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OPEN

Postoperative Dysnatremia in Pediatric Patients Undergoing Palatoplasty

Ewyanna Lonfat, MD and Giorgio C. La Scala, MD, PD

Objective: Identifying predisposing factors to dysnatremia to improve perioperative care after cleft surgery.
Design: Retrospective case series. Patient data were obtained through the electronic medical records of the hospital.
Setting: Tertiary care university hospital.
Patients: The inclusion criterion was the measurement of an abnormal natremia value, defined as Na >150 or <130 mmol/l after a cleft lip or cleft palate repair procedure. The exclusion criterion was natremia between 131 and 149 mmol/l.
Results: Natremia measurements were available for 215 patients born between 1995 and 2018. Five patients presented with postoperative dysnatremia. Several predisposing factors to dysnatremia have been identified: drugs, infection, administration of intravenous fluids, and postoperative syndrome of inappropriate antidiuretic hormone secretion. Although the hospital environment contributes to dysnatremia development, the fact that only patients undergoing cleft palate repair develop natremia anomalies suggests that this surgery may be itself a risk factor.
Conclusion: Children undergoing palatoplasty may be at higher risk to develop postoperative dysnatremia. Early recognition of symptoms and risk factors, postoperative monitoring, and prompt treatment of dysnatremia diminish the risk of neurological complications.

Keyword: cleft palate, diabetes insipidus, hypernatremia, hyponatremia, inappropriate ADH syndrome, plastic, postoperative complications, surgery

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Abnormal natremia (dysnatremia) is a frequent problem in the pediatric population, particularly in the perioperative period.[1,2] Sodium imbalance can be paucisymptomatic, making it challenging to diagnose and treat; therefore, it is not rare that errors may occur while managing the natremia. Rapid natremia correction can cause preventable irreversible neurological damage or even death.[3]

Several studies showed that in the postoperative period, children are more subject to plasma electrolyte changes.[2,4–6] This can be explained by the loss or dysfunction of homeostatic mechanisms during the postoperative period but also by the multiple therapeutic interventions potentially iatrogenic. Neurosurgery and cardiac surgery are known to cause dysnatremia;[7,8] only 3 cases have been reported after cleft lip or palate repair and in 2 cases after palatoplasty.[9–11] In our hospital, we have observed several cases of dysnatremia after palatoplasty in children, suggesting that patients undergoing this type of surgery may be at risk of postoperative dysnatremia.

This retrospective study aims to identify possible links between primary cleft lip or palate surgery, predisposing factors, and the development of dysnatremia. The recognition of predisposing factors could allow for improving the perioperative management of those patients.

METHODS

Study Population

This retrospective study identified children who underwent primary cleft lip or palate repair and presented postoperatively natremia anomalies in the division of pediatric surgery of the Geneva University between July 1995 and May 2019.

The inclusion criterion was the measurement of a natremia >150 or <130 mmol/l after a palatoplasty. Those values were chosen because they are the usual limit before natremia becomes symptomatic. The exclusion criterion was normal natremia between 131 and 149 mmol/l.

Data Collection

The electronic health care records were used to identify patients with postoperative dysnatremia and to retrieve information, such as the type of operation, associated syndromes, genetic anomalies, previous natremia anomalies, postoperative natremias, end of operation to measurement of abnormal natremia interval, type of perioperative and postoperative intravenous fluids used, drugs used, concomitant symptoms, and dysnatremia etiology.

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Operative Settings

A trained pediatric anesthesiologist always conducted the anesthesia. The drugs for sedation and analgesia, along with the perioperative fluids, were used at the physician's discretion. An intravenous dose of amoxicillin-clavulanic acid (co-amoxiclav, 50 mg/kg amoxicillin) was administered at induction. The surgeries were performed by different surgeons during the study period. Before the incision, Lidocaine 1% or Bupivacaine 0.25% diluted in adrenaline 1:200,000 was injected into the palate for local anesthesia and to diminish blood loss.

Postoperatively, patients were allowed to drink clear liquids from day 0, milk on day 1, and were allowed to eat pureed food from day 2 to 3. In addition, a perfusion of 100 ml/kg/day was used, at least during the first 24 hours. Before 2011, hypotonic fluids were administered according to the hospital guidelines. After 2011, the guidelines changed to recommend the systematic use of isotonic solutions. Co-amoxiclav was given intravenously during the hospital stay and orally after discharge for variable durations.

After discharge, all patients were followed up regularly in consultation and are still in active follow-up because of their cleft.

Ethics Approval

Due to the low number of patients included in the study, the Swiss ethics committee waived the requirement to submit a request for approval.

The study was conducted in accordance with the declaration of Helsinki.

STATISTICS

Descriptive statistics report data as average ± SD. Data were analyzed with Graphpad Prism version 9.4.1 (Graphpad Software, San Diego, CA).

RESULTS

Natremia measurements were available for 215 patients born between 1995 and 2018. Of those, 20 children (9.3%) had abnormal natremias in their charts. However, only 5 of those 20 (25%) had abnormal values after cleft surgery, in all cases after a palatoplasty. The excluded 15 patients presented natremia anomalies in other settings (perinatal, infection, dehydration, renal no, or adrenal pathology) (Fig. 1).

Of the 5 patients identified, 3 girls and 2 boys, none of them was previously known for natremia anomalies. Three patients had cleft palate and 2 had cleft lip and palate. Three patients were subsequently diagnosed with a syndrome or chromosomal anomaly.

Case reports data is detailed in Annex 1, Supplemental Digital Content 1, http://links.lww.com/SCS/E963.

The average age at operation was 12 ± 0.6 months, and the average weight was 8.5 ± 1.2 kg (see Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/SCS/E964). Two patients presented hypernatremia with a maximum value of 176 mmol/l, while 3 had hyponatremia, with a minimum of 126 mmol/l. Most of the abnormal values were measured in the first 24 hours after surgery (36 ± 20 h), with the following natremia usually in the following 3 hours (interval to second natremia check 5.9 ± 5.8 h).

Perioperatively, the most frequently used intravenous fluid was Ringer's acetate with glucose 1% (RA-G1). Postoperatively only one of the patients received hyponatremic fluids in accordance with the hospital guidelines at that time (see Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/SCS/E964).

Using patients' data, other than palatoplasty surgery, several concomitant risk factors for dysnatremia were identified: medication, infection and administration of intravenous fluids. Data on fluid management and on drugs received and concomitant factors are reported in Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/SCS/E964.

A treatment to correct the dysnatremia was necessary in two cases. The cause of the dysnatremia was identified in only two cases, syndrome of inappropriate secretion of antidiuretic hormone secretion (SIADH) and diabetes insipidus (see Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/SCS/E964). Only the patient diagnosed with diabetes insipidus presented further dysnatremia events.

DISCUSSION

The purpose of this study is to raise awareness of the risk of dysnatremia in children undergoing primary cleft surgery. In our cohort of patients, about 2% presented with significant postoperative natremia alterations, in all cases after a palatoplasty. Although the hospital environment contributes to dysnatremia development, the fact that only patients undergoing cleft palate repair developed natremia anomalies suggests that this surgery may be itself a risk factor.

Dysnatremias are often overlooked by physicians and may be inadequately treated. For this reason, routine blood tests should be part of the standard postpalatoplasty care.

Among hospitalized children, 1% to 3% present severe hyponatremia,[3,12] and hypernatremia ranges between 0.22% to 1%.[13] Although common, dysnatremia is frequently underdiagnosed, leading to increased morbidity or even fatal outcomes, with extreme values of sodium associated with >25% mortality.[2]

The sodium-water balance is governed by water intake, renal excretion, and vasopressin release. Therefore, multiple pathologies affecting sodium homeostasis can cause hypernatremia or hyponatremia, as shown in Supplemental Table 3, Supplemental Digital Content 2, http://links.lww.com/SCS/E964 and 4, Supplemental Digital Content 2, http://links.lww.com/SCS/E964. The resulting neurological symptoms are caused by a water shift between intracellular and extracellular compartments, leading to either swelling or shrinking of brain cells.

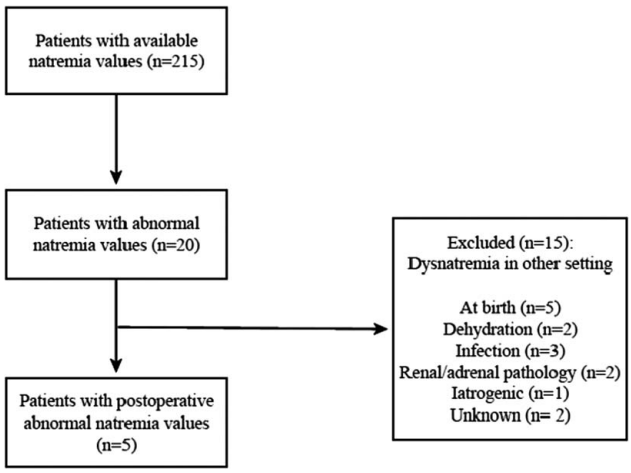

FIGURE 1. Flowchart of inclusion and exclusion criteria for the study.

Nausea, vomiting, muscular weakness, headache, lethargy, and ataxia appear with the progression of cerebral oedema in case of severe hyponatremia.[3] Altered mental status, lethargy, irritability, restlessness, seizures, muscle twitching, hyperreflexia, fever, nausea, and vomiting can appear with hypernatremia.[14,15]

These symptoms may be difficult to recognize, especially in toddlers. Moreover, they are often attributed to the disease motivating admission rather than to an electrolytic disorder.[16] In our study, all patients presented with symptoms that could suggest dysnatremia; however, blood tests were often delayed (interval to second natremia check 5.9 ± 5.8 h). Only patient 5, who presented with severe symptoms of hyponatremia, was promptly tested and treated.

Therefore, the treatment of dysnatremia and the prevention of neurological complications relies on the early recognition of symptoms, but even more so on the identification of patients at risk of dysnatremia.[5]

In the hospital environment, diseases and possible iatrogenic interventions favor the development of dysnatremia.[1,17] All patients in this study were exposed to some extent to those risk factors.

Infections can cause both hyponatremia and hypernatremia. Respiratory infections, especially pneumonia and bronchiolitis, are known to cause hyponatremia in up to 20% of children, possibly due to the development of SIADH.[18,19] Of these children, about 4% will develop seizures.[18,20–22]

Hypernatremia is known to develop during severe gastroenteritis with an increased loss of free water. Less frequently, systemic infections (eg, tuberculosis) or central nervous system infections (eg, meningitis, encephalitis) cause hypernatremia due to the development of acquired diabetes insipidus.[17,23]

All of our patients presented with a postoperative fever suggesting a possible infection. In two cases of hyponatremia, a viral infection was diagnosed (croup and RSV), possibly playing a role in the development of dysnatremia.

Although often forgotten, multiple drugs can cause sodium imbalance. Antibiotics (eg, penicillin derivates, aminoglycosides), corticosteroids, lactulose, and diuretics are all drugs causing water loss that can result in hypernatremia.[24] Similarly, nonsteroidal anti-inflammatory drugs, opiates, diuretics, antihypertensive, antiepileptic, antidiabetic, antiarrhythmic, antidepressants, antipsychotic, and some anticancer agents can all result in hyponatremia due to either water retention or loss of sodium.[25]

All patients were given morphine PCA and co-amoxicillin antibiotics. One patient received a diuretic and another dexamethasone (see Supplemental Table 4, Supplemental Digital Content 2, http://links.lww.com/SCS/E964). It is uncertain whether these drug administrations contributed to the development of dysnatremia.

One of the most debated topics in the literature regarding in-hospital dysnatremia is the administration of intravenous maintenance fluids. Since the 1950s, the rate and composition of parenteral fluids for hospitalized children were based on the recommendation of Holliday and Segar, whose theoretical calculations were not considering changes in the sodium homeostasis in ill or postoperative children. Those recommendations led to the widespread use of hypotonic solutions for maintenance infusion in children.[26]

Throughout the years, it has been recognized that the administration of hypotonic fluids can be responsible for iatrogenic hyponatremia and lead to catastrophic complications with hyponatremic encephalopathy.[27–34] For this reason, the American Academy of Pediatrics published new guidelines in 2018 to unify the use of isotonic intravenous fluids. There are still, however, uncertainties about the appropriate fluid management for pediatric patients with neurosurgical disorders, congenital or acquired cardiac disease, hepatic disease, cancer, renal dysfunction, diabetes insipidus, abundant watery diarrhea, severe burns, neonates younger than 28 days, and critically ill patients in the ICU.

During the period in which hypotonic fluids were used in our hospital, only 1 child (patient 5) developed severe symptomatic hyponatremia, suggesting that it is rather the combination of several risk factors that leads to the development of dysnatremia instead of hypotonic fluids on their own. Patient 1 of our study, who was later diagnosed with diabetes insipidus, developed hypernatremia after the administration of an isotonic solution. Indeed, in diabetes insipidus, the renal absorptive capacity is reduced, and therefore an improper administration of isotonic fluid may lead to dehydration and hypernatremia. For this reason, isotonic fluid may not be appropriate for this specific population.[35]

Drew et al compared a series of 25 patients undergoing a pharyngeal flap to patients undergoing secondary cleft lip correction. In the pharyngoplasty group, 48% of patients had increased postoperative ADH, with 8% developing SIADH, versus none in the other group. The authors suggest that neck hyperextension may stimulate the hypotalamo-hypophysary system, possibly by an ischemic mechanism.[36] Patients undergoing palatoplasty have the same position during the surgery, suggesting that if this mechanism holds some responsibility in the development of dysnatremias, neck hyperextension should be avoided, and it may be useful to monitor cerebral perfusion by near-infrared spectroscopy.

It can also be postulated that extensive dissection along the medial pterygoid plate toward the skull base may possibly induce regional and intracranial blood flow alterations leading to dysnatremias.

The postoperative period itself puts patients at risk to develop dysnatremia. Pain, stress, nausea, and certain types of drugs, which are all present in the postoperative period, are some of the triggers of high secretion of ADH, potentially leading to SIADH and, therefore hyponatremia.

On the contrary, hypernatremia is rarely seen in recently operated patients, except in neurosurgical patients who underwent an intrasellar resection, leading to the development of an acquired diabetes insipidus.

Certain types of surgery are prone to induce postoperative dysnatremias: among neurosurgical patients, the incidence of dysnatremia varies between 12% and 50% depending on the type of neurological pathology and the type of surgery performed. This high incidence is explained by the disruption of the cerebral mechanism involved in the control of the salt-water balance. Hyponatremia is attributed to either SIADH or Salt-wasting syndrome, while hypernatremia is caused by diabetes insipidus.[8,37] More recently, Kaufman reported that half of all children undergoing cardiac surgery present postoperative dysnatremia. This higher incidence in the pediatric population compared with the adult population may be partially explained by iatrogenic interventions such as fluids and diuretic administration.[7]

Concerning cleft palates, only two cases of natremia disorder have been reported after palatoplasty.[9–11] A hypothesis suggested in the few published case reports is that in addition to risk factors related to the perioperative setting, there may be a possible link between cleft palates and midline anomalies and brain malformations. This connection could explain the susceptibility of patients with cleft palate to develop dysnatremia.

Embryological studies have already proved that the development of the brain and the face are intimately related.[38–41] Recently, a large study conducted on 5500 infants presenting cleft lip with or without cleft palate reported that nearly 30% of them had associated central nervous system anomalies.[42] Although the patterns of those cerebral anomalies are not yet known, development failures of the hypothalamo-pituitary pathway become particularly relevant when considering dysnatremia.[43] Embryological studies proved that the development of the midline structures, such as the pituitary gland and the palate, are closely related, and therefore craniofacial anomalies are frequently associated with hypothalamo-pituitary dysfunction.[44–47] Holoprosencephaly is an example of cerebral anomaly associated with craniofacial (80%) and hypothalamic/pituitary abnormalities, mainly causing diabetes insipidus (70%).[48] Diabetes insipidus is, therefore, probably secondary to a structural abnormality, leading to failure of hypothalamic function affecting osmoreception and vasopressin release.[45] Other rare cases of congenital hypothalamo-pituitary dysfunction are subtypes of SIADH called "reset osmostat," which probably result from altered hypothalamic osmoreceptors.[22,49–53]

For these reasons, patients with a cleft palate may be intrinsically at a higher risk of developing postoperative dysnatremia, favored by multiple mechanisms secondary to the operative management. Therefore, early detection of natremia variations should probably become part of the standard postoperative care.

There is currently a lack of recommendations concerning the appropriate laboratory surveillance for pediatric patients after surgery.[29,34,35] Dysnatremia is thought to appear early postoperatively, mostly 24 hours after surgery.[5] Similarly, in our study, the most extreme values of natremia were measured between 20 and 60 hours after the end of the operation. Apart from patients who were symptomatic, the other patients were not frequently monitored. Nonetheless, given the potentially fatal consequences of dysnatremia and the potentially higher risk for patients undergoing a palatoplasty to develop it, it may be reasonable to adopt systematic monitoring of natremia during the first 24 to 48 hours after this surgery.[16]

Treatment

Hypernatremia treatment relies on addressing the underlying cause (listed in Supplemental Table 4, Supplemental Digital Content 2, http://links.lww.com/SCS/E964) and correcting the serum sodium level and free water deficit. Treating the etiology may include stopping gastrointestinal or cutaneous losses, controlling fever, hyperglycemia, and glycosuria, withholding diuretics, treating other electrolyte disorders, adapting feeding formula, or in case of diabetes insipidus, replacing vasopressin.[54,55] Fluid management requires correction of the free water deficit and replacement of the ongoing losses, which can be calculated as follows (desired natremia change in mmol/l). Free water deficit (ml) = 4 ml × lean body weight (kg) × (desired natremia change in mmol/l).[3,56]

To avoid correction errors and subsequent neurological symptoms, one should aim for a natremia change of 1 mmol/h or 15 mmol/24h. In case of severe hypernatremia (Na > 170 mmol/l), the correction should not go below 150 mmol/l in the first 48 to 72 hours. It is necessary to monitor sodium levels at 1 to 4-hour intervals early in the treatment to ensure a gradual decrease of sodium level.[56] The development of seizures may be a sign of cerebral oedema due to the rapid correction of hypernatremia. Administration of hypertonic saline to slightly increase sodium concentration usually permits to slow the rate of correction and resolves the neurological symptoms.[3]

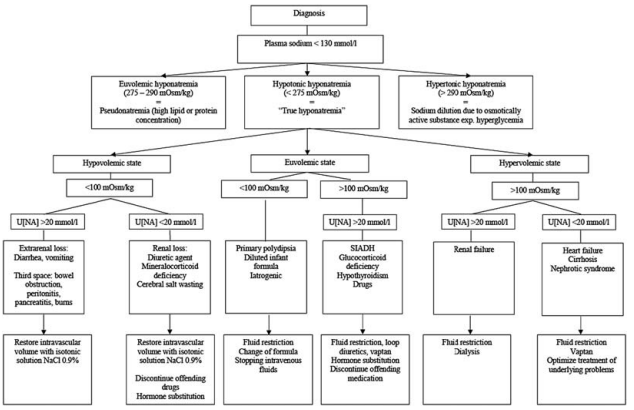

FIGURE 2. Hyponatremia treatment.

The treatment of hyponatremia requires analysis of serum osmolality, volume status, and urine osmolality.[57,58]

Measurement of serum osmolality identifies "true hyponatremia", hypotonic hyponatremia. Euvolemic hyponatremia is a pseudohyponatremia caused by a high concentration of proteins in the plasma,[3] while hypertonic hyponatremia appears in the case of hyperglycemia.[14,55]

Once hypotonic hyponatremia is confirmed, the extracellular volume status of the patient should be evaluated. Clinical history of fluid imbalance, weight changes, drugs, and underlying medical conditions and clinical examination permit to identify the etiology and type of hyponatremia (see Supplemental Table 3, Supplemental Digital Content 2, http://links.lww.com/SCS/E964).[3] In addition, assessing the urinary sodium concentration permits one to distinguish between renal (U[Na] > 20) and nonrenal causes (U[Na] <20) of hyponatremia.[14] It is the classification of the natremia that defines its treatment (Figure 2).

A patient with hypovolemic hyponatremia needs isotonic saline to replace any sodium and water deficit; this restores intravascular volume and interrupts the non-osmotic release of ADH.

A patient with hypervolemic hyponatremia presents an excess of both water and sodium. Therefore, the therapy is based on water and sodium restriction and on treatment or stabilization of the underlying diseases (eg, heart failure, chronic liver disease, or renal failure).[14,55]

In patients presenting euvolemic hypovolemia, the underlying cause should be addressed (see Supplemental Table 3, Supplemental Digital Content 2, http://links.lww.com/SCS/E964). Chronic hyponatremia due to poor solute intake should be corrected with appropriate feeding formula and restricting water intake. A patient presenting hypothyroidism or cortisol deficiency should receive appropriate hormone therapy.[58] SIADH treatment relies on treatment of the etiology and progressive correction of the serum sodium level through fluid restriction.[59]

Acute symptomatic hyponatremia should be promptly treated with the administration of hypertonic 3% saline solution (Fig. 3).[60] The rate at which hyponatremia should be corrected depends on its duration (acute or chronic) and should be adapted to avoid disastrous neurological consequences.

Acute symptomatic hyponatremia (< 48 h) can be corrected as fast as 2 mmol/l per hour until symptoms resolve.[14] Usually, symptoms improve after the administration of 4–6 mmol/kg of NaCl 3%, reversing hyponatremic encephalopathy.[55,60] For a

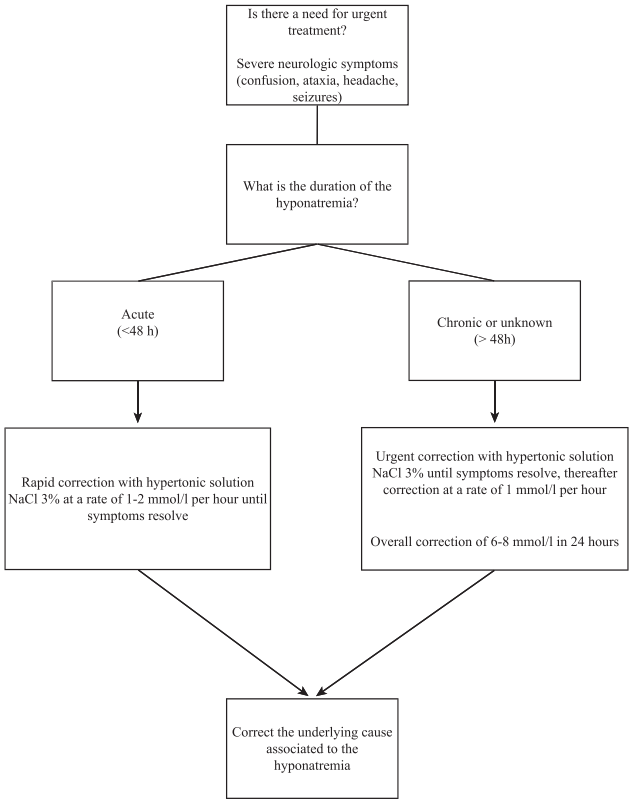

FIGURE 3. Treatment of symptomatic hyponatremia.

more aggressive therapy, boluses of NaCl 3% can be administered at a rate of 2 ml/kg to a maximum of 100 ml. One bolus results in a maximum of 2 mmol/l acute increase in natremia, which quickly reduces brain oedema. This approach has the advantage of an immediate and controlled increase in sodium levels, with little to no risk of overcorrection.[61]

Chronic hyponatremia (> 48h or duration unknown) should be corrected with caution to avoid central pontine myelinolysis. After 48 hours, brain cells lose osmolytes to maintain their volume, and therefore a rapid correction of hyponatremia can cause hypertonic stress, triggering apoptosis and eventually demyelination.[62] Up to 7 days after overcorrection, patients may present confusion, quadriplegia, pseudobulbar palsy, or even death.[61]

To prevent overcorrection, the maximal recommended rate should be 1 mmol/l/h and an overall correction of 6–8 mmol/l in 24 hours.[63]

LIMITATIONS

The findings of this study are based on a small number of patients and on retrospective data, limiting their interpretation. Furthermore, the links between cleft lip/palate and brain alterations are not yet fully understood, leaving open a vast field for research. Nonetheless, raising awareness for the higher risk of postoperative dysnatremia in children undergoing palatoplasty can help prevent serious complications.

CONCLUSION

This study suggests that children undergoing cleft palate repair may be at higher risk of developing dysnatremias due to the numerous elements that disrupt the homeostatic regulation systems postoperatively and possibly because of underlying brain anomalies. Consequently, clinical and laboratory monitoring should be an essential part of the perioperative management of these patients to recognize and treat dysnatremias quickly, avoiding neurological sequelae.

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