

# An unusual case of oral surgical management in a patient with isovaleric acidemia and schizophrenia: A case report

SHO MIYAMOTO<sup>1</sup>, EDWARD HOSEA NTEGE<sup>1,2</sup>, YASUTSUGU CHINEN<sup>3</sup>, TAKAHIRO GOTO<sup>1</sup>,  
JUMPEI SHIRAKAWA<sup>1</sup>, SHIMPEI GOTO<sup>1</sup>, TOSHIHIRO KAWANO<sup>1</sup>, YUSUKE SHIMIZU<sup>2</sup>,  
KOICHI NAKANISHI<sup>3</sup> and HIROYUKI NAKAMURA<sup>1</sup>

Departments of <sup>1</sup>Oral and Maxillofacial Functional Rehabilitation, <sup>2</sup>Plastic and Reconstructive Surgery, and  
<sup>3</sup>Child Health and Welfare (Pediatrics), Graduate School of Medicine, University of the Ryukyus,  
Nishihara, Okinawa 903-0215, Japan

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**Abstract.** Oral/dental surgical care in patients with chronic medical comorbidities, such as isovaleric acidemia (IVA), can be challenging. In addition to technical complications, different comorbidities also present a complex range of concerning factors/challenges, which can increase the incidence of morbidity and mortality associated with surgery. IVA, a congenital error of metabolism, is a rare organic acidemia with a predisposition towards acute acidosis and life-threatening metabolic decompensation during stressful conditions, such as prolonged fasting and surgery. In addition, schizophrenia, a major neurological disorder, can result in manifestation of severe dental or periodontal conditions, including pericoronitis. The condition is associated with significant risk factors of postoperative complications, such as dangerous behaviors and adverse interactions between antipsychotic drugs and anesthetic agents. A case of comorbid dental disease with two coexisting chronic and life-threatening medical conditions, one of which is rare, is an unusual encounter in oral/dental surgery that is seldomly published. Moreover, implementing a safe and effective surgical intervention in such patients requires several informed considerations. However, only a few reported experiences or guidelines exist, reporting appropriate

perioperative management strategies to minimize risks. Hence, in this case report, our experience of managing one of these rare encounters of a 20-year-old man who suffered from bilaterally partially erupted third molars, associated with chronic pericoronitis and dental caries of both the maxilla wisdom teeth with coexisting IVA and schizophrenia comorbidities is described. Additionally, the presentation and anticipated complications of the comorbid disorders of the patient are briefly reviewed. In this case, the pericoronitis and dental caries were treated by surgically removing the impacted third molars and the antagonist maxilla wisdom teeth under regional anesthesia and application of antibiotics for 3 days. The patient recovered without any postoperative complications after 1 year of follow-up.

## Introduction

Pericoronitis is the inflammation of soft tissues around the crown of an erupting or partially erupted tooth (1-3). Based on the published guidelines for chronic pericoronitis treatment and prevention of chronic or acute exacerbation (1,4), surgery and the application of antimicrobial agents are recommended as the most appropriate interventions. Furthermore, the health status of the patient should be considered during the evaluation. For example, removing an impacted third molar helps reduce pain and other symptoms, and improves oral health and function for patients (5,6). However, information remains limited regarding considerations for the safe and effective implementation of oral/dental surgical interventions in patients with chronic medical comorbidities, such as schizophrenia and isovaleric acidemia (IVA).

Schizophrenia, recently renamed integration dysregulation syndrome in Japan (*togo-shitcho-sho*) (7), is a severe mental disorder resulting from an interplay of multiple factors, including genetic causes, and several environmental and psychosocial factors. The disease is a public health problem, which affects ~24 million people or 1 in 300 people (0.32%) worldwide and is associated with significant morbidity and premature mortality in individuals between the ages of 10 and 20 years old (8,9). It has been reported that patients with schizophrenia present profound alterations in thought,

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*Correspondence to:* Dr Sho Miyamoto, Department of Oral and Maxillofacial Functional Rehabilitation, Graduate School of Medicine, University of the Ryukyus, 207 Uehara, Nakagami, Nishihara, Okinawa 903-0215, Japan  
E-mail: miya-sho@med.u-ryukyu.ac.jp

*Abbreviations:* IVA, isovaleric acidemia; IVD, isovaleryl-CoA dehydrogenase; CBCT, cone-beam computed tomography; ECG, Electrocardiography; LAST, local anesthetic systemic toxicity; MIM, Mendelian inheritance in man; GC/MS, gas chromatography/mass spectrometry; GA, general anesthesia; RA, regional anesthesia

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language, perception and sense of self, with impaired social and occupational functioning (9). The manifestation and progression of symptoms also vary between individuals (10). Additionally, it has several subtypes, including paranoid, catatonic, disorganized and undifferentiated (9), diagnosed through the primary presenting symptoms. These symptoms are classified into three main categories: i) Positive symptoms, including delusions, hallucinations, disordered thoughts and behavior; ii) negative symptoms, such as apathy, social withdrawal and blunted effects; and iii) cognitive symptoms, such as impairment of attention, information processing and memory (1,11). Furthermore, schizophrenia can result in severe dental and periodontal diseases, including chronic pericoronitis requiring surgery. In addition, the management of comorbid dental diseases is associated with several challenges, especially anesthesia-related complications during surgery. Such challenges include the coexistence of physical illnesses, dangerous behaviors and serious side effects from drug interactions between antipsychotic and anesthetic agents (12,13).

IVA (MIM #243500) is a rare autosomal recessive congenital metabolic disorder categorized as organic acidemia (14). Homozygous mutations cause IVA in the isovaleryl-CoA dehydrogenase gene (IVD; MIM #607036) on chromosome 15q14-15 (14). Furthermore, IVA is relatively uncommon, with a frequency of 1:250,000, 1:365,000 and 1:62,500 births in the United States, Taiwan and Germany, respectively (15,16). IVA disorder results from an accumulation of isovaleric acid in the body, which is toxic to the central nervous system (17). During IVA crises, detoxification is achieved through alternative pathways that produce isovaleryl glycine, 3-hydroxyisovaleric acid and other metabolites excreted via the urinary system. Gas chromatography/mass spectrometry (GC/MS) is the ideal means of identifying the organic acidemia metabolites (18,19). IVA exists in two forms: The acute neonatal form, which leads to substantial metabolic acidosis from the first days of life, and results in an individual succumbing to the disease fairly rapidly (20), and a chronic state in which severe ketoacidosis occurs intermittently in older age groups (14). In both IVA forms, acute episodes of metabolic decompensation can appear during catabolic states due to impaired protein and fatty acid metabolism, infection, fasting and other physiological stresses (21,22). Patients with IVA requiring surgery also present various challenges to the choice of anesthesia, as certain anesthetics can trigger metabolic crises, including poor nutrition, electrolyte imbalance, prolonged periods of fasting and other forms of stress (23). Despite various studies on IVA, there are few reports on its perioperative management. Moreover, there are no reports on adult surgery in patients with IVA, to the best of our knowledge.

Through careful perioperative evaluation and management strategies, significant challenges to dental surgery in patients with coexisting comorbidities, such as schizophrenia and IVA, can be minimized (1). The present case report describes the unusual encounter and management of a 20-year-old man suffering from bilaterally and partially erupted third molar associated with chronic pericoronitis and dental caries of the maxilla wisdom teeth with coexisting schizophrenia and IVA. The pericoronitis was treated through surgical removal of the third molar and the antagonistic maxilla wisdom teeth under

regional anesthesia. The patient recovered well without any reported complications after 1 year of follow-up.

## Case report

*Patient information.* A 20-year-old Japanese male patient was referred to the Oral and Maxillofacial Department at Ryukyu University Hospital in December 2020, with a history of bilateral chronic pericoronitis. The patient was previously diagnosed with IVA at the age of 5 years and 6 months old, as reported by his accompanying mother - the next of kin. He had repeated fever, anemia, vomiting and thrombocytopenia since the neonatal stage. GC/MS was performed since the symptoms persisted, including vomiting, the distinct odor of sweaty feet and general malaise, which were indicated by isovaleryl glycine (114.7 ratio/mg; creatinine > undetected), 3-hydroxy-isovaleric acid (20.7 ratio/mg; creatinine >0.72), 4-hydroxy-isovaleric acid, 2-methyl succinic acid and 2-methyl fumaric acid levels in the patient's urine specimen. Furthermore, the patient was under treatment for undifferentiated schizophrenia disorder, diagnosed in May 2020 at the Psychiatry Department of Ryukyu University Hospital. The treatment for IVA included L-aspartate Ca (one tablet, every 8 h daily), levocarnitine 250 mg (twice daily with meals) and glycine 6.5 g daily. Additionally, the treatment for schizophrenia was a second-generation antipsychotic drug, Zyprexa (olanzapine) 10 mg, one tablet a day. He had neither history of smoking nor drug addiction, no family history of congenital anomalies and denied having any allergies. On examination, although slightly nervous and anxious, he was not agitated, uncooperative, or violent when approached by the healthcare providers. Moreover, he was in good general condition, with no pallor, oedema, jaundice, cervical or generalized lymphadenopathy. His systemic examinations were also within normal limits. Nevertheless, intraoral investigations revealed incomplete eruption of the mandible wisdom teeth (also referred to as mandibular or lower third molars) bilaterally with only a part of the tooth's crown exposed in the oral cavity (Fig. 1). The operculum, the soft tissue covering the partially visible crowns, also appeared slightly inflamed. Additionally, we observed dental caries affecting the fully erupted maxilla wisdom teeth bilaterally.

*Investigations.* Panoramic radiographic examination and cone-beam computed tomography revealed that both lower third molars had incomplete root development and were close to the mandibular canal without bone involvement (Figs. 2 and 3). Alternatively, electrocardiography (ECG) and echocardiogram did not indicate any abnormalities. The blood biochemistry hematology results are shown in Table I. As shown, no abnormalities were observed in blood cells, renal function, and liver function. Although some amino acid values were slightly outside of reference values, a correction was not necessary.

*Treatment and follow-up.* Considering published reports (1,4), the appropriate treatment/prevention strategy for comorbid dental diseases in IVA and schizophrenia diagnosis was surgery and antibiotic administration. Notably, the patient and his next of kin also preferred surgery under general anesthesia (GA). However, considering his medical history, the following

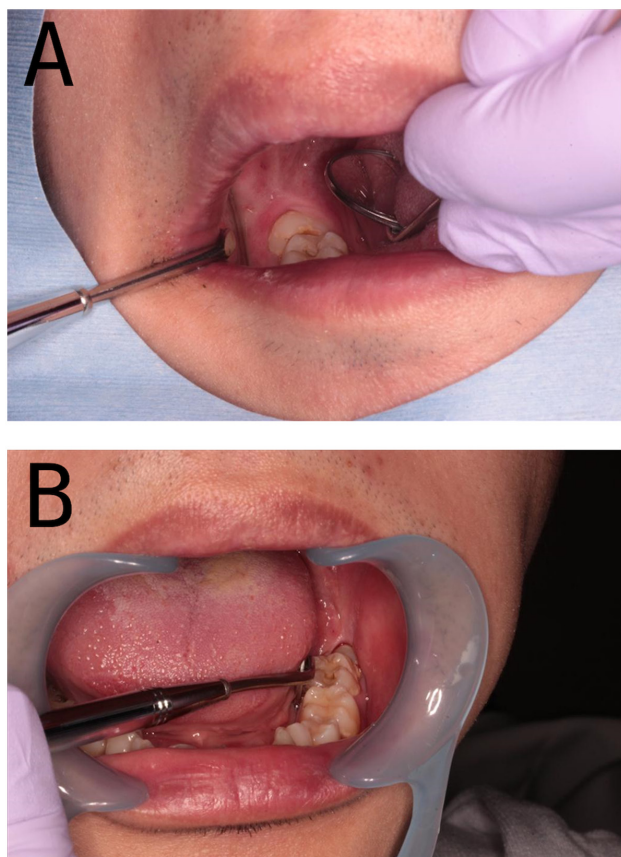


Figure 1. Preoperative intraoral view of the mandible. (A) Right wisdom teeth were horizontally impacted, and only a part of the crown was exposed; (B) Left wisdom teeth were horizontally impacted and only a part of the crown was exposed.

perioperative management strategies were implemented to minimize the risk factors of complications: i) The surgical team chose regional anesthesia (RA) to avoid IVA crises of disordered metabolism, including glucose disturbances, hyperammonemia, hypocalcemia and non-anion gap metabolic acidosis due to GA-associated prolonged fasting, poor nutrition, electrolyte imbalance and other physiological stresses; ii) 3% mepivacaine, and not bupivacaine or lidocaine, was selected as the preferred drug for RA to reduce the risk of developing local anesthetic systemic toxicity (LAST) based on the report of a patient having a reduced threshold for developing malignant dysrhythmias due to IVA-associated carnitine deficiency (24,25); iii) since IVA can cause bone marrow suppression during crises, postoperative infection was considered a risk factor for IVA crises. Therefore, although bone marrow suppression was not observed in blood biochemistry hematology results, we planned to adequately prevent infection with antibacterial agents before and after surgery (21,22); iv) antibiotics other than pivalate-containing medications were used as IVA raises acylcarnitine levels, and antibiotics containing pivalate already have the possibility of increasing acylcarnitine levels (26); v) tooth extraction was conducted in stages to avoid trismus related to removing all four teeth immediately and seizures of IVA crisis due to poor eating; vi) the patient was managed as an outpatient to reduce psychological stress related to the coexisting pandemic restrictions for preventing coronavirus disease-2019 caused by severe



Figure 2. Preoperative panoramic radiographic examination findings. Bilateral maxillary wisdom distally had erupted, and bilateral mandibular wisdom was horizontally impacted. L, left; R, right.

acute respiratory syndrome coronavirus 2; and vii) although investigations revealed normal ECG and echocardiogram findings, the continuation of antipsychotic therapy, olanzapine, was evaluated in consultation with the attending psychiatrist to avoid side effects of drug interactions. The first stage involved removing the right mandibular wisdom tooth, the second stage involved removing the left mandibular wisdom tooth and the third stage involved removing the bilateral maxilla wisdom teeth. During and shortly after surgery, all the patient's vitals, including his level of consciousness, pulse rate, percutaneous oxygen saturation and blood pressure, were regularly monitored. To further reduce psychological stress, the patient's favorite music was played. Infection prevention involved 1,000 mg cefazolin sodium, administered intravenously 30 min before the operation and oral amoxicillin (250 mg) every 8 h for 3 days after the operation.

Tooth extraction was performed as previously described (27). A minimum of two ampoules of 3% mepivacaine was used for each extraction stage. Then, the gingiva was incised with a scalpel to show the alveolar bone clearly. Next, we split a portion of the mandibular bone around the exposed crown to extract the tooth by dividing the crown and root. The incised soft tissue part was subsequently closed with a suture. Finally, the maxilla wisdom teeth were extracted with an elevator. Skilled oral surgeons performed the surgery to shorten the operation time. Therefore, we completed all three different stages of the operation within 30 min. Hemostasis was also confirmed 30 min after surgery. Upon completing each surgical procedure, the patient was instructed to avoid strenuous exercise, drinking alcohol and long baths for a week. Pain medication, which included 60 mg of loxoprofen sodium hydrate every 8 h for 7 days, was also prescribed. However, no specific dietary restrictions were applied.

Follow-up of the patient was done a day after surgery and 7 days later. We physically examined the patient during the scheduled 7th-day visit and removed the sutures simultaneously. The patient recovered well after surgery without prolonged pain, infection or loss of neurological function (Fig. 4) and he remained symptom-free after 1 year of follow-up.

## Discussion

The past several decades have shown growing interest in managing oral/dental diseases in patients with comorbid

Table I. Preoperative hematology and biochemistry laboratory test results.

Analyte	Patient results	Reference intervals	Units	Notes
White blood cell count	6.7	3.3-8.6	$\times 10^3/\mu\text{l}$	-
Neutrophils	44.1	40.0-71.0	%	-
Lymphocytes	41.2	26.0-46.0	%	-
Monocytes	9.4	2.0-7.0	%	High
Eosinophils	4.6	0.0-6.0	%	-
Basophils	0.7	0.0-1.0	%	-
Red blood cell count	5.03	4.35-5.55	$\times 10^6/\mu\text{l}$	-
Hemoglobin	15.5	13.7-16.8	g/dl	-
Biochemistry				-
Blood urea nitrogen	10	8.0-20.0	mg/dl	-
Serum creatinine	0.72	0.65-1.07	mg/dl	-
Estimated glomerular filtration rate	117.6			-
Total bilirubin	0.7	0.4-1.5	mg/dl	-
Aspartate aminotransferase	25	13-30	U/l	-
Alanine aminotransferase	41	10-42	U/l	-
$\gamma$ -glutamyl transferase	13	13-64	U/l	-
Taurine	37.9	39.5-93.2	nmol/ml	Low
Aspartic acid	2.7	<2.4	nmol/ml	High
Hydroxyproline	15.3	<21.6	nmol/ml	-
Threonine	108.5	66.5-188.9	nmol/ml	-
Serine	108.2	72.4-164.5	nmol/ml	-
Asparagine	37.0	44.7-96.8	nmol/ml	Low
Glutamic acid	31.0	12.6-62.5	nmol/ml	-
Glutamine	477.9	422.1-703.8	nmol/ml	-
Sarcosine	TR	TR	nmol/ml	-
$\alpha$ -Amino adipic acid	ND	ND	nmol/ml	-
Proline	225.9	78.8-272.7	nmol/ml	-
Glycine	324.0	151.0-351.0	nmol/ml	-
Alanine	348.7	208.7-522.7	nmol/ml	-
Citrulline	29.7	17.1-42.6	nmol/ml	-
$\alpha$ -Aminobutyric acid	11.6	7.9-26.6	nmol/ml	-
Valine	259.4	147.8-307.0	nmol/ml	-
Cystine	10.6	13.7-28.3	nmol/ml	Low
Cystathionine	ND	TR	nmol/ml	-
Methionine	20.7	18.9-40.5	nmol/ml	-
Isoleucine	96.8	43.0-112.8	nmol/ml	-
Leucine	147.4	76.6-171.3	nmol/ml	-
Tyrosine	58.4	40.4-90.3	nmol/ml	-
Phenylalanine	58.1	42.6-75.7	nmol/ml	-
$\gamma$ -Amino $\beta$ -hydroxybutyric acid	ND	ND	nmol/ml	-
$\beta$ -Alanine	3.9	TR	nmol/ml	-
$\beta$ -Amino-iso-butyric acid	ND	TR	nmol/ml	-
$\gamma$ -Aminobutyric acid	ND	ND	nmol/ml	-
Monoethanolamine	9.4	<10.4	nmol/ml	-
Homocysteine	ND	ND	nmol/ml	-
Histidine	90.1	59.0-92.0	nmol/ml	-
3-Methylhistidine	4.0	<5.0	nmol/ml	-
1-Metnylhistidine	TR	<18.5	nmol/ml	-
Carnosine	ND	ND	nmol/ml	-
Anserine	ND	ND	nmol/ml	-
Tryptophan	54.8	37.0-74.9	nmol/ml	-
Hydroxylysine	ND	ND	nmol/ml	-

Table I. Continued.

Analyte	Patient results	Reference intervals	Units	Notes
Ornithine	56.9	31.3-104.7	nmol/ml	-
Lysine	177.3	108.7-242.2	nmol/ml	-
Arginine	96.4	53.6-133.6	nmol/ml	-

ND, not detected; TR, trace.

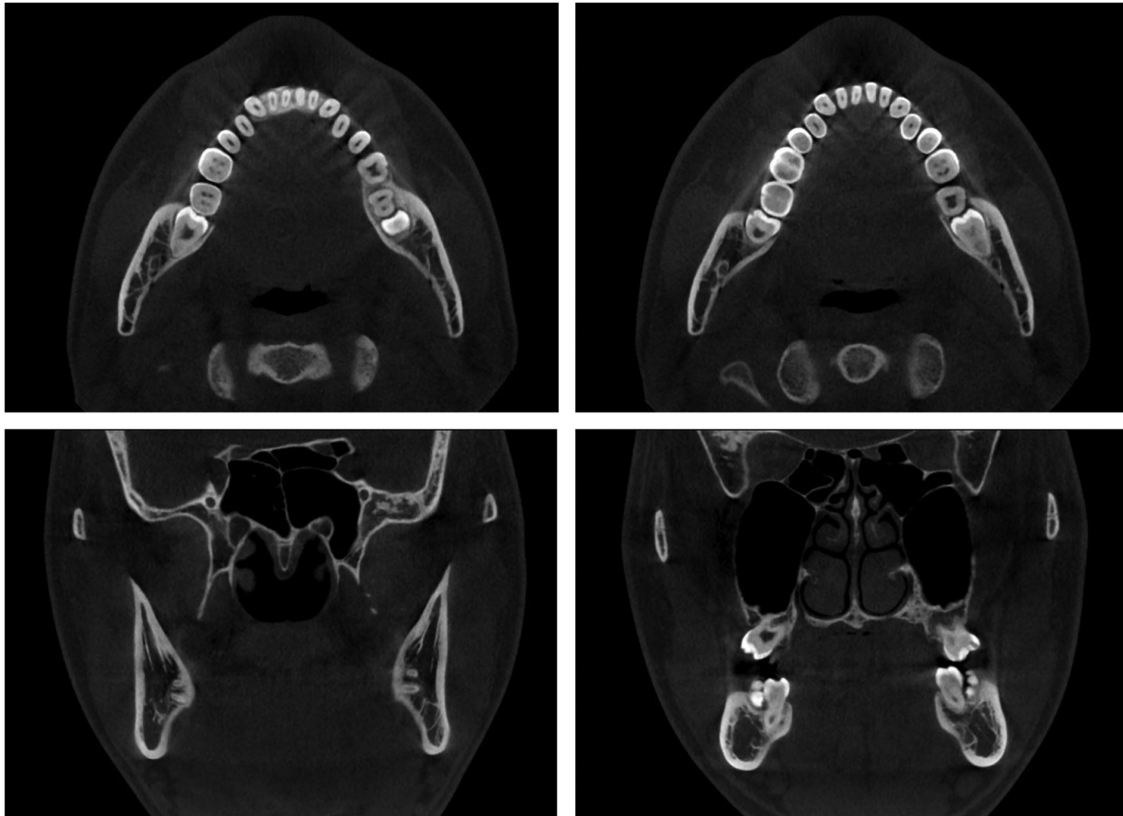


Figure 3. Cone-beam computed tomography image. Bilateral mandibular wisdom teeth were close to the mandibular canal. The growth of the root of all wisdom teeth was incomplete.



Figure 4. Postoperative panoramic radiographic examination, indicating successful removal of the lower third molar and antagonistic maxilla wisdom teeth. L, left; R, right.

mental and/or somatic disorders (28-30). However, the practice of safe and effective oral/dental medicine in patients

with chronic and rare medical comorbidities remains challenging. This case report describes a patient who suffered chronic pericoronitis associated with bilateral lower third molar impaction and dental caries in the antagonistic maxilla wisdom teeth amid a coexistence of two medical conditions: Schizophrenia and a rare congenital error of metabolism, IVA. These comorbid dental diseases, coupled with two chronic and life-threatening medical conditions, one of which is rare, is an unusual encounter in dental surgery that is seldomly published. Nevertheless, the case considers careful perioperative management strategies despite the limited number of published guidelines or information on the subject.

Schizophrenia is a complex, multifactorial disorder with varying clinical presentations and progression of symptoms in different individuals (10). Therefore, the disease has several subtypes, including the undifferentiated subtype diagnosed in this patient. However, the patient appeared stabilized with prescribed antipsychotic agents, given the relative calmness

and cooperation exhibited in each of the three stages of the surgical intervention. Second-generation antipsychotic agents for management of schizophrenia, such as olanzapine, can affect several receptor sites, including histamine, serotonin, acetylcholine,  $\alpha$ -adrenergic and dopaminergic receptors. They also cause blurred vision, constipation, dry mouth, urinary retention, sedation, hypotension and extrapyramidal movements. Furthermore, the preoperative use of antipsychotics makes schizophrenic patients more susceptible to the hypotensive action of GA (13). However, discontinuing antipsychotics can increase psychotic symptoms, such as hallucinations and agitation. Therefore, patients with chronic schizophrenia should continue their antipsychotics pre-operatively, as abrupt withdrawal may cause psychotic symptom recurrence (31). Here, although the choice of RA was the most appropriate approach for the surgical removal of the impacted third molars and the antagonist maxilla wisdom teeth in this case, regular consultations with the attending psychiatrist revealed that the patient was on glycine treatment; whose short-lasting impact on serotonin levels can reduce the side effects of the second-generation antipsychotic drugs. Therefore, there was no need to discontinue antipsychotics in the perioperative period.

Additionally, the patient had a congenital error of metabolism, an organic acidemia of the IVA type. Patients with IVA can successfully be treated with GA using agents like sevoflurane, nitrous oxide, thiopental, fentanyl, desflurane, nitrous oxide and vecuronium (23). However, reported incidences of development of ventricular tachycardia shortly after bupivacaine and epinephrine injection (25), and cardiac arrest following the use of lidocaine as an RA agent have also been reported (24). Similarly, a report of a patient having a reduced threshold for developing malignant dysrhythmias due to IVA-associated carnitine deficiency has been described (25). Moreover, patients with IVA are at risk of acute acidosis and metabolic decompensation, largely due to intercurrent illnesses or other physiological stresses, including fasting (21,22). Furthermore, IVA is a disease that raises acylcarnitine levels (32). Therefore, avoiding antibiotics containing pivalate, which can increase acylcarnitine levels is recommended (26). It has also been reported that pancytopenia, isolated neutropenia and thrombocytopenia can occur due to bone marrow suppression (33).

For the above reasons, it is paramount that patients with IVA are subjected to a detailed management action plan that can effectively reduce the risks of complications of surgery. Here the patient requested surgery to be performed under GA. However, prolonged fasting before GA poses a high risk of acute acidosis and life-threatening metabolic decompensation. Hence, surgery was performed under RA instead. Furthermore, the extraction of multiple highly invasive wisdom teeth at once would have resulted in deficient nutrient intake due to trismus and bleeding. Therefore, surgery was divided into three stages to avoid stress and dietary problems. When selecting local anesthetics, bupivacaine and lidocaine were not considered to prevent the risk of the development of LAST, which can trigger an IVA crisis (34). Moreover, the use of olanzapine for schizophrenia also contraindicated adrenaline-containing lidocaine as an RA agent (35). Hence, 3% mepivacaine was chosen as a local anesthetic instead due

to its superior anesthetic effect and limited probability of severe side effects. Similarly, although bone marrow suppression was not observed in blood sampling, adequate plans were made to prevent infection using broad-spectrum antibacterial agents. Furthermore, while avoiding pivalate-containing options, antibiotics comprised of intravenous cefazolin sodium (1,000 mg) 30 min before the operation and oral amoxicillin were administered 3 days after the procedure. Finally, efforts were made to minimize psychological and other stresses due to surgery. First, the surgery was performed while playing the patient's favorite music and taking breaks from time to time. Secondly, all operations were performed by experienced dentists familiar with oral surgery to shorten the operational time, and finally the operating procedure was divided into three stages.

Here, the unusual case of successful oral surgical treatment in a patient with two coexisting chronic medical conditions is described. The surgical management of comorbid dental diseases in mental and metabolic disorders is associated with an increased risk of postoperative complications. However, safe and effective treatment is achievable with careful perioperative considerations, as highlighted above.

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#### **Availability of data and materials**

The datasets used and/or analyzed for the case report are available from the corresponding author on reasonable request.

#### **Authors' contributions**

SM and EHN contributed to the drafting of the manuscript. SM, EHN, YC, TG and KN performed the literature search. SM, EHN, TG, JS, SG, TK and HN collected the data and assisted in drafting the case report section. SM was the primary surgeon. SM, EHN, YS, KN and HN critically revised the manuscript. All authors have read and approved the final manuscript. All authors confirm the authenticity of all raw data.

#### **Ethics approval and consent to participate**

Not applicable.

#### **Patient consent for publication**

Written informed consent was obtained from the patient for both the surgical treatment and publication of any accompanying images.

#### **Competing interests**

The authors declare that they have no competing interests.



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