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Perioperative Management of Patients with Down Syndrome: A Review

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Abstract

Introduction: Down syndrome (DS) or Trisomy 21 is associated with a higher morbidity, mortality and surgery need. This syndrome presents a characteristic set of morphologic features regarding several systems: cardiovascular, respiratory, gastrointestinal, nervous, musculoskeletal, immune, hematologic, endocrine, ophthalmic and hearing. Therefore, special care is required to maximize safety before, during and after surgery.

This study's objective is to systematically review these needs in the perioperative (pre, intra and postoperative) period, and how to approach them.

Methods: PubMed and Web of Science were searched and 32 articles selected for this revision.

Results: DS patients have commonly pulmonary arterial hypertension and congenital heart defects.

They may have swallow function abnormalities or gastro-esophageal reflux disease. Airway and respiratory tract conditions, such as aspiration pneumonia, obstructive sleep apnea, congenital tracheal stenosis, and recurrent infections, are common.

In addition, cervical instability and nociception disorders may be present.

Discussion: In order to prevent perioperative complications, several practices are suggested. In the preoperative period: assess the surgical risk using Aristotle and RACHS-1 scoring systems, analyze a recent echocardiogram, consider prophylactic antibiotic therapy and take strict aseptic precautions. Performing an X-ray looking for cervical instability is a controversial topic.

In the intraoperative period: administer intravenous sedation in dental treatments, have anticholinergic agents available, consider aspiration prophylaxis, and position the neck particularly. However, there is no agreement on the best airway device.

In the postoperative period: provide longer hospitalizations or stay in intensive unit care, remove catheters as soon as possible, assess the pain with specific tools, administer lower weight-adjusted doses of dexmedetomidine (controversial topic) and use morphine, once no opioid resistance was found.

Conclusion: There are variations in the approach to the perioperative period, and even lack of agreement in some topics, making clear the need for specific guidelines to standardize this process and reduce morbidity.

Keywords: Down syndrome anesthesia; Down syndrome surgery; Perioperative management; Down syndrome

Abbreviations: DS: Down Syndrome; PA: Pulmonary Artery; CHD: Congenital Heart Defects; PAH: Pulmonary Artery Hypertension; ASD: Atrial Septal Defect; HAPE: High-Altitude Pulmonary Edema; ES: Eisenmenger's Syndrome; GERD: Gastro-Esophageal Reflux Disease; OSA: Obstructive Sleep Apnea; ILD: Interstitial Lung Disease; ICU: Intensive Care Unit; GABA: Neurotransmitter Gamma-Aminobutyric Acid; ADI: Atlantodens Interval; MRI: Magnetic Resonance Imaging; AAP: American Academy of Pediatrics; ASA: America Society of Anesthesiologists; ECG: Electrocardiography; RSI: Rapid Sequence Induction; RTI: Respiratory Tract Infections; LMA: Laryngeal Mask Airway; ETT: Endotracheal Tube; PLMA: ProSeal LMA; NIOM: Neurophysiologic Intraoperative Monitoring; MAC: Minimum Alveolar Concentration; SpO_2: Peripheral Oxygen Saturation

Introduction

Down syndrome (DS) or Trisomy 21, is the only known autosomal aneuploidy consistent with a prolonged survival into adulthood [1] and was first described by Dr. John Langdon Down in 1866 [2]. This trisomy occurs mainly when the disjunction of the chromosome 21, in meiosis, does not occur. A nonviable gamete, lacking chromosome 21, and a gamete with two chromosomes 21 is the consequence. When this diploid gamete merges with a normal gamete, a zygote with three chromosomes 21 is produced and this pattern is usually preserved in all subsequent mitotic divisions. This is the most common mechanism by which this extra chromosomal material arises, resulting in a total of 47 chromosomes, which are present in all cell lines [1].

The second mechanism responsible for DS is the translocation of chromosome 21 to another chromosome, resulting in zygotes with an excess of chromosomal material, indistinguishable from regular DS, or with a normal number of chromosomes phenotypically normal (having either a normal karyotype or a balanced translocation), aka zygotes "carriers" of DS. Mosaicism is the last mechanism responsible for the arising of DS and consists in the presence of trisomy 21 in some but not in all cell lines. Their phenotypic expression varies from typical DS to clinically normal individuals, which are only diagnosed after having parented several DS offspring [1].

DS incidence is approximately 1 per 800 live births and is associated with a higher mortality rate [2]. However, medical care improvement and surgical correction of congenital defects have greatly reduced mortality in the postnatal period, so that survival past early adulthood is no longer uncommon [1].

DS patients present a large but inconsistent set of typical morphologic features. These anatomic and physiologic features appear even before birth. DS babies are usually small for their gestational age and born prematurely, although their placentas have a normal size and morphology [1,3]. Growth remains depressed in infancy and throughout childhood [1]. Besides this, they usually present different features in several systems: cardiovascular, respiratory, gastrointestinal, nervous, musculoskeletal, immune, hematologic, endocrine and ophthalmic and hearing [4-6]. The phenotype is also variable, both in terms of associated anomalies and degree of cognitive impairment, ranging from mild (IQ: 50-70) to moderate and, occasionally, to severe (IQ: 20-35) [7].

Cardiovascular system

The majority of congenital defects observed in DS are in the cardiovascular system, with an incidence of heart malformations about 44% [8]. A fetal study found an even higher rate of 56%, which is explained by the higher loss rate of chromosomally abnormal fetuses [9]. Regarding cardiovascular malformations, the atrioventricular septal defect is the most common finding [10,11].

Most of cardiovascular abnormalities involve a left to right shunt that leads to increased pulmonary blood flow and consequently to pulmonary hypertension [4]. Pulmonary hypertension is defined as a mean pulmonary artery (PA) pressure over 25 mmHg at rest, along with the absence of left atrial hypertension, and with a pulmonary capillary wedge pressure below 15 mmHg [12].

Gastrointestinal system

The second most common group of congenital abnormalities in DS patients concerns the gastrointestinal system. The Duodenal atresia is well known for being associated with DS. Hirschsprung's disease and gastro-esophageal reflux disease (GERD) are also more frequent and often found in this group [4].

Respiratory system and airway

The most frequent anatomic features found in DS patients are macroglossia, crowding of the midfacial structures, a high arched, narrow palate, micrognathia, a short broad neck and a high incidence of tonsillar and adenoidal hypertrophy [4]. Other authors also refer flattened nasal bridge, shallow hypopharyngeal dimensions, tracheal and congenital subglottic stenosis, airway malacia, pharyngeal muscle hypotonia, increased secretions and frequent infections [10].

Immune and hematologic system

DS patients have a relative immune deficiency leading to an increased susceptibility to all infections, especially those of the respiratory tract. There is also an increased incidence of positive hepatitis B surface antigen in DS individuals [4].

Up to 80% of newborns with DS have neutrophilia, up to 66% have thrombocytopenia and up to 34% have polycythemia. Although these events occur most frequently during the first month of life, the risk remains increased during the first year [10]. Leukemia (acute lymphoblastic and myeloblastic) is 20 times more frequent in DS than in general population [4]. Approximately 10% of neonates will also have transient myeloproliferative disorder, or transient megakaryoblastic leukemia, which usually resolves within 3 months of life [10].

Endocrine system

It has been shown that DS individuals have more propensities for organ specific autoimmune dysfunction, in particular congenital hypothyroidism. In fact, 40% of adults with trisomy 21 have evidence of hypothyroidism. Relatively low blood catecholamine levels have also been reported [4].

Central nervous system

In different degrees mental retardation is universal in DS. However, these people are usually friendly and gregarious. It is also known that the muscle tone is abnormal in many patients, with hypotonia being reported in up to 75% of DS. Strabismus incidence is also higher than in normal children and epilepsy is present in up to 10% of individuals [4]. DS patients do not always exhibit signs of distress in reaction to noxious stimuli, when compared to general population, which may be a consequence of anatomical and neurotransmitting alterations that may play a role in nociception and in the pain-control system [13].

Peripheral nervous system

In addition, DS patients have an exaggerated mydriatic response to ocular atropine (including following conjunctival instillation), and an increased heart rate response to parenteral atropine has been documented. On the other hand, some studies have not found cardiac sensitivity to atropine [2,4]. DS individuals have also decreased sympathetic nervous system activity and circulating catecholamines [2,4].

Cervical instability

An association between atlantoaxial instability and DS is well documented, with an incidence of between 12% and 50%, depending on the definition of instability, cohort age, and the imagological exams used in studies [4,14].

In addition, a wide variation in the rate of atlantooccipital and atlantoaxial instability in patients with DS arises in the literature. Atlantooccipital and/or atlantoaxial instability are referred as having a frequency of 15% [15], while a later review has found craniocervical instability reported in 8-63% of the cases and atlantoaxial instability in 10%-30% [16]. The frequency of osodontoideum (separation of the odontoid process from the body of the axis) may be as high as 6%, which could contribute to instability [10].

Due to all conditions mentioned above, most of DS patients will need a surgery in their lives. The gastrointestinal and cardiac malformations often require surgery within the first days to weeks of life [7]. Other surgical conditions occur with higher rates, such as Hirschsprung disease, polydactyly, clef palate, and cataracts. Multiple malformations occur in some patients, and the repair of one needs to be considered in light of the other abnormalities [10].

In fact, it is required special care to maximize safety before, during and after surgery. The incidence of anesthesia-related complications was found to be significantly higher in DS patients, in a large retrospective study [17]. However, no current consensus exists regarding the evaluation and management of these issues [10]. This lack of agreement in the anesthetic approach of DS patients exists due to the limited data available to guide practice, as patients with potential cognitive or neurological impairments are usually excluded from controlled analgesic trials [7].

The objective of this study is to systematically review the special needs of this population in the perioperative period, and its management to meet these special needs. Regarding the preoperative, the intra-operative and the postoperative period, individualized needs of these phases will be discussed, towards the safest surgical experience.

Methods

A search was performed on PubMed using the following keyword combinations: "Down syndrome", "anesthesia" and "surgery"; "Down syndrome", "postoperative", "preoperative" and "anesthesia". Another search was performed on Web of Science using "Down syndrome", "anesthesia" and "management" as keywords.

From a total of 199 studies found using the mentioned keywords, 32 were selected to this revision. Inclusion criteria for the study were: written in English and being a systematic revision, a retrospective study, an observation prospective study, a case study, or a guideline. Both pediatric and adult populations were accepted, since the main features are commonly present in both ages. Relevant papers cited in the selected articles were added to the group, ending up with 66 articles being analyzed in this review.

Some studies were not included such as: studies regarding other syndromes than DS; studies approaching specific features present in DS but not focusing on this pathology; studies about special needs but not related to DS; general issues on genetic diseases but not focusing on DS; specificities of subsidiary methods of diagnostic or treatment of abnormalities present in DS; hospital costs; epidemiologic issues; specific surgery details (Figure 1).

Results

Cardiovascular system

Structural congenital heart defects (CHD) are found in over 40% of infants with DS [18]. In a population of children with CHD, DS patients had a significantly higher mean PA pressure (51 *vs.* 26 mmHg) and rate of pulmonary arterial hypertension (PAH) (51,4% *vs.* 18,4%) [19]. PAH also develops significantly earlier in DS patients [20].

The development of PAH is explained by increased pulmonary flow, which intensifies the shear stress on pulmonary endothelial cells, resulting in a pathological process of progressive intimal fibrosis [10,21]. Eventually, this fibrosis will obstruct the lumen of the arteries, further increasing the pulmonary vascular resistance. In addition, Chi and Krovetz [20] found higher rates of PAH in children with a primum atrial septal defect (ASD) and DS (5 out of 6) when compared to those with a primum ASD without DS (4 out of 14).

However, PAH may develop even in the absence of congenital heart disease in DS [4,11]. The other mechanism responsible for PAH in DS is not fully understood but is thought to be related with hypoxia secondary to recurrent respiratory tract infections (RTI), upper airway obstruction, obstructive sleep apnea and hypoventilation due to muscle hypotonia [2,4].

Another possible manifestation of the pulmonary vasculature vulnerability in DS is high-altitude pulmonary edema (HAPE) [18]. The presence of specific symptoms and signs of pulmonary edema, in the context of a recent altitude gain, defines HAPE. It has been described as occurring in children with DS, CHD, left to right shunts and known chronic PAH, but also in children without any history of CHD or PAH. Indeed, HAPE may represent the first manifestation of pulmonary hypertension in DS.

Lower airway abnormalities in DS have also been extensively studied as risk factors for PAH [10]. Authors have found that a diminished alveolar count, commonly present in DS patients, significantly reduces the internal surface area of the lung and the vascular bed itself, contributing for an early development of PAH. Other abnormalities in lung morphology were found, such as reduced airway branching, reduced number of airway generations (75% of the expected value), and reduced inflated lung volumes after 6 months of age.
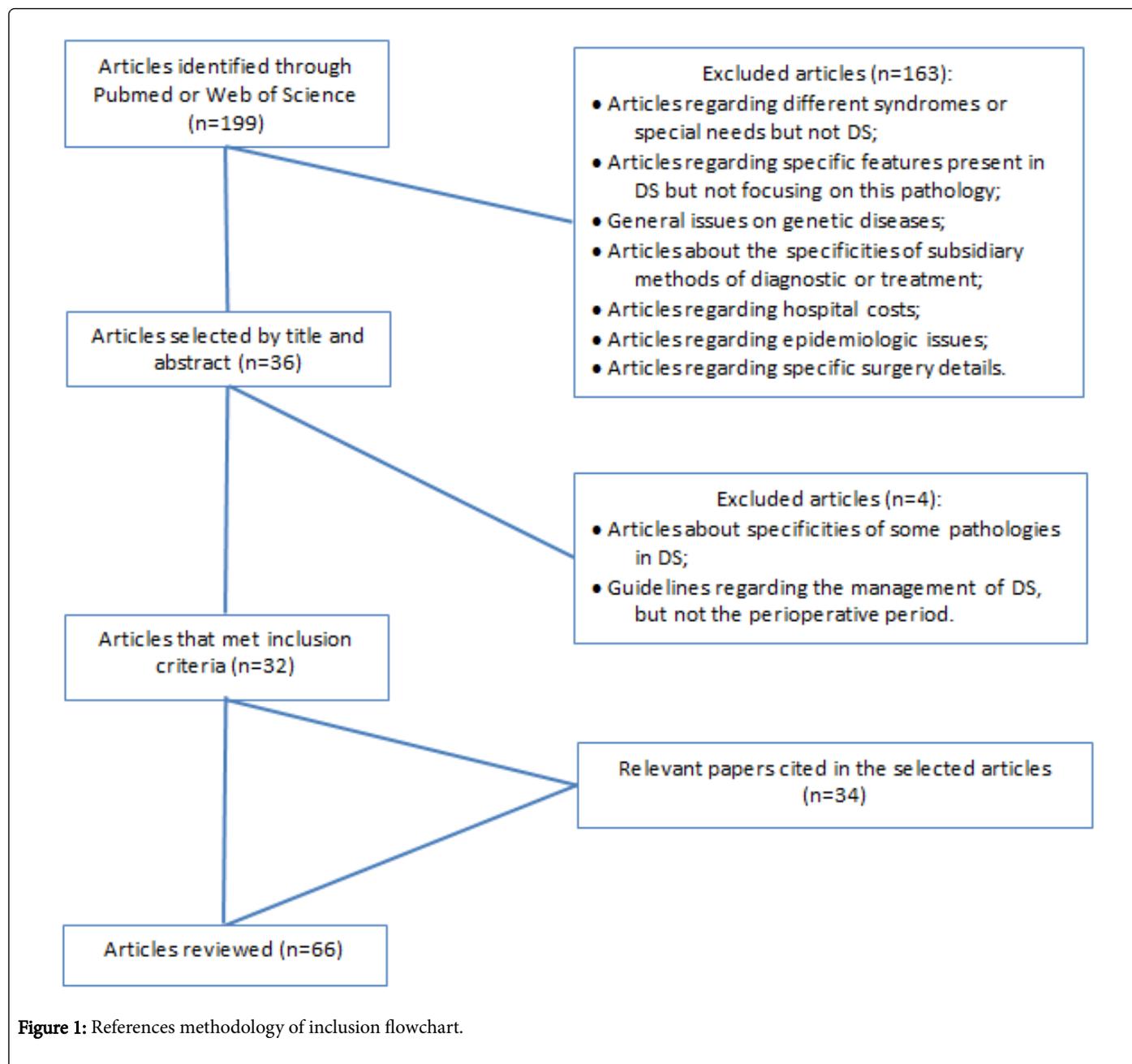
Figure 1: References methodology of inclusion flowchart.

Regarding cardiac malformations, 50% of endocardial cushion defects in general population are associated with DS [2]. Malformations include a range of defects characterized by involvement of atrial septum, ventricular septum, and one or more AV valves. The ostium primum defect is a consequence of the lack of superior and inferior cushion fusion, resulting in septum intra atrial communication, thus shunting blood from left side to right side. In a complete defect, not only large ventricular septal defect may happen but also valvular defect may occur, resulting in volume overload of both the right and left ventricles.

Other cardiac anomalies may include Tetralogy of Fallot and ductus arteriosus persistence. As aforementioned, all these cardiac malformations result in pulmonary overload, pulmonary vascular disease and congestive heart failure [2].

Eisenmenger's syndrome (ES) is a usually rare condition but with a higher incidence in DS. ES is characterized by: a high pulmonary vascular resistance, secondary to long-standing left-to-right shunt causing PAH; and a reversed (right-to-left direction) or bidirectional shunt at the aortopulmonary, interatrial or interventricular level [22,23]. As a result, these patients develop cardiomegaly, chronic hypoxemia and polycythemia [23]. It will become rarer as more of the predisposing congenital cardiac lesions undergo corrective surgery [22].

Patients with DS, due to heart lesions, have an increased risk of infective endocarditis [11]. The association of DS with Morgagni hernia (herniation of the abdominal organs into the chest cavity through a retrosternal defect) was reported in 20%-30% of patients

with DS, and it was suggested that muscle hypotonia plays a role in this relationship [24].

Turhan et al. [25] reported two cases of DS patients, with 24 and 19 years old, submitted to surgical repair of secundum ASD and Tetralogy of Fallot, respectively. The surgical treatment was successful in both cases, although the high risk comorbidities. 5 years and 4 years later the surgeries, heart failure of both patients was functionally classified in level 1 of New York Heart Association, and echocardiographic controls showed intact interatrial and interventricular septum, respectively. Moreover, in Tetralogy of Fallot's patient a blood gradient of 20 mmHg was detected on the pulmonary valve. These case-reports alert for the importance of an early diagnosis and early surgical treatment in the prognosis of CHD in DS.

Gastrointestinal system

Patients with DS may have abnormalities of swallow function, esophageal dysmotility or GERD [18], which may often require surgical repair at a young age [26].

Swallowing dysfunction may origin aspiration, the inhalation of foreign material into the lower airway, which particularly occurs with liquids? Frequently DS children aspirate silently, which means that no cough or choking symptoms are observed at the time of aspiration. Esophageal scintigraphy shows a significantly increased retention of liquid and semisolid boluses in the esophagus, and a higher incidence of achalasia. Chronic recurrent aspiration consequent to swallow dysfunction may cause children to present wheeze, chronic cough, recurrent pneumonia, pulmonary scarring or an impaired lung function [18].

GERD is common in DS and is defined as a condition that evolves when the reflux of stomach contents causes uncomfortable symptoms and/ or complications. Its physiopathology is probably based on pathological changes in the nervous system. GERD in children with DS may lead to a number of serious complications, including aspiration pneumonia and obstructive sleep apnea (OSA) in children with DS [18,27]. Since a wide range of treatment options are now available, this disease should be considered as a probable diagnosis in any child with DS with important or recurrent respiratory problems [18].

DS is related to a number of congenital gastrointestinal defects, such as esophageal atresia, duodenal atresia, ano-rectal malformations and Hirschsprung's disease [18]. Among these, esophageal atresia, which has an incidence of 0.5-0.9%, may influence pulmonary function [28]. Even after surgical repair, respiratory problems may persist following the initial postoperative period, including bronchitis, cough, pneumonia and wheezing [18].

In addition, there is an association between Hirschsprung's disease and congenital central hypoventilation syndrome. However, patients with DS and Hirschsprung's disease are not more likely to present congenital central hypoventilation syndrome [18].

Respiratory system and airway

Respiratory illnesses (aspiration, pneumonia and influenza) were found to be the second most common cause of death for children with DS aged up to 19 years, and the most common cause across all age groups [18].

Patients with DS may have problems related to the upper respiratory tract: structural problems, laryngomalacia, tracheomalacia, subglottic stenosis, and sleep-related breathing disorders. It is frequent to find, in addition, problems related to the lower respiratory tract: congenital and structural abnormalities, RTI, immunological defects, and wheeze. Moreover, problems related to CHD or pulmonary vasculature may have an important impact on the respiratory system, being addressed on the cardiovascular section [18]. However, DS patients, even with a normal heart, may develop pulmonary vascular disease and right heart failure secondary to airway or respiratory problems [11].

Upper respiratory tract: The upper airway is frequently narrow in children with DS, which may result from a range of phenotypic features or associated conditions, including macroglossia, midface hypoplasia, choanal stenosis, a narrow nasopharynx, enlarged tonsils and adenoids, lingual tonsils, shortening of the palate, a smaller trachea and subglottic stenosis [18].

Tracheal bronchus is a congenital anomaly observed in DS consisting of an aberrant or accessory bronchus arising from the trachea, being the right tracheal lobe bronchus more frequent [2,18]. This may be associated with respiratory disease, particularly with recurrent right upper lobe pneumonia [18]. Other anomalies associated with DS were described, such as tracheoesophageal fistula [2].

In addition, both laryngomalacia (the most common cause of airway obstruction in children with DS under the age of 2 years) and tracheomalacia are associated with DS and may present stridor [18].

Moreover, congenital tracheal stenosis has been reported in patients with DS, being segmental 'hourglass' stenosis the most common type [2,18]. In addition, the presence of vascular rings and a hypoplastic aortic arch has been found in up to 50% of patients with congenital tracheal stenosis [2]. Still, most cases of subglottic stenosis appear to be acquired post-intubation [18].

OSA has a prevalence of 30% to 50% in children with DS, increasing to 90% in adults with DS, as compared with the 2% to 4% prevalence observed in the general population [27]. It appears to arise usually in the second or third year of life. This happens more frequently in DS children in consequence of the narrow upper airway, probable reduction in pharyngeal muscle tone in relation to generalized hypotonia, and tonsillar and adenoid hyperplasia [18]. The sleep induced ventilatory dysfunction, which includes OSA [27], manifests itself in children through snoring, unusual sleeping position, increased fatigue during day time and behavioral changes [2].

Lower respiratory tract: Several structural abnormalities were identified in DS, although their contribution to respiratory morbidity is unclear [18]. The authors [29] have found a particular pattern of pathological and histological abnormalities of general porosity in DS. Once these findings were not observed in late gestation, they appear to be related to a failure of alveolar multiplication in the postnatal period. In addition, the authors frequently found a double capillary network in DS patients [29].

Moreover, DS has been associated with subpleural cysts. These have limited clinical significance and are often not diagnosed, since they are not normally apparent on a plain chest radiograph [18]. However, there are reports of patients with DS and subpleural lung cysts who suffered adverse outcomes, such as rapid development of severe PAH, recurrent RTI and bronchiectasis, leading to respiratory failure [30].

These cysts are thought to adversely affect lung mechanics and cause hypoxia, and also contribute to the development of PAH [18,30].

Though subpleural cysts are associated with lung hypoplasia, interstitial lung disease (ILD) is not frequent in DS but it was described in one case report [31]. In this case, in the preoperative period, besides the known comorbidities, the DS child did not present any symptom or sign suggestive of ILD. However, the child desaturated in the postoperative period and a high-resolution computed tomography chest revealed ILD features. Recurrent RTI and aspiration might have predisposed the ILD development [31].

Respiratory infections are the second most common cause of mortality after CHD in children with DS until 19 years old. In fact, they seem to be more susceptible to RTI, having a 30% increased risk of death from sepsis [18]. In a study on hospital admissions of children with DS, respiratory pathology was responsible for 54% of admissions and was also the most common reason for admission to the pediatric intensive care unit (ICU) (43%) and for ventilation (50%) [32]. These children were mainly diagnosed with pneumonia and their length of admission was 2-3 times longer than non-DS children [32]. Respiratory syncytial virus is a relevant cause of lower respiratory tract infection in this subgroup. In addition, they tend to require hospital admission with this viral infection and are likely to have a more severe course and an increased length of stay [18]. As a consequence, in these situations of preoperative RTI, it is likely to find postoperative atelectasis [31].

Similarly, children with DS admitted to ICU present an increased risk of acute lung injury and acute respiratory distress syndrome; however, the cause of this higher risk is not clear and a relation with the increased morbidity from RTI has not been proved [18].

The higher incidence of RTI is thought to be multifactorial: structural abnormalities of the airways; increased mucus secretions; reduced ciliary beat frequency (although ciliary dysfunction is likely to be acquired and may be the result rather than the cause of increased RTI) [18]; chronic aspiration; and presence of CHD associated with the syndrome [31]. In addition, a number of immune defects have been identified which may be at the basis of the recurrent infections [31]: reduced T and B lymphocyte subpopulations, decreased neutrophil chemotaxis and thymic abnormalities, abnormalities of B-cell function resulting in alterations of levels of immunoglobulin subclasses. Alterations in response to vaccinations were also reported and it has been suggested that pneumococcal polysaccharide vaccine may be beneficial to children with DS as well as checking functional antibodies and repeat immunizations as necessary [18].

Wheeze is usually noticed in children with DS but a different etiology than asthma has been suggested. DS children are frequently considered as having asthma, but only a few meet the international diagnostic guidelines. Whereas chronic rhinitis is commonly observed, DS children are less likely to be diagnosed with atopic diseases such as eczema or hay fever than non-DS children. Positive skin prick tests are less frequent among DS children [18]. It was investigated whether wheeze was related with a previous infection with respiratory syncytial virus, but this association was not found [33]. However the high incidence of wheeze in DS may be explained by a number of possible factors: congenital lung abnormalities, tracheomalacia and upper airway collapse secondary to hypotonia or CHD [33].

Immune and hematologic system: The high incidence of pulmonary infections and relative frequency of positive hepatitis-associated antigens in DS patients might be explained by thymus dependent immune system depression more than by humoral immune system [2].

Polycythemia with hematocrit values above 70% has been reported in children with DS. In fact, hematocrit values higher than 80% are an indication for immediate phlebotomy to prevent circulatory failure. Thus, this condition may potentiate circulatory failure in these patients [2].

Endocrine system: About a half of the patients with DS who reach adulthood develop autoimmune hypothyroidism. Consequently, they are prone to have hypothermia and there are chances of a delayed recovery, due to the thyroid status of these patients, even though the effect of neuromuscular blocking agents is not prolonged in this group of patients [2].

Central nervous system/Nociception: The main anatomic and neurotransmitting alterations of the central nervous system in DS patients involve the decreased cholinergic and serotoninergic systems, which may play a role in the nociception. Trying to find the mechanism that decreases the serotoninergic system, accumulated evidence indicates a decreased active transport of 5-HT, possibly due to lowered activity of Mg^{++}-dependent Na^+-K^+-stimulated adenosine triphosphatase. Moreover, other alterations that involve neurotransmission in subjects with DS include the neurotransmitter gamma-aminobutyric acid (GABA) system, the noradrenergic system, and glutamate transmission [13].

Some authors found out that DS patients showed a limited capacity for verbal and behavioral expression in reaction to the painful stimulus [13], being of great importance the use of adapted and correct tools to evaluate their pain.

Cervical instability: The cervical instability involves the atlantoaxial instability and the atlantooccipital (aka craniocervical) instability [34]. This happens due to laxity of the transverse atlantal ligament, which holds the odontoid process close to the anterior arch of the atlas. 6% of DS patients present bony abnormality of the atlas and axis, which may increase the potential for instability. [4]

Cervical instability can be acquired or precipitated by upper respiratory infections. Rotation of the head may also result in C1C2 subluxation and general anesthesia has the potential for joints' subluxation, during laryngoscopy, positioning and transport. [14].

The normal distance between the odontoid process and the anterior arch of the atlas on lateral cervical spine X-ray is less than 4.5 mm [4,14]. If there is a subluxation the diameter of the cervical canal narrows and may cause spinal cord compression [4]. This atlantodens interval (ADI) changes with neck position, and is typically greater in flexion than extension [10]. Most patients with an ADI of less than 6 mm are asymptomatic but if greater than 7 mm it is almost always associated with neurological manifestations [4]. For other authors, 3-5 mm is considered to be reference values for the ADI, and the values of 12-13 mm are usually associated with symptoms [14]. These symptoms include walking fatigue or a new preference for sitting games, abnormal gait, increased clumsiness [4], neck pain limiting neck mobility and torticollis [2]. Physical signs may also be present such as hyperreflexia, clonus, quadriparesis, extensor plantars, neurogenic bladder, hemiparesis, ataxia and sensory loss [4]. These signs and symptoms may remain stable for months and years, but in the worst case scenario they can result in death [2].

Moreover, laxity of other joints such as fingers, thumb, elbows and knees tends to correlate well with the presence of atlantoaxial dislocation [14].

Ophthalmological problems: Among DS patients there is a high prevalence of ocular disorder: refractive errors and/or squint may be present from an early age and persist into childhood, and most children with DS have reduced accommodation at near. Congenital cataract is ten times more frequent than in general population and infantile glaucoma may also occur. In addition, nystagmus is present in at least 10% of DS patients. Cataracts and keratoconus may evolve in adolescence and are suggested to be 4 times more frequent than in the adult general population. If untreated most of these conditions are a significant cause of preventable secondary handicap at all ages. Consequently, it is of great importance extra vigilance at all ages [5].

Hearing issues: Up to 50-70% of DS patients will experience impaired hearing at some point in their life. Hearing losses may be conductive, sensorineural or mixed in nature, and may be temporary or permanent. The patterns of hearing loss presenting in these patients change throughout life, with otitis media with effusion (glue ear) being the most common cause in childhood, and sensorineural deafness becomes more prevalent with age [6].

Discussion

Preoperative period

The authors [10] consider that surgeries in DS children should occur in a specialized pediatric hospital, and/or include an overnight stay for observation after surgery. Preoperative evaluation should also consider combining two or more compatible surgical procedures under the same anesthetic event. Therefore, the potential complications of anesthesia induction, emergence from anesthesia, extubation, and postoperative pain control may be reduced.

Cardiovascular system

Congenital heart disease is an important preoperative concern, especially when DS is present. The surgical risk assessment may include lesions' severity and repair status, including whether the defect was completely or partially repaired and whether any residual defect remains [10]. This information is important once repaired atrioventricular canal, Tetralogy of Fallot, and ventricular septal defect may result in fibrosis of the tract, and atrial rhythm anomalies are common after repair of great vessels transposition with an atrial baffle [2]. Regarding this complex task of assessing surgical risk, some authors propose several scoring systems, such as Aristotle [35] and RACHS-1 [36]. These systems evaluate risk not only for DS but for all pediatric patients [10].

Carmosino et al. [37] reviewed the medical records of children with PAH undergoing non-cardiac surgical procedures or cardiac catheterizations, observing the risk of major complications, including cardiac arrest or pulmonary hypertensive crisis, was 4,5%. Patients with baseline suprasystemic PAH were at highest risk [37]. Lewanda et al. [10] classify patients with PA pressure below 30% systemic pressure (no PAH) as low risk; those medicated to keep their PA pressure below 50% systemic pressure as moderate risk; those with PA equal or greater 50% of systemic pressure, regardless of medication status, were classified as high risk. Those with PA pressures between 30% and 49% of systemic pressure, and non-medicated, have a risk category individually determined, considering right ventricular function and

the presence or absence of a shunt to allow maintaining cardiac output in case of a PAH crisis. The authors suggest a pediatric cardiac anesthesiologist should evaluate all moderate or high-risk DS children, even if the planned surgery is not cardiac in nature [10]. Concerning these risks, during the preoperative period of a patient with DS, the symptoms of ES are to be analyzed and paramount importance should be given to respiratory system evaluation, which will result in smoother intraoperative course [2].

Moreover, it is suggested to consider a recent echocardiogram evaluation to look for undiagnosed or residual heart disease and the presence of PAH. If PAH or unrepaired CHD are present, the patient should be hospitalized for the surgery aiming a close postoperative monitoring. For children with high or moderate risk, the services of pediatric intensivists should be available as needed [10].

At last, prophylactic antibiotics are indicated in patients who had aortic valvulotomy, resection of aorta coarctation, pulmonary valvulotomy or any valve replacement of great vessels [2].

Gastrointestinal system

Given the high prevalence of GERD in children with DS, it is suggested to preoperatively assess some symptoms, such as: vomiting, esophagitis, respiratory symptoms like apnea, wheezing and aspiration pneumonia [14].

Respiratory system and airway

Sinha et al. [31] suggest recording the preoperative air saturation in DS patients once it may help to suspect of ILD. This concern is based on a case report in which prolonged postoperative desaturation occurred due to undiagnosed ILD.

Bronchoscopy is indicated in patients suspected of having tracheal stenosis, in order to visualize the area of stenosis and complete tracheal rings, if present. This may help during intubation, and in stenotic lesions management [2].

Before adenotonsillectomy, in patients with DS, a full airway evaluation and a sleep study should be performed [27]. In addition, it is suggested to make other studies such as sleep endoscopy and cine magnetic resonance imaging (MRI), both of which to evaluate the entire airway during a state of induced sleep, to identify sites of dynamic airway collapse. The outcomes of these studies are used to drive the surgical management [27].

Immune and hematologic system

Regarding the higher risk of infections in DS patients, it is advisable to take strict aseptic precautions during intravenous cannulation [2].

In what concerns the high incidence of hematologic disorders in DS, it is important to perform a simple blood count before surgery. In the presence of significant cytopenias or peripheral blasts an appropriate evaluation is required, including a bone marrow examination prior to any elective surgery [10]. Due to the incidence of polycythemia associated with DS, preoperative hematocrit should also be measured. Phlebotomy, if needed, is mandatory in order to prevent circulatory failure [2].

If a neonate with DS has transient myeloproliferative disorder, and needs a surgery within the first days or weeks, special precautions have to be taken. The two main issues are the risk for thrombosis and stroke, due to the very high white blood cells count, and the decrease in other

hematologic cell lines, producing anemia or thrombocytopenia. Authors suggest the use of plasmapheresis to lower the white cells count to an acceptable level, but in general it is only considered when the count is extremely high, namely over 125 000 per microliter. Red blood cell or platelet transfusion may be indicated to correct anemia or inadequate clotting [10].

Endocrine system

Some authors recommend the preoperative biochemical screening of thyroid function, once physical signs may not be helpful to diagnose an unknown hypothyroidism, so frequent in DS. Thyroid antibodies are found in up to one third of patients [4].

Cervical instability

Some authors say that relying on symptomatology to identify patients with cervical spine instability is problematic once only 1-2% will actually show significant symptoms [10]. This means that a large number of patients may not be detected on history and physical examination by itself. For Bhattarai et al. [14], lateral radiographs of cervical spine in flexion, extension and neutral position are sufficient for the diagnosis of atlantoaxial instability. However, radiologic assessment is a controversial way of diagnosing this condition [10]. On the one hand, if atlantoaxial instability is revealed in the radiographic examination, Bhattarai et al. consider that the child should be referred to a neurosurgeon and orthopedic surgeon for further evaluation and stabilization of cervical spine is necessary before any surgery is undertaken [2]. On the other hand, this diagnostic method has some limitations, as explained below.

In young children (under age 3), the spine is often inadequately ossified to allow good measurements [10]. Nevertheless, there is a reported clinical case with a 16-day-old symptomatic baby whose cervical spine films revealed atlantooccipital instability [38]. Behavioral issues in children with intellectual disability can be a problem for the right positioning for the imaging. Some authors suggest using a wedge-shaped neck support with the patient supine to guarantee the correct position. Some authors suggest that spinal canal width together with the ADI may be a good way to provide an accurate risk prediction for cervical spine instability [10].

Another point to consider is whether the structural integrity of the cervical spine changes over time, which is relevant for example when considering if radiographs taken at age 3 are valid for a patient undergoing anesthesia and surgery at age 10. A 5-year long study found a reduction over time in the ADI and none of the children with normal X-rays had developed cervical instability in the subsequent 5 years [39]. However, there was one exception: a child with previous normal films (ADI of 3 mm) who suffered from an acute rotatory dislocation at the atlantoaxial joint after anesthesia and ear, nose and throat surgery (ADI of 7 mm) [39]. So, the authors concluded that normal screening radiographs do not guarantee against injury. And they suggest that all DS patients should wear soft collars prior to anesthesia, alerting staff for the potential of cervical spine injury [10].

The American Academy of Pediatrics (AAP) previously suggested cervical X-rays for children with DS between 3 and 5 years old [40]. However, as said above, more recent studies show that such films do not provide guaranteed information on which patients are actually at risk. Therefore, the newest AAP guidelines, as well as the guidelines designed by the UK Down Syndrome Medical Interest Group, no longer recommend routine cervical X-rays for asymptomatic DS children [10,34].

Litman et al. [41] surveyed pediatric anesthesiologists to enquire how they evaluate and manage patients with potential cervical instability, such as DS patients. With 171 respondents, the results can be summarized as follows: in asymptomatic DS children, 18% required preoperative X-rays and/or subspecialty consultation (9%); in symptomatic children, 64% obtained radiographs and/or preoperative consultation (74%). The authors concluded that respondents based their decisions on symptoms and signs, an approach supported by the literature but contrary to recommendations made in previous reports [10].

Lewanda et al. [10] conclude that although the probability of a spinal injury from intubation or surgery in a patient with DS is low, the consequences of an adverse event may be severe, so the decision of requiring preoperative X-rays remains at the discretion of the anesthesiologist and surgeon. In a retrospective study [42], other authors concluded that general anesthesia is a safe alternative to facilitate MRI in children with a higher America Society of Anesthesiologists (ASA) classification status and those with a history of failed sedation.

Other abnormalities

The use of alternative therapy to address the cognitive aspects of DS has existed since a long time ago, persisting today with a large number of products marketed directly to the families with DS children: carnitine, folic acid, gingko biloba, piracetam, MSB Methyl Plus, NuTriVene, and Speak are some examples [10].

It is important to question if the patient is consuming any of these products before a surgery once they potentially cause problems. For example, piracetam, promoted as a substance to enhance cognitive function, also acts as a platelet inhibitor, what increases the bleeding risk at a surgery. None of these products is endorsed by the main organizations for DS patients, so the authors propose considering discontinuing them several days before surgery [10].

Intraoperative period

930 anesthetic procedures in children with DS were reviewed and it was found that the most common anesthetic-related complications, in the intraoperative period, included bradycardia, which was severe in 3.66% of the cases, airway obstruction in 1.83%, difficult intubation in 0.54%, and post-intubation croup in 1.83% [17]. In the following section, these and other complications will be described.

Cardiovascular system

Children with DS have more propensities to present bradycardia after sevoflurane induction. Of 11201 pediatric individuals, Bai et al. [43] observed that 28% of DS patients experienced bradycardia after sevoflurane anesthesia compared to 9% in controls. In most cases, decreasing the volatile agent and airway instrumentation corrected the heart rate. Although DS patients presented higher incidence of bradycardia, there was no difference in hypotension, pharmacologic interventions, or outcomes. It seems prudent to have anticholinergic agents, such as atropine, available during induction with sevoflurane. Bhattarai et al. [2] consider it is advisable to use a vagolytic dose of atropine once these patients have decreased sympathetic activity (although there is increased incidence of atropine hypersensitivity). In

any case, it is suggested to have a variety of options available for anesthesia at the time of surgery [10].

If the patient with DS also presents ES, it is recommended by The American Heart Association and the American College of Cardiology guidelines that the anesthetic approach should be individualized [44]. The basis of anesthetic management is to promote oxygen delivery by preventing arterial desaturations, maintain balance between the systemic and pulmonary blood flow, optimize hematocrit, and monitor for and treat promptly right ventricular decompensation [23].

In a case report, regional anesthesia was considered by the authors and rejected for several reasons [22]. However, more recently both general and regional anesthesia has been used successfully in patients with ES, although both techniques have the potential to produce hypotension and vasodilation, which will increase the reversed shunt. Recently, regional anesthesia has been reported to have a slightly lower mortality, although the authors suggest that is more related to the surgical procedure and the disease than with the anesthesia [23].

Conventional non-invasive perioperative monitoring is recommended in DS patients with ES, which includes pulse oximetry, electrocardiography (ECG), and capnography. Pulse oximetry is particularly useful as it can be used to assess the degree of right-to-left shunting because of raised pulmonary vascular resistance [23].

Invasive arterial pressure monitoring allows for rapid detection of changes in systemic vascular resistance in DS patients with ES. In addition, trans-esophageal echocardiography can be useful to assess ventricular function, preload and shunting [23].

Gastrointestinal system

Given the high incidence of GERD in DS patients, aspiration prophylaxis with modified rapid sequence induction (RSI) may be used along with the agents to decrease pH in the stomach [2]. The components of a classic RSI consist of oxygen administration, cricoid pressure application, and mask ventilation avoidance before inserting an endotracheal tube (ETT) to secure the airway. In certain clinical circumstances, a modified technique is implemented in an attempt to optimize patient outcomes and decrease excess risk exposure [45]. The agents used to reduce gastric pH, to avoid regurgitation, may vary on an institutional basis [2].

Respiratory system and airway

Regarding the high incidence of subglottic stenosis and recurrent RTI in patients with DS, there are always controversial opinions on using ETT or the supraglottic air device [10,31]. Lewanda et al. [10] say the use of a laryngeal mask airway (LMA) should be considered for short procedures. Although endotracheal intubations may lead to chronic inflammation and scarring of the subglottic airway [2], if intubation is required it is suggested to use initially an ETT at least two sizes smaller than would otherwise be chosen [10,24]. Some physicians use a small cuffed tube, which allows successful intubation and avoids an unacceptably large air leak [10]. Tait et al. [46] suggested that LMA is as acceptable as ETT regarding perioperative airway complications in children with upper RTI. Von Ungern et al. [47] showed higher incidence of laryngospasm, desaturation and cough with the use of LMA in children with recent upper RTI compared to healthy children.

In a case reported by Sinha et al. [31], physicians used ProSeal LMA (PLMA), a modification of Classic LMA, which has a gastric drainage tube placed lateral to the main airway tube, which allows the regurgitated gastric contents to bypass the glottis and prevents pulmonary aspiration. They preferred it over ETT to reduce intubation and extubation response as the child had ASD, and referred that in their experience PLMA in children with recurrent RTI did not increase airway complications in comparison to ETT.

Obesity, especially if extreme, can affect soft tissues of the upper airway and hinder oxygenation and ventilation during and after anesthesia [10]. If sedation or spontaneous ventilation is used, the patient should be carefully monitored as hypoventilation frequently occurs [4]. Sleep induced ventilatory dysfunction in DS patients may be exaggerated by narcotic induced sedation and residual anesthetic concentration in the body [2].

A case of difficult airway was reported in a patient with DS, OSA and other comorbidities [48]. Physicians were not able to use rigid laryngoscopy to visualize the epiglottis because of hypertrophied tonsillar tissue, and mask ventilation became difficult when spontaneous breathing stopped. They avoided using a LMA given a slight bleeding tendency, consequent to a preoperative antiplatelet therapy. After all, it was fiberoptic bronchoscopy through the nasal cavity in combination with jet ventilation that was able to successfully identify the glottis and allowed nasotracheal intubation to be accomplished.

A study with 239 children with DS, reported that 13,8% had one airway diagnosis with airway symptoms of sufficient severity to require airway endoscopy under general anesthesia [49].

Cervical instability

When a child has an increased ADI, some anesthesiologists prefer to use fiberoptic intubation, while others feel that inline stabilization of the neck provides adequate protection of the cervical spine [10,24].

Common procedures in DS children, including tonsillectomy and tympanostomy tube placement, involve more extensive manipulation of the neck than do general surgical procedures. Therefore, positioning for intubation and surgery should be given additional consideration in DS patients. Several authors recommend a procedure to minimize the injury risk, which is to strap the patient to the operating table, place supports alongside the head, and roll the table to the side, rather than turning the head [10,14,50].

Besides its importance in avoiding respiratory complications, LMA has proven to be a valuable tool in allowing these children to keep their neck in a neutral position [14]. Although some authors have reported up to 95% success rate in insertion of LMA in neutral position in child with atlantoaxial instability [51], others concluded that fiberoptic laryngoscopy is the more suitable technique when cervical movement is not desired, although it involves neck movement [52].

Patel et al. [53] studied whether neurophysiological monitoring during complex spine procedures in children with DS may reduce risk of injury by providing feedback to the surgeon. They concluded neurophysiologic intraoperative monitoring (NIOM) during neurosurgical procedures in children with DS may be reliably and safely implemented. In addition, changes in neurophysiologic parameters during surgery must be carefully interpreted and discussed with the neurosurgeon, neurophysiologist, and neuroanesthesiologist, and may not correlate with postoperative clinical changes. At last, these changes may be related to abnormal physiology rather than an inflicted injury during surgery. Nonetheless, the authors advise routine

NIOM for children with DS undergoing neurosurgical spine procedures.

In a case report, the authors consider that protective motor and somatosensory evoked potential monitoring of intubation and neck extension is an obvious consideration when DS patients with cervical instability undergo already-monitored spinal surgery [54]. However, they consider this monitoring may be useful even if they undergo other normally unmonitored procedures. They report a case of monitoring of these maneuvers for the unusual indication of thyroidectomy in a DS boy with atlantoaxial instability. Evoked potential stability correlated with normal postoperative neurological function.

Pain management

Regarding the potential alteration in nociceptive processing in DS, 45 cases of neonates undergoing duodenal surgery were described, concluding that pain scores and analgesic requirements did not differ from a subgroup of 15 patients with DS [55]. In fact, perioperative analgesic requirements are influenced by variability in pain sensitivity and analgesic efficacy in DS, but there is limited evidence of differences [7]. Studies with rodent models were performed in order to identify these impairments, describing variable changes [56]. Clinical studies are also currently inconclusive, once altered behavioral responses suggestive of either decreased or increased sensitivity have been reported [7].

Opioid efficacy has not been widely evaluated in DS, however morphine dose-response curves were not significant altered in a mouse model [56], and data from Walker's paper sustains the use of similar morphine doses in neonates with or without DS [7].

Observer-based measurements, through behavioral and physiological responses, are used to evaluate pain and analgesic efficacy in neonates and infants. Accordingly, they should be applicable to neonates having or not potential for cognitive impairment [7]. In fact, the COMFORT-Behaviour scale has been validated not only for use in ICU, but also, more recently, it has been reported to be reliable in children aged 0-3 years with DS [26]. When using this scale, although there were some differences between children with and without DS, they were not clinically significant. The COMFORT-Behaviour scale assesses the intensity of six behavioral manifestations: alertness, calmness, facial tension, body movements, muscle tone, and respiratory response, if children are ventilated, or crying if they are spontaneously breathing [7]. These results in a score between 6-30, with ≥ 17 considered to be moderate-to-severe pain, requiring additional analgesia [57]. Facial actions have been reported as the main indicators of pain in neonates at risk of neurological impairment. The authors reported that facial response needs further investigation to be considered a reliable tool in assessment of pain in adults with DS [7].

Numeric Rating Scale is another validated option to assess pain in children aged 0-3 yrs with DS: a score ranging from 0 to 10, where ≥ 4 represents moderate-to-severe pain, requiring additional analgesia [26,57]. Additional studies are also required to evaluate the measurement tools' ability to effectively titrate bolus analgesic administration, once it is more frequently used than continuous infusions [7].

Another study explored several methods for assessing pain during venipuncture in children, using classic and modified scales (Visual Analog Scale, Eland Scale, Faces Scale, Cube Test, Modified Eland Scale, and Modified Faces Scale) to evaluate the children's response to simplified tools. The modified Eland Scale proved to be easier, especially for DS children, when compared to its classic version [13].

The side effects related to opioid use as analgesic are particularly relevant for children with DS, as many have associated cardiorespiratory anomalies. However, the author considers that a larger series is required to determine if DS, the associated anomalies, or both, increase the risk of opioid-related complications [7].

Nervous system

Decreased catecholamine levels have been demonstrated in children with DS, which may result in minimum alveolar concentration (MAC) decrease of inhaled anesthetic agents [58]. However, during anesthesia, heart rate and blood pressure are stable in all these patients, which suggest that deeper level of anesthesia is achieved with the same MAC of inhaled anesthetic agents [59]. Levels of dopamine beta hydroxylase do not increase in the plasma following stress tests [60]. Thus, the blood pressure is lower in DS patients as compared to healthy children. Thus, these patients require less volatile anesthetic agents than normal patients. Keeping in mind the possibility of anesthesia awareness, bispectral index (BIS) monitoring may be used if available [2].

Drugs management

Management of neonates with DS generally does not differ from other neonates, although anesthetists may anticipate possible airway management difficulties in this subgroup. After 2008 there were some changes in the choice of anesthetic drugs and techniques: atracurium (neuromuscular blocking agent) was replaced by cisatracurium; barbiturates (thiopental or Pentothal) used as the hypnotic agent was replaced by propofol and a singleshot caudal block was used more frequently as anesthetists became familiar with this technique [55].

Intravenous Sedation

Dental practices are currently a challenge in patients with disabilities, once the excessive mental strain during the treatment can cause systemic complications such as vasovagal reflex, neurogenic shock, pain shock, and hyperventilation. If the patient has a cardiovascular condition, serious complications can be encountered. Therefore, intravenous sedation is often used to relieve the mental strain during the dental treatment. Conscious sedation is generally preferred, however these patients may require behavioral control in order to avoid refusal reactions. In these cases, deeper levels of intravenous sedation are a safer option. The doses must consider the individual case and the deepness of sedation anesthesiologists want to achieve. Consequently, the use of intravenous anesthesia requires a careful perioperative management once these drugs have strong systemic actions on the nervous, respiratory and circulatory systems [61].

Yoshikawa et al. [61] consider that patients with disabilities have lower peripheral oxygen saturation (SpO_2) and delayed recovery after intravenous sedation in a dental procedure, being DS in higher risk when compared to mental retardation and cerebral palsy. Midazolam was also found to be a risk factor for prolonged recovery time. It is usually used in these situations for its amnesic effect, behavior control and provision of a longer duration of action, comparing to propofol for example. To prevent the decreased SpO_2 oxygen: emergency equipment must be kept ready; consciousness, ventilation, oxygenation, and circulation statuses should be carefully monitored; and airway management has to be carefully performed.

Postoperative period

It is proved that children with DS undergoing a cardiac surgery have a higher rate of mortality and morbidity [4], playing the postoperative period an important role on its control.

Cardiovascular system: The early postoperative care of patients with ES should be provided in an ICU [23].

Respiratory system and airway: DS patients who have had a thoracic or abdominal surgery are at particular risk of postoperative RTI and benefit from regular physiotherapy and close monitoring [4].

As the incidence of postextubation stridor following prolonged ventilation is 30-40% in DS, compared to 2% in other children [62], some centers administer a short course of steroids prior to extubation of DS patients. The duration of postoperative ventilation, intensive care stay and total period spent in hospital, all tend to be longer than for other children [4].

Presenting comorbidities, craniofacial abnormalities, and moderate to severe OSA are all considered indications for postoperative hospital observation in children undergoing adenotonsillectomy. Thus, DS children after this surgery should be supervised in the hospital (ICU if obesity and/or severe OSA are present) in opposite to their peers who are generally managed as outpatients. Because of the high rate of persistent OSA in children with DS, a postoperative sleep study is indicated 2-3 months after adenotonsillectomy [27].

Immune system: Regarding the increased risk of infections, strict asepsis is advisable for invasive procedures, and venous and arterial cannulas, urinary catheters, and others, should be removed postoperatively as early as possible, to minimize the possibility of serious infection [4,2].

Cervical instability: All individuals with DS exposed to a surgery should have not only a preoperative, but also postoperative basic neurologic examination to identify any patient that might have sustained a cervical spine injury [10].

Pain management and sedation: There is a high incidence of postoperative agitation in DS patients which may occasionally warrant sedation [4].

Evaluation of pain and analgesic efficacy in children with DS from the age of 3 to 4 years onward may be done with some validated tools for the postoperative period [26]: the Non-communicating Children's Pain Checklist-Postoperative Version; the Paediatric Pain Profile; the revised Faces, Legs, Activity, Cry and Consolability; and the Checklist Pain Behavior. These scales require a long observation period, up to 10 min, or require description of idiosyncratic behaviors.

In 1998, a study [63] concluded that children with DS are: likely to receive more morphine following cardiac surgery, especially on day 3; likely to receive more additional sedatives and paralytic agents; and more likely to still be on morphine on day 3 compared with children without DS.

More recently, Terada et al. [64] selected patients with and without DS who underwent through cardiac surgeries according to some inclusion criteria. They concluded pulmonary-systemic artery pressure ratio after cardiac repair and intraoperative anesthetic doses did not differ between the two groups. Postoperative sedation score, stay in ICU and duration of mechanical ventilation were equivalent. Also equivalent were maintenance and cumulative dose of midazolam, dexmedetomidine and fentanyl, and times of rescue administration.

Valkenburg et al. [55] did not find any substantial differences in anesthesia and analgesia, for congenital duodenal obstruction repair, between neonates with and without DS, nor in pain scores or in the duration of mechanical ventilation. Children with DS received more often a bolus midazolam before transport to the ICU. In addition, COMFORT-B scores at day two were lower in DS children, but the difference is clinically not significant.

In another study [65], Van Driest et al. found results consistent with Valkenburg et al. [55] indicating no difference in the opioid doses administered after cardiac surgery, and do not support the hypothesis that patients with DS are opioid resistant. Instead, these findings indicate that patients with DS (44 in 121 individuals) in this cohort were managed with similar doses of opioids as patients without DS. Non-opioid medication (such as nonsteroidal anti-inflammatory drugs and sedatives) management was similar across the two groups (DS patients and non-DS patients) with the exception of dexmedetomidine, which DS patients received in lower weight-adjusted doses. The authors also concluded that DS children had lower pain scores after surgery which indicates that they achieved the same or better level of analgesia than the non-DS patients. Analysis of the outcomes of time to extubation and length of hospitalization revealed no difference between groups for the former, but patients with DS had longer hospitalizations.

Valkenburg et al. [57] also showed that children with DS have comparable analgesic and sedative requirements after cardiac surgery, compared with non–DS controls. Pain and distress assessment showed no statistically significant differences between the two groups, apart from the finding that children with DS are more at risk for oversedation. No differences were observed in the volume of distribution and clearance neither of morphine, nor in the numbers of boluses of midazolam or chloral hydrate and numbers of children requiring a midazolam infusion. According to the authors, there is no evidence for the optimal morphine infusion rate after cardiac surgery in children. It seems common practice to start with 40 µg/kg/hr after a loading dose of 100 µg/kg and next to titrate the dose on the guidance of pain scores. In this same study, the authors found out that morphine pharmacokinetics did not differ between the two groups, concluding that morphine is still the preferred opioid after cardiac surgery in children because it is the most commonly used and best-studied analgesic in children.

Very recently [66], the pharmacokinetics of fentanyl in children after cardiac surgery has been evaluated. Although there is a large international experience using fentanyl for postoperative analgesia in the congenital cardiac population, there is still pharmacokinetic data lacking to guide optimal dosing algorithms.

Key Learning Points

Preoperative period

1. The authors agree that physicians should try to combine two or more compatible surgical procedures under the same anesthetic event. It should also be planed an overnight stay after the surgery to offer a close monitoring postoperatively.

2. Regarding the cardiovascular anomalies, the assessment of the surgical risk may be performed using scoring systems such as Aristotle and RACHS-1. In addition, a pediatric cardiac anesthesiologist, before any kind of surgery, should evaluate the moderate or high-risk DS children. A recent echocardiogram evaluation should be performed

and services of pediatric intensivists should be available. We consider that prophylactic antibiotic therapy is indicated in DS patients who had valvulotomies or resection of aorta coarctation.

3. It is suggested to preoperatively assess gastrointestinal symptoms given the likelihood of GERD presence.

4. The respiratory system and airway should be taken into account to avoid complications. It is suggested to register the preoperative air saturation, to provide bronchoscopy if suspicion of tracheal stenosis, and to perform a full airway evaluation and a sleep study.

5. Regarding the high risk of infections, we advise to take strict aseptic precautions during venous cannulation. Prior to any elective surgery, we consider important to perform a simple blood count, followed by a bone marrow examination if needed. Physicians may require plasmapheresis to lower the risk of thrombosis and stroke, red blood cell or platelet transfusion if anemia or inadequate clotting, or phlebotomy to correct some polycythemias.

6. Similarly, physicians should require biochemical screening of thyroid function, looking for unknown hypothyroidism.

7. We did not find an agreement in the preoperative management of cervical instability in DS.

• The authors agree in assessing cervical spine instability based on symptoms and physical examination.

• We also suggest to require a subspecialty consultation if symptomatic patients.

• However, the use of radiologic assessment is controversial once it is has some limitations in young children and may not be a good predictor of this condition. Nowadays, performing a cervical X-ray in asymptomatic patients is not advisable. In symptomatic cases, although the probability of a spinal injury from intubation or surgery is low, the consequences of an adverse event may be severe, so the decision of requiring preoperative X-rays remains at the discretion of the anesthesiologist and surgeon.

• The authors suggest, anyway, the use of soft collars prior to the anesthesia, alerting staff for the potential of cervical spine injury.

Intraoperative period

1. Regarding the cardiovascular comorbidities, if the patient experience bradycardia after induction, we suggest reducing sevoflurane anesthesia and airway instrumentation. Moreover, monitoring the depth of anesthesia with BIS may avoid this complication. It is useful to have anticholinergic agents (such atropine in a vagolytic dose) available during this procedure, to use if necessary.

2. When DS patients present CHD, the authors advise an individualized anesthetic approach, followed by a close monitoring focusing on the efficient oxygenation of the tissues. Both general and regional anesthesia may be used in DS patients with ES and conventional non-invasive perioperative monitoring is recommended (pulse oximetry, ECG, and capnography). Some authors also consider invasive arterial pressure monitoring or trans esophageal echocardiography in this group.

3. Given the high incidence of GERD, the authors suggest aspiration prophylaxis with modified rapid sequence induction and the use of agents to decrease the pH in the stomach.

4. In the respiratory and airway system, there is no agreement on the best airway device.

• We consider LMA is useful for short procedures, and if ETT is needed it should be at least two sizes smaller than the predicted. A small-cuffed tube is one more option to have in consideration.

• Generally, LMA is as acceptable as ETT regarding the airway complications. However, in children with recent RTI there is a higher incidence of complications using LMA.

• In some cases ProSeal LMA may be preferred over ETT, to prevent pulmonary aspiration, and does not increase airway complications.

• In difficult airway cases, fiberoptic bronchoscopy through the nasal cavity in combination with jet ventilation might be the last and only alternative to identify the glottis and allow intubation.

5. Considering the so frequent cervical instability in DS, we recommend some attitudes to prevent spinal injury such as:

• The use of LMA or fiberoptic intubation (the better option) in neutral neck position;

• Inline stabilization of the neck;

• Strapping the patient to the operating table, place supports alongside the head, and roll the table to the side, rather than turning the head.

• Some authors also suggest routine NIOM and motor and somatosensory evoked potential monitoring in children with DS undergoing neurosurgical spine procedures.

6. Regarding the potential alteration in nociceptive processing in DS, to assess the pain and analgesic efficacy in children with DS we recommend the use of the following tools: COMFORT-Behaviour scale (0-3 years), Numeric Rating Scale (0-3 years), and the modified Eland Scale. It seems there is no difference in the morphine doses required in this condition, although further investigation is needed due to the relevance of side effects.

7. Still about drugs management, intravenous sedation is recommended in dental treatments, despite its risk of a low SpO2 and a delayed recovery. This risk may be minimized with careful monitoring.

Postoperative period

DS patients with ES should be provided early postoperative care in an ICU. Moreover, simple procedures such as adenotonsillectomy may require hospitalization in DS.

Respiratory and airway system: In order to prevent postextubation stridor, we suggest administering a short course of steroids before this maneuver. Given the high incidence of OSA, a postoperative sleep study is indicated 2-3 months after adenotonsillectomy.

All invasive procedures require strict asepsis and removal of catheters may be done as early as possible, trying not to increase the risk of infection.

Regarding the pain management in the postoperative period, sometimes the agitation of these patients may require sedation. To assess the pain and analgesic efficacy in children (≥ 3 years) there are a high number of validated tools.

The majority of the analyzed studies concluded that there is no significant difference in anesthesia or analgesia in postoperative period in DS, namely in: postoperative sedation score, pain scores, stay in

ICU, duration of mechanical ventilation and cumulative doses of midazolam, fentanyl, chloral hydrate and opioids.

• However, DS patients were found to achieve the same or better level of analgesia than the non-DS patients, meaning this a higher risk for oversedation and to have longer hospitalizations. Some authors prescribed lower weight-adjusted doses of dexmedetomidine while others did not agree with this point.

• Focusing on opioids, we may infer there is no opioid resistance in DS. There is no evidence for the optimal morphine infusion rate after cardiac surgery in children, but it is still the preferred opioid because it is the best-studied analgesic (comparing with fentanyl) in children.

Conclusion

In conclusion, there are several variations in the approach of patients with DS through their perioperative period, including some topics with lack of agreement, such as: cervical instability management in the preoperative period; choice of the best airway device in the intraoperative period; and doses of opioids administered in the postoperative period. This reflects the need of specific guidelines to homogenize this approach.

In addition, it seems very clear the lack and need of these conducts once DS presents a high amount of comorbidities that, if not well approached, may even result in death. Moreover, it is frequent the need of surgical corrections in this syndrome, which exposes these patients to a higher number of perioperative periods.

With this review, we notice there is more information regarding the anesthetic management in DS children than regarding DS adults. It would be of interest a further investigation on the correct applicability of this data to both children and adults.

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