'Osmotoxicity' in Type 2 Diabetes Mellitus: a retrospective comparative analysis of the effect of pre-treatment with IV 0.9% saline on glycemic control in Subcritical hyperglycemia

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ABSTRACT:

BACKGROUND: Studies showed an increase in serum osmolality (Osm) contributes to hyperglycemia by increasing hepatic glucose output and suppressing peripheral glucose utilization and reversing hyperosmolality decreases blood glucose (BG). This is not therapeutically exploited. **AIM:** To assess the effect of pre-treatment with IV 0.9% saline (NS) on glycemic control and medication requirement in type 2 diabetes mellitus (T2DM) with subcritical hyperglycemia (SCH) not amounting to DKA or HHS. **METHOD:** A retrospective comparative data analysis of T2DM patients (198) with SCH, pre-treated with NS before diabetic specific therapy (group 1) and compared with those who were not pre-treated with NS (group 2). Differences in glycemic control and drug dosage were assessed. **RESULTS:** In group 1, 1500ml of NS reduced BG from baseline of 496.3±67.1 to 283.3±83.8 (mg/dL), p=0.000, mean reduction of 43% and reduced the Osm by 11mOsm/kg [313.8±8.1 to 302.9±8.5, p<0.001]. There was a significant correlation between BG and Osm (r=0.322, p=0.001). Fluid pre-treatment enabled reduction in BG during 4 weeks of follow up {[FBS 298.9±73.7 to 158.9±58.7 in group 1 v/s 265.6±70.7 to 171.48±66.5 in group 2, p=0.00] and [RBS 496.3±67.1 to 228.3±80.7 in group 1 v/s 450.5±47 to 282±112.4 in group 2, p=0.001]}. There was a trend of decrease in dosages of anti-diabetic medications in group 1 and increase of the same in group 2. **CONCLUSIONS:** Fluid pre-treatment reduced BG and drug dosage in T2DM patients presenting with SCH and the benefit persisted for a minimum of 4 weeks. **KEY WORDS:** IV 0.9% saline, glycemic control, hyperosmolality**,** Osmotoxicity, pre-treatment, serum osmolality, subcritical hyperglycemia

BACKGROUND:

The global prevalence of type 2 diabetes (T2DM) in adults has been increasing over recent decades [1]. Most often diabetes related complications are more likely to occur as a result of poor control and management of hyperglycemia. However people with appropriate management are also at ultimate risk of developing complications. Acute or short term complications of diabetes result from extremes of blood glucose (BG) levels (hyperglycemia and hypoglycemia) which can lead to severe illnesses and even death [2]. Control and maintenance of blood glucose as close to normal as possible prevents chronic complications of diabetes mellitus mainly micro vascular complications and to a certain extent macro vascular complications [3], [4]. Apart from this, diabetes also imposes a significant economic and social impact [2].

The current routine management of T2DM includes various stepwise methods like intensive lifestyle modification, suppressing hepatic glucose output and reducing insulin resistance with metformin and glitazones, suppression of glucose reabsorption from urine by SGLT2 inhibitors, inhibition of glucosidase absorption from intestine with alpha glucosidase inhibitors, promotion of incretin activity, augmenting insulin secretion by secretagogues and finally by the use of Insulin itself [5], [6].

In T2DM, glucose builds up due to either absolute or relative insulin deficiency or the lack of insulin action (insulin resistance) [7], [8]. Building up of glucose will be resisted by the body by flushing out of glucose through urine. Along with glucose, there will also be loss of water causing an increase in serum osmolality (Osm). Glucose being an 'osmogenic' substance, the Osm increases parallel to the increase in BG [9]. Studies have shown that hyperosmolality further interferes with glucose metabolism by enhancing hepatic glucose output and suppressing its peripheral glucose utilization and thus precipitating more hyperglycemia [29].

In Duke EPESE survey (1992-1996) conducted in non diabetic community dwelling older adults (70+years), serum hyperosmolality/hypertonicity has been reported to be independently associated with increased odds of developing diabetes (OR = 2.0, 95% CI: 0.9-4.2) [10]. Studies of Berneis K et al (1999) proved that endogenous hepatic glucose production was higher in hyperosmolar than iso- and hypo-osmolar state (P<0.05) [11]. Pathophysiological attributes of hyperosmolality in relation to hyperglycemia have also been proven in experimental animal studies, where exposure of isolated hepatocytes to hyperosmotic media was found to increase activated glycogen phosphorylase enzyme (GPase a) activity up to 7-fold and thereby increasing hepatic glucose production. Such enzymatic activation by hyperosmolality was reported to be almost equal to that caused by glucagon (2.7 fold

vs 3.1). Conversely, hypo-osmotic medium leads to significant decreases in GPase a activity and curtailed glucose output [12].

In liver cells, hyperosmolality impairs the Ptdins-3-kinase-dependent K(+) uptake and cell swelling in response to insulin, leading to resistance of MAP-kinases and proteolysis regulation by insulin and this interferes with glucose metabolism as well [13]. Likewise, it was also reported that dehydration caused by loop diuretics like Furosemide and Bumetanide can induce a reduction of insulin-induced cell swelling causing insulin resistance by interfering with the same mechanisms (MAP-kinase activation and proteolysis control) [14]. These in vitro results are in congruence with clinical observations by Hellerstein (1995) which showed that dehydration and hyperosmolality in decompensated diabetes mellitus was associated with protein catabolism and insulin resistance of glucose metabolism [15].

There are also evidence from experimental studies that hyperosmolality can interfere with cellular oxidative metabolism which can compromise glucose oxidation [16].Thus in short, hyperosmolality and dehydration caused by increasing hyperglycemia can further impair insulin function and thus worsen hyperglycemia and precipitate the diabetic status. Converse is also shown in experimental studies that reduction in Osm even by less than 10 mOsm/kg significantly reduced hyperglycemia [17] which supports the clinical observations of BG levels dropping during fluid replacement in critical hyperglycemic conditions like Diabetic ketoacidosis(DKA) and Hyperglycemic hyperosmolar state (HHS)[18],[19],[20],[21].

Generally the initial fluid therapy is directed towards the correction of dehydration and restoration of renal perfusion [22],[23] and not for its above mentioned metabolic benefits. Here, the glucose lowering accompanies the use of IV 0.9% sodium chloride solution (NS) at the rate of 15–20 ml/ kg/ hr as the principal fluid which restores circulating volume, corrects osmolality and reverses dehydration. But this effect of glucose lowering during fluid administration was not explored for its therapeutic benefits in Subcritical hyperglycemia (SCH)-severe hyperglycemia not amounting to DKA or HHS.

The US food and drug administration has approved over 40 new treatment options for T2DM since 2005 [24]. Despite this, the proportion of patients with good glycemic control (<7%) remains around 50% [25] and results from the National Health and Nutrition Examination Survey (NHANES) indicates that only 64% are reaching individualized glycemic goals [26]. This trend predicts that the search for a perfect medication for diabetes control will continue for a long time.

According to our knowledge, no previous study had investigated the therapeutic efficacy of fluid administration in reducing glucose levels in SCH. So we decided to retrospectively analyze the data of patients presented with SCH who were pre-treated with NS before anti-diabetic therapy and standard lifestyle modification advises (group1) and to compare the data with another group of SCH patients who were not pre-treated with NS before anti-diabetic therapy and standard lifestyle modification advises (group 2).

AIM:

To assess the effect of pre-treatment with NS on glycemic control and medication requirement in T2DM patients presenting with SCH.

ASSESSMENTS:

PRIMARY ENDPOINT:

- Change in BG and change in Osm from baseline to after 1500ml of NS administration in group 1 and the relative change in BG from the baseline to follow up visits between the two groups (group 1 and group 2)

SECONDARY ENDPOINTS:

- Change in BG after each 500ml of NS in group 1
- The relative changes in drug dosage prescribed in group 1 versus group 2 between the baseline and follow up visits

MATERIALS AND METHODS

This is a retrospective comparative data analysis. The data for the study was collected from the electronic health records of patients who visited the outpatient department of "Dr.Suresh's, Diabcare India", an outpatient secondary care diabetic clinic and research center at Calicut, Kerala, India from July 2018 to January 2021. All patients were hailing from north Kerala. We collected data of two groups of T2DM (99 in each group, total 198) presented with BG more than 400mg/dL and Osm greater than 300mOsm/kg. The first group (Group 1) was those patients who were pre-treated with NS for correction of hyperosmolality before giving diabetes specific medications and the second group (Group 2) was those patients who were directly prescribed anti-diabetic medications without pre-treatment with NS.

INCLUSION CRITERIA:

- Patients with T2DM more than 18 years of age presenting with BG more than 400 mg/dL and Osm equal to or greater than 300mOsm/kg (overt hyperosmolality)

EXCLUSION CRITERIA:

- Patients presenting with BG less than 400 mg/dL
- Patients whose records do not contain serial BG values during fluid administration, RFT, Serum electrolytes
- Patients whose follow up data was unavailable

Baseline data collected included available clinical history, relevant clinical examination findings, anthropometric measurements, laboratory investigation results {including BG values, Osm, C peptide, complete blood count (CBC), lipid profile, renal function tests (RFT), urine analysis, serum glutamic- pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), Thyroid stimulating hormone (TSH) and serum electrolytes}, drugs and dosages of previous, baseline and follow up prescriptions. Details of comorbidities and long term diabetic complications like retinopathy (DR), peripheral neuropathy (DPN), nephropathy (DKD), coronary artery heart disease (CAD), stroke, transient ischemic attack , peripheral vascular disease were also collected. In group 1, we collected only the data of patients

whose records contain at least BG values, RFT, Serum electrolytes.

Omron HBF 212 Digital full body Composition Monitor was used for weight (kg) and BMI (kg/m^2). Osm was calculated using the formula:
Osm (mOsm/kg) =2[Sodium (mmol/L) + Potassium (mmol/L)] + Urea (mg/dL)/2.8 + Blood glucose (mg/dL)/18.
TURBO CHEM PRIME fully auto analyzer, CPC Diagnostics, Chennai, India was used for biochemical analysis. Fasting and random plasma glucose values were estimated by Glucose oxidase (GOD) - peroxidase (POD) end point and kinetic assay using Autospan glucose- lyophilized reagent and diluent. Random capillary glucose measurement was done using Glucometer (One touch Select plus, Lifescan Europe GmbH, Gubelstrasse 34, Switzerland). Cholesterol was measured by CHOD-PAP Enzymatic End Point Assay, Triglycerides (TGL) by GPO-PAP End Point Assay, High density lipoproteins (HDL) by Polyethylene glycol- CHOD-PAP End point Colorimetry and Low density lipoproteins (LDL)was estimated by Friedewald formula: LDL=Total cholesterol – (HDL+TGL/5). Serum Creatinine was done by modified Jaffe's method, SGOT and SGPT were done by modified UV-IFCC Kinetic Assay, serum Uric Acid by uricase- POD method and serum Urea by urease-GLDH method. Complete blood counts were measured by VECTOR CBC-BC-2300 haematology analyzer of MINDRAY, Chennai, India. Serum electrolytes were assessed by PATHOLYTE PLUS electrolyte analyzer of ORBIT, PV Enterprises, Pune. Vibration perception threshold (VPT) was done using Vibrosense Digital Biothesiometer of Genesis Medical Systems Pvt. Ltd, Hyderabad
Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI formula: {eGFR=141* min (Scr/K,1)α* max(Scr/k,1)-1.209* 0.993Age*1.018 [if females]*1.159[if black]}. Scr is serum creatinine (mg/dL), k is 0.7 for females and 0.9 for males, a is -0.329 for females [27].

'*Osmotoxicity'* refers to the metabolic, physiological and biochemical effects of hyperosmolality. SCH is defined as severe hyperglycemia not amounting to DKA or HHS. CAD was diagnosed as having a history of myocardial infarction (MI), typical chest pain or using nitrates or ECG changes suggestive of CAD validated against Minnesota code for Classification System for Electrocardiographic Findings [28] or Echocardiography showing regional wall motion abnormalities suggestive of past MI or myocardial ischemia or positive Treadmill stress test (TMT). CKD was defined as GFR < 60 ml/min and/or abnormal urinary albumin excretion. DR was diagnosed by means of retinal fundus photographs taken and reported by qualified Ophthalmologists through tele reporting. Presence of DPN was diagnosed based on symptoms of peripheral neuropathy, positive vibration perception threshold (VPT) [>15 mv] or negative monofilament test using 10-g Semmes-Weinstein monofilament. Hypertension was diagnosed if there was a previous diagnosis of hypertension or treatment for hypertension or if the Blood pressure (BP) was ≥ 140/90 mm Hg. BP was measured by ELKO EL-510 FDA approved upper arm fully automatic digital BP machine with smart inflation technology.

Group 1 received a total of 1500 ml of NS (500ml x 3) at the rate of 15-20 ml/kg/hour in 60-90 minutes. Serial capillary BG values were monitored using a glucometer in the beginning and after every 500 ml of fluid administration. Osm values at the beginning and at the end of fluid administration were calculated. The data during follow up after 4 weeks in both groups were also collected. Changes in glucose values, percentage glycemic changes and anti-diabetic medications from baseline to follow up were analyzed. Only drugs from four major classes (Metformin, SU, DPP4 inhibitors and insulin) were considered for comparison of drug dosage. For comparison purposes of different molecules within the same class, drug dosages were converted into 'dose units' {for SU, 1 unit =Glimepiride 1mg=Gliclazide 40mg=Glipizide 2.5mg=Glibenclamide 2.5 mg, for DPP4 inhibitors, 1 unit= Vildagliptin 100 mg = Sitagliptin 100 mg = Linagliptin 5 mg= Teneligliptin 20 mg} except for Metformin which was expressed in milligrams and Insulin was expressed in number of units.

STATISTICAL ANALYSIS:

Descriptive statistics for demographic and clinical data are reported as number (*n*) and percentage *(%)* of the cohort for categorical variables. For continuous variables, data are reported as mean ± SD for data with normal distribution. A *p* value of less than 0.05 was considered statistically significant. Statistical similarities were observed between the two groups in all parameters except age, gender and presence of comorbid conditions like hypertension, CAD, CKD, DPN and DR.

The significance of baseline characteristics between two groups of patients including FBS and RBS were estimated by unpaired student t test. One way ANOVA and post-hoc Tukey HSD was done to evaluate the difference in glucose values during and after fluid administration in Group 1. Paired student t test was used to estimate the change in serum osmolality before and after fluid administration in Group 1. Pearson's correlation was used to evaluate the correlation between random plasma glucose and serum osmolality. ANCOVA was done to compare the glycemic changes from baseline to follow up visit between the two groups.

RESULTS

We analysed the data of a total of 198 patients (99 each in Group 1 and Group 2) with 54% males in Group 1 and 62% males in Group 2. For group 1 and group 2 the mean age was 52.2±12.9 and 55.7±10.2 (*P*=0.0355); BMI (kg/m^2) was 25.2±4.3 and 25.6±4.6 (*P*=0.9494); mean duration of diabetes (years) was 10.13±8.9 and 12.8±8.74 (*P*=0.8307); fasting C-peptide (ng/ml) was 1.85±0.65 and 1.7±0.52 (*P*=0.9701); SBP (mmHg) was 134.6±18.8 and 132.8±22.7 (*P*=0.9514) and eGFR was (ml/min) 85.7±17.7 and 75.5±20.5 (*P*=0.7067) respectively. In group 1 and 2, 25% and 31% of patients had CAD, 39% and 44% had hypertension and 33% and 55% had CKD respectively. Detailed baseline characteristics of the participants are given in table 1:

Table 1: Baseline characteristics of participants:

Characteristics	Group 1 Values	Group 2 values	P value
Age	52.2±12.9	55.7±10.2	P=0.0355
Male sex	54(54.5)	61(61.6)	-
Female sex	45(45.5)	38(38.4)	-
Weight (kg)	65.1±12.1	66.4±12.5	P=0.5696
BMI (kg/m^2	25.2±4.3	25.6±4.6	P=0.9494
SBP (mm Hg)	134.6±18.8	132.8±22.7	P=0.9514
DBP (mm Hg)	79.6±11.4	78.9±11.9	P=0.9662
Duration of diabetes (years)	10.13±8.9	12.8±8.74	P=0.8307
CAD	25(25)	31(31)	-
Hypertension	39(39.4)	44(44.4)	-
CKD(GFR<60)	33(33.3)	55(55.2)	-
DPN	38(38.4)	56(56.6)	-
DR	14(14.1)	23(23.2)	-
Total cholesterol (mg/dL)	219.5±50	203.1±49.3	P=0.8238
Triglycerides(mg/dL)	159.5±72.6	166.3±122	P=0.9654
High density lipoproteins (mg/dL)	50.3±4.96	52.6±11.8	P=0.8747
Low density lipoproteins (mg/dL)	130.8±45.5	116±44	P=0.8247
Very low density lipoproteins (mg/dL)	32.06±14.5	31.8±16.2	P=0.9909
Total cholesterol-HDL ratio	4.25±1.03	4.32±3.14	P=0.9854
LDL-HDL ratio	2.6±0.97	2.3±0.96	P=0.8302
Non- HDL cholesterol (mg/dL)	161.5±46.2	147.3±45.43	P=0.8309
Creatinine (mg/dL)	0.92±0.17	1.01±0.23	P=0.7530
eGFR (ml/min)	85.7±17.7	75.5±20.5	P=0.7067
Blood urea (mg/dL)	26.9±4.8	31.3±11.6	P=0.7263
Uric acid (mg/dL)	4.51±1.28	5.3±1.8	P=0.7165
Sodium (mEq/L)	134.24±3.98	135.8±4.6	P=0.7979
Potassium (mEq/L)	4.45±0.34	4.3±0.4	P=0.7754
Chloride (mEq/L)	101.5±2.8	101.8±3.12	P=0.9432
TSH (mIU/L)	3.1±3.7	2.13±1.85	P=0.8124
SGOT (Units/L)	30.1±17.6	24.9±11.5	P=0.7964
SGPT (Units/L)	39.97±32.3	33.2±19	P=0.8474
Fasting C- peptide (ng/ml)	1.85±0.65	1.7±0.52	P=0.9701
Random C- peptide (ng/ml)	2.4±1.29	2.9±2.28	P=0.8423

Data are mean ±SD or n (%); BMI- body mass index; SBP-systolic blood pressure; DBP-diastolic blood pressure; eGFR- estimated glomerular filtration rate; CAD-coronary artery disease; CKD- chronic

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kidney disease; DPN- diabetic peripheral neuropathy; DR- diabetic retinopathy; Analysis done by Unpaired student t test.

The mean FBS and RBS at baseline in Group 1 and 2 were 298.9±73.7 mg/dL, 265.6±70.7 mg/dL (p=0.0056) and 496.3±67.1 mg/dL, 450.5±47 mg/dL (p<0.001) respectively. The change in BG values on pre-treatment with NS in Group 1 were as follows. After the first 500ml of NS, it decreased from a mean of 496.3±67.1 mg/dL to 357.1±84.8 mg/dL (p= 0.00) and after second 500 ml and third 500 ml to 325.4±82.3 mg/dL (p=0.02) and 283.3±83.8 mg/dL (p=0.00) respectively (Fig 1). Mean percentage reduction of glucose from baseline to after 1500 ml of NS was 43% (p<0.001). Mean Osm of group1 reduced from baseline of 313.8±8.1 to 302.9±8.5 (p<0.001) after 1500ml of fluid administration showing a mean reduction in Osm of 11 mOsm/kg (Fig 2). There was a significant correlation between the reductions of BG and Osm (r=0.322, p=0.001).

Change in the means of FBS and RBS from baseline to follow up in group 1 was significantly higher compared to group 2{[FBS from 298.9±73.7 to 158.9±58.7 in group 1 and from 265.6±70.7 to 171.48±66.5 in group 2, p=0.00] and [RBS from 496.3±67.1 to 228.3±80.7 in group 1 and 450.5±47 to 282±112.4 in group 2, p=0.001]} (table-2, Fig 3). The percentage reduction of FBS and RBS from baseline to follow up was 47% and 54% in group 1 and 35% and 37% in group 2 respectively.

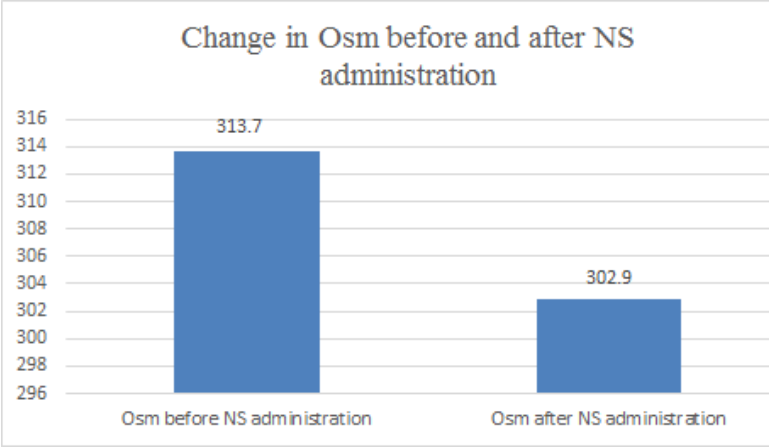

Fig 1: Mean serial BG values after each pint of NS in Group 1

Groups	Baseline mean FBS	Follow up mean FBS	*P* value	Percentage reduction (%)	Baseline mean RBS	Follow up mean RBS	*P* value	Percentage reduction (%)
Group 1	298.9±73.7	158.9±58.7	*P*<0.001	47	496.3±67.1	228.3±80.7	*P*<0.001	54
Group 2	265.6±70.7	171.48±66.5	*P*<0.001	35	450.5±47	282±112.4	*P*<0.001	37

Table 2: Mean baseline and follow up BG values of two groups:

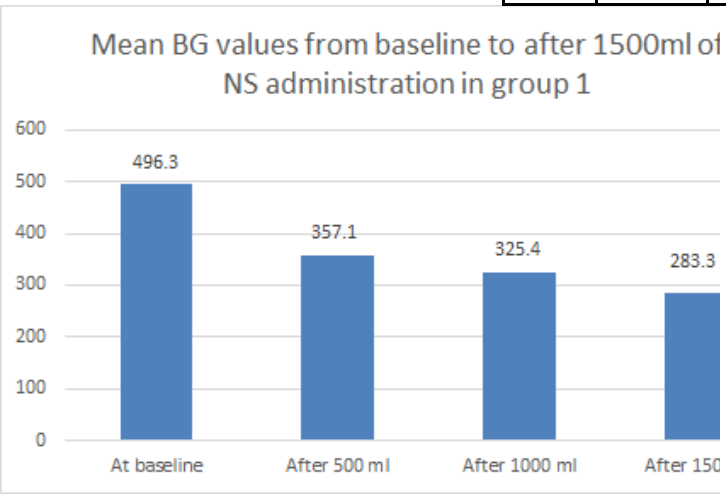

Fig 2: change in Osm values in Group 1

Fig 3: Comparative change in BG from baseline to follow up in two groups:

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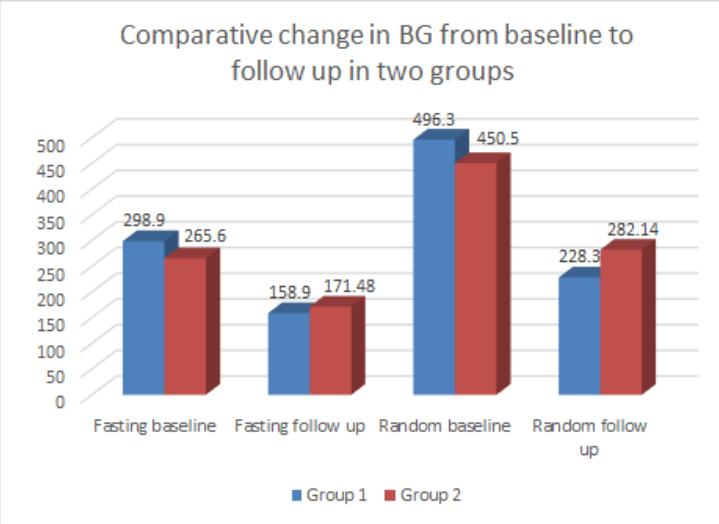

Different antidiabetic medications used in each group at baseline and follow up visits are as follows : Metformin-84%, 86% (group 1) and 76%,76% (group 2), Sulfonylureas (SU)-90%, 89% (group1) and 87%, 89% (group 2), DPP4 inhibitors-96%, 98% (group 1) and 90%, 94% (group2), Insulin-46%, 42% (group 1) and 55%, 60% (group2). With regard to the anti-diabetic dose titration from baseline to follow up visits, Metformin dose was reduced by 1.7% in group 1 but increased by 5% in group 2 (p=0.075), SU reduced by 3.5% in group 1 but increased by 1.2% in group 2 (p=0.859), DPP4 inhibitors reduced by 3.26% in group 1 but increased by 1.6% in group 2 (p=0.00), dose of Insulin reduced by 3% in group 1 while increased by 7% in group 2 (p=0.758). Overall there was a general trend of decrease in the dosages of anti-diabetic medications in group 1 and increase of the same in group 2. The change was statistically significant only for DPP4 inhibitors. Mean dosages of medication prescribed at baseline and follow up visits in both groups are given in table 3.

Table 3: mean dosage of anti-diabetic medications of two groups during baseline and follow up visits:

Groups	visits	metformin	SU	D ir
Group 1	Baseline visit	1358.3±511	3.6±1.4	1.
	Follow up visit	1334.8±544	3.7±1.5	1.
Group 2	Baseline visit	1171±526	3.54±1.5	1.
	Follow up visit	1233.6±464.3	3.59±1.62	1.

DISCUSSION

Studies have shown that hyperosmolality interferes with glucose metabolism by enhancing hepatic glucose output and suppressing its peripheral glucose utilization [29]. Studies by Paul R and Ralph A (1983) showed that moderate elevations in Osm, even less than 10%, can cause a significant decrease in insulin-mediated glucose metabolism [17]. And Grauso M et al (2019), had reported impairment of oxidative metabolism of intestinal epithelial cells in in vitro hyperosmolar environment [16] indicating that hyperosmolality can suppress glucose metabolism. This reflects in clinical situations where hyperosmolality due to increasing BG creates a vicious cycle of *'hyperglycemia-dehydration-hypertonicity-hyperglycemia'*. Theoretically, by interfering with insulin action on glucose metabolism it can reduce the effectiveness of therapy and simple interventions like fluid administration can reverse this. But the utility of this simple but effective therapeutic option was not explored yet. This appears to be the first such attempt to demonstrate that correction of hyperosmolality using pre-treatment with NS can significantly reduce glycemic load and thus contribute to reduction in drug requirement in SCH.

There was progressive reduction in mean glucose values with NS administration. After 1500 ml of fluid administration, mean BG reduction corresponded to the reduction in mean Osm. Compared to group 2, group 1 showed significant reduction of both FBS (p=0.00) and RBS (p=0.001) from baseline to follow up. Though the baseline glucose values were higher in group 1 than group 2, the percentage reduction was better in group 1 (54% vs 37%).During serial fluid administration, the change in BG was highest b/w the baseline and after the first 500 ml (mean-139.2mg/dL, 28%, p=0.00) and the reduction continued unabated during the second and third 500mls. There was also a consistent reduction (significant for DPP4 inhibitors, p=0.00) in requirement of anti diabetic medications in group 1. This further underscores the importance of IV fluid administration in the management of SCH.

The benefit of fluid administration persisted for a mean period of 4 weeks though the long term benefit is not clear from this analysis as mean data analysed here was only of about 4 weeks. This proves to be an easy, scientific and universally feasible intervention in conjunction with drugs for controlling BG which can be done even in a primary care set up without much infrastructural requirement in a very cost effective manner.

Apart from the need for longer prospective controlled studies to evaluate the long term effects of Osm correction in patients presenting with SCH, studies using investigations like

fructosamine and glycated albumin to monitor short term glycemic control and Ambulatory Glucose profile (AGP) metrics like glucose management index (GMI) and coefficient of variability (CV) will give a better understanding about the effects including glycemic variability.

This study showed that pre-treatment with NS in SCH can reduce both glycemic load and drug burden. A minimum of 1500ml of NS can safely be administered in SCH to correct hyperosmolality and hyperglycemia. This may bring down the cost of treatment and hyperglycemia mediated acute and chronic complications. Based on this report, there is a perceived need for utilizing IV fluid for managing SCH with overt hyperosmolality (>300mOsm/kg). The decision to administer IV fluids can be made on the basis of calculated osmolality at baseline in SCH. So we propose that IV fluid pre-treatment be included as an important initial modality in the management of SCH. Prospective, randomized controlled trials with long term follow ups are needed to explore the long term benefit.

DECLARATIONS:

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Availability of data and material (data transparency): Available

Code availability (software application or custom code): Not applicable

Consent to participate (include appropriate statements): Not applicable

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