

## Original Article

# Choice of fluid therapy in patients of craniopharyngioma in the perioperative period: A hospital-based preliminary study

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## Abstract

**Background:** Electrolyte imbalance and acute diabetes insipidus (DI) are the most common complications in patients undergoing craniopharyngioma surgery. Improper management of water and electrolyte imbalance is common cause of morbidity and mortality. Data is sparse and controversial regarding the choice of fluid therapy in this population during perioperative period.

**Methods:** In this retrospective-prospective study involving 73 patients (58 retrospective), the type of fluid therapy was correlated with occurrence of hypernatremia, hyponatremia, DI, morbidity, and mortality. In the retrospective study, 48 patients received normal saline and 10 received mixed fluids as per the prevailing practice. In the prospective group, five patients each received normal saline, half normal saline, and 5% dextrose randomly.

**Results:** The sodium values were significantly higher in first 48 h in the group that received normal saline compared with other groups ( $P < 0.001$ ). The use of normal saline was associated with higher incidence of hypernatremia, DI, and mortality ( $P = 0.05$ ), while the group that received 5% dextrose was associated with hyponatremia, hypoglycemia, and seizures. There was no perioperative hypotension with use of any of the fluids.

**Conclusion:** Our results indicate half normal saline was fluid of choice with diminished incidence of water and electrolyte abnormalities without increase in mortality during postoperative period.

**Key Words:** Craniopharyngioma, diabetes insipidus, hypernatremia, half normal saline

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## INTRODUCTION

Craniopharyngiomas are sellar and/or suprasellar and locally invasive tumors compressing critical neural and

vascular structures. Surgery for these tumors may be challenging given the significant potential for harms with any intervention involving these critical structures and young age at presentation.<sup>[12,22]</sup> Acute diabetes

insipidus (DI) is the most common complication of craniopharyngioma surgery with estimated postoperative incidence as high as 76% in children<sup>[12]</sup> and syndrome of inappropriate antidiuretic hormone secretion (SIADH) occurs in 4% of patients in a large series.<sup>[5,16]</sup>

In the postneurosurgical settings, the differentiation of central DI from polyuria as a result of diuresis due to intraoperative fluid administration is important.<sup>[17,27]</sup> The DI may be differentiated from polyuria by the assessment of plasma osmolality. Central DI is more likely if plasma osmolality is more than 300 mosm/kg and urine osmolality less than 700 mosm/kg.<sup>[2,11]</sup> SIADH is considered when spontaneous oligouria (urine output of less than 0.5 ml/kg/h) with concurrent hyponatremia (serum sodium <135 mEq/L) in the absence of renal insufficiency, glucocorticoid, and thyroid hormone deficiency.<sup>[20]</sup>

Careful history of perioperative fluid intake and output, laboratory investigations such as urine specific gravity, urine and serum osmolality and serum electrolytes are required to make correct diagnosis of DI. In settings of DI and polyuria due to excessive administration of isotonic fluid, hypernatremia (serum sodium  $\geq$ 150 mmol/L) is usually observed. This poses potential risk of serum hyperosmolality and if uncorrected, may lead to serious complications like stupor, seizures, renal failure, and very high values can potentially be fatal.<sup>[17,27]</sup>

The study by Shucart and colleagues showed that dextrose in water solution for an intravenous fluid or tap water for oral administration was better for the management of DI in neurosurgical setting.<sup>[27]</sup> There is controversy about infusion of saline solution in the postoperative period. Few authors believe that use of normal saline (NS) deliver continuous solute load to the kidney aggravating renal water loss since solute concentration cannot be increased in absence of antidiuretic hormone.<sup>[4,20,24]</sup> However, this hypothesis has been challenged by another study done in patients who underwent craniopharyngiomas surgery. In immediate postoperative period, hypernatremia and hypokalemia due to hyperaldosteronism cause sodium retention and potassium excretion with the normal hypothalamic-pituitary axis.<sup>[8,9,13]</sup> Surgery for craniopharyngioma disturbs the normal hypothalamic-pituitary axis resulting in postoperative electrolyte abnormalities. This controversy in the selection of intravenous fluid in the postoperative period prompted us to carry out this study.

## PATIENTS AND METHODS

### Patient selection

The study was an analytical prospective and retrospective, conducted on patients of histo-pathologically verified craniopharyngiomas in different age groups

at Postgraduate Institute of Medical Education and Research, Chandigarh, India, a leading tertiary care institute in north India. The patients for prospective study were recruited from January 2012 to January 2013 and the retrospective study patients underwent surgery between January 2002 and January 2010. The surgeries were performed by a single neurosurgeon (KKM) by transcranial route. Patients in whom transsphenoidal surgery was performed were excluded from the study. All patients were managed in the postoperative setting by specialist intensivist (HB). Written informed consent was taken from all the patients and the study was approved by Institute's Ethics Committee. The patients in the prospective group were allotted randomly from computer generated random numbers to receive different types of fluids. They were divided into three subgroups (five in each) according to the type of fluids infused during intraoperative period. In the retrospective group, the type of fluid was analyzed from hospital records. Patients were deemed to receive fluid boluses for hypotension in the perioperative period. The exclusion criteria were mere biopsy, ventriculoperitoneal (VP) shunt or only reservoir placement in tumor, patients having diabetes mellitus, or known DI.

### Perioperative evaluation

All patients were evaluated by computerized tomography (CT) scan and contrast enhanced magnetic resonance imaging (CEMRI) of hypothalamo-pituitary area. Preoperative serum and urinary sodium levels, serum and urine osmolality, urine specific gravity, history suggestive of preoperative DI, fasting plasma glucose, Glasgow coma scale (GCS), visual acuity and field, neurological deficits, and hormonal parameters were recorded. If patients were deficient of pituitary hormones, they were replaced adequately for at least one month before taking decision for surgery.

The intraoperative evaluations included extent of excision of tumor, type of fluid used for first 7 days following craniopharyngioma surgery, total amount of fluid given, intraoperative intake/output and central venous pressure (if applicable).

Postoperative evaluation (daily till the end of first week or normalization of patient's clinical and biochemical parameters) included serum and urine sodium, serum and urine osmolality, urine specific gravity, incidence of DI, SIADH, serum sodium, use and dose of desmopressin administered, plasma glucose, postoperative GCS, vision, neurological deficits and serum thyroxine and serum cortisol. Postoperative DI was managed with desmopressin subcutaneously at an initial dose of 5  $\mu$ g when urine output was 200-250 ml/h for  $\geq$ 2 h with urine specific gravity <1.005 or urine osmolality <200 mosm/kg of water as per standard protocol.<sup>[27]</sup>

### Laboratory methods

The urinary and serum osmolality were measured by principle of freezing point depression method (Fiske® 210 Micro-Sample Osmometer, USA). All the hormonal parameters were done by immunochemiluminiscence method (COBAS 6001, Roche Diagnostic, Germany). Serum and urine sodium were measured by immunochemiluminiscence method (ELCYS 2010, Roche Diagnostic, Germany)

### Statistical analysis

The sample size of 5 per group was required to detect a difference of 10 mmol/L in serum sodium value with variance of 25. The alpha was set to 0.05 and adjusted for Bonferroni corrections for multiple comparisons. The power was set to 80%. Continuous data was expressed as mean (standard deviation). Categorical data was expressed as numbers or percentage. Parametric data was compared using analysis of variance and nonparametric data was done using Chi-square test. A P value less than 0.05 was considered as significant. Repeated measure data was analyzed with repeated measures of analysis of variance (ANOVA) (Friedman’s test for nonparametric data) with Bonferroni correction for comparison between groups. Proportional data was analyzed with Z test. Correlation of data was analyzed by Pearson’s or Spearman’s correlation based on the distribution of data.

### RESULTS

The study included a total of 77 patients (58 in retrospective group, male: female 40:18) and 19 in the prospective group. Seventy-three patients were available for final analysis (15 in the prospective group, male: female 6:9). The concert of flow of patients is shown in Figure 1.

#### Prospective group

In the prospective group, young children (7, 47% were less than 20 years of age) were the most commonly affected by the disease. There was no significant difference in the age between the subgroups receiving different category of intravenous fluids. Loss of vision was the most common preoperative complaint of the patients, followed by

headache and vomiting. The visual acuity and field defect was significant among all the patients ranging from mild field defect to total absence of vision. Short stature was present in 13 (90%) children, hypothyroidism in 2 (13.7%), and hypocortisolism in 6 (40%). Only one patient (5%) out of the total number of patients in the prospective group had preoperative DI and was excluded from the final analysis. Fifteen patients had sellar and suprasellar components and 4 had only sellar component, 13 had mixed solid and cystic components and 5 had calcification [Table 1]. Primary surgical resection with gross total removal was attempted in all cases. In the postoperative period, patients who received NS had sodium values higher in first 48 h than preoperative values ( $P < 0.001$ ). Intraoperatively to prevent hypotension, all patients received fluid boluses and the amount of fluid given in each subgroup was comparable. The mean cortisol was comparable in all three subgroups. The postoperative sodium was independent of use of desmopressin and glucocorticoid therapy. The trend of sodium values in the three groups are depicted in Figure 2. In other two groups, serum sodium values in the immediate postoperative period did not rise compared with the preoperative values and followed the same trend for next 2 days ( $P = 0.26$ , Figure 3). In patients who received 5% dextrose, two out of five patients had significant hyperglycemia with maximum plasma glucose of 289 and 388 mg/dl, respectively. They received short period of insulin to keep plasma glucose normal. The serum sodium values in these two patients were 129 and 126 mmol/L, respectively, at the end of surgery. One of them had generalized tonic chronic seizures in the immediate postoperative period for 5-6 s without any neurological deterioration.

There was one death observed in the prospective group following left hemispheric infarct on second postoperative day with sodium levels at the time of

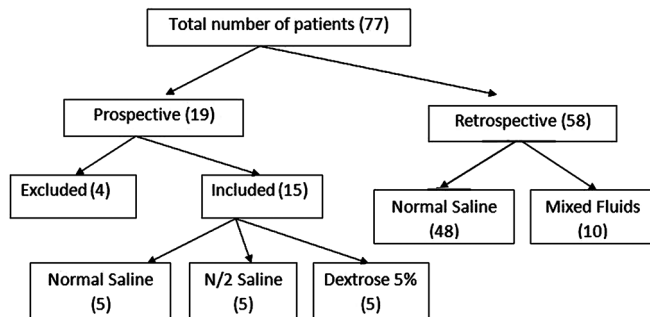


Figure 1 : Concert of flow of patients

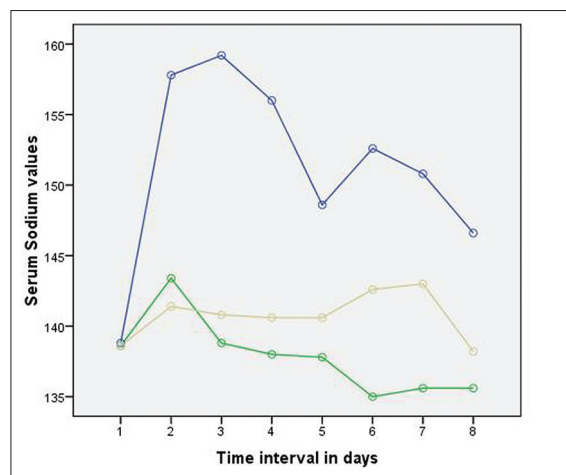
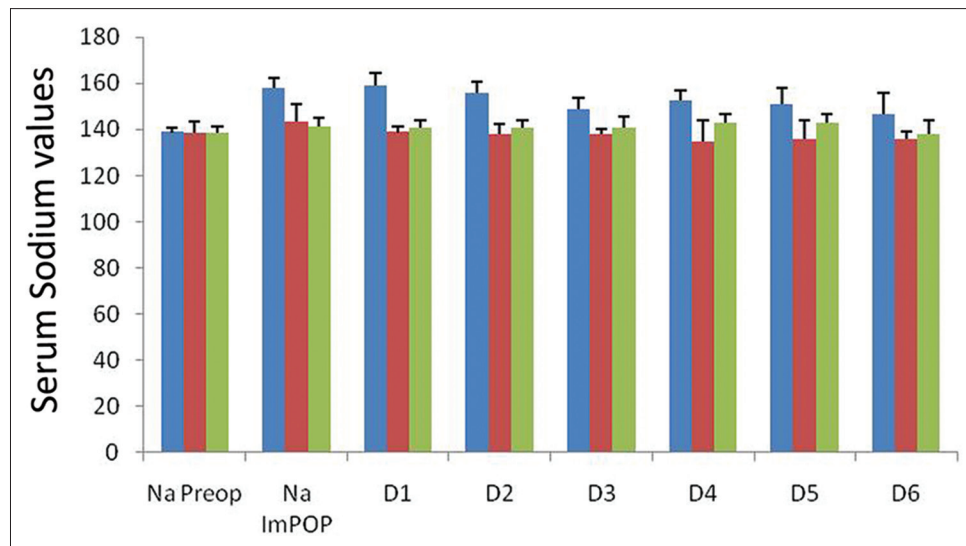


Figure 2: Serum sodium levels preoperative and different postoperative days. Group 1: NS, Group 2: Half normal, Group 3: 5% Dextrose



**Figure 3: Trend of sodium profile in the three subgroups in the prospective study from Day zero to Day 6. Blue – normal saline, Red – N/2 saline, Green -5% dextrose, ImPOP: Immediate post operative period**

deterioration approaching 160 meq/l. He also had associated DI. There was no evidence of intraoperative vascular insult, hypoxia, or any other known aggravating factors in this patient. The trend of sodium values, occurrence of hypernatremia, DI in three subgroups are depicted in Tables 1 and 2.

### Retrospective group

The clinical presentation and radiological finding were comparable to the prospective group [Table 3]. Fifty-eight patients were available for final analysis, comparable number of them were in the pediatric age group (34, 59% were less than 20 years of age). In this group, 12% were hypothyroid and 15% were hypocortisolic. In none of the patients previous removal was attempted. Forty-eight patients received NS as the sole intraoperative fluid and 10 patients were given mixed fluid in random succession (all three types) not by design but by default. Forty-five patients (93%) in the NS group and 10 (100%) in the mixed fluid group received fluid boluses with the mean volume of fluid being 1.8 and 1.7 L, respectively. Twenty-nine of 48 patients in NS group and 9 out of 10 patients in mixed fluid group underwent gross total resection. Of 48 patients in whom NS was used as the sole intraoperative fluid in the immediate postoperative period, 29 had hypernatremia, 22 of whom had DI ( $P = 0.01$ ). In patients in whom there was no hypernatremia, 6 of the 19 had DI ( $P$ , not significant). The occurrence of DI and hypernatremia in the first two postoperative days is shown in Table 4. The requirement of desmopressin had no significant effect on the postoperative sodium values. The odds of getting DI in patients undergoing near total resection was 4.8 times more than patients undergoing subtotal resection ( $P = 0.008$ ).

**Table 1: Different parameters of patients in the prospective group**

Parameters	Group (n=5)			P value
	1	2	3	
	Normal saline	N/2 saline	D5	
Age (SD)	24.8 (1.90)	11.2 (9.36)	20.4 (9.91)	0.253
Male: female	2: 3	3: 2	1:4	0.43
Headache	5 (100%)	3 (60%)	5 (100%)	0.09
Visual deficit	5 (100%)	4 (80%)	5 (100%)	0.34
MRI				
Suprasellar	2 (40%)	3 (60%)	1 (20%)	0.99
Sellar+Suprasellar	3 (60%)	2 (40%)	4 (80%)	0.77
Cystic	4 (80%)	4 (80%)	5 (100%)	0.56
Calcification	1 (20%)	1 (20%)	3 (60%)	0.30
Tumor volume (cm <sup>3</sup> )	47.42	51.07	39.60	0.90
Resection	Gross total	Gross total	Gross total	1.00
No. of patients receiving fluid bolus	5 (100%)	5 (100%)	5 (100%)	1.00
Mean volume of fluid bolus (L)	1.72	1.14	1.71	1.00
Hyperglycemia (Intraoperative)	0	0	2	0.09
Hyponatremia (Intraoperative)	0	0	2	0.09
Hypothyroid	1	1	0	NS
Hypocortisolic	2	2	2	NS
Hypernatremia (Na $\geq$ 150 mMol/L)	5	0	0	0.05
DI	5	5	5	
Death	1	0	0	

DI: Diabetes insipidus, MRI: Magnetic resonance imaging, NS: Normal saline, SD: Standard deviation

**Table 2: Trend of sodium profile in the three sub groups in the prospective study from Day zero to Day 6**

	1		Hypnatremia	2		Hypnatremia	3		Hypnatremia
	Mean	SD		Mean	SD		Mean	SD	
Na Preop	138.8	1.64	0	138.6	4.56	0	138.6	2.8	0
Na Inop	157.8	4.20	5	143.4	7.73	2	141.4	3.36	1
D1	159.2	5.06	5	138.8	2.58	0	140.8	3.27	0
D2	156	4.52	5	138	4.58	0	140.6	3.36	0
D3	148.6	4.87	4	137.8	2.48	0	140.6	5.12	1
D4	152.6	4.27	5	135	8.71	0	142.6	4.15	1
D5	150.8	7.32	3	135.6	8.29	0	143	3.67	2
D6	146.6	9.39	2	135.6	3.36	0	138.2	5.49	0
Cortisol	690.08	617.68		663.23	323.61		465.83	257.90	

Na=Sodium, Preop=pre-operative, InOP=intra-operative, D1-D6=Day 1 to Day 6, SD: Standard deviation

There was no significant difference in serum sodium in patients receiving NS and the fluid-mix ( $P = 0.60$ ). There were six deaths and all of them had received NS in their perioperative period. All of them had hyponatremia (serum sodium  $\geq 150$  mEq/L) in the immediate postoperative period and before deterioration. The patients died primarily due to cerebral infarcts at various locations, which were attributed to hyponatremia. The tumor volume and extent was comparable both in pediatric and adult patients (46 vs 42.4 cm<sup>3</sup>,  $P = 0.67$ ).

Both in retrospective and prospective groups (multivariate analysis), even though there were deaths observed in NS groups, the sample size was not sufficiently powered to detect a significant difference in mortality between the groups but on univariate analysis, the portion of deaths in NS group (retrospective group) was significantly more than the mixed fluid groups ( $P = 0.02$ ).

## DISCUSSION

Use of NS as an infusible in perioperative period has high risk of hyponatremia and DI, 5% dextrose has hyperglycemia and hyponatremia. The use of N/2 saline is associated with lower risk of fluctuating serum sodium and hyponatremia. Therefore, it is favorable to use half NS as the sole intraoperative fluid in patients undergoing craniopharyngioma surgery. All deaths happened in patients receiving NS.

In the present study, in the prospective group, prevalence of hyponatremia in the patients who received NS was 100%. In the other two groups, it was zero. Two patients (40%) who received 5% dextrose developed hyponatremia. The incidence of sodium disturbance was reported between 12% and 76% in previous studies.<sup>[16,18,27]</sup> However, these studies are silent regarding the nature of perioperative fluid used.

In the prospective study, preoperative central DI was present in only one patient (5%) but present in all patients in the peri- and immediate postoperative

**Table 3: Different parameters of patients in the retrospective group**

Variables	Group		P values
	Normal Saline (N=48)	Mixed Fluids (N=10)	
Age (mean)	20.7		0.94
Gender			
Male	35		
Female	13	5	0.18
Headache	44	9	0.87
Vision loss	37	7	0.65
MRI			
Sellar+Suprasellar	26	6	0.70
Suprasellar	22	4	0.70
Cystic	48	10	0.99
Calcification			
Yes	16	3	0.84
Tumor volume (cm <sup>3</sup> )	42.63	40.32	0.90
Tumor resection			
Near total	29	9	0.09
Subtotal	19	1	0.01
Mean volume of fluid bolus (L)	1.8	1.7	0.94
Hyperglycemia	0	1	0.94
Hyponatremia	0	3	0.94
Hypothyroid	5	2	0.38
Hypocortisolic	4	1	0.21
Desmopressin-immediate postoperative	23	3	0.48
Desmopressin - D1	26	7	0.20
Desmopressin - D2	27	3	0.10
Outcome			
Death	5	0	0.02

period. In the retrospective group, 80% had DI in the perioperative period. The classical textbook triphasic pattern of endogenous vasopressin secretion was uncommon (10%). Overzealous glucocorticoid and phenytoin therapy complicates the risk of life



threatening hyper or hypo natremia and DI.<sup>[25]</sup> In our study, patients with glucocorticoid deficiency were put on replacement weeks before surgery and phenytoin was sparingly used (only in patients who developed seizures: One in the prospective group and two in retrospective group).

In the prospective study, there was significant hypernatremia in all patients in whom NS was used as a sole intraoperative fluid as compared with N/2 saline or 5% dextrose in first 48 h of postoperative period. There was no significant difference in biochemical or hormonal profile of patients who received either of N/2 saline or 5% dextrose during this time frame. Being hypotonic these later two fluids theoretically pose increased chances of cerebral edema but no such thing was observed in our study. The other fear was that of hyperglycemic during surgery with 5% dextrose. Use of dextrose is also associated with higher risk of ischemia therefore it is not a preferred intraoperative fluid in cranial surgery. As stated earlier, hyperglycemia was observed in two patients who received 5% dextrose requiring insulin for a short period of time. It did not pose any problem in patient's recovery from general anesthesia. Their hemoglobin A1c values were in the nondiabetic range. The same two patients had hyponatremia, which is comparable to the incidence in identical circumstances.<sup>[23]</sup> There was only one death in prospective group who received NS infusion. He died of hemi cerebral infarct requiring decompression surgery on second postoperative day perhaps due to hypernatremia.

In our retrospective study, NS had been the choice of intraoperative fluid, irrespective of the postoperative sodium values. We tried to analyze the patient outcome in relation to serum sodium values with the intraoperative type of fluids, particularly in the first 48 h, since a lot of other factors come into play later. Approximately 80% of patients had significant hypernatremia in the immediate postoperative period. Patients (20%) who did not have hypernatremia but DI, nearly half of them were found to be hypo cortisolic. This is due to masking of hypernatremia in presence of hypocortisolism.<sup>[7,25]</sup> The occurrence of DI and hypernatremia was concordant in remaining 10 patients in whom all the three fluids were given in a variable manner [Table 4]. However, there was no mortality in any of these patients (5 vs 0,  $P = 0.001$ ). As the retrospective group was by default and not by design, therefore there was no bias regarding patient selection and management. Conventionally, it is believed that in the postoperative period, each patient will have different fluid requirement based on presence of DI, SIADH, or other hypothalamo-pituitary axis dysfunction. However, in our study very small subset of patients had SIADH and none had disorders of thirst mechanism. Therefore we can make a broad generalization about fluid management in this patient population.

**Table 4: Occurrence of diabetes insipidus and hypernatremia retrospective group**

	Hypernatremia		P value	No Hypernatremia		P value
Immediate post op	29		<0.001	19		0.034
	DI	No DI		DI	No DI	
	22 (76)	7 (24)		6 (33.33)	13 (66.67)	
Day 1	29		<0.001	19		<0.001
	DI	No DI		DI	No DI	
	26 (88.89)	3 (11.11)		3 (17.64)	16 (82.35)	
Day 2	26		<0.001	22		<0.001
	DI	No DI		DI	No DI	
	22 (82.6)	4 (17.4)		4 (19)	18 (81)	

DI: Diabetes insipidus

All deaths in retrospective group happened in patients who received NS as the sole fluid in the perioperative period. They had significant hypernatremia particularly at the time of deterioration with average serum sodium value of 160mmol/L. The possible causes of death in these patients was due to acute cerebral infarcts at various sites with variable severity, directly correlating to hypernatremia as all other predisposing factors for infarcts were absent.

Among the immediate causes of morbidity and mortality, DI, and hypernatremia pose a significant effect on outcome of patients undergoing craniopharyngioma surgery.<sup>[1,3,15,19,21,26,30]</sup> When the excision of the tumor is planned after hormonal work up, many a times perioperatively electrolyte abnormalities are ignored. Though the complications and predictors related to water and electrolyte homeostasis following pituitary surgery in general and craniopharyngioma surgery in particular is well known, there is paucity of data regarding the choice of intraoperative fluid.<sup>[6,10,14,29]</sup> Studies have addressed the type of postoperative fluids with controversial results.<sup>[17,27]</sup> In a study Leurenbecher *et al.* had used NS as the sole postoperative fluid, causing serum sodium values to rise erratically in immediate postoperative period in the setting of ongoing DI.<sup>[17]</sup>

In normal physiology daily salt intake varies from 50 to 90 mmol as sodium chloride. Water and sodium homeostasis is maintained primarily by kidneys and skin under conditions of reduced salt intake or excessive extra renal losses. The normal kidneys can reduce sodium excretion to less than 1 mmol/day in acute stressful condition. Postoperatives state is a condition of reduced salt intake and apparent mineralo-corticoid excess. The increased excretion of aldosterone is influenced by reduced extracellular volume, low sodium diet, and excessive potassium administration. Such kind of mechanisms work under the normal hypothalamo-pituitary axis.<sup>[8,9]</sup> We presume that in craniopharyngioma surgery, the normal hypothalamo-pituitary and adrenal axis are disturbed leading to erratic electrolytic abnormalities. Though aldosterone is predominantly regulated by renin-angiotensin system,

serum sodium, potassium, and ACTH plays a minor role. Good understanding of this patho-physiology is required for appropriate management and avoidance of life threatening and disabling electrolyte disturbances.

The clinical presentation and radiological findings in our studies were comparable to historical data by various authors.<sup>[1,3,21,28]</sup> As all of the patients included in the study underwent transcranial resection and both adult and children had comparable tumor volume, the chances of stalk and hypothalamic damage was equal in both the groups. However, the prevalence of hormonal insufficiency other than growth hormone deficiency was relatively less in the retrospective group in our study.<sup>[18,30]</sup> In neurosurgical practice, generally Hartman's solution is not preferred at induction, and NS/ plasmalyte is the preferred solution. None of our patients had any baseline sodium abnormality that is why we ventured to categorize them in to three different types of fluid groups.

The strength of this study is that this is a randomized controlled trial. Equal number of patients in either group had similar size and type of tumor (sellar/suprasellar) and all were operated by transcranial route, as the location of the tumor and damage to hypothalamus will have a profoundly different impact on postoperative serum sodium. Similarly, comparable number of patients received fluid boluses and the amount of fluid was also not different. Therefore, the occurrence of mortality, DI, and hypernatremia is unlikely to be influenced by this. The limitations of this study are that this was a heterogeneous study design (retrospective and prospective), small number of subjects as a whole in the prospective group and in the subgroups, absence of blinding, and lack of autopsy in patients who died of cerebral infarcts. Since the study has involved the measurement of objective parameters mostly absence of blinding would not have biased the results.

## CONCLUSION

The type of intraoperative fluid should be given utmost importance while planning craniopharyngioma surgery. Use of NS promotes occurrence of hypernatremia, DI, and mortality, while 5% dextrose promotes hyponatremia hyperglycemia and seizures. This study results indicate half NS as the fluid of choice with diminished incidence of water and electrolyte abnormalities without increase in mortality during postoperative period. In future, a large prospective blinded study is required to determine the consistency of our results and make more clear recommendations.

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