

Anaesthesia recommendations for **Ehlers-Danlos syndrome**

Disease name: Ehlers-Danlos syndrome (EDS)

ICD 10: Q79.6

Synonyms: none

Disease summary: Ehlers-Danlos syndrome comprises a group of clinically and genetically heterogeneous, inherited connective tissue diseases [22]. Different defects in the synthesis of collagen lead to an increased elasticity within different types of connective tissue (skin, joints, muscles, tendons, blood vessels and visceral organs). Depending on the specific subtype and individual aspects, defects are mild to life-threatening. The incidence of EDS is estimated as 1:5000, in which the hypermobility-type has the highest prevalence affecting 1 in every 10.000 to 15.000 individuals [20]. It affects men and women of every race and ethnicity but is known to be more common among non-white populations and women [31].

The Villefranche classification from 1998 recognizes six major genetic subtypes: classic (type I and II according to the old “Berlin classification” from 1988), hypermobility (type III), vascular (type IV), kyphoscoliotic (type VI A), arthrochalasia (type VII A&B) and dermatosparaxis (type VII C), most of which are linked to mutations in one of the genes encoding fibrillar collagen proteins or enzymes involved in post-translational modification of these proteins.

Over the last decades, a whole spectrum of novel EDS subtypes and mutations have been identified via next-generation sequencing in an array of new genes. Therefore, in 2017 an international EDS consortium proposed a revised EDS classification, which recognizes 13 clinical subtypes: classical EDS (cEDS), classical-like EDS (clEDS), cardiac-valvular (cvEDS), vascular EDS (vEDS), hypermobile EDS (hEDS), arthrochalasia EDS (aEDS), dermatosparaxis EDS (dEDS), kyphoscoliotic EDS (kEDS), brittle cornea syndrome (BCS), spondylo-dysplastic EDS (spEDS), musculocontractural EDS (mcEDS), myopathic EDS (mEDS) and periodontal EDS (pEDS).

Since many previous literature still refer to the older Villefranche classification [17,31]. For each subtype, a set of clinical major and minor criteria are proposed and are suggestive for diagnosis [17]. However, individual symptoms and severity need to be investigated for each specific patient.

Major criteria for the classic type include severe skin hyperextensibility, atrophic scarring and generalized joint hypermobility (GJH), whereas the classical-like type presents with easy bruisable skin, spontaneous ecchymoses and also skin hyperextensibility (in the absence of atrophic scarring) and GJH with or without recurrent dislocations [17]. GJH in hypermobility-type may be diagnosed via Beighton score, whereby recurrent joint dislocations, mild skin

hyperextensibility, striae and chronic pain are further exemplary diagnostic criteria in this type. Probably the most severe type is the vascular subtype with extreme fragile blood vessels and internal organs. Major criteria include arterial rupture at a young age, spontaneous sigmoid colon perforation, uterine rupture (during third trimester in absence of C-section) and carotid-cavernous sinus fistula [17]. Beside skin and joint pathologies, the cardiac-valve type presents with severe progressive cardiac-valvular problems, especially in aortic and mitral valve. The arthrochalasia type may present with congenital bilateral hip dislocation, whereas short limbs, hand and feet occurs in dermatosparaxis EDS. Muscle hypotonia may be present in myotonic, kyphoscoliotic and spondylodysplastic EDS. Musculocontractural EDS is among other things characterized by congenital multiple contractures and different cutaneous pathologies. Major criteria of periodontal EDS include severe and intractable periodontitis of early onset (childhood or adolescence) and a lack of attached gingiva [17]. Nevertheless, specific symptoms must be given respect for each individual patient due to overlapping phenomena. In addition to these selected clinical signs, we refer to the new classification mentioned above for detailed major and minor clinical criteria [17].

When compared with the other subtypes of EDS, the vascular type has largely been recognized as having the worst prognosis due to vessel/organ rupture and is associated with early mortality [9]. It accounts for less than 4% of all EDS [21].

On an operational perspective, surgical and anaesthetic pitfalls relate to a mixture of common features shared by most subtypes and complications related to specific variants. Therefore, an accurate patients' classification should be planned before any invasive procedure. Subtypes are caused by autosomal-dominant or autosomal-recessive mechanisms. Approximately 50% of all patients have de-novo mutations with negative family history.

Medicine in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong



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Typical surgery

Most EDS subtypes (particularly hypermobility subtypes): operative therapy of joint instability (fingers, wrist, elbow, shoulder, knee, hip) as well as joint debridement, tendon replacement, arthroscopy, arthroplasty, corrective surgery for scoliosis or pectus deformity.

EDS subtypes with vascular fragility: vascular complications with operative/interventional therapy like valve replacements, aortic dissection, rupture of medium-sized arteries, (vessel dissections), and haematoma evacuation, carotid-cavernous fistula.

EDS with vascular subtype: rupture of organs, perforations of intestines, spontaneous pneumothorax, uterine rupture, liver rupture, spleen rupture.

EDS of all subtypes: Ceasarean section.

Miscellaneous: ophthalmologic disorders like retinal detachment, corneal / scleral rupture (in EDS kyphoscoliotic type or in the related brittle cornea syndrome) lens luxation (the latter is infrequent and not typical for EDS, it is more frequent in Marfan syndrome).

Type of anaesthesia

There is no definite recommendation for either general or regional anaesthesia [28]. There are several case reports and case series of spinal and epidural anaesthesia as well as peripheral nerve blocks without any complication.

However, local anaesthetics might have reduced or no effects in some patients [1,2]. Tissue scarring or some other unidentified mechanism results in reduced spread of the local anaesthetics and block failure [11]. This includes the use of EMLA cream (and its use e.g. in paediatric anaesthesia for pain-reduction in venous puncture). Reports of block failure are often with respect to local anaesthesia for dental surgery and peripheral nerve blocks.

Besides, performance of peripheral nerve blocks in patients with (especially vascular type) EDS is controversial, due to easy bruising and haematoma formation after injections. Nevertheless, they were performed successfully in different EDS subtypes [20,29]. Especially hEDS patients are often candidates for peripheral nerve blocks due to orthopaedic surgical intervention. Generally, clinicians should remain cautious and use appropriate clinical judgement when presented with a patient with severe presentations of EDS, regardless of subtype. Using ultrasound guidance in peripheral regional anaesthesia is recommended and may help to reduce the risk of haematoma [20,23]. Using needle approaches that avoid muscle and vessel trespass, prophylactic pressure application to the site immediately after the procedure and monitoring for the signs of haematoma are further precautionary measures [23].

No reports for block failure are published with regard to neuraxial blocks. However, when neuraxial anaesthesia is selected for patients with EDS, a combined spinal epidural or epidural catheter may allow additional doses of local anaesthetic in case of local anaesthetic

resistance [7]. Nevertheless, meningeal involvement, in form of isolated or multiple Tarlov cysts, is a feature of specific EDS subtypes (i.e. classic, hypermobility and kyphoscoliotic). Therefore, particularly in patients with these subtypes, spinal anaesthesia should be performed with particular care in order to avoid post-dural puncture headache. However, most Tarlov cysts are primarily located in the S1 to S4 region of the spinal cord and therefore there is regularly no contraindication for the performance of a spinal anaesthesia or thoracic or lumbar epidural anaesthesia. Scoliosis and/or severe spondylosis might hamper epidural spread of local anaesthetics or performance of spinal anaesthesia.

Thorough bleeding anamnesis and individual decision making with the patient are pivotal, especially for neuraxial blocks like spinal or epidural anaesthesia. Some recommendations against the performance of neuraxial anaesthesia have been made in the light of the theoretical risk of spinal haematoma formation in vascular type EDS [9].

General anaesthesia can be performed as balanced anaesthesia with volatile anaesthetics, nitrous oxide or as total intravenous anaesthesia (TIVA). Monitoring of neuromuscular blockade is advised before emergence of the anaesthesia (because some patients present with muscular weakness). However, depolarising (succinylcholine) as well as non-depolarising agents can be used in patients with EDS with regard to concomitant disease or disability. Hypertensive response to intubation includes potential complications encountered in vascular EDS patients, i.e. arterial dissection or cerebral haemorrhage [5].

Postural orthostatic tachycardia syndrome (POTS) is described as a feature in some patients with EDS subgroups with hypermobility secondary to abnormal aortic baroreceptor responses [10,19]. A sufficient volume therapy may help to mitigate this aspect in the perioperative management [10].

Avoidance of central venous access and arterial puncturing is recommended in Type IV (and some patients of other subtypes) due to high risk for vascular dissection whenever possible. If those lines are needed (high risk surgery, emergencies), ultrasound guidance is strictly recommended including visualisation of correct wire localisation within the blood vessel [25].

Adequate prophylaxis of postoperative nausea and vomiting is recommended as spontaneous esophageal rupture may result, especially in EDS of vascular type [21].

Intraoperative patient positioning should focus on optimal padding of the patient, reduction of shear forces, protection of the eye with respect to the risk for retinal detachment due to direct force (e.g. by the surgeon's elbow). Adhesive tapes for fixation of cannulas, tubes etc. should be easily removable or avoided when possible because of the risk of severe skin damages in many patients.

Necessary additional pre-operative testing (besides standard care)

A thorough history is required including complete bleeding anamnesis. Conventional coagulation tests are usually within normal range, bleeding time might be prolonged in affected patients. Patient history and bleeding anamnesis are usually quite helpful in estimating the degree of bleeding risk [14,16,22]. Physical examination of difficult airway, muscular weak-

ness and signs of aortal and mitral insufficiency are important. Actual echocardiography results might be helpful for estimating the patient's individual risk. Depending on anamnesis, an MRI may reveal presence or progress of cerebral aneurysm [5].

Particular preparation for airway management

Careful mask ventilation is advised to avoid the high risk of temporomandibular joint luxation. Tissue fragility can cause bleeding in repeated intubation attempts. Smaller endotracheal tube than in healthy patients might reduce mucosal damage in the trachea. Check cuff pressure thoroughly. Laryngeal mask airway is feasible. Reduce airway pressure whenever possible due to the risk for spontaneous pneumothorax. Due to affected cartilaginous tissues of e.g. the trachea and larynx in hEDS, intubation difficulties may also arise secondary to the collapse of fibro-elastic tissues and cartilaginous rings in the trachea [7]. Therefore, the BURP technique should be avoided or at least used carefully, because it may occlude the trachea and further obscure the view [7]. In addition to a greater predisposition to periodontal disease, tooth and gingiva may be particularly vulnerable, which has been connected to defects of collagens in oral tissues (especially in EDS periodontal type) and xerostomia may hinder placement of laryngeal mask [13,15].

Many adult patients with various forms of EDS develop temporomandibular dysfunction and block, as well as premature spondylosis or occipitalatlantoaxial instability of the cervical spine. This may lead to difficult intubation and/or to difficult airway management [12]. Sub-clinical cervical spine instability should be taken into account also in patients with preserved neck flexibility and temporomandibular joint mobility in order to prevent post-operative complications, such as neck pain and compression neurologic symptoms, related to temporomandibular joint luxation and occipitoatlantoaxial instability. These complications can be minimized with the use of video laryngoscopy or fibreoptic bronchoscopes [7].

Particular preparation for transfusion or administration of blood products

Prematching of RBCs is advised for patients with high risk for bleeding (Type IV EDS as well as patients with unknown or positive bleeding history). Inform your local transfusion specialist in advance for storage of sufficient numbers of blood products. In acute bleeding type IV EDS patients, aggressive haemostatic therapy is advisable. Use of desmopressin (DDAVP) might be helpful in reducing transfusions [2,18,26,31], also in other EDS subtypes with positive history of bleeding. In high-risk surgery as well as with high risk patients, cell saving strategies might be advisable. Anecdotal reports discuss the use of tranexamic acid to prevent re-bleeding and recombinant FVIIa for patients with massive haemorrhagia and coagulopathy [3,8].

Particular preparation for anticoagulation

Not reported.

Particular precautions for positioning, transportation and mobilisation

Careful transport is needed for patients with EDS. Mobilisation should be done with respect to the danger of easy skin damage, haematoma formation and luxation of joints [22]. Shear forces should be reduced due to tissue fragility whenever possible.

Fracture and wound healing is often compromised in EDS patients, again with moderate to severe extent.

Interactions of chronic disease and anaesthesia medications

Not reported.

Anaesthetic procedure

Optimal padding of the patient in the OR is an important issue. Extent of matched blood products (as well as the provision of cell saver even for small surgical procedures for patients with abnormal coagulation) should be discussed with the team.

Avoid tourniquets (this topic should be discussed with the surgeon) whenever possible - high risk for haematoma and compartment syndrome (and unstoppable diffuse bleeding especially in EDS subtypes with vascular fragility). The authors have anecdotal knowledge of lethal complications due to the use of tourniquets in elective minor surgery.

Avoid insertion of central venous catheters and arterial lines whenever possible. If needed, ultrasound guidance of each procedural part is strictly recommended to avoid vessel dissection [25].

Laryngeal mask and intubation are possible. Reduce cuff pressure whenever possible, use a smaller-than usual endotracheal tube to reduce potential mucosal damage. Difficult airway status should be anticipated.

Particular or additional monitoring

Prefer non-invasive monitoring whenever possible. Some patients develop extensive haematoma even by repetitive non-invasive blood pressure measurements. On the other hand, invasive blood pressure monitoring is exposing the patient to the risk of vascular wall dissection with high morbidity and mortality (especially for EDS subtypes with vascular fragility).

Possible complications

Patient positioning: plexus neuropathy, postoperative visual loss due to direct pressure to the eye. Skin damage and haematoma formation when patient was insufficiently padded and positioned or due to shear forces to the skin.

Spontaneous pneumothorax due to mechanical ventilation and airway bleeding during repeated intubation attempts. Difficult airway status can be observed in some patients with atlantooccipital instability as well as higher risk of temporomandibular joint luxation due to mask ventilation or intubation.

Postdural puncture headache (PDPH) might occur more often in EDS patients than in other population in neuraxial blockades and should be discussed with the patient. However, this is solely an expert opinion with regard to the fragility of (dural) tissue and to a case series of patients with spontaneous CSF leaks with high rates of underlying EDS [24].

Post-operative care

Postoperative care should focus on the development of bleeding and haematoma at the operation site. Furthermore, some patients report muscular weakness after extubation. Careful patient positioning and mobilisation is advised to reduce the risk of joint luxation. In all EDS subtypes, but particularly in the hypermobility subtype, early mobilization is a key point in order to prevent excessive deconditioning and unexpected deterioration of the musculoskeletal system and cardiovascular reactivity.

Approximately 90% or more suffer from chronic widespread neuropathic or musculoskeletal pain as well as migraine or similar [31]. In patients with hEDS this is mainly due to recurrent subluxations and joint dislocations [10,27]. Adequate analgesia in addition to careful physiotherapy may be challenging in these patients and a careful evaluation and consideration as well as an extensive multimodal concept is necessary for sufficient treatment [6,31].

Disease-related acute problems and effect on anaesthesia and recovery

Emergency-like situations: Acute vascular dissection (e.g. aortal dissection, peripheral arterias & veins) may be caused spontaneous or iatrogenic (especially during angiographic interventions) [4]. Compartment syndromes can be caused by vasculare puncture and resulting haematoma. High risk of pneumo(haemo-)thorax must be anticipated during ventilation as well as central venous access. Spontaneous rupture or rupture after bagatell trauma of intestines, organs or other tissues (bowel, uterus, oesophagus, vagina) are reported. However, these situations are most often encountered in patients with EDS subtypes of vascular fragility and unusual in patients with other subtypes.

Differential diagnostics: Marfan syndrome.

Ambulatory anaesthesia

Not reported. We strongly encourage to operate patients in centres with expertise for EDS and the special conditions within this syndrome. Crossmatching of RBCs is important for patients with EDS with vascular fragility and those with high bleeding risk even for minor surgery.

Obstetrical anaesthesia

There are case series with parturients for all types of delivery (vaginal, forceps, caesarean section and all common types for anaesthesia (general, epidural, spinal). However, mode of delivery and anaesthesia remain controversial [9].

Uterine or bowel rupture, extensive perineal trauma and delayed wound healing are complications for both vaginal delivery and cesarean section [9]. Severe bleeding - especially for patients with EDS with vascular fragility must be anticipated for both vaginal delivery as well as cesarean section. There's a report of pre-emptive dispense of tranexamic acid and deamino-D-arginine vasopressin (DDAVP) in women with EDS of the vascular type before undergoing elective Cesarean section in spinal anaesthesia [5]. Mortality rates in parturients with vascular EDS have been estimated at 12-25 % [9]. In the hypermobility subtype, episiotomy is related to pelvic prolapse. Therefore, Cesarean section may be considered as first delivery option in this EDS subtype.

In summary, a multidisciplinary approach and consideration to peripartum decision-making and management is indispensable in the setting of EDS [9]. A multidisciplinary team including obstetricians and anaesthesiologists together with cardiologists, cardiothoracic and vascular surgeons, neonatologists should discuss an individual patient-specific approach for an optimal and maximum safe peripartum management. [5].

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