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Opioid-Free Anesthesia Plus Postoperative Management Focused on Anti-Hyperalgesia Approach in Patients with Joint Hypermobility Syndrome Undergoing Occipital-Cervical Fixation: A Narrative Review and Authors' Perspective

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ABSTRACT

Cranio-cervical instability has been well identified in diseases with connective tissue like Ehlers-Danlos Syndrome-Hypermobility Type/Joint Hypermobility Syndrome. It is frequently associated with functional gastrointestinal disturbances, mast cell activation syndrome, and autonomic symptoms as postural orthostatic tachycardia syndrome. These patients suffer from chronic fatigue, and severe widespread pain of exceedingly difficult management and poor control with opioids. Chronic neuroinflammation, opioid-induced hyperalgesia, and Central Sensitization phenomena may explain this complex and painful condition.

The aim of this narrative review is to present updated information on the peri-operative considerations of patients with Ehlers-Danlos Syndrome-Hypermobility Type/Joint Hypermobility Syndrome and cranio-cervical instability who are undergoing Occipital-Cervical Fixation/Fusion. Our protocol of opioid-free total intravenous anesthesia will also be described. Acute post-operative pain management includes the use of a combination of anti-hyperalgesic coadjuvants (lidocaine, ketamine and dexmedetomidine) with an opioid-sparing effect.

Keywords
Opioid-free-anesthesia, Central Sensitization, Hyperalgesia, Craniocervical-instability, Craniocervical-fixation, Occipitocervical-fixation, Ehlers-Danlos Syndrome-Hypermobility type/Joint Hypermobility Syndrome.

Abbreviations List
BIS: Bispectral Index; Ce: Concentration at pharmacokinetic effect compartment; CCF: Cranio-cervical fixation/fusion surgery; CCI: Cranio-cervical instability; CCU: Critical Care Unit; CFS: Chronic fatigue syndrome; CMS: Cervical-Medullary Syndrome; CS: Central Sensitization phenomena; EDS: Ehlers-Danlos Syndrome; EDS-HT/JHS: Ehlers-Danlos Syndrome-Hypermobility Type/Joint Hypermobility Syndrome; EMG: Electromyography; ERAS: Enhanced Recovery After Surgery protocols; HR : Heart Rate; GABA: Gamma-aminobutyric acid; K^+_A: Potassium channels type A; LA: Local anesthesia; JHS: Joint Hypermobility Syndrome; MCAS: Mast cell activation syndrome; ME: Myalgic Encephalomyelitis; MMEPs: Motor-evoke potencials; NFRT: Nociceptive Flexion Reflex Threshold; NMDAr: N-Methyl-D-Aspartate receptors; NMR: Neuromuscular relaxants; NK-1r: Neurokinin-1 receptors; NSAIDs: Nonsteroidal anti-inflammatory drugs; PCA: Patient Controlled Analgesia; OCF: Occipito-cervical fixation/fusion surgery; OFA: Opioid-free anesthesia; OIH: Opioid-induced hyperalgesia; PKC: Protein Kinase C; PONV: Postoperative nausea and vomiting; POTS: Postural orthostatic tachycardia syndrome; SD: Standard Deviation; SSEPs: Somato-sensitive-evoke potencials; TCI: Target Controlled Infusion mode; TMJ: Temporo-maxilar joint; VAS: Visual Analogue Scale score; VGSC: Voltage-Gated Sodium Channels.

Introduction
The aim of this article is to present updated information on the peri-operative considerations of patients with Craniocervical instability (CCI), Joint Hypermobility Syndrome (JHS) and widespread chronic pain who are to undergo Occipital-Cervical Fixation/Fusion (OCF). Our protocol of opioid-free total intravenous anesthesia (OFA-TIVA), and acute post-operative pain management using a combination of the opioid-sparing coadjuvants (lidocaine, ketamine and dexmedetomidine) will also be laid out.

Physiopathology
Genetic condition, chronic neuro-inflammation plus central sensitization as common pathways to bringing onneuronal damage and severe widespread pain

Craniocervical instability (CCI), considered as instability between the skull and usually the first two cervical vertebrae, has been well identified in diseases with connective tissue disorders such as Systemic Lupus, Rheumatoid Arthritis and genetic disorders like Ehlers-Danlos Syndrome-Hypermobility Type/Joint Hypermobility Syndrome (EDS-HT/JHS), Marfan Syndrome, Loeys Dietz Syndome, Stickler Syndrome, Cleidocranial Dysostosis, MorquioSyndrome, Osteogenesis Imperfecta and Down's Syndrome. This broad group of genetic diseases with collagen abnormalities characterized by generalized joint hypermobility can exhibit laxity of the ligaments of the spine and a propensity to have severe symptoms due to CCI [1,2].

CCI may give rise to microtraumas on cranio-cervical joints surfaces and musculoskeletal inflammation with repetitive peripheral sensitization that ultimately result in the complex phenomenon of Central Sensitization (CS) and hyperalgesia [3]. Both CCI and EDS-HT/JHS can lead to adaptation to and compensation of movement patterns. Consequently, they cause overloading in other areas with additional microtraumas to other joints, ligaments, and tendons of the movement apparatus characterized by generalized soft tissue laxity [4-7]. Another important factor relative to biomechanical issue is the lack proprioceptive acuity [8]. It has been suggested that that lack plays an important role in bringing on gait abnormalities, generalized joint and soft tissue microtrauma and musculoskeletal pain. Cervical Medullary Syndrome (CMS) may be involved in the development of more severe proprioceptive disturbances.

In adults with EDS-HT/JHS, the generalized microtrauma of soft tissues and joints leads to a reduction of physical activity as a self-preservation behavior. Therefore, patients tend to do less activity due to a fear of increased pain that leads to deconditioning, body fragility, fatigue and widespread pain. Factors such as proprioception and reflex inhibition may also be implicated as factors causing reduced muscle strength and muscle atrophy [9,10].

Undoubtedly, when considering the multi-systemic nature of generalized joint hypermobility, there is some overlap with all hereditary diseases of the connective tissue. However, interestingly the clinical characteristics of most patients who are going to undergo occipital-cervical fixation and fusion (OCF) by our surgical team present with JHS accompanied by CCI. There is also fatigue, severe occipital-cervical pain, severe widespread pain with a poor response to opioids, functional gastrointestinal disturbances, mast cell activation syndrome (MCAS) and autonomic symptoms like postural orthostatic tachycardia syndrome (POTS) [11]. On the other hand, it is striking that some studies seem to suggest that there is a common genetic condition related to germline excessive duplications and triplications in the allelic TPSAB1 gene encoding α-tryptase that provokes an increase in serum basal tryptase levels from mast cell activity (tryptase ≥8.0 ng/ml). It is a common autosomal dominant inheritance that may partially explain the coexistence of these multi-system symptoms affecting the skin, gastrointestinal tract, circulation and musculoskeletal system as well as for the coexistence of MCAS, POTS and EDS-HT/JHS [12,13].

Furthermore, CMS may explain some of the neurological and ancillary symptoms of the patient with CCI and JHS, particularly when Chiari Malformation is present. An unstable cervical spine may cause functional brainstem compression that is possibly influenced by neck movements and axonal damage due to deformative stress [14].Cervical Medullary Syndrome (CMS),

defined as a group of bulbar symptoms and myelopathy, has been well described in a recent Consensus Statement on Craniovertebral instability [15]. CMS may be explained by the traumatic deformation of axons that induces abnormal sodium influx through mechanically sensitive Na^+ channels that subsequently triggers an increase in intra-axonal calcium via the opening of the voltage-gated calcium channel, up-regulation of glutaminergic pathway, chronic neuro-inflammation and apoptosis. CMS symptoms include altered vision (particularly photophobia, diplopia), altered hearing (peculiar misophonia), altered speech and swallowing, the presence of vertigo, dizziness, numbness (i.e., peripheral hypo/anesthesia), dysesthesias (e.g., allodynia, hyperalgesia, burning sensations, etc.), paresthesia, tremulous limbs, muscle weakness, lack of balance and coordination, abnormal movements (e.g., fasciculations, periodic limb movements, dystonia), altered sleep architecture, mood changes, emotional and cognitive disturbances (minor memory and concentration disturbances). There may also be signs of dysautonomia like POTS, sensory loss, and bladder dysfunction. Some of these symptoms coincide with those observed in chronic fatigue syndrome (CFS), Myalgic Encephalomyelitis (ME), or a combination of both (ME/CFS) [1,14-17].

On the other hand, the presence of migraines and Temporo-Mandibular Joint (TMJ) dysfunction syndrome in patients with JHS are factors that make the diagnosis of craniocervical pain produced by CCI difficult. They also increase the severity of pain. A migraine is considered the most common type of headache in EDS-HT/JHS. Vascular dysfunction may be a trigger of a headache due to either an underlying arteriopathy or cardiovascular dysautonomia. EDS-HT/JHS is associated with a high rate of orthostatic hypotension and POTS. Therefore, it may be postulated that a vascular headache is the main symptom of chronic orthostatic intolerance [11,18,19]. Although infrequent, we have also performed OCF on patients with symptomatic CCI and Vascular-EDS or kyphoscoliotic-EDS with disabling universal spinal pain, hyperalgesia and a medical history of multiple thoraco-lumbar spinal surgeries. Vascular EDS is associated with a high prevalence of severe migraines and arterial aneurysms (Table 1). The routine use of ultrasound for vascular access has allowed us to see an increased tendency to peripheral arterial dissections during the procedure. It also makes it possible to identify central vein abnormalities, particularly unilateral or sometimes bilateral hypoplasia of the internal jugular veins. In those circumstances, echo-guided subclavian vein access is preferred [1,11].

In patients with EDS-HT/JHS and CCI, it is common to find TMJ dysfunction with recurring subluxation which is associated with microtrauma of the joint and a high rate of temporal/occipital and myofascial neck pain. TMJ dysfunction is another condition strongly associated with CS and severe headaches as well as neck pain brought on by increasing pericranial muscle stress and repetitive masticatory and paravertebral muscle damage.

Table 1: The 2017 International Classification of the Ehlers–Danlos syndromes (EDS), Adapted from Malfait F, Francomano C, et al. 2017. [11].

Clinical subtype and Abbreviation	**IP**	**Gen**	**Protein (s)**	**Group**
		Implicated	Implicated	Pathogenesis
Classical EDS (cEDS)	AD	Major: COL5A1	Type V collagen	A
		Rare: COL1A1	Type I collagen	
Classical-like EDS (clEDS)	AR	TNXB	Tenascin XB	C
Cardiac-valvular (cvEDS)	AR	COL1A2	Type I collagen	A
Vascular EDS (vEDS)	AD	Major: COL3A1	Type III collagen	A
		Rare: COL1A1	Type I collagen	
Hypermobile EDS (hEDS)	AD	Unknown	Unknown	Unresolved
Arthrochalasia EDS (aEDS)	AD	COL1A1	Type I collagen	A
		COL1A2		
Dermatosparaxis EDS (eEDS)	AR	ADAMTS2	ADAMTS2	A
Kyphoscoliotic EDS (kEDS)	AR	PLOD1	LH1	B
		FKBP14	FKBP22	
Brittle cornea syndrome (BCS)	AR	ZNF469	ZNF469	F
		PRDM5	PRDM5	
Spondylodysplastic EDS (spEDS)	AR	B4GALT7	β4GalT7	D
		B3GALT6	β3GalT6	F
		SLC39A13	ZIP13	
Musculocontractural EDS (mcEDS)	AR	CHST14	D4ST1	D
		DSE	DSE	
Myopathic EDS (mEDS)	AR or AD	COL12A1	Type XII collagen	C
Periodontal EDS (pEDS)	AD	C1R	C1r	E
		C1S	C1s	

IP: inheritance pattern, **AD**: autosomal dominant, **AR**: autosomal recessive.
Groups according to pathogenetic mechanisms
Group A: defects in collagen primary structure and processing.
Group B: defects in collagen folding and cross-linking
Group C: defects in structure and function of myomatrix, the interface between muscle
Group D: defects in glycosaminoglycan biosynthesis
Group E: defects in complement pathway. **Group F**: disorders of intracellular processe

Frequently, patients with EDS-HT/JHS along with CCI have myofascial trigger points, dizziness, tinnitus and poor body balance when the paravertebral muscles are involved [20]. Relative to joint laxness, the symptoms of the patients overlap in EDS-HT and Joint Hypermobility Syndrome (JHS). Experts have recently considered these two disorders indistinguishable at the clinical level [21,22]. It is important to clarify that the terms EDS-HT or JHS are used indistinctly herein. Although this concept still needs stronger genetic demonstration, we agree with recent evidence that suggests that EDS-HT and JHS might be the same disorder at the genetic level [23].

Management

Perioperative management focusing on Hyperalgesia and Central Sensitization

JHS is highly prevalent among patients diagnosed with widespread chronic pain and hyperalgesia. In patients with JHS who developed CCI, both severe craniocervical pain and widespread pain (i.e. somatic/neuropathic/visceral) have multi-factorial causes, and are strongly related to chronic nociceptive neuro-inflammation, glial activation and neuronal plasticity in the spinal cord, brainstem and brain that lead to a common final pathway, the Central Sensitization phenomena (CS) [1,3,15,17,24].

Moreover, many of the patients with CCI, JHS, chronic fatigue and severe chronic pain receive different types of opioids, which further complicates pain due to opioid-induced hyperalgesia (OIH) [25,26]. Sometimes, these patients may suffer from a category of pain known as central intractable pain, a painful condition that does not respond to opioids and their use may even be detrimental to the patient [27].

Therefore, considering the probable mechanisms of the chronic pain (CS and OIH) that affect patients with JHS and CCI, and considering their frequent association with MCAS and POTS, the use of opioids in total intravenous anesthesia (TIVA) during the OCF was halted. Intra-operative opioid-based analgesia has been replaced by infusions of lidocaine, ketamine and dexmedetomidine. They are coadjuvants with known anti-hyperalgesic properties. This anesthetic protocol tries to improve postoperative pain control, minimize postoperative opioid rescues, and reduce preoperative opioid doses in those patients who have been prescribed these drugs over a long period. The infusions of lidocaine, ketamine and dexmedetomidine are continued at lower doses during the post-operative period (for a maximum of one week) as part of a multimodal analgesia plan.

Pre-anesthetic consideration

Routinely, patients scheduled for OCF come to the pre-anesthetic check-up with a complete evaluation by the neurosurgeon team and the Ehlers-Danlos Syndrome (EDS) experts. The EDS subtype, the diagnose of JHS, the severity of the CCI as well as the concomitant presence of diagnoses such as POTS and MCAS are checked. Triggers and allergies (particularly antibiotics, some opioids and NSAIDs) are taken in consideration for the anesthetic management. In addition, the presence of fatigue, deconditioning, gastrointestinal dysfunction, behavioral or cognitive disturbances is evaluated, and a list of chronic medications is made (Table 2). Additionally, a detailed assessment is carried out to evaluate pain severity and its characteristics, the presence of hyperalgesia/allodynia, the use of mono or multi-therapy with opioids and its effectiveness to pain control. It is important to verify whether the patient has tendency to increase the use of opioids. The current dose, types of opioids, side effects, and the use of coadjuvant drugs for pain control are recorded.

Interrogation focused on Ehlers-Danlos Syndrome (EDS) complications, particularly regarding previous surgeries like orthopedic procedures for articular luxations or kyphoscoliosis, varicose vein surgery, obstetrical procedures or abdominal surgeries is carried out. The patients are also asked about the previous ineffectiveness of infiltrative local anesthetics or failed regional anesthesia. The literature has described some resistance to local anesthesia and shorter duration of its affect in patients with EDS, particularly during dental surgery or obstetric procedures. However, other reports on successful neuraxial anesthesia have also been published. As for EDS patients, there are some hypotheses that suggest the presence of differences in the structure or function of the voltage-gated sodium channels (VGSC) in pain signaling causing some alteration the drug binding sites [28-30].

A thorough bleeding anamnesis is carried out to evaluate the tendency to bruising, difficulties in vascular access, capillary fragility and surgical complications from bleeding. On the MRI or Tomography scanner, the radiologist alerts us to be careful if there are any vascular anomalies or anatomical variants of central veins.

Laboratory test are usually within the normal range and are generally not helpful at estimating the risk of bleeding. In terms of anesthetic planning, the use of desmopressin and tranexamic acid for patients with positive bleeding history is considered [28,31-33]. Cross-matching of RBCs is solicited for all patients (minimum 2 packages).

The Basal tryptase test is already included by EDS experts, and frequently altered.

A medical history of difficult tracheal intubation, a mast cell crisis or hemodynamic instability during previous surgeries are asked about. The evaluation of the airway to plan the best option to manage it, either by means of the video-laryngoscope (we use Glide-Scope®) or with a flexible fiberoptic bronchoscope (FOB), is particularly important. Because of symptomatic CCI and cervical hyper-laxity, we no longer use the direct laryngoscope to avoid potential spinal damage due to hyperextension during laryngoscopy. Some patients represent a challenge to airway management because they suffer from extreme TMJ subluxation or limited mouth opening due to painful TMJ dysfunction and ankylosis, dental crowding and a high or narrow palate as well as fragility of the oral mucosa with easy bleeding. They can also have a complex and chronic craniocervical antalgic posture, or may have external craniocervical fixations that make either facial mask ventilation as tracheal intubation difficult (Figure 1).

Treatment related to POTS.
Alpha-adrenergic drugs (midodrine or dihydroergotamine).
Beta-blockers (metoprolol, atenolol, bisoprolol, or propranolol).
Clonidine (POTS-hyperadrenergic type).
Pyridostigmine.
Fludrocortisone.
Oral sodium/potassium supplements.
Selective serotonin /norepinephrine reuptake inhibitors (SSNRI).

Treatment related to chronic pain, anxiety, and sleep disorders.
Fentanyl (patch, oral), oral morphine, oral oxycodone, buprenorphine (patch).
Pregabaline, gabapentin, carbamazepine.
Benzodiazepines. Mitarzapine, quetiapine.
Treatment related to MCAS.
Anti-H1: Cetirizine, levocetirizine, desloratadine,fexofenadine, diphenhydramine, chlorpheniramine.
Anti-H2: ranitidine,famotidine.
Leukotriene modifying agents (LTMA): Montelukast, zafirlukast, zileuton.
Mast cell stabilizer: Cromolyn sodium, ketotifen, rupatadine, omalizumab.
EpiPen (SOS)
Glucocorticoids (prednisone).
Chemotherapy: Interferon Alfa-2b, cladribine, masitinib, imatinib.

Treatment related to gastro-intestinal dysfunction
Trimebutine, metoclopramine, domperidone,cromilyn sodium, probiothic, prometazine, omeprazol, pantoprazol, esomeprazol.

Warning on management.
Medication that can worsen POTS.
Alpha adrenergic antagonists, calcium antagonist, diuretics, nitrates, hydralazine, opiaces, phenothiazines, angiotensin receptor blocking agents, angiotensin converting enzyme inhibitors.
Some potential MCAS triggers
Cold or sudden temperatures changes.
Stress: emotional, environmental, physical.
Pain.
Drugs: NSAIDs, some opiates, some antibiotics, and contrast dyes.
*COX2: etoricoxib or celecoxib may be safe.
Chemical odors, perfumes and scents.
Infections, venoms.
Sun/Sunlight.
Mechanical irritation, friction, vibration.

Table 2: Chronic medication frequently prescribed to patients with EDS-HT/JHS, POTS, MCAS and widespread pain.

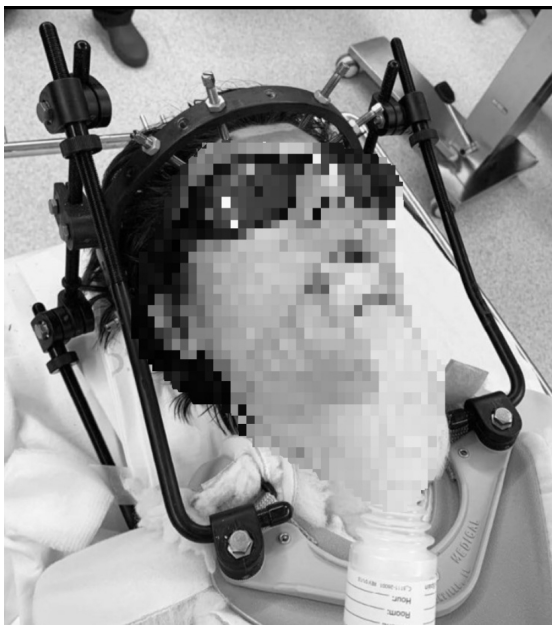

Figure 1: Patient with external craniocervical fixations and difficult facial mask ventilation. To rescue the ventilation/oxygenation, the patient had to be ventilated with Laryngeal Mask Airway previously to perform the tracheal intubation with fibro-optical bronchoscope.

Besides standard laboratory tests and thorax X-rays, an echocardiogram to rule out a possible cardiac pathology (e.g., valve insufficiency or aortic root dilatation) is requested.

Monitoring

Typically, monitoring consists of NIBP, EKG, SpO_2, $EtCO_2$, BIS, the esophageal temperature, neuromuscular relaxation, diuresis, arterial/central venous blood gas testing, and the parameters of mechanical ventilation. NIBP is initially measured during anesthetic induction and oro-tracheal intubation.

An invasive arterial blood pressure line and a central vein line are accessed after tracheal intubation. Preferably, an internal jugular vein is accessed to administer vasopressor drugs and for CVP measuring. All vascular lines, including two peripheral venous lines (18 or 16 gauge, if possible), are carefully accessed under ultrasound guidance. Before puncturing, a thorough ultrasound evaluation is done to determine the feasibility of accessing the arterial and central venous lines. There is always a potential for iatrogenic arterial dissection or venous rupture, with catastrophic complications, due to tissue fragility. Interestingly, we have had some patients with unilateral or bilateral hypoplasia of the internal jugular vein that led to accessing a subclavian vein [28,34]. These patients have more of a possibility of bleeding due to compensatory hypertrophy of the posterior cervical venous return.

Somatosensory Evoked Potentials (SSEPs), muscle Motor Evoked potential (mMEPs), and electromyography (EMG) are measured. Therefore, we must administer TIVA without neuromuscular relaxants (NMR) during the surgical procedure [35].

Specific care and positioning of patients

These patients suffer from a high level of anxiety and pain. Therefore, all patients are supported by a team of top-notch psychologists throughout the peri-operative period. It includes an educational program on CS control [36].

The patients know their long-term medication and their MCAS triggers very well. As result, the patients often show fear of being pre-medicated with any other drug they do not know. In consequence, we give just oral midazolam/pregabalin early in the morning. Upon arriving in the pre-anesthetic room and a peripheral venous line has been accessed, prophylactic intravenous antibiotics (cefazoline 2grs) and intravenous medications like ranitidine (50 mg), methylprednisolone (5-10mg/kg) and dexchlorpheniramine (5-10mg) are administered. Teicoplanin, vancomycin or another antibiotic are prescribed by infectious disease experts if there is PNC-allergy.

The transfer to the operating room and surgical positioning (prone) must be done very carefully. These patients are very susceptible to recurring joint dislocations, severe elongation injury to the brachial plexus, pressure injuries of the peripheral nerves (i.e., radial, cubital, popliteal nerves) or skin pressure injures over certain bone points like the shoulders, elbows, wrists, pelvis, antero-superior iliac prominences, knees and ankles .Patient handling must be performed with a maximal reduction of shear forces to the skin. Padding and cushioning must be used to reduce shear forces and external tissue pressure. Furthermore, special oral protection is used to avoid TMJ luxation and to prevent a motor stimulation-induced bite injury to the tongue during neuro-monitoring.

Due to the heightened risk of retinal detachment and globe rupture, the eyes should be well-protected. Fortunately, a special surgical table with a craniocervical stabilizer/fixer that reduces the aforementioned complications is used. All patients are protected with a graduated compression stocking to increase venous return and reduce deep vein thrombosis. Additionally, a forced-air warming blanket is routinely used. These patients often lack efficient thermo-regulatory balance.

Anesthetic management

Anesthetic induction consists of midazolam 0.04mg/kg, ketamine 0.2mg/kg and propofol administrated by TIVA-TCI (Target Controlled Infusion) to achieve a BIS between 40-60. A bolus of lidocaine is administrated at 1.5mg/kg followed by cis-atracurium 0.15mg/kg to facilitate orotracheal intubation. If the basal heart rate (HR) is greater than 90 beats per minute, esmolol (0.5-1mg/kg) is administrated before intubation. Phenylephrine 50-100mcg can be used to maintain the blood pressure (BP) close to the basal level (±15-20%).

Once the patient is stabilized, a dexmedetomidine infusion is started at 2.0 mcg/kg/h over 20 minutes, and a bolus of 20ml/kg of NaCl 0.9% and 50mg/kg of $MgSO_4$ [37,38] is administered. We use "Hotline™" to infuse warming fluids.

The opioid-free anesthesia is maintained with the following protocol:
Propofol by TCI (Schnider model): 2.0-3.0mcg/ml to keep the BIS between45-55.
Lidocaine:2.0-2.5mg/Kg/h
Ketamine: 0.2mg/kg/h
Dexmedetomidine: 0.2-0.5mcg/Kg/h
No other neuromuscular blocker is used after induction until the surgery is finished.

Paracetamol (1gr), ondansetron(8mg), dexamethasone(8mg), pantoprazole(40mg) and tranexamic acid (2gr) are also administered [32,33] (Figure 2).

If necessary, a carefully titrated phenylephrine infusion (0.1-0.5 mcg/kg/min) is administered to maintain the BP close to the basal value (±15-20%). Low doses of norepinephrine (0.02-0.05mcg/Kg/min) have been carefully used in patients with a poor response to phenylephrine. Ephedrine is not recommended because it can cause unpredictable beta-adrenergic hyperactivity. Keeping normal BP and oxygenation, normocapnia, normothermia and avoiding anemia are essential to obtaining adequate neuro-monitoring records. Metoprolol (2.0-5.0 mg iv) may be used to control persistent high HR unrelated to hypovolemia. Labetalol may also be an option.

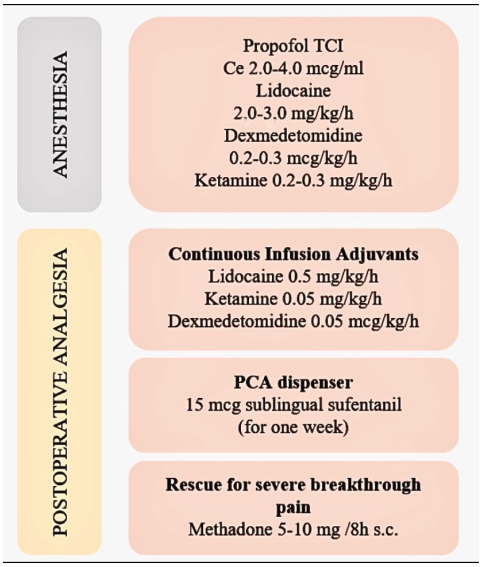

Figure 2: Opioid-Free Anesthesia (OFA) protocol plus postoperative anti-hyperalgesic management.

The CVP in maintained at between 8-10 mmHg and diuresis at between 0.5-1.0ml/Kg/h with NaCl 0.9% perfusion. To decide on blood transfusion, the parameters to analyze are the following: hemodynamic status, amount of bleeding, presence of heart disease, SvO_2, Hb^+/Hct,pH, $HCO3^-$/base-excess, lactic acid. Generally, we use a transfusion cut-off at Hb^+8.0mg/dL but insist that this cut-off value must be comprehensively analyzed. Desmopressin (0.2-0.3 mg/kg) is administered in patients with a surgical history of bleeding as well as when the surgeons consider that there are difficulties with hemostasis (i.e., continuous layered bleeding). On the other hand, higher doses of tranexamic acid and cell-saver (blood salvage) are used in patients that reject blood transfusions, or in cases in which there is documented hypertrophy of the posterior cervical venous return that may predict abundant bleeding [28,31,39].

Post-operative period.

Once the surgery is finished, the propofol dose is lowered to 1.0mcg/Kg/min, lidocaine is reduced to 1.0 mg/kg/h, ketamine to 0.15mg/Kg/h, and dexmedetomidine to 0.15 mcg/Kg/h (Figure 2).

When the patient is repositioned face-up, a check is made for the presence of pressure injuries, bruising or skin tears as well as any luxation or joint dislocation. Moreover, the eyes, tongue and the whole oral mucosa is checked to rule out any injury.

The still intubated and sedated patient is transferred to the Critical Care Unit (CCU).The infusions of lidocaine, ketamine and dexmedetomidine are continued at the same dose during the CCU-stay, and ventilation weaning is performed by the CCU team after stopping propofol.

If it is possible, those infusions are maintained at the same dose for 2 days. Then, they are gradually reduced and administered for no more than one week of the hospital-stay and monitored by the nurse pain-team and anesthesiologists.

Sublingual sufentanil as pain-relief rescue is used. The sufentanil is self-administered by the patient with a special portable PCA-dispenser (Zalviso™: 15mcg/mini-pills, 20min lock-out). The frequency of opioid rescue/24 hours is recorded [40].

Other indications are Bemiparin 3.500Ud/day s.c. (started at 24h of P.O), baclofen (10-25mg every 8 hrs.), diazepam (5mgevery 8-12 hrs.), paracetamol, methylprednisolone (40mg e/8 hrs.), dexchlorpheniramine and ranitidine (SOS) and pantoprazole. The graduated compression stocking is used until the patient begins mobilization.

Despite the possibility of opioid-related histamine release in patients suffering breakthrough pain, methadone (opioid-NMDA effects) has been used as a pain-killer rescue after administering dexchlorpheniramine and ranitidine. Until now, there have not been any MCAS events after methadone rescue [41,42]. In addition, by increasing oral baclofen dose (25mg e/8hrs), we have noticed an improvement in these patients with "uncontrolled pain". Furthermore, intensive psychological support is given in difficult cases. That fact has leaded us to consider cervical-dorsal muscular spasticity or muscle contracture as an additional component of a pain crisis. Given "the new ergonomic status" because of OCF along with an altered descending inhibitory GABAergic pathway, baclofen may act in the same way as it does in cases of spasticity due to spinal cord damage [44,45].

Afterward, when the lidocaine, ketamine and dexmedetomidine infusions have been stopped, oral ketamine is administered to patients with widespread pain that is difficult to control, a preoperative history of treatment with opioids, OIH, an important neuropathic component, or tendency to use high sublingual sufentanil rescue doses.

Discussion

Over last decade, many articles about the benefits of OFA have been published, particularly related to ERAS protocols for patients undergoing laparoscopic gastrointestinal surgery. Otherwise, studies of OFA in patients undergoing spinal surgery show controversial results in term of the postoperative reduction of opioids, the recovery time, the complications and the duration of the hospital stay [46-48]. However, there seems to be more agreement about the perioperative use of non-opioid coadjuvants infusions as part of a multimodal analgesia protocol to achieve enhanced recovery after spine surgery [49-51].

Although the anti-nociceptive and anti-hyperalgesic effects of the coadjuvants used in OFA ("opioid-substitutes") have been well studied, there are still questions about their clinical analgesic efficacy during surgery compared to opioids. Questions about what combination of coadjuvants to use have also arisen. Lacking reliable monitoring of nociception (maybe defined as sympathetic/parasympathetic balance monitors in response to surgical stress) is an important barrier to changing the paradigm in spine surgery.

Monitoring of nociception based on heart rate variability and vagal tone (HRV) have been validated to measure intra-operative opioid-induced analgesia(i.e. ANI, NoL Index, STAN index) but they have not been validated for OFA [52]**.** To monitor nociception in patients under opioid-free total intravenous anesthesia (OFA-TIVA) without NMR, the Nociceptive Flexion Reflex Threshold (NFRT) might be useful. NFRT is a promising method, which is based on EMG and BIS, that allows for the prediction of movement as responses to surgical stimulus under propofol mono-anesthesia. This fact may confirm its utility to predict movement responses under TIVA [53].

The present article shows a propofol-based OFA-TIVA protocol in these special patients (EDS-HT/JHS) with widespread pain and SC who are undergoing OCF (a major spinal surgery) due to CCI. The intra-operative analgesia is provided by infusions of lidocaine, ketamine and dexmedetomidine, coadjuvants with well-known anti-hyperalgesic properties and multiple mechanisms of analgesic action. Moreover, due to mandatory needs of neuro-monitoring (SSEPs, mMEPs, EMG), anesthesia is performed without NMR during the surgical procedure. EMG records have allowed us to confirm no movements related to surgical stimulus throughout surgery in all patients. On the other hand, BIS was kept between 40-55 with propofol-TCI at Ce. Of 2.3 ± 0.5mcg/ml, a fact that indirectly suggests a state of appropriate surgical analgesia.

The doses of lidocaine, ketamine and dexmedetomidine proposed in our protocol seems to be a combination with balanced anti-nociceptive synergism which coincides with recent publications that describe lidocaine, ketamine, dexmedetomidine and $MgSO_4$ as the best options [54-56].

In term of the reduction of postoperative opioid requirements and a better recovery, the controversies around the benefits of OFA in major spinal surgery may be due to the diversity of surgical procedures, the varying degrees of complexity of the cases and the exceptionally varied use of coadjuvants for PO multi-modal analgesia. There is strong evidence that opioid-inclusive anesthesia does not reduce postoperative pain, but is associated with more side effects in comparison with OFA. OFA management should be pondered on a case-by-case basis [48,59].

Since the use of the OFA protocol plus peri-operative infusions of lidocaine, ketamine and dexmedetomidine has been in place, the patients have shown better pain control, a noticeable reduction on the postoperative Visual Analogue Scale (VAS) and a reduction in methadone rescues. Moreover, the postoperative patient-comfort has improved. Our data will be further analyzed and presented in a subsequent publication.

In patients with EDS-HT/JHS, some authors have described the possibility of local anesthesia (LA) allergy as well as some resistance to the LA effect, particularly related to infiltrative techniques, nerve blocks or epidural anesthesia in dental, orthopedics and obstetrics procedures. As we mentioned before, pre-anesthetic evaluation carefully covers the possibility of a lidocaine allergy [60-62]. Regarding resistance to LA, it seems to be due to alterations in LA dispersion because of the special characteristic of EDS-collagen fibers, or because of the presence of differences in the structure or function of the voltage-gated sodium channels (VGSC) in pain signaling that causes some alteration the LA binding sites [28-30].

Until now, we have not had any complication that has led us to think about resistance or the lack of an intravenous lidocaine analgesic effect. It may be because intravenous lidocaine analgesic mechanisms are mediated by an strong systemic anti-inflammatory effect and other multiple anti-nociceptive pathways (i.e., reduction of inflammatory biomarkers by direct action on cell membrane of monocytes, neutrophils and mast cell, PKC-mediated reduction of Ca^{++}intracellular influx and K^+_A-channels, action over cholinergic, adrenergic, GABAergic, NMDAr, and NK-1r pathways, etc.). Lidocaine has a non-relevant analgesic effect mediated by Na^+-channel blocks at therapeutic plasmatic concentrations [55,63,64].

The most important reasons that drove the use OFA in these particular patients are the presence of widespread chronic pain, CS and OIH, a high prevalence of gastrointestinal disturbances and the reduction of MCAS triggers during surgery (also avoiding NSAIDs) [26,66]. Avoiding NMR in OFA-TIVA has been a challenging, but also a strength. The absence of movements related to surgical stimulus and further documented by EMG suggests that the infusions provide good clinical analgesia. Moreover, the continued postoperative use of lidocaine, ketamine and dexmedetomidine infusions and the gradual reduction of the doses over one week might overcome the peak of the inflammatory surgical-response, and therefore its effect on pain and CS [53,64,66].

To be consistent with OFA management, there are still doubts as to whether to continue administering opioids (sufentanil or methadone) to relieve severe postoperative breakthrough pain or to consider non-opioid options involving different nociceptive pathway like sublingual medicinal cannabinoid rescues, pre-operative and the post-operative use of memantine, dextromethorphan, or another one [67-70].

Conclusion

Patients with EDS-HT/JHS and CCI suffer from severe chronic widespread pain and hyperalgesia that are strongly related with the Central Sensitization phenomena.

The use of OFA-TIVA is feasible, and safe to use in patients who are undergoing OCF with EDS-HT/JHS associated with POTS, MCAS, and gastrointestinal dysfunction.

The infusion of lidocaine, ketamine, and dexmedetomidine seems to provide adequate analgesia to use in combination with propofol for TIVA without NMR. The neuro-monitoring (BIS, EMG, SSEPs, mMEPs) records suggest that the it is proper.

The post-operative pain control of patients who are undergoing OCF is quite difficult and complex. The use of lidocaine, ketamine

and dexmedetomidine infusions during the post-operative period can be a useful tool to improve pain management while bringing the total amount of opioids used down during the hospital-stay.

Until now, it has been difficult to completely eliminate the use of opioid rescues to control severe post-operative breakthrough pain. It is important to continue studying more non-opioid therapeutic options to reduce gastro-intestinal side-effects, OIH and opioid tolerance and dependence.

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