inf}-[Na]_1}{TBW+1}$	14,15
4	$V_{Inf1}=\frac{Required\ [Na]_2-[Na]_1}{[Na]_2-[Na]_1\ from\ formula\ 3}$	21,22
5	$TBW\times[Na]_1+V_{Inf}\times[Na]_{Inf}=(TBW+V_{Inf})\times[Na]_2$	2,23*
6	$V_{Inf2}=TBW\times\frac{[Na]_2-[Na]_1}{[Na]_{Inf.}-[Na]_2}$	23,24
7	$[Na]_2=\frac{TBW\times[Na]_1+V_{Inf}\times[Na]_{Inf.}}{TBW+V_{Inf.}}$	2,23*
8	$TBW=V_{Inf}\times\frac{[Na]_{Inf}-[Na]_2}{[Na]_2-[Na]_1}$	

$[Na]_{SW}$, sodium concentration in serum water; $TBNa_{Exch}$, total body exchangeable sodium; TBK_{Exch}, total body exchangeable potassium; TBW, initial (presaline infusion) body water; $[Na]$, serum sodium concentration, $[Na]_1$, presaline infusion, $[Na]_2$, postsaline infusion; $[Na]_{Inf}$, sodium concentration in the infused hypertonic saline; $TBNa$, total body natrium; TBK, total body potassium; V_{Inf}, volume of hypertonic saline required for a desired increase in serum sodium concentration, V_{Inf1}, computed from the increase in serum sodium after infusion of 1 L of hypertonic saline computed by the Adrogué-Madias formula (formula 4); V_{Inf2}, computed from the sodium conservation formula 5. * According to the Rose formula (formula 2) [Na]xTBW = TBNa + TBK. Formula 8 computes TBW as a function of VInf and the changes in [Na]. Inserting a saline volume of 1 L for VInf and the desired increase in [Na] allows computation of the TBW at which the [Na]2 computed from formula 7 is the same for formulas 4 and 6.

osmotically inactive compartment, for example, in subjects with hereditary multiple exostoses.[42,48] The influence of genetic factors on correction of hyponatremia by hypertonic saline infusion is another area needing further research.

Osmotic inactivation of part of infused hypertonic saline, hydrophilic polymer water binding, and genetic factors affect the application of formulas determining V_{Inf} but represent determinants of change in $[Na]$ not included in most formulas. The Nguyen-Kurtz formulas were created to account for osmotic inactivation.[21] However, the accuracy of these formulas may be questioned because of the following two reasons: (1) the Edelman formula was developed without data from changes in $[Na]$[5] and (2) a repeated statistical analysis of the data used in the Edelman study by Oppelaaar and coinvestigators produced regression results substantially different from the Edelman formula.[49]

Two of the quantities of determinants of the change in $[Na]$ entered in formulas are potential sources of error. Formulas which contain terms for gains or losses of water, sodium, and potassium, other than through infusion of saline, in the estimation of V_{Inf} fail to accurately assess these gains or losses. Formulas that include these gains or losses after they have been quantitated during treatment or development of dysnatremias are more accurate.[50,51] Finally, inaccurate TBW values entered in the formulas are a major source of errors.[5] Several reports have stressed the need for accurate estimates of TBW when using formulas to compute the required V_{Inf}.[6,22,23] Studies reporting inaccurate estimates of postinfusion $[Na]$ using multiple formulas[52] illustrate the need for great caution.[53]

The last potential limitation listed in Table 2 applies only to the Adrogué-Madias formula and is not the result of not including determinants of the change in $[Na]$ or entering in this formula, a wrong value of a determinant, but rather the result of wrong calculation of V_{Inf} using this formula.[24] The magnitude of this error is addressed below.

Curvilinear Relationship between Volume of Hypertonic Saline Infused and Increase in Serum Sodium Concentration

V_{Inf} is computed using the Adrogué-Madias formula by dividing the desired increase in $[Na]$ by the computed increase in $[Na]$ if 1 L of hypertonic saline were infused, as shown by formula 4 in Table 1.[21,22] Chen and coauthors indicated that formula 4 implies a linear relation between V_{Inf} and increase in $[Na]$, whereas the relationship between the two variables is curvilinear.[24] This curvilinear

Table 2. Reported limitations of the Adrogué-Madias formula

Limitation	References
Not accounting for changes in body water, sodium, and potassium, other than those due to saline infusion, during correction of hyponatremia	8,22,23,25–30
Not accounting for exchanges of sodium between osmotically active and nonosmotically active sodium stores during correction of hyponatremia	5,7,8,33–43
Not accounting for potential changes in water binding to hydrophilic biopolymers during correction of hyponatremia	5,44,45
Not accounting for potential genetic influences on sodium exchanges between osmotically active and nonosmotically active stores during correction of hyponatremia	5,46–48
Not accounting for the curvilinear relationship between the infused volume of hypertonic saline and the rise in serum sodium concentration	24

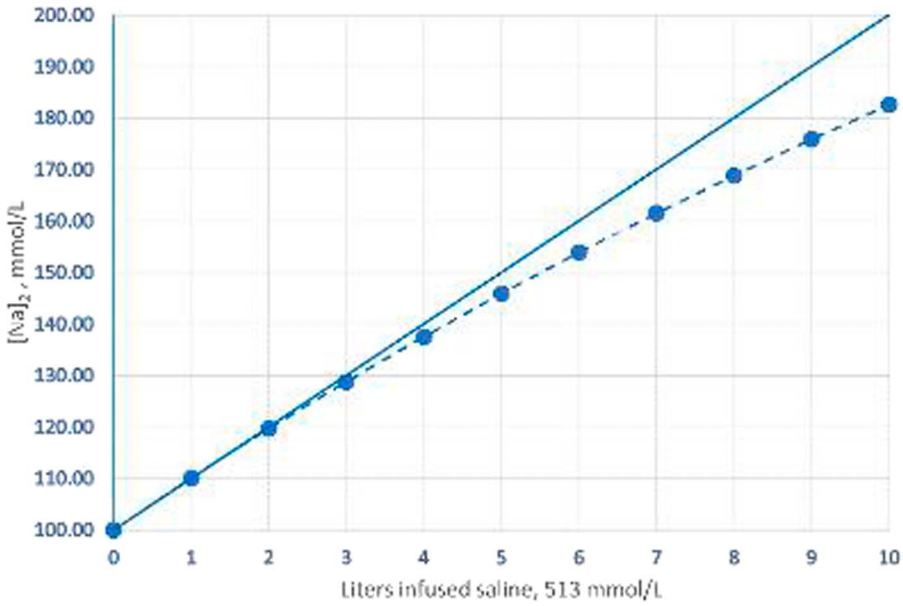

Figure 1. Sequential increases in serum sodium concentration after ten successive boluses on 1 L hypertonic saline, with sodium concentration of 513 mmol/L, in a subject with body water of 40 L and serum sodium concentration of 100 mmol/L computed using the Adrogué-Madias formula. Continuous line: increase in [*Na*] with the first bolus increase extended to the 10th bolus. Interrupted lines: Increases in [*Na*] after each bolus, computed using as $[Na]_1$ the $[Na]_2$ of the previous bolus and as *TBW* the sum of *TBW* plus V_{Inf} (1 L) of the previous bolus. The [*Na*] increase is 10.1 mmol/L after the first 1 L bolus. If the rise in [*Na*] was linear, [*Na*] after the infusion of the tenth 1 L bolus, it would be 201 (100+10.1×10) mmol/L. However, the increase in [*Na*] becomes progressively less after each saline bolus, resulting in final [*Na*] of 182.6 mmol/L after the tenth bolus. Note that the calculation of V_{Inf} for a $[Na]_2$ of 182.6 mmol/L by formula 4 using a denominator of 10.1 mmol/L provides a V_{Inf} of 8.178 L, which by formula 7 will provide a $[Na]_2$ of 170.1, not 182.6, mmol/L. Formula 6 computes appropriately a V_{Inf} of 10 L for a $[Na]_2$ of 182.6 mmol/L.

relationship is an important concept. Equal sequential boluses of hypertonic saline add the same amount of sodium diluted in progressively larger volume of water, resulting in diminishing increases in [*Na*].

The nonlinear relation between V_{Inf} and increase in [*Na*] can be shown by computing the sequential changes in [*Na*] after bolus increments of hypertonic saline. Figure 1 shows the changes in [*Na*] in a hypothetical patient with *TBW* of 40 L and $[Na]_1$ of 100 mmol/L infused with 10 1-L boluses of 3% saline (sodium concentration of 513 mmol/L). The Adrogué-Madias formula was used to compute the increase in [*Na*] after each saline bolus. Sequential computations using formula 3 were performed. In each computation, we entered the *TBW* plus V_{inf}(*TBW*+!) of the previous bolus as the *TBW* and the $[Na]_2$ value of the previous bolus as $[Na]_1$. For example, in the second bolus, the values entered in formula 3 were 41 (40+1) L for *TBW* and 110.1 mmol/L (the $[Na]_2$ value computed by formula 7 for the first bolus) for $[Na]_1$. Figure 1 presents a progressive decrease of the change in [*Na*] produced by sequential V_{Inf} loads of 1 L calculated by the Adrogué-Madias formula.

The question about the magnitude of the error from calculating V_{Inf} by formula 4 when clinical conditions dictate the required increase in [*Na*] can be addressed as follows: Formula 6 computes the V_{Inf} without interference from its nonlinear relation with the rise in [*Na*] and contains the same determinants of V_{Inf} as the Adrogué-Madias formula. Therefore, the accuracy of estimates from formula 4 can be evaluated by comparing them to corresponding estimates from formula 6.

Table 3. Body water at which the infused volume of hypertonic saline (sodium concentration of 513 mmol/L) for a desired increase in serum sodium concentration is 1 L

$[Na]_1$, mmol/L	Desired $[Na]_2 - [Na]_1$, mmol/L	TBW, L
90	4	104.750
120	4	97.250
90	6	69.500
120	6	64.500
90	8	51.875
120	8	48.100
90	10	41.300
120	10	38.300
90	12	34.250
100	12	33.417
120	12	31.750

Comparison of Estimates of Required Infused Volume and Postinfusion Serum Sodium Concentration by Formulas 4 and 6

This section presents a comparison of estimates of V_{Inf} computed by formulas 4 and 6 for a range of *TBW* between 5 and 200 L, a range of $[Na]_1$ between 90 and 120 mmol/L, and a range of desired increase in [*Na*] between 4 and 12 mmol/L. Note that an increase in [*Na*] between 4 and 6 mmol/L has been proposed by Sterns and coauthors for the infusion of hypertonic saline.[51,52] The $[Na]_2$ value corresponding to each V_{Inf} was computed by formula 7 in Table 1.

Table 4. Hypertonic saline (513 mmol/L) volumes for raising serum sodium by 6 mmol/L computed by two different formulas and corresponding serum sodium concentrations

TBW (*L*)	$[Na]_1$, mmol/L	V_{Inf}, L Formula 4	$[Na]_2$, mmol/L Formulas 4 and 7	V_{Inf}, L Formula 6	$[Na]_2$, mmol/L Formulas 6 and 7
5	90	0.085	97.08	0.072	96.00
5	120	0.092	127.07	0.078	126.00
10	90	0.156	96.50	0.144	96.00
10	120	0.168	126.49	0.155	126.00
20	90	0.298	96.21	0.288	96.00
20	120	0.321	126.20	0.310	126.00
40	90	0.582	96.06	0.576	96.00
40	120	0.626	126.06	0.620	126.00
60	90	0.865	96.01	0.863	96.00
60	120	0.931	126.01	0.930	126.00
80	90	1.147	95.99	1.151	96.00
80	120	1.237	125.09	1.240	126.00
100	90	1.433	95.97	1.439	96.00
100	120	1.542	125.97	1.550	126.00
120	90	1.716	95.96	1.727	96.00
120	120	1.847	125.96	1.860	126.00
160	90	2.284	95.95	2.302	96.00
160	120	2.458	125.95	2.481	126.00
200	90	2.851	95.95	2.878	96.00
200	120	3.069	125.94	3.101	126.00

TBW, initial total body water; $[Na]_1$, initial serum sodium concentration; V_{Inf}, required volume of 513 mmol/L saline; $[Na]_2$, final serum sodium concentration. Formulas 4, 5, and 6 are from Table 1.

The only V_{Inf} at which the same $[Na]_2$ is provided by formulas 4 and 6 is at 1 L. At $V_{Inf}<1$ L, the estimates of formula 4 and the corresponding estimates of $[Na]_2$ exceed the estimates produced by formula 6. At $V_{Inf}>1$ L, the estimates of formula 6 exceed those of formula 4. Formulas 4 and 6 provide the 1 L V_{Inf} value at specific combinations of *TBW*, $[Na]_{Inf}$, $[Na]_1$, and desired $[Na]$ increase. Table 3 presents *TBW* values for V_{Inf} of 1 L, $[Na]_{Inf}$ of 513 mmol/L, $[Na]_1$ of 90 and 120 mmol/L, and desired $[Na]$ increase between 4 and 12 mmol/L. These values were computed by formula 8 in Table 1, which is obtained by solving formula 6 at a V_{Inf} of 1 L. The values of *TBW* required for a V_{Inf} of 1 L decrease with higher desired increases in $[Na]$ and, for the same desired increase in $[Na]$, with higher values of $[Na]_1$.

Table 4 presents estimates of V_{Inf} of 3% saline calculated by formulas 4 and 6 for an increase in $[Na]$ of 6 mmol/L in subjects with $[Na]_1$ 90 and 120 mmol/L and the corresponding values of $[Na]_2$ calculated by formula 7. Practically, almost all values of V_{Inf} computed by formulas 4 and 6 were equivalent, and the corresponding values of $[Na]_2$ were very close. V_{Inf} values computed by formula 4 for a *TBW* of 5 L were moderately larger than those computed by formula 6. Calculations using a desired increase in $[Na]$ of 4, 6, 8, 10, or 12 mmol/L for $[Na]_1$ of 90, 100, 110, and 120 mmol/L produced similar results.

Conclusions

Formulas 4 and 6 provide extremely close estimates of the required V_{Inf} for the desired rises in $[Na]$ when hypertonic saline is infused, except only in small children (Table 4). The potential errors of the Adrogué-Madias formula, as well as of other formulas computing the required V_{Inf}, stem from not inclusion of important determinants of $[Na]$ in the formulas and erroneous estimates of *TBW* and/or of external changes in water, sodium, and potassium, other than the infused saline, entered in the formulas. Monitoring $[Na]$ and these external changes during correction of hyponatremia with any method are critical.[23,54,55]

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