CASE REPORT OLGU SUNUMU

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Novel Approach to Perioperative Management of a Child with Nonketotic Hyperglycinemia

Nonketotik Hiperglisinemili Çocuk Hastanın Perioperatif Yönetimine Yeni Yaklaşımlar

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ABSTRACT Nonketotic hyperglycinemia is a rare condition that requires a specialized approach. Perioperative management remains uncertain due to both the rarity of the disease and the limited literature available. A 7-year-old girl was admitted for a surgical dental procedure. She remained fasting for 6 hours without receiving any intravenous dextrose-containing fluids. Oral dexmedetomidine at a dose of 4 mcg/kg was selected for premedication. Sevoflurane was used as the sole agent for both induction and maintenance of anesthesia. The patient awakened 20 minutes after the discontinuation of sevoflurane. In this case, we emphasize that the use of dexmedetomidine for premedication may reduce preoperative anxiety and the potential for postoperative delirium. Furthermore, preoperative glycine concentrations are likely proportional to the duration of awakening. To avoid prolonged emergence, the use of Bispectral Index monitoring is recommended. Additionally, it has been shown that preoperative fasting without intravenous fluid supplementation can be safe.

Keywords: Nonketotic hyperglycinemia; dexmedetomidine; perioperative care; pediatric anesthesia

ÖZET Nonketotik hiperglisinemi, özel yaklaşım gerektiren nadir bir durumdur. Perioperatif yönetimi hem hastalığın ender görülmesi, hem de literatür azlığından dolayı hâlâ belirsiz bir konudur. Yedi yaşında bir kız hasta cerrahi dental prosedür için başvurdu. Hastaya, intravenöz dekstroz içeren sıvılar verilmeden 6 saatlik açlık sağlandı. Premedikasyon için 4 mcg/kg oral deksmedetomidin seçildi. Anestezi indüksiyonu ve idamesinde sadece sevofluran kullanıldı. Hasta, sevofluran kesildikten 20 dk sonra uyandı. Bu olguda, deksmedetomidinin premedikasyonda kullanımı ameliyat öncesi anksiyeteyi ve postoperatif deliryum potansiyelini azalttığını vurgulamaktayız. Ayrıca preoperatif glisin konsantrasyonları muhtemelen uyanma süresi ile orantılıdır. Uyanma süresinin uzamaması için Bispektral İndeksi kullanılması önerilmektedir. Bir diğer taraftan intravenöz, sıvı takviyesi olmadan preoperatif açlığın güvenli olduğu gösterilmektedir.

Nonketotic hyperglycinemia (NKHG) is an autosomal recessive disorder caused by a defect in the glycine cleavage system, which results in accumulation of large quantities of glycine in all body tissues. Children with NKHG have the onset in the neonatal period that manifests as progressive lethargy evolving into profound coma.[1]

CASE REPORT

A female, 7 years old, admitted for dental procedure. She achieved her diagnosis at neonatal period. She stayed 3 weeks under close observation for respiratory impairment. At discharge, a diet, with close calculation of carbohydrate and protein amounts, was

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prescribed. She was started on sodium benzoate and dextromethorphan. Seizure activity was last recorded at the age of 7 months. Clobazam was discontinued at the age of 6 years. Developmental delay with mental retardation and hyperactivity attention deficit disorder were present. After detailed explanation of planned approach, a written consent was obtained from both parents.

The patient stayed null peros for 6 hours. Sodium benzoate and dextromethorphane were continued. Pediatric Sedation Agitation Scale measurements prior to premedication were recorded as "very agitated" and the patient didn't calm in spite of reassurance. 4 mcg/kg dexmedetomidine was administered peros for premedication. No bradycardia or hypotension were recorded. 30 minutes after premedication, Pediatric Sedation Agitation Score was recorded as "agitated" (the patient anxious, but easily calmed by verbal reassurance). The separation from parents was unproblematic and Parental Separation Scale was recorded as "excellent".

In this exclusive case, anesthesia team decided to escape multidrug administration and hypnotics, opioids and muscle relaxants were sparred. Appropriate deep sevoflurane induction and its central myorelaxative effect promoted to successful nasotracheal intubation. Anesthesia maintenance was provided by sevoflurane with low fresh gas flow of 0.8 lpm and remifentanyl infusion of 2,5 mcg/min. Mechanical ventilation properties were as follows: Fio2=50%, Peep=0 mmHg Peak pressure=14 mmHg, Respiratory rate=17/min. Venous blood gas analysis, revealed no metabolic issue (Figure 1).

The operative manipulation lasted for 45 minutes with average sevoflurane Minimum alveolar concentration (MAC)=0.9. The volatile anesthetic was switched off at MAC=0.2 and it took 20 minutes, while the patient sustained her spontaneous breathing. Pediatric Sedation Agitation Scale at arousal was recorded as "very sedated" (the patient moved extremities in response to physical stimuli, but did not awake or sustain eye contact). This score, reevaluated at the time point of patient discharge from postoperative unit, was recorded as calm and cooperative. No combative behavior or agitation were recorded.

ACID/BASE	37.0 °C	
pH	7.430	
pCO_2	43.3	mmHg
pO_2	41.8↓	mmHg
HCO_3^-act	28.1	mmol/L
HCO_3^-std	27.0	mmol/L
BE(B)	3.3	mmol/L
BE(ecf)	3.8	mmol/L
$ctCO_2$	29.4	mmol/L
CO-OXIMETRY		
Hct	38	%
tHb	12.8	g/dL
sO_2	75.7	%
FO_2Hb	75.1↓	%
FCOHb	0.6	%
FMetHb	0.2	%
FHHb	24.1↑	%
nBili	<2	mg/dL
OXYGEN STATUS	37.0 °C	
BO_2	17.6	mL/dL
p50	27.9	mmHg
$ctO_2(a)$	13.5	mL/dL
ELECTROLYTES		
Na^+	141.0	mmol/L
K^+	4.79	mmol/L
Ca^{++}	0.99↓	mmol/L
$Ca^{++}(7.4)$	1.00	mmol/L
Cl^-	103	mmol/L
AnGap	14.7	mmol/L
METABOLITES		
Glu	104	mg/dL
Lac	1.58	mmol/L
pAtm	752	mmHg

PATIENT RANGES	
pH	7.370 – 7.450
pCO_2	35.0 – 46.0
pO_2	70.0 – 100.0
Na^+	135.0 – 145.0
K^+	3.60 – 4.80
Ca^{++}	1.15 – 1.35
Cl^-	95 – 105
Glu	70 – 115
Lac	0.00 – 2.00
tHb	12.0 – 18.0
FO_2Hb	95.0 – 100.0
FCOHb	0.0 – 2.0
FMetHb	0.0 – 2.0
FHHb	0.0 – 5.0
nBili	0.0 – 16.0

↓,↑=out of range

FIGURE 1: Venous blood gas analysis

No respiratory complications and mechanical ventilation support was required.

DISCUSSION

Although glycine is primarily an inhibitory neurotransmitter, it also acts as a co-agonist with glutamate for N-methyl D-aspartate receptor. The inhibitory effects of glycine are prominent in spinal cord, brainstem and retina. The action mechanism includes postsynaptic hyperpolarization of intrinsic dorsal horn neurons that transmit nociceptive information via spinothalamic pathways. On the other hand, NMDA co-agonistic behavior of glycine in cerebral cortex, cerebellum and hippocampus, results in over triggering of neurons in these areas. Clinically, this results in hyperactivity, excitability and seizures. In our case, proper treatment with clobazam, sodium

benzoate, strict diet and dexmetromethorphane promptly restored clinical stability. Although there is a very scarce literature, reflecting the anesthetic management of such a rare condition, several outcomes, we supervised during the perioperative period, gain special importance.

Firstly, we didn't support the patient with intravenous dextrose infusion during the fasting period. It is well-known, that hypoglycemia is not a central feature of NKHG, but these children usually lack necessary glycogen stores due to feeding difficulties and poor energy uptake. Preoperative fasting is the period, when the body relies on glycogen and fat stores to produce glucose. Theoretically, hypoglycemia is unanticipated (as no metabolic pathway of glucose synthesis is affected) in patients with NKHG. Although, if the glycogen and fat stores are severely reduced, the patient may become hypoglycemic due to fast exhaustion of reserves. Generally, practitioners prefer glucose containing additives for every patient with metabolic disease, even if insufficient research is available upon preoperative fasting protocols for patients with this rare condition. Absence of supportive dextrose solution did not affect the amounts of glucose in blood, as was noted by blood gas analysis. Therefore, we suppose that no supportive intravenous therapy is needed and fasting for 6 hours doesn't interfere with metabolic state.

Secondly, we premedicated the patient with dexmedetomidine. The reason for this preference is complete sparing of central nervous system receptors, sensitive to glycine. Barker and Jefferson suggest ketamine as an effective drug both for premedication and for anesthesia induction.[1] However, preoperative levels of plasma and cerebrospinal fluid glycine may be crucial. Too high basal glycine levels may lead to resistance to ketamine and benzodiazepines. No case of patient with hyperglycinemia, premedicated with ketamine or benzodiazepines is present in literature. Possibly, it is should be tenable to measure glycine levels at least in the plasma, before planning premedication method. Unfortunately, literature doesn't cover the recommendations for preoperative glycine levels. In our case, the patient's plasma glycine concentration was 587 μmol/l. This value is slightly above the upper limit, so we couldn't anticipate, if ketamine or benzodiazepine premedication would be effective. With dexmedetomidine, we witnessed smooth separation from parents and absence of emergence delirium.

Another notable perioperative issue for patients with NKHG is the delayed emergence.[3,4] Liu and Fan reported a case of 3-year-old boy, undergoing bronchoscopy under sevoflurane anesthesia.[3] Awakening and return of spontaneous respiration lasted for 45 minutes. Factors that prolong emergence from general anesthesia include non-depolarizing muscular blockers, premedication agents and hypothermia. Though none of these were carried out, delayed recovery was linked to interference between glycine and trace anesthetics. Thereby, the concentration of glycine may be proportional to the duration of awakening.[5]

Another case, conducted by Allee and Tobias, represents a 4-year-old boy with glycine encephalopathy, admitted for adenoidectomy and tonsillectomy.[6] The authors planned anesthetic management without premedication. They inducted anesthesia with propofol and cis-atracurium and maintained with remifentanyl and nitrous oxide. Awakening lasted for 10 minutes after discontinuation of remifentanyl and nitrous oxide. The patient had basal awake [Bispectral Index (BIS)] of 41. Consequently, effects of residual concentrations of long-acting anesthetic agents would possibly prolong the emergence period.

The anesthetic management of a patient with NKGH is still a complex and not well studied issue for practitioners. We hope our case report may serve as a beneficial supplement to what was experienced previously.

We recommend BIS monitor for MAC titration. Premedication with dexmedetomidine-possibly reduces postoperative emergence agitation and assists smooth separation from the parents. Still its efficacy in NKGH population should be supported by research.

We consider that glycine concentration is proportional to patient's response to premedication and the duration of awakening.

Safety of 6 hour preoperative fasting, without dextrose-containing intravenous additives, was also

witnessed and strengthens the data, proposed in previous case discussions.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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