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Agreement Status of Measured versus Calculated Osmolality in the Patients receiving Mannitol or Hypertonic saline infusion for Raised Intracranial Pressure in a tertiary care Teaching Hospital

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Abstract

Raised intracranial pressure (ICP) is one of the most devastating complications following neurological injury. Measurement of serum osmolality is the only surrogate marker to check the effect of hyperosmolar agents like mannitol or hypertonic saline to reduce raised intracranial pressure. Several studies have shown that during a mannitol or hypertonic saline (HTS) infusion, calculated serum osmolality may lead to a systemic bias compared to measured osmolality. Therefore, accurate measurement is important to determine their clinical efficacy, dosage and avoid serious adverse effects like acute renal failure. The study group was comprised of a total of 102 patients above 18 years of either gender receiving mannitol or hypertonic saline over the period of 1 year. Measured osmolality by using the osmometer with the principle of the freezing point depression method and calculated osmolality by the Dorwart and Chalmers formula. Intraclass correlation coefficient is used to check the correlation or agreement between the measured osmolality and calculated readings. Using the limits of agreement analysis developed by Bland and Altman, we were able to determine the robustness of the estimated serum osmolality calculated for each of the three formulas used. In our study, we found, that Dorwart's Formula I and Formula III showed a relevant correlation with the measured osmometer value. Thus, this study recommends validating formulas I and III for osmolality prediction with raised intracranial pressure.

Keywords: Intracranial pressure, Osmolality, Mannitol, Hypertonic saline

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1. Introduction

Since the early 1960s, osmotic therapy has played an important role in the treatment of patients with high intracranial pressure (ICP) [1]. Brain edema and elevated intracranial pressure (ICP) are potentially devasting complications following head injury, craniotomy, cerebral edema, cerebral tumors, etc. An appropriate treatment improves cerebral perfusion and reduces damage by local compression of brain tissue [2]. Hyperosmolar agents have been used to ameliorate brain edema and raise intracranial pressure. Mannitol and hypertonic saline (HTS) are the two most extensively used hyperosmolar agents in clinical practice. An increased osmotic gradient across the blood-brain barrier during medication infusion facilitates the evacuation of water from brain tissue to the vascular space, which is the main mechanism by which hyperosmolar medicines manage brain oedema. In clinical practice, serum osmolality can be used as a surrogate measure of the effect of hyperosmolar agents, with either mannitol or hypertonic Saline [3-5]. Therefore, measurement of serum osmolality during hyperosmolar agent infusion is of clinical importance to determine clinical efficacy, adjust dosage, and avoid serious adverse effects like acute renal failure [6]. Clinicians usually calculate serum osmolality by using formulas derived from the estimation of blood glucose, blood urea nitrogen (BUN), and serum electrolytes (Na+, K+) by routine biochemistry analyzers [7-8]. However, direct measurement of osmolality by a freezing point depression osmometer is considered as a reference method [9]. However, in a clinical setting, routine measurement of serum osmolality is not feasible at the bedside, neither in the intensive care unit (ICU) nor in the neurosurgical ward. In these circumstances, physicians typically calculate serum osmolality using formulas derived from serum osmoles that can be determined by regular laboratory chemical analysis or bedside blood gas

analysis, such as serum sodium, potassium, urea, and glucose [10-11]. Several studies have shown that during mannitol or hypertonic saline (HTS) infusion, calculated serum osmolality may lead to a systemic bias compared to direct measurement [3, 4, 5]. This poor correlation between calculated and measured osmolality during hyperosmolar agent infusion might be due to the osmolal gap [2]. Osmolal gap is a rough definition of the difference between actual serum osmolality (measured in the laboratory) and the calculated (estimated) osmolarity values [12]. The drug infusion will involve measuring and computing serum osmolality. The objective is to ascertain how accurate the assessment of serum osmolality is when hyperosmolar drugs are administered. An osmometer is an instrument that works on the principle of freezing point depression and can measure direct osmolality quickly, and is expensive. Keeping this in mind, we formulated the following aim and objectives. To compare measured and calculated osmolality in patients receiving mannitol or hypertonic saline infusions for raised intracranial pressure in a tertiary care Teaching Hospital. The objectives are as follow: To measure serum osmolality by Cryobasic osmometer in patients with raised ICP receiving mannitol or hypertension saline infusion. To calculate serum osmolality using the Dorwart and Chalmers formula in patients with raised ICP receiving mannitol or hypertension saline infusions. To calculate the osmolar gap by finding the difference between measured and calculated osmolality. To compare and correlate the difference between measured and calculated serum osmolality in patients with raised ICP receiving mannitol or hypertension saline infusion. PICOTS: P: Raised intracranial pressure patients receiving mannitol or hypertonic saline infusion at a Tertiary care teaching hospital. I: Receiving mannitol or hypertonic saline infusion. C: Measured osmolality vs calculated osmolality. O: Accuracy of method. T: Nil. S: Observational study at Tertiary care teaching hospital.

2. Materials and Methods

2.1. Study Setting

A tertiary care teaching hospital with NABL-accredited laboratory.

2.2. Study Design

Observational study.

2.3. Study Duration

1 year from 01/08/2022 to 30/07/2023.

2.4. Selection of Participants

A total of 102 patients admitted in ICU for raised intracranial pressure were included as participants after taking informed consent. The samples were collected for one year as per mentioned criteria and analyzed. Ethical approval obtained from institutional ethics committee.

2.5. Inclusion Criteria

Patients admitted in ICU above 18 years of age either gender receiving mannitol or hypertonic saline infusions for the prevention of raised intracranial pressure over the period of one year are included.

2.6. Exclusion Criteria

History of known cases of diabetes, alcohol abuse, herniation of the brain, unstable hemodynamic condition: systolic blood pressure (BP) less than 90 mmHg or need for continuous infusion of vasopressor, presence of oliguric renal failure, serum sodium concentration below 130 mEq/L or above 155 mEq/L.

2.7. Method for estimation of serum osmolality

2 ml of blood was collected under aseptic precautions and separated for estimation of Blood Glucose (fluoride vacutainer), Blood Urea nitrogen, and serum electrolyte (Plain vacutainer or gel tube).

2.8. Methods for Estimation of Serum Osmolality

1. Direct method by Osmometry: freezing point depression method [1].

Instrument: Cryobasic Osmometer.

2. Calculation method: Using Dorwart and Chalmers formula [10],

Formula I = [1.86 sodium (mEq/l) + glucose (mg/dl)/18 + blood urea nitrogen (mg/dl)/2.8] + 9

Formula II = 1.89Na (mEq/l) + 1.38K (mEq/l)+1.03urea (mg/dl)+1.08Glucose (mg/dl)+7.45

Formula III = 2[Sodium (mEq/l)+Potassium (mEq/l)]+Glucose (mg/dl)/18 +Urea (mg/dl)/6

2.9. Facilities

The above facilities are available in the Central Clinical Laboratory (CCL) of Bharati Hospital and Research Centre.

2.10. Statistical analysis

Data was obtained and statistically analyzed using SPSS software version 29.0. Categorical variables were presented as frequencies and percentages and analyzed by the $\chi 2$ test. Continuous variables were given as mean and SD or, if suitable, median and IQR after being examined for normal distribution. The Student t test for normally distributed data and the Mann-Whitney U test for non-normally distributed variables were used to compare continuous variables. The intraclass correlation coefficient is used to check the correlation or agreement between the measured osmolality and calculated readings. We used Bland and Altman's limits of agreement analysis to clarify the accuracy of the estimated serum osmolality calculated by each of the three formulas listed above. The mean of the difference between the calculated and measured values (measured minus calculated) was used to define bias. Based on the concordance between measuring techniques with many observations per subject,

the standard deviation of the mean bias was computed. Upper and lower limits of agreement were defined as bias ± 1.96 SD of the mean bias. P value <0.05 was considered significant.

3. Results and discussion

A total of 102 patients included in the study received a hyperosmolar solution or mannitol for the treatment of raised intracranial pressure. Out of 102 total patients 68(66.7%) were males and 34 (33.3%) were females with a mean age of 56 years. We measured osmolality directly with an Osmometer and compared values with calculated osmolality using Dowarts formulas I, II, and III.

Formula I = [1.86 sodium (mEq/l) + glucose(mg/dl)/18 + blood urea nitrogen(mg/dl)/2.8] + 9

Formula II = 1.89Na(mEq/l) + 1.38K(mEq/l) + 1.03urea(mg/dl) + 1.08Glucose(mg/dl) + 7.45

Formula III = 2[Sodium(mEq/l) + Potassium(mEq/l)] + Glucose(mg/dl)/18 + Urea(mg/dl)/6

All analyses are categorized in 3 groups with the above formula. The tendency of change in measured and calculated osmolality did not differ from reading-1 and reading-2 (Table 3). The serum osmolality by measured reading (267.26 ± 47.35) was not statistically significant with calculated reading-1 (265.07 ± 31.03, p=0.555), it was deviated and statistically significant from calculated reading-2 (413.93 ± 62.99, p<0.001) and not different from calculated reading-3 (271.67 ± 28.62, p= 0.224). There was higher reliability or agreement found in measured and calculated osmolality readings (as ICC= 0.566, p<0.001). Our study showed the difference between the direct value by osmometer and the calculated value by Dorwart's formula was significant for formula II but the comparison with measured osmometer value was deviating. In our study, we found, that Dorwart's Formula I and Formula III showed relevant correlation with direct osmometer value but Formula II does not show any comparison with measured osmometer value. Thus, we recommend not proposing Formula II for calculating osmolality. We were used Bland and Altman's limit of agreement analysis to clarify the accuracy of measured serum osmolality with calculated osmolality by each of the formulas, which are listed above. In table-3 the data are presented as bias and lower to upper limits of agreement. The differences between measured and calculated osmolality were calculated in each reading. Bias was defined as the mean of difference between the measured and calculated values. SD of the mean bias was calculated according to the agreement between methods of measurement with multiple observations per individual. Upper and lower limits of agreement were defined as bias ± 1.96 SD. In Bland and Altman's Plot Fig-1 and fig-3 the data points are very close to mean of difference so it represents that there is good level of agreement between measured and calculated Osmality by reading-1 and Reading-3; but in fig-2 we conclude that there is week agreement between measured and calculated Osmality by reading-2. Osmolality is widely used to characterize the body's water-electrolyte balance and may be useful in identifying electrolyte abnormalities, which can result from a variety of illnesses, including heart or renal problems as well as certain types of poisoning [13]. A crucial laboratory test for identifying illnesses that could compromise body homeostasis and worsen the acid-base and electrolyte balance is serum osmolality measurement [14]. The laboratories measured serum osmolality ranging from 278 to 298 mOsmol/kg. Many formulas have been developed for calculating serum osmolality, however, Dorwat-Chalmer's formula was deemed most appropriate due to its ability to compute osmolality. However, we use a direct innovative approach in our laboratory that is based on the freezing point depression osmometer method. This study was conducted to evaluate real data because we discovered some differences between the calculated and direct measurements of osmolality. The term "osmolar gap" refers to the discrepancy between calculated and direct measured osmolality; this gap is deemed acceptable if it is less than 2 mOsmol/kg H_2O. Our findings indicate that, use of Formulas I and III, does not differ values, statistically substantially for calculated osmolality from the direct measured osmolality, rather Formula II, values do differ statistically significantly from the measured osmolality and the calculated osmolality values. According to Qian Li and et al, calculated osmolality can be used as reliable substitute for measurement of osmolality with use of hypertonic saline to treat brain edema, their results are correlates with our study findings [2]. Qian Li and et al, carried out randomized controlled trials to find out correlation of calculated and measured osmolality during infusion of mannitol and hypertonic saline in craniotomy patients with four calculated formulas and also Bland and Altman limit of agreement to assess accuracy of calculated osmolality. This study is similar to our study and summarizes same findings [6]. Dringer MN and et al, have given light on osmotic therapy and its clinical experience through various literature search and concluded osmolality is not predictive of mannitol levels, on contrary osmolal gap may be useful in monitoring clearance of mannitol for cerebral and renal toxicity [1]. Numerous investigations employing various tools can produce a range of confirmed formulas. These computed formulas must be validated [9]. Four different formulas were used by Acikgoz S and etal as like our objectives for validation of calculated osmolality over measured osmolality and they suggested to use Formula 1 and Formula 4 to evaluate osmolality in intracranial hemorrhage and head injury [9]. CI Bhagat and et al, conducted study for calculated versus measured plasma osmolalities and study recommends use of Dorwart and Chalmer formula for calculation of osmolality and suggested calculation formula too (1.86 (Na + K) + glucose + urea + 10) to reduce calculation errors [8].

Table 1. Comparison of measured and calculated serum osmolality

		N	Mean	Std. Deviation	Std. Error Mean	Mean difference	t value	P value
Pair 1 (Formula I)	**Osmometer reading**	102	267.255	47.3491	4.6883	2.1872	0.592	0.555
	Calculated I (Dorwart and Chalmers formula I)	102	265.068	31.0316	3.0726			
Pair 2 (Formula II)	**Osmometer reading**	102	267.255	47.3491	4.6883	-146.6708	-25.979	<0.001
	Calculated II (Dorwart and Chalmers formula II)	102	413.926	62.9900	6.2369			
Pair 3 (Formula III)	**Osmometer reading**	102	267.255	47.3491	4.6883	-4.4187	-1.224	0.224
	Calculated III (Dorwart and Chalmers formula II)	102	271.674	28.6164	2.8334			

Table 2. Intra-class Correlation Coefficient

Intraclass Correlation	**95% Confidence Interval**		**F Test with P Value**
	Lower Bound	**Upper Bound**	
0.566	0.418608	0.685036	<0.001

Table 3. Bland and Altman's limits of agreement analysis between measured and calculated serum osmolality by the three formulas

Readings	**Bias**	**Limits of Agreement**	
		From	**To**
1	4.80	-47.60	57.20
2	-144.30	-246.10	-42.50
3	-1.79	-50.91	47.34

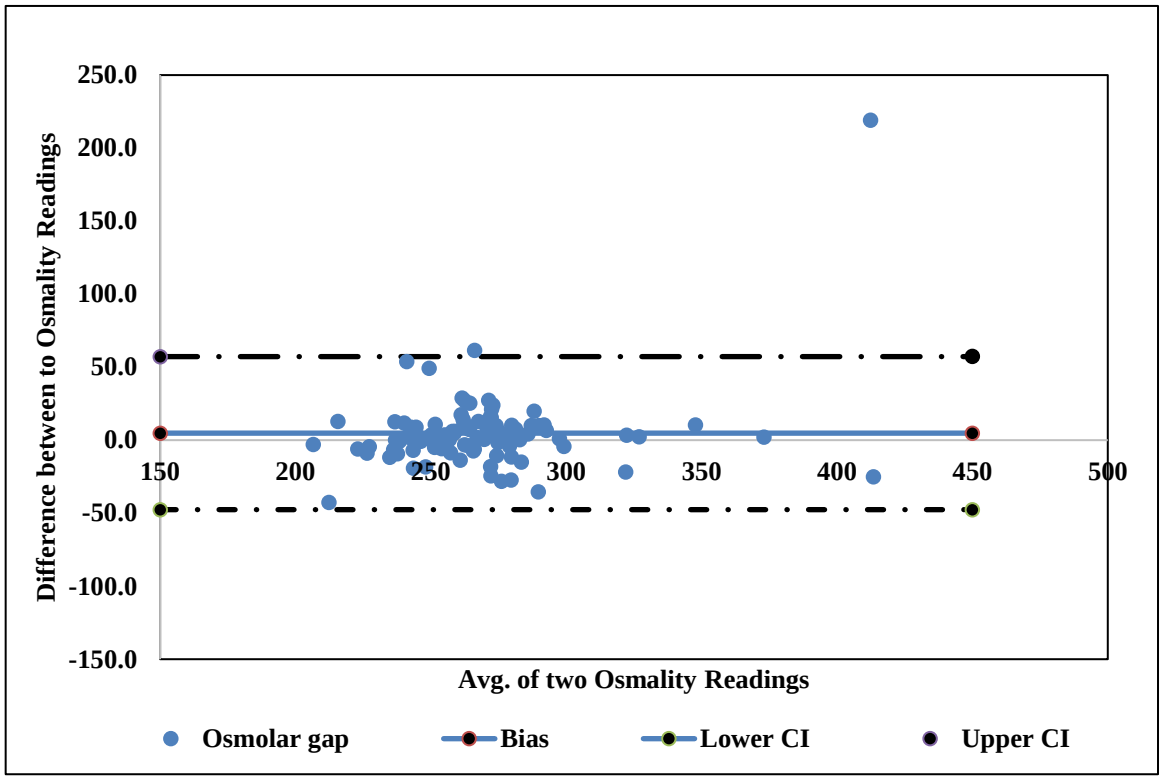

Figure 1. Bland Altmann Plot for measured and Calculated reading 1

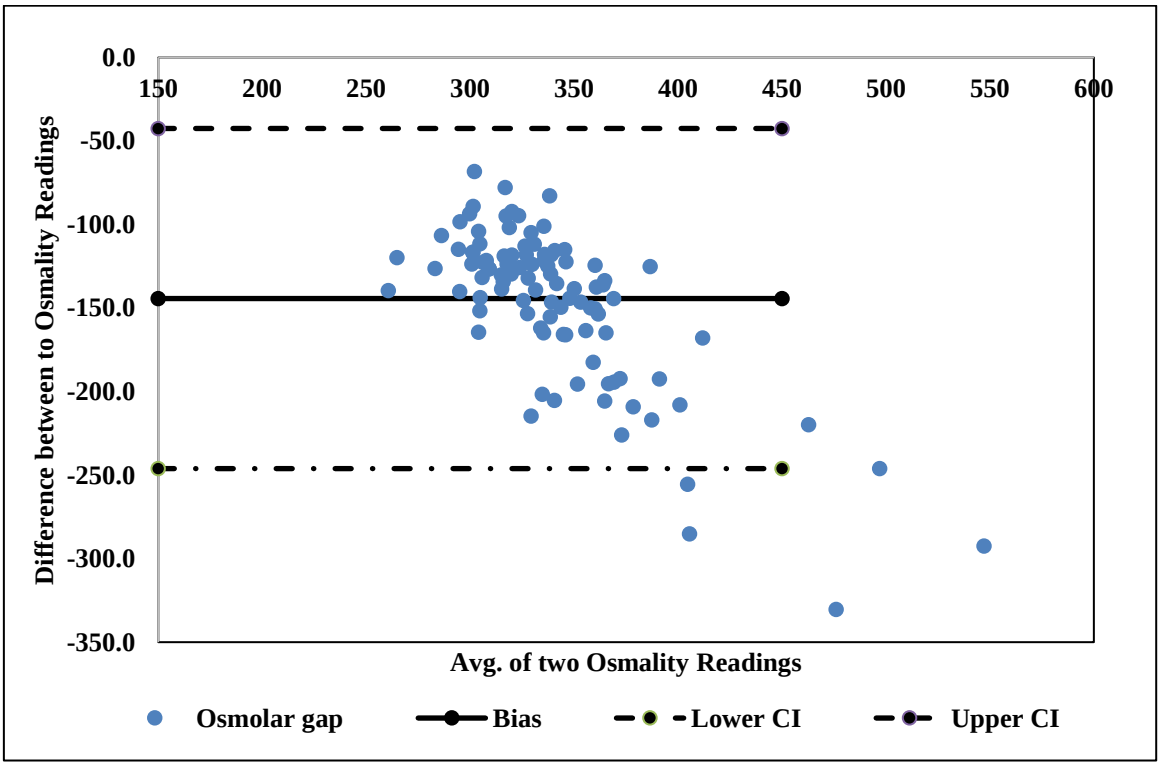

Figure 2. Bland Altmann Plot for measured and Calculated reading 2

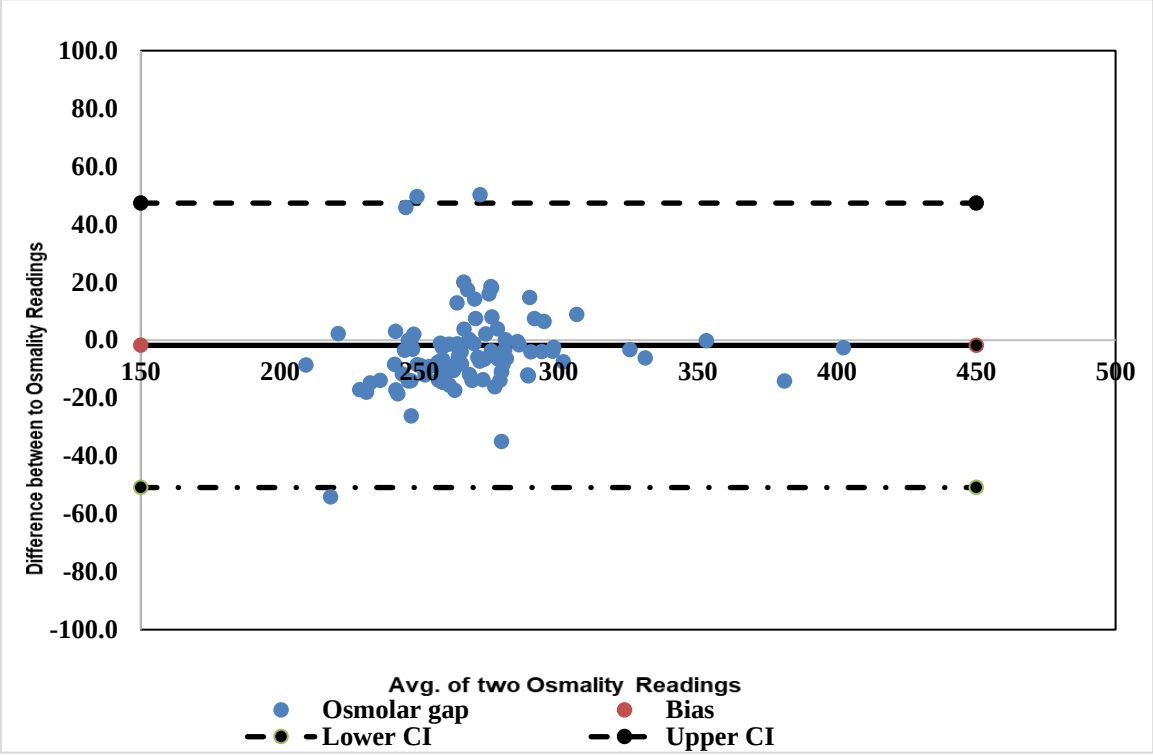

Figure 3. Bland Altmann Plot for measured and Calculated reading 3

Table 4. Methods used for estimation of analytes.

Sr. No	Test Parameter	Method	Instrument used
1	Blood Glucose	Glucose Oxidase peroxidase method	Abbott Alinity c4000 integrated platform
2	Serum Urea	Urease Method (BUN=Blood Urea/2.14)	
3	Serum Electrolytes (sodium, Potassium, Chloride)	Ion selective electrode method	
4	Direct measurement of osmolality	freezing point Depression Osmometer	Osmometer

Accuracy of calculated versus measured urine osmolality was estimated by Vidal-Mayo JJ and et al, and recommendations approves calculated osmolality using factor 33.5 over measured osmolality if osmometer is not available from urine density,on the other hand factor 32 with adjusted urine density had closest proximity to measured urine osmolality [15]. Evaluation of 36 published formulas for calculating plasma osmolality has been used by Fazekas AS and et al, and 9 out of 36 formulas showed mean difference of < 2 mosmol/kg H2O which is desirable, and only 4 formulas out of 36 showed mean differences of < 1mosmol/kg H2O. Even Zander's new formula for Osmolality quantification demonstrated good correlation with measured Osmolality which allows for more accurate diagnosis based on a blood gas analyzer [11]. The goal of our study shows the same findings with Kristen Heaven et al (2014) study that were to determine the most effective formulas to apply in a healthy population to prevent unknown bias, caused by uncertain osmolality [16]. Kristen Heaven and et al, conducted cohort study and evaluated 36 equations for validation of formula for osmolality measurement and found 5 equations were shown acceptable or optimal results for predicting osmolality in healthy population and could be used as aid for identifying osmolal gaps [16]. Berska J evaluated accuracy of calculated osmolality over measured osmolality in pediatric population by using different formulas and suggested calculated osmolality may be used by formula 1.86*(Na+K)+ 1.15*Glu+Urea+14 (S No 6 listed in Table 1 of cited reference) between age group 3month to 2 years [13]. Kar E and et al, compared measured and calculated osmolality levels and not found significant correlation for all age groups, rather they suggested large scale studies with different age groups and different calculations are required to get closer results. Also evaluation of calculated and measured osmolality in different pathological conditions may give more clarification [14]. When monitoring patients with neurological disorders who should get osmotherapy with mannitol or hypertonic saline, serum osmolality measurement can be utilized as a laboratory parameter [17]. Thus Daniel K. Faria and et al, measured serum osmolality and its applications in clinical practice and laboratory. This study recommend, if it is not possible to measure osmolality by using direct osmometer calculated formulas could be applied because use of calculated formula gives good correlation with clinical picture and thus could be effective measure for osmolality in diagnosis of hyperglycaemias, adrenal insufficiency, therapies with hypertonic solutions in neurological lesions, and in physical exercise in athlete for hydration status [17]. This study finding are correlating with few of above discussed findings obtained by various authors after literature search. Few studies were used formulas, which are different from formulas we used in our study for calculation of osmolality. Few study evaluated osmolality measurement by using Dorwart and Chalmer formulas, which were used in our study too. Thus by considering this and other study findings, we can recommend the calculated osmolality can be used over measured osmolality and this can be done by using formula I and III if osmometer is not available in laboratory for direct measurement.

3.1. Limitations

Large-scale studies with different formulas are required to give closure for results for directly measured osmolality. Apart from raised Intracranial pressure, other clinical conditions are necessary to include for closure about the use of Dorwart's formula.

4. Conclusions

Finally, it was found that, of the three formulae that were analyzed, two Dorwart's formulations seemed to be the best at forecasting osmolality. Utilizing formula II may result in larger osmolar- gap in our group, although a pilot study may indicate a strong link between direct and formula II-calculated osmolality. The study's recommendations could validate formulas I and III for osmolality prediction.

Conflict of Interest

Nil.

Authors Contribution

First and corresponding author: Contributed for concept, test performance and data analysis and writing of article. Second author: Contributed for data analysis and writing of article, plagiarism check and other formatting. Third author: Contributed for concept and formatting of article.

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