orphanaesthesia

Anaesthesia recommendations for

Tuberous sclerosis complex

Disease name: Tuberous sclerosis complex

ICD 10: Q85.1

Synonyms: Tuberous sclerosis, Bourneville disease, Epiloia

Disease summary: Tuberous sclerosis complex (TSC) is an uncommon, neurocutaneous multisystem genetic disorder. It was classically described as presenting in childhood with a pathognomonic triad (Vogt triad) of seizures (absent in one-quarter of individuals), intellectual disability (up to half have normal intelligence) and adenoma sebaceum (only present in about three-quarters of patients) [1]. The full triad is only seen in a minority of patients (~ 30 %). Therefore, diagnostic criteria have been developed to aid the diagnosis of tuberous sclerosis.

There are 2 genetic loci: TSC1, found on chromosome 9q34; and TSC2, found on chromosome 16p13 [2,3,4] coding for the proteins Hamartin and Tuberin, respectively. These proteins act as tumour growth suppressors, regulating cell proliferation and differentiation. In TSC patients, TSC1 or TSC2 mutations give rise to hyperactivation of the mTOR pathway, inducing several abnormalities in numerous cell biochemical processes such as cell cycle regulation and control at transcriptional, translational, and metabolic levels [5]. More recently, mTOR inhibitor drugs, such as everolimus, have been licensed for use in the treatment of specific clinical manifestations of TSC in certain countries, e.g., subependymal giant cell astrocytomas, renal angiomyolipomas, therapy of refractory epilepsy [6] and in patients with cardiac or pulmonary involvement. Everolimus can take over the function of the proteins hamartin and tuberin, which are missing due to the genetic defect. Approximately one third of the patients inherit mutations via the autosomal dominant route with the remaining two thirds of patients born with new sporadic mutations. The TSC2 gene is more common in both the familial and sporadic forms of the condition. The incidence is approximately 1 in 5,000 – 10,000 live births [7].

The condition is characterised by cellular hyperplasia, tissue dysplasia, and multiple organ hamartomas (benign tumours). TSC shows wide phenotypical variability with patients harbouring the TSC2 gene exhibiting the more severe clinical manifestations. The benign tumours seen in TSC can occur in almost all organ systems, e.g., on the skin, brain, kidneys, heart, lungs, liver, spleen, pancreas, gastrointestinal tract, gingivae and the retinas. Clinical symptoms may include epilepsy, which can be refractory, developmental delay, behavioural problems, and autism. Three types of brain tumour are commonly associated with the condition: giant cell astrocytoma, cortical tubers (after which the disease is named) and subependymal nodules. The growths on the kidneys can be angiomyolipomas (AMLs) or renal cysts. Renal AMLs can produce pain and haemorrhage in adulthood, whereas the cysts are more likely to cause damage to the renal parenchyma causing hypertension and chronic kidney disease which is exhibited in < 5 % of patients overall [8,9]. Cardiac rhabdomyomas are single or multiple and can be seen antenatally. If symptomatic, they present in the neonatal period, but this is rare. They tend to regress in childhood without the need for intervention [2,8]. Lymphangioleiomyomatosis (LAM) of the lungs occurs in 40 % of women with TSC and

appears to be hormonally sensitive. It can cause recurrent pneumothoraces [10] and in some cases leads to progressive, irreversible cystic cavitations within the lungs. For certain patients, this can ultimately lead to death without lung transplantation.

The main anaesthetic concerns in the treatment of patients with TSC are related to cardio-respiratory complications secondary to progressive damage to the lung parenchyma in adults and the potential for arrhythmias, outflow tract obstruction and venous thromboembolic events in children. Consideration must also be given to anaesthetic drug choices in view of possible renal impairment and medications that the patients may have been prescribed to take long term. Oral lesions on the tongue, palate and less commonly the pharynx and larynx may interfere with anaesthetic airway management [11,12]. In addition, practical difficulties may arise when anaesthetising patients with developmental delay and challenging behaviour. Despite ongoing research into TSC, certain aspects related to its diagnosis and treatment remain unexplained, therefore the anaesthetist is presented with challenges when planning the peri-operative management of these patients.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

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Typical surgery

Common surgeries seen in patients with TSC include: acute decompressive neurosurgical procedures [13,14], resective neurosurgery and vagal nerve stimulator implantation for epilepsy. In the case of renal AMLs, selective arterial embolisation [15,16] is often the preferred treatment method to minimise bleeding whereas previously partial nephrectomy was commonly performed in preference to total nephrectomy. Sometimes a combined radiological and surgical approach may be employed to treat these lesions. Thoracic procedures such as pleurodesis and video-assisted thoracic surgery (VATS) [17,18] are seen more commonly than lung transplantation [13,19]. In certain cases, patients may require resection of jaw and oral lesions.

Anaesthesia may also be necessary for diagnostic and minimally invasive procedures such as MRI scans in children who in addition to TSC may exhibit signs of developmental delay. Other surgical procedures requiring anaesthesia include resection of jaw and oral lesions and surgery to the skin or laser treatment for facial AMLs.

Type of anaesthesia

There is no definite recommendation for general or regional anaesthesia in patients with Tuberous sclerosis complex [20] and both gaseous and intravenous induction of anaesthesia are considered to be safe. The spinal cord and peripheral nerves are very rarely known to be involved in the condition and therefore regional anaesthesia may be a viable anaesthetic option [21]. No specific anaesthetic agents or techniques are absolutely contraindicated in patients with TSC [20].

When considering any paediatric anaesthetic, it is often found that the presence of parents and carers is very helpful in reducing a child's anxiety prior to and during induction. If additional anxiolysis is required, oral or buccal premedications such as midazolam can play an important role in the pre-operative period in children with TSC. These children often have behavioural difficulties and developmental delay so may be anxious and uncooperative when presenting for anaesthesia.

Necessary additional pre-operative testing (beside standard care)

Tuberous sclerosis complex is a multi-system disorder which is associated with significant neurological, cardio-respiratory and renal dysfunction in the patient population. These pathologies must be fully investigated pre-operatively.

1. Upper airway lesions are present in 11 % of patients with TSC [21,22], and may be evaluated with imaging such as ultrasound or CT scan and where possible awake nasendoscopy.
2. If pulmonary involvement is suspected, pulmonary function testing and arterial blood gas analysis should be performed. Chest X-rays may miss the characteristic cysts found in LAM. If the patient is female and of child-bearing age, baseline pulmonary function testing, 6-minute walk test, and high-resolution chest computed tomography (HRCT), along with serial spirometry are indicated in addition to evaluate pulmonary structural and functional abnormalities related to LAM [14,23,24]. These tests will also aid decision making regarding the need for post-operative ventilation and Intensive Care admission.

3. All patients should have an electrocardiogram to rule out dysrhythmias, conduction defects or pre-excitation [20]. Echocardiography and a chest X-ray should be performed in patients who are thought to have cardiac involvement caused by cardiac rhabdomyomas. This is primarily the paediatric population.
4. Renal function should be assessed by measuring serum creatinine and/or cystatin C and by taking the patient's blood pressure. A renal ultrasound, CT or MRI should take place to detect complications of lesions such as haemorrhage, rupture or malignant transformation [7].
5. A CT or MRI of the brain should be performed to look for any signs of hydrocephalus or raised intracranial pressure caused by sub-ependymal giant-cell astrocytomas (SEGAs) which are observed in 5–15 % of patients with TSC [19].
6. For those TS patients with epilepsy, pre-operative blood tests should be taken to measure and evaluate the platelet count. Platelet aggregation studies should also be considered to look for any abnormalities of platelet function.

Particular preparation for airway management

Airway management can be complicated in patients with TSC if oral manifestations of the disease are present. These have been described in 11 % of cases [11] and can include; dental enamel pitting (48 % – 100 %), gingival fibromas (50 %), bifid uvula, cleft lip and palate, high arched palate, macroglossia, thickening of the alveolar bone and pseudocystic lesions of the mandible [39,40]. Lesions on the pharynx and larynx occur less commonly, however. Significant airway obstruction can be caused by these lesions and they also have the potential to bleed if traumatised.

Diligent assessment of the airway should be performed pre-operatively and any airway imaging reviewed. An opinion from an Ear, Nose and Throat surgeon should be sought to assess the extent of any airway lesions and awake nasendoscopy performed pre-operatively if possible.

The Difficult Airway Trolley should be available for the induction of anaesthesia, and if the patient needs intubating, then an alternative to direct laryngoscopy should be considered. Video laryngoscopy or an Airtraq Optical Laryngoscope could be useful. The preferred approach for patients with significant airway lesions is awake fibreoptic intubation although this technique can be performed asleep in children or in patients with developmental delay [20].

Particular preparation for transfusion or administration of blood products

TSC patients with renal angiomyolipomas (AMLs) are at increased risk of requiring blood products perioperatively due to the likelihood of haemorrhage from these lesions [42]. They may rupture and cause large volume retroperitoneal haemorrhage especially in cases of rare giant renal AMLs. Renal AMLs are hormone sensitive and therefore tend to grow during pregnancy thus increasing the risk of rupture and subsequent haemorrhage during pregnancy and delivery [36]. In addition, TSC patients with significant renal impairment may be anaemic pre-operatively.

There is evidence in a small study that paediatric patients with TSC may exhibit platelet function abnormalities. Platelet aggregation studies should be considered in these patients having surgery with anticipated blood loss [32].

Sodium Valproate can decrease platelet count and function, as well as affecting the coagulation cascade. Furthermore, when patients are taking multiple AEDs, there is an impact on the ability of the liver to synthesise coagulation factors. Studies performed in children undergoing epilepsy surgery demonstrated abnormalities in platelet aggregation and coagulation in up to 25 % of the patients, many of these children had an underlying diagnosis of TS [43].

Particular preparation for anticoagulation

There is no evidence to support any particular method of anticoagulation in patients with TSC, but there is an increased risk of thrombus formation in neonatal patients with cardiac rhabdomyomas. This is due to the turbulent flow created around these lesions [26]. A rare case of pulmonary embolism in a neonate secondary to cardiac rhabdomyomas has been reported [44].

Particular precautions for positioning, transportation and mobilisation

Careful attention to pressure areas should be maintained peri-operatively particularly in view of the many dermatological manifestations of TSC. Facial angiofibromas are present in 75 % – 80 % of patients with TSC [19], therefore care should be taken when securing airway devices.

Interactions of chronic disease and anaesthesia medications

One of the main characteristics in patients with TSC is epilepsy which can be refractory to treatment and very disabling. 90 % of these patients suffer from seizures that require more than one type of antiepileptic drug (AED) to achieve adequate symptomatic control. Notable pharmacokinetic and pharmacodynamic interactions exist between AEDs and common anaesthetic drugs [25]. The induction and inhibition of the Cytochrome P450 isoenzymes in hepatic metabolism being the most significant interaction [25,28]. This alteration in cytochrome P450 activity will alter the pharmacokinetics of many anaesthetic drugs where their metabolism takes place in the liver. Some first-generation AEDs, e.g., carbamazepine, phenobarbital and phenytoin have potent enzyme inducing properties resulting in decreased plasma concentrations of many common anaesthetic drugs; thus the anaesthetic requirements of these drugs will be greater. Examples of such drugs are propofol, thiopentone, midazolam, non-depolarising muscle relaxants such a rocuronium and vecuronium and opioids. Topiramate and felbamate are newer AEDs with mixed inducer and inhibitor properties [25,28] and notably cause relative resistance and to and higher requirements for opioids and non-depolarising neuromuscular blockers [19]. However, in comparison to the first-generation AEDs, they appear to have a lesser effect on liver enzyme activity. Sodium valproate is an inhibitor of the hepatic microsomal enzyme system thus leading to a reduction in the required dose of anaesthetic drugs. It is important to note the interaction between sodium valproate and the carbapenem group of antibiotics. Carbapenems significantly decrease the plasma concentration of sodium valproate thus exposing the patient to an increased risk of uncontrolled seizures. For this reason, the use of carbapenem antibiotics in patients taking sodium valproate should be avoided where possible. Where the combination is unavoidable then increasing the dose of sodium valproate should be considered or a second AED should be added [46].

In recent years, the mTOR inhibitor everolimus has been approved for use in the treatment of certain clinical manifestations of TSC in some countries. This in an immunosuppressant drug which is taken orally and has multiple adverse side effects such as; Non-infectious pneumonitis, stomatitis, infections, thrombocytopenia, rash and multiple metabolic abnormalities [47,48]. They are metabolized by CYP3A4, with enzyme inducers and inhibitors affecting the level of resultant immunosuppression [48]. CYP3A4 is a member of the cytochrome P450 family of oxidizing enzymes which is instrumental in drug metabolism. Anaesthetic volatile agents are enzyme inducers and etomidate is an enzyme inhibitor. Use of these drugs during the peri-operative period may adversely affect the patient taking everolimus therefore.

For the small proportion of TSC patients with significant renal failure, the recommendations regarding the use of anaesthetic agents and analgesics are comparable to those of patients with chronic kidney disease stages 3b – 5. In the case of patients with TSC, the administration of desmopressin prior to surgery could decrease the seizure threshold and interact with lamotrigine and carbamazepine [29].

Anaesthetic procedure

Most induction agents are considered safe to use in patients with TSC although ketamine should be avoided as there is evidence to suggest that it lowers the seizure threshold in TSC patients and increases intracranial pressure [26,27]. Hypnotic agents such as propofol can be used with extreme caution in patients with any significant cardiac pathology and likewise arrhythmogenic drugs should be avoided in such cases. In neonates with cardiac failure, hypnotic agents may not be appropriate for induction.

Either a gaseous or intravenous induction of anaesthesia is considered to be safe in most patients with TSC. Volatile agents and hypnotic agents are broadly considered to be anti-convulsant in their effects as is nitrous oxide so these drugs are all useful in those patients who are epileptic. Sevoflurane and enflurane have been rarely reported to have proconvulsant activity at low inspired concentrations [25,28]. However, higher inspired concentrations of enflurane, e.g., above MAC 2 have been associated with seizure activity [29]. Similarly, sevoflurane is considered to be safe providing inspired concentrations achieving MAC 1.5 or greater are avoided. When performing an inhalation induction with sevoflurane, an inspired concentration of approximately 4 % should not be exceeded to avoid the possibility of triggering seizures [31]. A slow inhalation induction of anaesthesia in TSC patients could be a safe option therefore or if possible, an intravenous induction would be preferable [29]. Isoflurane and Halothane have primarily anticonvulsant properties. Nitrous oxide has been shown to suppress epileptiform activity [30] but should be avoided in those patients with pulmonary cysts due to the risk of rupture due to expansion [41]. It is essential to maintain normocapnia, normovolemia and normothermia in patients with TS to avoid triggering seizures during surgery. TIVA has been used safely in patients with TSC [45]. Maintenance of anaesthesia can be achieved by using a volatile agent or TIVA.

Anticholinergics such as atropine or scopolamine can produce central cholinergic blockade (or central anticholinergic syndrome). This manifests as agitation with seizures, hallucinations, and restlessness or stupor, coma, and apnoea. The most effective treatment for this is physostigmine. Glycopyrrolate does not cross the blood–brain barrier, so does not produce these effects [25].

Non-depolarising neuromuscular blocking agents and succinylcholine have been used safely in patients with TSC [19] although care must be taken regarding drug interactions with certain AEDs. There may be a relative resistance and higher dosing requirement for non-depolarising

neuromuscular blocking agents. Atracurium and cisatracurium could be considered the ideal neuromuscular blocking agents due to their metabolisms being independent of the liver and kidneys. There may be prolonged action of muscle relaxants in those TSC patients with renal failure.

There is no specific pain management method for patients with TSC although fentanyl, alfentanil, sufentanil, and morphine have been reported to cause generalised seizures in patients after administration of low-to-moderate doses, so should be used with caution [32,33]. Doses of opioids should be adjusted for TSC patients with renal disease as accumulation may also occur leading to over-sedation and respiratory depression. Non-steroidal anti-inflammatory drugs are contraindicated in patients with renal pathology.

Local anaesthetics can be used safely at specific, therapeutic, doses. At higher doses, they can cause neurotoxicity which has the potential to give rise to generalised seizures. The rate of systemic absorption of local anaesthetics depends on the administration site as well as the toxic dose so this must also be considered. The rate of absorption is greatest when a local anaesthetic is injected intraarterially, then intravenously, tracheally, intercostally, paracervically, epidurally, into brachial plexus, into the sciatic plexus and finally subcutaneously. Alterations in metabolism and excretion of the aminoamide local anaesthetics (lidocaine, bupivacaine, mepivacaine, and ropivacaine) may be noted in patients with TS affecting the kidneys. Additionally, certain antiepileptic drugs may alter the enzymatic activity of the liver. Aminoamide local anaesthetics are hepatically metabolised and renally excreted. There can therefore be an increase in their plasma concentrations and consequently their systemic toxicity. Neuraxial techniques can be employed, providing advance imaging of the brain and spinal cord has been performed. Regional anaesthesia can be performed safely.

Glycopyrrolate and neostigmine can be used safely for the reversal of neuromuscular blockade at the end of surgery. The literature advises general caution when using sugammadex in cases of patients with renal failure.

Certain other drugs used during the peri-operative period should be considered specifically in the case of providing anaesthesia for a patient with TSC. High dose tranexamic acid can potentially lower seizure threshold. The most commonly used dose in cardiac surgery is 10 mg/kg intravenous (iv) bolus, followed by an infusion of 1 mg/kg/hr. Higher doses do not offer a greater haemostatic effect, yet a 25 % reduction in the total dose administered significantly reduces the risk of seizures [35].

Certain classes of antibiotics must also be used with caution. Beta-lactam antibiotics can trigger seizure activity when their beta-lactam ring acts as a competitive antagonist of the GABA receptor. Cephalosporins have been associated with a lower risk of seizures than Penicillins, but seizures have been described at toxic concentrations. Particular attention should be paid to carbapenems, specifically Imipenem, whose incidence of seizures varies from 3–33 %. In contrast, the seizure rate associated with Meropenem is less than 1 % [37].

Flumazenil should be used with caution due to its competitive antagonism of the benzodiazepine binding site on the GABA/benzodiazepine receptor complex. It can trigger seizures in patients on chronic benzodiazepine treatment, or if benzodiazepines have been used as part of anaesthetic premedication.

Particular or additional monitoring

In patients with more severe manifestations of the disease (e.g., significant hypertension, cardiac disease or renal failure), undergoing major procedures, invasive monitoring is

indicated, i.e. arterial line and central venous catheter placement. A urinary catheter should also be inserted in such cases. Central temperature monitoring should be mandatory in all surgical interventions lasting more than 30 minutes in order to avoid hyper-/hypothermia and thus an increased risk of triggering perioperative seizures. In addition, a method of peri-operative electrolyte monitoring should be available to avoid physiological situations which may alter the seizure threshold of the patient with TSC, e.g., hypoglycaemia, hyponatraemia, hypomagnesaemia and hypocalcaemia.

Depth of anaesthesia monitoring is very useful in TSC patients as it may provide information whereby sub-clinical seizure activity can be detected. Bispectral Index (BIS) is commonly used for intra-operative depth of anaesthesia monitoring, but to detect seizure activity in this instance, the BIS would also need to include the Spectral Density Matrix (SDM). The SDM is a coloured graph where the amplitude and frequency of brain waves are represented over time, and whose range varies from blue (minimum amplitude) to red (maximum amplitude). The anaesthetist could then identify a seizure by observing a range of low frequencies and high amplitudes on the monitor [34].

Neuromuscular blockade should be measured using a peripheral nerve stimulator due to the unpredictable nature of neuromuscular blocking drugs in TSC patients on AEDs or with renal failure.

Possible complications

General complications which may occur during the peri-operative period in patients with TSC include arrhythmias, thromboembolic events, hypertension, increased bleeding risk and complications related to surgical positioning.

Obstruction on extubation can occur in those TSC patients who have oropharyngeal lesions.

Neonatal patients are at risk of cardiac arrhythmias and thromboembolic events secondary to cardiac rhadomyomas. These can be exacerbated by certain anaesthetic agents and dehydration.

For patients taking certain anti-epileptic drugs, there is a relative resistance to non-depolarising neuromuscular blocking drugs so that higher doses are required. These drugs may also be prolonged in their action in patients with renal failure. Epileptic patients are at increased risk of seizures if they are in a state of hyper- or hypocapnia [26]. Normocapnia should be maintained.

There is potential for respiratory depression and increased sedation if opioids, e.g., morphine are administered to those patients who have renal failure. Short acting opioids and regional techniques would be more advantageous in these cases.

Post-operative care

A short observation period post-operatively is often all that is required following minor procedures. Many can be discharged home the same day. Others are safely discharged to normal surgical wards following inpatient surgery.

In cases where there is significant organ failure or the patient has required major surgery, admission to a critical care setting post-operatively should be considered21. Arterial blood gas sampling should be conducted post-operatively in those TSC patients with respiratory

involvement and significant renal failure to assess acid-base balance. This can help to avoid post-operative seizures.

Narcosis is a complication in patients with significant renal failure due to their altered drug metabolism and excretion. Post-operative analgesia should follow a multi-modal approach including the use of regional anaesthetic techniques and local anaesthetic to infiltrate wounds. This will help decrease the opioid requirements. NSAIDs should be avoided in these patients.

Disease-related acute problems and effect on anaesthesia and recovery

The three main complications that must be considered during the post-operative period in TSC patients are the development of seizures, severe hypertension and bradyarrhythmias. These must be recognised quickly and treated accordingly with anti-epileptic medications, vasodilator drugs and appropriate antiarrhythmics.

Ambulatory anaesthesia

Ambulatory anaesthesia is entirely appropriate in several surgeries in patients with TSC, particularly in common procedures such as resection of cutaneous lesions.

Obstetrical anaesthesia

Anaesthetists may need to provide analgesia during labour and delivery and anaesthesia and post-operative pain relief if caesarean section is performed [49]. Epilepsy may be triggered by pain, anxiety and excitement, which are all frequent during delivery. For those with epilepsy, epidural analgesia can be beneficial, since hypocarbia induced by maternal hyperventilation during painful uterine contractions lowers the seizure threshold, therefore it should be avoided [50]. Spinal lesions are rare, but cerebral lesions are more common. Pregnant women with TSC should have an MRI of their brain and spine early on in the pregnancy. The result of these scans, along with neurosurgical consult will guide the decision to proceed with epidural or spinal anaesthesia [49]. Both have been used safely in TSC patients who have no evidence of raised intra-cranial pressure or any spinal lesions.

General anaesthesia can be performed for caesarean section in cases where a neuraxial technique is contraindicated.

It is important to note that renal AMLs are hormone sensitive and have a tendency to grow during pregnancy. This may lead to an increased risk of rupture during pregnancy and delivery and therefore an increased risk of associated maternal haemorrhage [36].

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Date last modified: **February 2022**

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Disclosure The authors have no financial or other competing interest to disclose. This recommendation was unfunded.

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Disclosure The reviewers have no financial or other competing interest to disclose.