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Von Hippel-Lindau disease

Zhu-Tokita-Takenouchi-Kim syndrome

orphananesthesia

a project of the German Society
of Anaesthesiology and Intensive Care Medicine

SUPPLEMENT NR. 12 | 2023

OrphanAnesthesia –
ein krankheitsübergreifendes Projekt des Wissenschaftlichen Arbeitskreises Kinderanästhesie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

Ziel des Projektes ist die Veröffentlichung von Handlungsempfehlungen zur anästhesiologischen Betreuung von Patientinnen und Patienten mit seltenen Erkrankungen. Damit will OrphanAnesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patientinnen und Patienten mit seltenen Erkrankungen benötigen für verschiedene diagnostische oder therapeutische Prozeduren eine anästhesiologische Betreuung, die mit einem erhöhten Risiko für anästhesieassoziierte Komplikationen einhergehen. Weil diese Erkrankungen selten auftreten, können Anästhesistinnen und Anästhesisten damit keine Erfahrungen gesammelt haben, sodass für die Planung der Narkose die Einholung weiterer Information unerlässlich ist. Durch vorhandene spezifische Informationen kann die Inzidenz von mit der Narkose assoziierten Komplikationen gesenkt werden. Zur Verfügung stehendes Wissen schafft Sicherheit im Prozess der Patientenversorgung.

Die Handlungsempfehlungen von OrphanAnesthesia sind standardisiert und durchlaufen nach ihrer Erstellung einen Peer-Review-Prozess, an dem eine Anästhesistin bzw. ein Anästhesist sowie eine weitere Krankheitsexpertin bzw. ein weiterer Krankheitsexperte (z. B. Pädiaterin bzw. Pädiater oder Neurologin bzw. Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, sodass die Handlungsempfehlungen grundsätzlich in englischer Sprache veröffentlicht werden.

Ab Heft 5/2014 werden im monatlichen Rhythmus je zwei Handlungsempfehlungen als Supplement der A&I unter www.ai-online.info veröffentlicht. Als Bestandteil der A&I sind die Handlungsempfehlungen damit auch zitierfähig. Sonderdrucke können gegen Entgelt bestellt werden.

Bisher in A&I publizierte Handlungsempfehlungen finden Sie unter:

www.ai-online.info/Orphsuppl
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OrphanAnesthesia –
a project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine

The target of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases in order to improve patients' safety. When it comes to the management of patients with rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists making it available for physicians worldwide free of charge.

All OrphanAnesthesia recommendations are standardized and need to pass a peer review process. They are being reviewed by at least one anaesthesiologist and another disease expert (e.g. paediatrician or neurologist) involved in the treatment of this group of patients.

The project OrphanAnesthesia is internationally oriented. Thus all recommendations will be published in English.

Starting with issue 5/2014, we'll publish the OrphanAnesthesia recommenations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via www.ai-online.info. As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

Find a survey of the recommendations published until now on:

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orphananesthesia

Anaesthesia recommendations for

Zhu-Tokita-Takenouchi-Kim syndrome

Disease name: Zhu-Tokita-Takenouchi-Kim syndrome

ICD 10: Q87.8

Synonyms: ZTTK syndrome

Disease summary: Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome is a rare multi-organ disease. First cases were mentioned in 2015. This syndrome is typically inherited in an autosomal dominant manner (typically de novo) and is caused by heterozygous mutations in the SON gene (21q22.11). Mutations in this gene lead to abnormal RNA splicing processes, which are essential for metabolic functions and neurodevelopment, including neural cell migration and/or renal development.

This disorder can be suspected prenatally through intrauterine growth retardation. ZTTK syndrome abnormalities include a delay of global development, brain abnormalities like corpus callosum abnormalities, ventriculomegaly or cerebellar abnormalities, seizures, and generalised hypotonia. Facial dysmorphism is presented by short philtrum, microcephaly, wide nasal bridge, and midface retrusion. Other abnormalities include scoliosis, joint and muscle contractures, joint hypermobility, visceral malformations like a horseshoe or unilateral kidney, gastrointestinal malformations, or cardiac disorders like an atrial or ventricular septal defect.

Patients suffering from ZTTK syndrome can be indicated for corrections of cardiovascular or urogenital abnormalities in addition to surgery for musculoskeletal deformations. Anaesthesiologists have to focus on continual close monitoring due to the potential risk of perioperative complications like difficult airway management (DAM), anaesthesia-induced rhabdomyolysis (AIR), or inspiratory stridor after extubation. Rhabdomyolysis represents a potentially life-threatening complication, especially in these patients suffering from a neuromuscular disorder. Anaesthesiologists should prefer total intravenous anaesthesia (TIVA), eventually with nondepolarising myorelaxants and, avoid volatile anaesthetics and succinylcholine.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

▶ **Citation:** Hudec J, Kosinová M: Zhu-Tokita-Takenouchi-Kim syndrome. Anästh Intensivmed 2023;64:S332–S339. DOI: 10.19224/ai2023.S332

Typical surgery

Typical procedures include musculoskeletal corrections for scoliosis or extremities deformations, invasive and minimally invasive corrections of cardiovascular defects, or surgical repair of visceral malformations. Patients with development delay require sedation for a central venous access or MRI.

Type of anaesthesia

Anaesthesia of patients suffering from Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome can be challenging for all members of a perioperative team. Theoretically, general and regional anaesthesia is possible. However, only general anaesthesia has been described in the literature so far. There are no data about the use of regional anaesthesia in these patients.

Regional anaesthesia in patients with ZTTK syndrome has no specific contraindications. Cardiovascular abnormalities can be contraindications when it comes to a neuraxial blockade. The same applies to patients with heart disease. Anaesthesiologists must be ready to deal with the limited cooperation of patients with developmental delay. Intravenous access, neuraxial blockade, or peripheral blocks can also be challenging due to musculoskeletal deformations. Ultrasound-navigated venous cannulation or regional anaesthesia can improve the success rate.

General anaesthesia, concretely total intravenous anaesthesia (TIVA), is a method of choice in patients with psychomotor development delay. Volatile anaesthetics as well as succinylcholine should be avoided because of the potential risk of severe rhabdomyolysis or hyperkalemia. TIVA, also in combination with non-depolarising muscle relaxants, has been described in the literature. The benefit of rocuronium in combination with sugammadex in patients with neuromuscular disease has been described. This combination allows a complete recovery from muscle relaxation. The data about the risk of malignant hyperthermia are not available, however, the association between these syndromes is unlikely. They have different gene localization (SON gene located on chromosome 21).

Analgosedation has no specific contraindications to this syndrome. This anaesthetic approach should be considered individually by all members of the perioperative team. The sedation is unsuitable for patients with a restrictive lung disease due to scoliosis, mental retardation, or muscular weakness with the risk of hypoventilation. But then, the potential benefits must be weighed against the risk of difficult airway management, especially in patients with facial dysmorphism.

Necessary additional preoperative testing (beside standard care)

The patient´s case history and the type of surgery are essential for determining the spectrum of preoperative assessment. ZTTK syndrome is typically associated with multi-organ involvement and anaesthesiologists must consider indications for each examination individually to identify cardiovascular, pulmonary, or visceral disorders and neurological deficits.

Neurological examination is a necessity, eventually including electroencephalography and a detailed description of the neurological deficit. Also, the neurologist should recommend any specific therapy needed for patients suffering from epileptic seizures. In addition, a

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neurological examination can be helpful for juridical reasons in patients with neurological deficits before surgery.

Electrocardiography is a standard part of the preoperative assessment. Patients with ZTTK syndrome can suffer from heart disease. Cardiologist examination with echocardiography should be indicated in patients with heart disease symptoms before high-risk surgery or, in case of doubts, e.g., a large scoliotic curve with possible pulmonary hypertension.

The evaluation of respiratory functions includes arterial blood-gas analysis by spirometry. This examination should be considered in patients with altered respiratory functions, for example, patients with restrictive lung disease due to musculoskeletal abnormalities, scoliosis, or muscle weakness. On the other hand, this examination will not be helpful in case of noncompliant patients.

Other specific preoperative testing includes patients with a hormonal imbalance and the recommendation of hormone substitution by an endocrinologist. Magnetic resonance imaging (MRI) to identify brain abnormalities can be helpful but is not strictly necessary before surgery.

Particular preparation for airway management

ZTTK syndrome is a disorder that typically involves dysmorphic features in patients. Typical facial dysmorphism includes macrocephaly with midface retrusion, short philtrum, and a wide nasal bridge. There is only one case that reports airway management. Endotracheal intubation was used in this case. The authors mentioned uncomplicated bag-mask ventilation. There were no complications with any airway securing method mentioned.

There is no more data about airway securing. Anaesthesiologists must expect possible difficult airway management (DAM) due to facial dysmorphism in patients with ZTTK syndrome. Authors recommend preparing the equipment for DAM and devising more alternative plans for airway securing before every anaesthetic care.

Particular preparation for transfusion or administration of blood products

One case report indicated a relatively high blood loss, about 20% of the total blood volume during long-time and extensive surgery. No other data about the administration of blood products are available. Some studies presented a higher blood loss in patients with neuromuscular disease compared to patients without these syndromes. Hence anaesthesiologists must expect higher blood losses in patients suffering from ZTTK syndrome with limited mobility and general hypotonia.

Particular preparation for anticoagulation

There are no data on thrombotic complications and the administration of anticoagulation therapy in the literature. However, patients with ZTTK syndrome often have limited mobility. Therefore, the perioperative team should expect a higher risk of thrombotic complications during the perioperative period and individually consider the potential risk-benefit ratio of anticoagulation therapy with higher blood loss as compared to thrombosis in low-mobility patients.

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Particular precautions for positioning, transportation and mobilisation

Patients with ZTTK syndrome can suffer from a low mobility associated with a neuromuscular disorder, endocrine dysfunction, and/or secondary osteoporosis. There is often an abnormal body constitution or contractures in these patients. The perioperative team should expect a higher risk of iatrogenic damage. We recommend using specific positioning pads and careful, coordinated positioning of patients with ZTTK syndrome.

Interactions of chronic disease and anaesthesia medications

There could be possible interaction with antiepileptic drugs, heart rhythm drugs, or other neurological medication, e.g., some interactions can cause prolonged QT symptoms, deepening the sedation. The perioperative team, in case of uncertainty, should consider consulting a neurologist or pharmacologist to plan the administration of drugs before surgery and in the postoperative period.

Anaesthetic procedure

General anaesthesia, especially total intravenous anaesthesia, is the preferred method for a patient with a severe mental alteration. The combination of propofol, opioid, and non-depolarising muscle relaxants was used safely in a patient with ZTTK syndrome. In case of need for muscle relaxation, rocuronium is a preferred relaxant because a prolonged neuromuscular blockade can be reversed by sugammadex.

On the contrary, depolarising muscle relaxants or volatile anaesthetics should be avoided due to the potential risk of rhabdomyolysis and severe hyperkalemia.

There are no specific contraindications for any type of regional anaesthesia. An anaesthetic team must consider a limited cooperation in patients with altered mental status. The usual places for invasive access can be modified due to the changed body proportions, joint contractures, or scoliosis. Ultrasound-guided cannulation can significantly reduce the incidence of invasive access insertion failure.

Particular or additional monitoring

There is a potential risk of prolonged muscle relaxation in patients with general hypotonia. The anaesthetic team should always monitor the depth of a neuromuscular blockade.

Invasive haemodynamic monitoring should be considered in high-risk or more extensive surgeries with major fluid shifts and in case of patients having undergone cardiovascular corrections.

TIVA should be administered according to the depth of anaesthesia monitoring. Standard doses of sedatives can lead to overdosing and wake-up time prolongation after anaesthesia in patients with an abnormal habitus. Monitoring the depth of anaesthesia is helpful, and it also shortens the time of anaesthesia.

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Possible complications

Difficult airway management should be expected in patients with facial abnormalities. The anaesthetic team has to be prepared for this life-threatening complication and have alternative plans for airway securing, e.g., awake fibre-optic intubation, or have a prepared kit with invasive techniques ready for securing the airways, such as bougie-assisted cricothyrotomy.

The inspiratory stridor with desaturation after extubation has been described in the literature. This complication has been treated as a standard.

There is a potential risk of rhabdomyolysis as well as other neuromuscular disorders, especially during long-time surgical procedures with a risk of muscle damage. Volatile anaesthetics or depolarising muscle relaxants should be avoided. Stress factors, like pain, should be eliminated. The rhabdomyolysis can be detected postoperatively by plasma creatine kinase and myoglobinuria monitoring.

postoperative care

Patients suffering from ZTTK syndrome will profit from monitoring in ICUs after surgery, especially in cases of high-risk or extensive surgery.

Rhabdomyolysis, as a possible postoperative complication, can be diagnosed by clinical examination in combination with the laboratory results.

Disease-related acute problems and effect on anaesthesia and recovery

There is no data about the risk of malignant hyperthermia. There are different gene localisations in these two syndromes, so the association between ZTTK syndrome and malignant hyperthermia is unlikely.

Other complications and problems are mentioned above.

Ambulatory anaesthesia

Ambulatory anaesthetic care has not been reported. The anaesthetic team should consider the potentially higher risk in ambulatory care settings for these patients.

Obstetrical anaesthesia

Not reported.

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