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Perioperative Management of Children With Autism Spectrum Disorder: A Review

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ABSTRACT

Introduction: Autism Spectrum Disorder is a neurodevelopmental disorder characterized by social communication difficulties, restricted interests, repetitive behaviours and occasional sensorial hypersensitivity. Associated comorbidities include: intellectual disability, psychiatric, gastrointestinal, oral health and motor problems, insomnia, epilepsy, self-injury and aggression and metabolic abnormalities. Therefore, perioperative period of autistic children is often challenging and require a careful and individualized management.

The aim of this work is to review the special needs of this population in the perioperative period and how to manage them.

Methods: This dissertation was based on scientific articles published between 2008 and 2018, available on PubMed, Google Scholar e Google.

Results: In order to prevent perioperative adverse events, numerous practices are suggested; preoperative period: early identification of the patient, interview with the parents to collect information about child's specific needs, prepare an individualized anesthetic plan, flexible hospital admission, place the child first on the operating list, provide a private room for the child and parents with reduced distressing sensory input, allow the use of distractions from daily family routines, consider alternative forms of communication, consider the administration of premedication to facilitate preoperative management. Intraoperative period: assess the possibility of parental presence during induction of anaesthesia, administer postoperative nausea and vomiting prophylaxis, provide an adequate and effective analgesia, consider additional medication to prevent emergence agitation/delirium. The best anesthetic agent is yet to be determined. Postoperative period: provide an isolated recovery room, allow parental presence as early as possible, remove peripheral intravenous line if possible, use a nonverbal pain scale for pain evaluation, minimize hospital stay.

Conclusion: Autistic children have individualized needs, which requires a specific approach and preparation for each patient. However, there is a lack of anesthesia literature regarding their perioperative care. Developing clinical practice guidelines for the management of this population is important to a successful surgical experience.

Keywords: Autism Spectrum Disorder; Autism anesthesia; Autism surgery; Perioperative management

RESUMO

Introdução: Introdução: A Perturbação do Espectro do Autismo é uma perturbação do neurodesenvolvimento caracterizada por défices ao nível da comunicação e interação social, interesses restritos, comportamentos repetitivos e, ocasionalmente, hipersensibilidade sensorial. As comorbilidades associadas incluem: défice intelectual, distúrbios psiquiátricos, motores, gastrointestinais e de saúde oral, insónia, epilepsia, comportamentos agressivos e auto-lesivos e anormalidades metabólicas. Assim, o período peri-operatório das crianças com Perturbação do Espectro do Autismo é muitas vezes desafiante e requer uma abordagem cuidadosa e individualizada.

O objetivo deste trabalho é rever as necessidades específicas desta população no período peri-operatório e a sua abordagem.

Métodos: Esta dissertação foi elaborada a partir de artigos científicos publicados entre 2008 e 2018, disponíveis no PubMed, Google Scholar e Google.

Resultados: Para prevenir eventos adversos peri-operatórios, várias medidas são sugeridas. Período pré-operatório: identificação prévia do doente, conduzir uma entrevista aos pais para obter informação sobre as necessidades especiais da criança, elaborar um plano anestésico individualizado, possibilitar uma admissão hospitalar flexível, colocar a criança em primeiro lugar na lista de cirurgias, providenciar um quarto privado para a criança e os pais, com o mínimo de estímulos sensoriais, possibilitar o uso de distrações provenientes do quotidiano familiar, considerar formas alternativas de comunicação, ponderar a administração de pré-medicação para facilitar a abordagem pré-operatória. Período intraoperatório: avaliar a possibilidade da presença dos pais durante a indução da anestesia, administrar profilaxia das náuseas e vómitos no pós-operatório, fazer uma analgesia eficaz e adequada, considerar medicação adicional para prevenir delírium/agitação de emergência. A escassez de informação não permite determinar o melhor agente anestésico. Período pós-operatório: providenciar um quarto de recobro privado, permitir a presença dos pais o mais cedo possível, remover acessos venosos periféricos se possível, avaliar a dor usando uma escala de avaliação não verbal e minimizar a estadia hospitalar.

Conclusão: As crianças com Perturbação do Espectro do Autismo apresentam necessidades individuais, o que requer uma abordagem e preparação específicas para cada doente. No entanto, na literatura atual, existe ainda carência de informação relativamente aos seus cuidados peri-operatórios. O desenvolvimento de orientações de prática clínica específicas para esta população é importante para uma experiência cirúrgica bem-sucedida.

Palavras-chave: Perturbação do Espectro do Autismo; Autismo anestesia; Autismo cirurgia; Abordagem peri-operatória

ABBREVIATIONS

ASD - Autism Spectrum Disorder
BIS - Bispectral Index
CI - Cognitively Impaired
EA - Emergence Agitation
ED - Emergence Delirium
EEG - Electroencephalography
FLACC - Face, Leg, Activity, Cry, Consolability
IP - Intellectually Impaired
PONV - Postoperative Nausea and Vomiting

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INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that was first described in 1943, by psychiatrist Leo Kanner [1]. ASD begins at an early age and its characteristics include social communication difficulties, restricted interests and repetitive behaviours and sometimes, touch, visual, taste, or sound hypersensitivity [2]. The prevalence of ASD continues to increase and according to the 2010 report by Center for Disease Control, 1 in 68 children is diagnosed with ASD. Males are more commonly affected than females with a ratio of 5:1 [1].

It has not been identified an exact causative factor for autism, but a combination of genetic, immunologic and environmental factors are thought to interact during vulnerable periods of the neurodevelopment [3]. Indeed, certain environmental factors such as nutrition, psychotropic drugs, parental age, maternal autoimmune disease, maternal viral infection during pregnancy, or psychological stress can origin epigenetic modifications leading to neurodevelopmental diseases, including ASD [4].

The symptomatology of ASD initiates before the third year of age and generally undergoes a firm course without remission through ageing, although important deficits may not always be recognized until a child becomes unable to meet expected milestones for social and educational demands [1,5]. Even though the manifestations of autism amongst children can vary significantly, they all present some characteristics that are the basis of the diagnosis. According to DSM-5, the diagnostic is based in two types of criteria: social communication difficulties and restricted and repetitive behaviours, with both required to be present in multiple contexts. In addition to it, symptoms should be present early in life, cause a clinically significant impairment and other explanations for developmental and behavioural problems must be excluded [2].

Social Communication

Children with ASD show deficits in social interaction and difficulties in developing reciprocal social understanding [2]. They may be able to speak, but may show difficulty in initiating or maintaining a conversation, struggle to understand the meaning of a conversation, experience difficulty with metaphors and words with several meanings, have limited vocabulary or present echolalia [2,6]. They may also have difficulties in understanding the nuances of language, such as nonliteral language and sarcasm [7]. On the other hand, they can also show a total lack of speech [2]. Furthermore, children with ASD may also struggle with nonverbal communication or body language, giving as example the difficulty in making eye contact or understand facial expressions and gestures [2,7].

Behaviour

Children with ASD exhibit restricted and repetitive patterns of behaviours, which include a need for routines and for the environment to be the same, stereotypic repetitive movements (for example, rocking, twirling, biting, head banging) and intense special interests [2,8]. Thus, they are more susceptible to become anxious and develop other unwanted behaviours if their routine or repetitive behaviour is interrupted and so, this can be minimized by making events and environment predictable [2].

Sensory problems, including hypo- or hyperresponsiveness, are also incorporated under restricted and repetitive behaviours in DSM-5 and present in as many as 80% of persons with ASD [2,7]. Many repetitive behaviours in ASD are actually adaptive behaviours for the sensory differences that are being experienced [7]. Owing to an overly sensitive nervous system, autistic children may exhibit extreme responses to tactile, auditory, visual, gustatory, and vestibular or proprioceptive input [2,4]. For instances, they are often very sensitive to smells (for example alcohol and blood), lights (especially bright or flashing), noises at any sound level, textures (for example unfamiliar sheets) and being touched or examined [7]. On the other hand, some sensory experiences can evoke intense pleasure, such as the visual input from toys with spinning lights. As a result of their difficulty managing sensory input, children may become very anxious or exhibit inappropriate behaviours in situations that could be considered pleasant by other children [2].

Besides the features described above, children with ASD also have commonly associated comorbidities, resulting in more health care visits and more medications prescribed [9]. Therefore, an understanding of these additional clinical features is vital for good perioperative care [2].

Intellectual Disability

Variable degree of intellectual disability can be found in children with ASD [10]. According to a study conducted by Charman et al. [11], of the 75 children with ASD evaluated, 55% of them had intellectual disability (IQ<70), 16% had moderate to severe intellectual disability (IQ<50), 28% had average intelligence (115>IQ>85) and 3% had above average intelligence (IQ>115).

Psychiatric Problems

In a study conducted by Simonoff et al. [12], 70% of 112 children with ASD evaluated had at least one concurrent psychiatric disorder, while 40% had two or more. Social anxiety disorder (29%), attention deficit/hyperactivity disorder (28%), and oppositional defiant or conduct disorder (30%) were the most common problems. Other less common disorders identified were generalized anxiety disorder (13%), panic disorder (10%), major depressive disorder (1%) and dysthymic disorder (0.5%).

Insomnia

Sleep problems are common in children and adolescents with ASD and its prevalence is reported to be 40–80%. Falling asleep, sleep duration and quality are the most common problems [3].

Seizures

Approximately 30% of children with ASD develop epilepsy [3]. According to Bolton et al. [13], generalized tonic–clonic seizures were the most predominant (88%) and, in the majority of individuals, they were controlled with one or two anticonvulsants. It was also reported that epilepsy was associated with gender (female), intellectual disability and poor verbal abilities.

Gastrointestinal Problems

About 50% of children with ASD have gastrointestinal, nutritional, or feeding issues [6]. This includes not only malabsorption, maldigestion, irritable bowel syndrome, celiac disease, food intolerance and food allergies, but also selective or obsessive eating, nonfunctional mealtime routines or oral aversion, or sensory processing difficulties. All this can lead to nutritional deficit [3,6].

Oral Health Problems

There is no association between ASD and specific dental problems. Nevertheless, children who have this condition have often a higher risk of caries due to the combination of several factors [14]. This includes poor oral hygiene, diet choices, use of sweet sticky foods as reward and xerostomia (as a side effect of psychoactive medications) [3,14]. In addition to this, child's behaviour towards simple dental procedures and treatments, cost of dental care, lack of dental insurance and limited availability of dental specialists capable of treating children with ASD have also been reported as important barriers to dental care access [5].

Motor Problems

Both fine and gross motor coordination can be affected. Some children may even exhibit hypotonia, toe walking or have motor apraxia [2].

Self-injury and Aggression

Head banging, biting the wrist and disruptive/challenging behaviour arising in response to stress are common in children with ASD [2].

Metabolic Abnormalities

Mitochondrial dysfunction is one of the most common metabolic abnormalities and according to a population-based study, its prevalence is 7.2% in children with ASD, while in the general population is only 0.01% [15]. Other metabolic abnormalities include folate cerebral metabolism dysfunction and disorders of creatine, cholesterol, pyridoxine, biotin, carnitine and uric acid [3].

Due to all conditions mentioned above, children with ASD are more likely to require procedures under general anesthesia than typically developing children, as it is necessary, not only for surgeries, but also for routine procedures, such as dental care or radiographic examinations [16-18]. These children also have an increased risk of adverse events occurring during hospitalization or procedures [2]. Besides this, behavioural challenges are common in perioperative period and require careful consideration of the diverse profiles of these patients [19].

Despite this, there is a lack of anesthesia literature regarding the perioperative care of autistic children and in what it differs from nonautistic children [16].

The aim of this work is to systematically review the special needs of this population in the perioperative period and its management to meet these special needs. Particular needs regarding the preoperative, intraoperative and postoperative period will be discussed, towards the safest surgical experience.

METHODS

An online search was performed on PubMed, Google Scholarship and Google, between September 2018 and October 2018. The following keyword combinations were used: "autism" "anesthesia" "surgery", "perioperative" "management" "autism", "anesthesia" "management" "autism", "autism" "anesthesia" "preoperative", "autism" "anesthesia" "postoperative", "autism" "anesthesia".

In this review, were eligible for inclusion articles written in English, which dated between 2008 and 2018. Also, only studies conducted in humans were used. 97 articles resulted from this research.

Thereafter, the selection of the articles was performed by reading their abstracts and, subsequently, by a complete reading. At this stage, were excluded studies regarding other syndromes/diseases than ASD; studies based in adult populations; studies related to specific features in ASD but not focusing on this pathology; hospital management; the role of general anesthesia in inducing the development or regression of ASD; etiologic issues; ASD pathophysiology; specific surgical details; specificities of treatment of abnormalities existing in ASD.

Applying these inclusion and exclusion criteria, 39 publications were selected to this revision.

Lastly, other articles were analysed, by consulting bibliographic references of the initially selected articles, where the year of their publication was not taken into account, ending up with 90 publications being analysed for this review (Figure 1).

RESULTS

The authors consider that autistic children are challenging patients in the perioperative period due to the high level of anxiety of the patient and family members and an uncooperative or combative behaviour of the child that can even become violent in more extreme cases [10]. Besides, for a positive surgical experience, it is vital to take into consideration child's routines, special interests, sensory sensitivities and level of understanding in order to prevent adverse events from occurring [2].

Thus, there must be careful planning which implies a specific approach and preparation for each patient [3,10].

Preoperative Period

Recently, Muskat et al. [20] found that the challenges faced by autistic children in the hospital setting lie in communication and sensory challenges and the degree of flexibility of the hospital and health-care providers.

Most of the times, the first contact between the child and the anaesthesiologist is on the day of the procedure which does not provide an adequate preparation [21]. Van der Walt et al. [22] suggested that children with ASD should be identified earlier so that the anaesthesiologist could conduct an interview with the parents, where an anesthetic questionnaire is fulfilled, to assist in the admission and anesthetic management. This questionnaire should include information regarding patient's autistic severity, developmental level, general health, medication, behaviour, likes and dislikes, phobias, favourite activities, objects and food, and coping techniques. The authors also focus the importance of placing autistic children first on the operating list in the morning, providing a flexible admission process to minimize preoperative waiting time and offering a quiet and private room for the patient and parents, with reduced amount of distressing sensory input (noise, movement and light).

Another study based on semistructured interviews to parents and medical staff identified that successful outcomes were facilitated by productive interactions between health care providers and families, mostly dependent on advanced provider preparation and alterations in the organization of health care delivery. This includes allotting more time to complete procedures for ASD children, minimizing waiting times and schedule appointments to reduce disruptions in child's routine and individualized modifications in the environment to avoid child's agitation (namely involving fewer people in child's care, providing a quiet room with warm colours, no fluorescent lights, turning lights down and closing doors) [23]. Changing the environment to accommodate ASD children was described in several studies [6,24].

Also, regarding the collaboration with the caregiver, Thompson and Tielsch-Goddard [6] conducted a study where forty-three caregivers of autistic children with an upcoming schedule surgery were interviewed before the surgery, to collect information to better help their children cope with their hospital visit. A postoperative call was performed to obtain feedback information about their child's surgical experience. The results obtained showed that, with the additional information provided, staff members could more quickly recognize potential stressors and help identify individual needs of these patients. It also increased staff interest in optimizing their surgical experiences. On the other hand, parents appreciated the individualized attention and focus on their child's issues.

In accordance to this, a hermeneutic study by Lindberg et al. [25] concluded that the parents experienced previous anesthetic care of their child in the absence of the perioperative dialogue as suffering and, on the contrary, the perioperative dialogue as alleviated suffering, which confirms the beneficial effects of the perioperative dialog from parental point of view.

Besides this, during the preoperative period, several forms of distractions can also be used, such as music, games, television, electronic devices [26,27] and allowing children to bring their own toys from home [24,26,28,29].

Using different forms of communication might also be helpful [3]. Children with ASD tend to be visually oriented and, thus visual tools can be useful, mainly for those with limited verbal skills [30]. Short et al. [31] suggested that autistic children may benefit from the use of symbol timelines and social stories. A randomized controlled trial conducted by Isong et al. [32] showed that certain electronic screen media technologies may reduce fear and uncooperative behaviours among children with ASD in preparation for dental visits, although additional studies using larger sample sizes are necessary, as well as, studies in other medical settings. Also, Vaz [33] developed a total of 150 visual symbols, representing treatment procedures, for use in healthcare settings and showed that its use before appointments improved understanding and cooperation of autistic children in clinical setting, though symbols were used in a small sample of children who were already familiar with the use of symbols in their daily life.

In addition to nonpharmacologic measures, usually ASD children will also require premedication to guarantee a smooth and safe pre-induction period [3,22]. Indeed, a prospective study comparing children with ASD to typically developing children in the perioperative setting showed that about 87.5% of youth with ASD received a premedication as compared to 64.3% of typically developing children [34]. Also, Swartz et al. [35] found that the need of preoperative sedation increased with increasing severity of ASD.

Oral midazolam is the most commonly used drug in the US and Europe in order to reduce anxiety with minimal sedative effects. It offers a rapid and reliable onset, short duration of onset, lack of major side effects and minimal delay in recovery room discharge time after anesthesia [10,36].

A prospective, randomized, doubleblinded study comparing three different doses of oral midazolam (0.25, 0.5 and 1.0 mg/kg, up to a maximum of 20 mg) found that the smallest dose was equally as effective as the higher two doses and overall 97% of patients achieved a satisfactory sedation, that was kept in 90% of patients for up to 45 min, although a larger proportion of children achieved satisfactory anxiolysis within 10 min at the higher doses (P=0.01). 86% had satisfactory anxiety ratings at face mask, however its acceptance was lower with the 0.25 mg/kg dose. There were no differences between any of the three doses regarding satisfactory separation from parents (88,2%), duration of recovery time, nausea, emesis, or respiratory events [37].

Prakash et al. [28] described a case of a 7-year-old autistic boy who required general anesthesia for dental treatment and was effectively premedicated with oral midazolam (0.5 mg/kg).

Finley et al. [38] observed that the use of oral midazolam to decrease anxiety during anesthetic induction was more pronounced in children with higher baseline levels of anxiety, while levels of trait impulsivity may contraindicate its use.

Although the oral route is preferred, other ways for midazolam administration can be used [39-41]. Kogan et al. [42] compared the following routes and doses of midazolam administration: intranasal (0.3 mg/kg), oral (0.5 mg/kg), rectal (0.5 mg/kg), and sublingual (0.3 mg/kg). They concluded that there were no significant differences in anxiety or sedation levels and face mask acceptance among the four different routes and, although the onset of peak sedation was faster in the intranasal group (20 min) than in the other three (30 min), 77% of the children cried after administration, presumably due to nasal irritation. Also in accordance to this, Yildirim et al. [43] found no significant difference in the effects of sedation between children premedicated with oral midazolam and those who received intranasal midazolam (P=0.583), as well as, no adverse effects.

Oral ketamine is a common alternative to oral midazolam [40,41]. Turhanoğlu et al. [44] showed that children who received 8mg/kg of oral ketamine were successfully sedated (80%), calm at the moment of separation from their parents (95%) and had an easy application of the anesthetic facemask. No child experienced emergence delirium (ED). Comparing to lower doses (4mg/kg and 6mg/kg), there were no differences in heart rate, blood pressure, respiratory rate and pulse oximetry, but nystagmus was more frequent with the highest dose. Other side effects associated with the use of ketamine were described in other studies, including emesis, vertigo, visual and auditory hallucinations [45] and hypersalivation [46].

Van der Walt et al. [22] conducted a retrospective chart review study from a hospital database in Australia with a total of 87 anesthetics in 59 children with ASD over a 4-year period. They suggested the use of oral midazolam for children with mild autism and oral ketamine for moderate and severe cases.

The combination of midazolam and ketamine can also be used in the more uncooperative children, as they improve compliance with minimal side effects [10,36,41,45].

In 2004, Darlong et al. [46] conducted a randomized controlled trial to evaluate if the combination of low dose oral midazolam (0.25 mg/kg) and low dose oral ketamine (3 mg/kg) offers a better premedication than oral midazolam (0.5 mg/kg) or oral ketamine (6 mg/kg) alone. The results showed that the combination provided a faster onset of sedation than the other two drugs alone ($P<0.05$), although at 30 minutes, there were no significant differences in sedation level. There were also no significant differences in the acceptance of the parental separation and response to induction with face mask.

Other double-blind study showed that combining intranasally ketamine (1–2 mg/kg) with midazolam (0.2 mg/kg) accelerated onset of sedation ($P<0.003$), compared to midazolam alone ($P<0.05$), with no adverse events. Also, no differences in the acceptance of parental separation were found [47].

On the other hand, in 2005, a prospective randomized double-blind study comparing the efficacy of oral midazolam alone (0.5 mg/kg) with a low-dose combination of oral midazolam (0.25 mg/kg) and ketamine (0.25 mg/kg) showed an uniform and acceptable sedation in both groups (95.9% and 97.96%, respectively) and comparable induction scores. However, the combination offered a significantly greater number of awake, calm and in a quiet state children during parental separation (73.46%) compared with oral midazolam alone (41%) [48]. The better acceptance of parental separation in children premedicated with this combination was also verified in other studies [45,49].

A case report showed a 16-year-old boy with severe autism and combative behaviour who was scheduled for dental rehabilitation under general anesthesia and was successfully premedicated with oral midazolam and ketamine [50].

Regarding recovery time, Darlong et al. [46] showed that patients who received the combination experienced an earlier recovery, compared to the midazolam and ketamine groups (P<0.001). However, other studies revealed no significant differences in recovery time [45,48,51]. Besides this, some studies show no difference in the incidence of postoperative nausea and vomiting (PONV) [45,46,48].

ASD children usually are more sensitive to certain textures and tastes which can limit the available premedication options [3]. Having this in mind, some authors have suggested the administration of the drug mixed in a flavoured drink [36,41,52]. According to this, Van der Walt et al. [22] stated that the incidence of rejection of premedication drugs by the patients became rare with parents' help and with the administration of midazolam or ketamine mixed in a flavoured drink and sharing the drink without the drug with their parents. In accordance to this, Shah et al. [50] described the case of a children with ASD undergoing dental rehabilitation under general anesthesia, whose acceptability to take midazolam and ketamine increased after mixing them in his favourite drink to mask the taste of the drugs.

The use of dexmedetomidine and clonidine in children with ASD has also been described by some authors [3,10,39].

A retrospective study about the use of oral dexmedetomidine as the main sedation in 315 individuals with ASD (83%) or other neuro-behavioral disorder showed that dexmedetomidine, alone or with midazolam, provided effective sedation in 311 of 315 children. Most patients (90%) received both drugs. Hypotension and bradycardia occurred in 9.5% and in 20.3% of patients, respectively, but only 2% required intervention [53].

In 2014, a prospective study comparing the efficacy of intranasal dexmedetomidine with intranasal midazolam concluded that children premedicated with dexmedetomidine were significantly more sedated than those with midazolam (77.8% vs 44.4%, respectively, P=0.002, CI 0.54–0.12) and had better acceptable compliance with mask application (80.6% vs 58.3%, respectively, CI 0.4209.01, P=0.035). However, the median onset of sedation was significantly shorter with midazolam than with dexmedetomidine (10–25 min vs 20–40 min, respectively, P=0.001). No cases of oxygen desaturation, respiratory depression or apnea were observed [54].

On the other hand, Akin et al. [55] found no difference in sedation score (P=0.36) or anxiety score (P=0.56) between these two drugs, but midazolam was superior to dexmedetomidine in providing satisfactory conditions during mask induction (82.2% vs 60%, respectively, P=0.01). No patient developed hypotension or hypoxemia.

The effectiveness of dexmedetomidine as a premedication prior to anesthesia induction was also described in other studies [56,57].

Regarding clonidine, a prospective study with 27 autistic children, who were undergoing electroencephalography (EEG), used oral clonidine as a sedative agent (dose ranging from 0.05 mg to 0.2 mg) and the results showed that sedation was achieved in 85% of the patients and the mean time to achieve it was 58 minutes, with a range of 15 to 135 minutes (SD 32.7).The mean time to recovery was 105 minutes with a range of 20 to 195 minutes (SD 40.9). 17% of successfully sedated children experienced mild and asymptomatic reduction in blood pressure and heart rate, recovering without any intervention [58].

Fazi et al. [59] compared the effects of oral clonidine (4 mg/kg) and midazolam (0.5 mg/kg) on the preanesthetic sedation in children during tonsillectomy with or without adenoidectomy. The results showed that children's anxiety at the time of separation from their parents and at mask induction was higher in the clonidine group. There were no clinically significant episodes of bradycardia, hypotension or hypoxemia in neither of the groups. However, in the clonidine group, the intraoperative averages of the mean blood pressure were lower (69 ± 10 vs 63 ± 7 mmHg, for midazolam and clonidine groups, respectively, $P<0.05$) and the duration of surgery and anesthesia were significantly shorter ($P<0.05$).

Though the goal is to avoid the intramuscular route as much as possible, instead of struggling with a combative child when oral premedication is not working, intramuscular ketamine may be indicated [2,27,36,41].

In fact, Elliott et al. [34] found that ASD children were more likely to receive a nonstandard premedication (34.4%) when compared with typically developing youth (RR=4.9, 95% CI=[2.0, 11.7], $P<0.001$) and the most commonly used nonstandard medication was intramuscular ketamine. Similar findings were shown by Arnold et al. [16].

Swartz et al. [35] observed good cooperation rates at separation and induction of anesthesia in children with ASD premedicated with intramuscular ketamine (88%) and found that this route was more likely to be chosen in more severe autistic patients.

Verghese et al. [60] evaluated the effects of intramuscular ketamine alone or combined with midazolam in uncooperative children during induction of anesthesia and concluded that in both cases children achieved satisfactory sedation in less than 3 minutes, however those who received both drugs had significant longer recovery and discharge times, when compared with children who received only ketamine.

Intraoperative Period

Allowing parental presence in the operating room during induction to help reduce child's anxiety has been suggested by some authors [1,26,28].

Several authors advise the administration of intravenous fluids and antiemetic agents to minimize PONV and allow early removal of the intravenous cannula and, thus provide a calm postoperative course [2,3,8,31,40].

In fact, regarding adequate hydration, Elgueta et al. [61] conducted a study, reporting that the group of children who received 30 ml/kg/h of intravenous fluids was associated with less emesis than the group that received 10 ml/kg/h of intravenous fluids (62% vs 82%, respectively), without any other prophylaxis. The same conclusion was reached by Goodarzi el all. [62].

Van der Walt et al. [22] used intravenous fluids and tropisetron (0.1 mg/kg up to a maximum of 2 mg) for antiemesis prophylaxis in children with ASD. Of the 51 patients included, 12 (24%) had postoperative vomiting.

Several authors also highlight the importance of a good analgesia. It must be carefully managed as children with ASD may have difficulty in expressing the location and intensity of pain postoperatively. Thus, it is recommended intraoperative use of simple analgesics, as acetaminophen and anti-inflammatory medications, supplemented by the utilization of regional anesthesia [3,31,40].

According to Tripi et al. [63], children who are more frequently clingy/dependent (χ^2=5.57, P<0.06) and children with temper tantrums (χ^2=7.44, P<0.02) are more likely to have emergence distress behaviour. In accordance to this, a study by Voepel-Lewis et al. [64] found that children who experienced emergence agitation (EA) were significantly less adaptable compared with nonagitated children. Besides poor adaptability, an increased incidence of EA was also associated with young age, no previous surgery, ophthalmology and otorhinolaryngology procedures, sevoflurane, isoflurane and sevoflurane/isoflurane anesthesia, analgesics, and short time to awakening. Other studies have shown that children with more intense preoperative anxiety are more likely to experience ED [65,66].

In order to decrease this phenomenon, additional medication in children with ASD may be required [2,3,40].

A meta-analysis involving 13 studies about the protective effect of propofol against EA in children showed that propofol given by continuous administration [OR=0.17 (0.11, 0.27), I^2=36%, P=0.13] and as a bolus dose at the end of anesthesia [OR=0.21 (0.09, 0.50), I^2=0, P=0.47] is effective in preventing EA. However, the administration of a bolus after induction was found to be ineffective in preventing this phenomenon [OR=0.46 (0.20, 1.06), I^2=40%, P=0.19] [67]. Similar results comparing the incidence of EA in children undergoing sevoflurane versus propofol anesthesia are reported in another recent meta-analysis of 14 studies [68].

A double blind study involving 85 children premedicated with acetaminophen and midazolam undergoing general anesthesia with sevoflurane for dental repair showed that only 16.6% of children who received ketamine intraoperatively (before surgery end) experienced EA, comparing to 34.2% in the placebo group [69]. Another study conducted by Tsai et al. [70] involving a total of 60 paediatric patients under sevoflurane general anesthesia premedicated with midazolam found that those who received intraoperative administration of ketamine (after induction) had a lower incidence of EA comparing with the placebo group (35% vs 55%, respectively, $P<0.05$). Dalens et al. [71] also found similar results with the injection of ketamine immediately before the discontinuation of sevoflurane administration in children for magnetic resonance imaging examination under general anesthesia. They found that the differences between the ketamine group and placebo group were observed at all times (5, 10, 15, and 30 min), especially at 30 minutes, after discontinuation of anesthesia.

A double-blind randomized prospective study was conducted to analyse the effects of a continuous infusion of dexmedetomidine on the incidence of ED in 50 children scheduled for sevoflurane-based general anesthesia. The results showed that the incidence of ED in children who received dexmedetomidine following inhalation induction was significantly lower than in the placebo group (26% vs 60.8%, respectively, $P=0.036$), as well as, the number of episodes (12 vs 36, respectively, $P=0.017$) [72]. Also, in accordance to this, Guler et al. [73] studied the effect of single intravenous dose of dexmedetomidine (given 5 minutes before the end of surgery) on EA in children undergoing adenotonsillectomy under general anesthesia (inducted and maintained with sevoflurane). They found that the median agitation score was better in the dexmedetomidine group than in the placebo group: score=2 - awake, calm vs score=4 - inconsolable crying, respectively ($P<0.05$). Also, a more recent study showed that giving dexmedetomidine (1 μg/kg), after induction with sevoflurane, intravenously over a period of one minute, plus a 1 μg/kg/hr continuous infusion was successful in preventing postoperative agitation (11% vs 46% in the placebo group, $P=0.011$) and severe agitation (4% vs 25% in the placebo group, $P=0.042$). Compared to ketamine, dexmedetomidine was also associated with a lower incidence of agitation (22% vs 11%, respectively) and severe agitation (7% vs 4%, respectively) although it was not considered significantly different. [74]. On the other hand, a study comparing a single dose of propofol (1 mg/kg) with dexmedetomidine (0.3 ug/kg) before the end of surgery, showed that the number of children who experienced ED was significantly higher with propofol than with dexmedetomidine at T0 (13 vs 5), T5 (9 vs 2), and T15 (4 vs 1) [75].

A study conducted by Saadawy et al. [76] showed that the incidence of EA in children who received a caudal injection of bupivacaine mixed with dexmedetomidine was significantly lower, compared to the incidence in the group that received only bupivacaine (27% vs. 7%, respectively, P<0,05).

In 2010, a randomised, double-blind and placebo controlled trial evaluated the effectiveness of intravascular clonidine in preventing post-sevoflurane EA in children premedicated with midazolam and undergoing surgery. Agitation was observed in 27,5% of children in the placebo group, compared to 5,1% and 0% in the groups that received clonidine 1 µg/kg and 2 µg/kg, respectively (P<0.001) [77]. Other studies demonstrate the reduction of EA associated with sevoflurane anesthesia in children who receive intravenous clonidine after anesthetic induction [78,79].

In 2011, Ghosh et al. [80] conducted a prospective randomised double-blind study to evaluate the effectiveness of caudal clonidine (1mg/kg) in reducing the incidence of sevoflurane-induced agitation in children undergoing surgery. The results revealed that post-anesthetic agitation was observed in 6.6% of the patients who received clonidine added to bupivacaine (0.75ml/kg) and in 40% of the patients in the control group (bupivacaine 0.75 ml/kg).

Regarding these two different routes for clonidine administration, Bock et al. [81] compared the effectiveness of caudal and intravenous clonidine in the prevention of postanesthetic agitation associated with sevoflurane anaesthesia. They verified that the incidence of agitation in the group that received clonidine (3 µg/kg) added to caudal bupivacaine (1 ml/kg) and in the group that received clonidine (3 µg/kg) intravenous and caudal bupivacaine (1 ml/kg) was 0% and 5%, respectively, while in the group receiving clonidine (1 µg/kg) added to caudal bupivacaine (1 ml/kg) and in the control group (caudal bupivacaine 1 ml/kg) the incidence was 22% and 39%, respectively.

On the other hand, in contrast to all the studies previously described, Lankinen et al. [82] observed no significant differences in the incidence of postoperative agitation between children who received intravenous clonidine (1.5 µg/kg) after anesthesia induction with sevoflurane and those in the placebo group (54% vs 62%, respectively, P=0,6).

The existent studies about intraoperative management of children with ASD have not found the best anesthetic agent yet [3].

Ma et al. [83] conducted a study comparing propofol and etomidate use after sevoflurane induction, for maintenance of general anesthesia in autistic children (N=60), during transplantation of stem cells. They found no differences in surgery and recovery time and degree of sedation. However, blood pressure and heart rate were significantly lower with propofol (P<0.05), which was also associated with higher occurrence of respiratory depression, bradycardia, hypotension and pain on injection (P<0.05), whereas the incidence of myoclonus was higher with etomidate (P<0.01).

Li et al. [84] investigated etomidate administration with or without flumazenil in autistic children (N=40) who underwent intrathecal transplantation of stem cells by lumbar puncture. All children received etomidate for induction and maintenance of anesthesia and, after operation, 20 patients received flumazenil. Blood pressure and heart rate measurements were not significantly changed in both groups, compared with baseline (P>0,05). Myoclonus was observed in the two groups, with no significant difference between them. Recovery time was significantly shorter in the group that received flumazenil compared to the control group (1.2 ± 1.15 vs 6.7 ± 2.27 min, respectively, P<0.01).

Asahi et al. [85] compared dose requirements for propofol anesthesia for dental treatment between autistic and intellectually impaired (IP) patients. Combative patients received oral midazolam premedication, while the others received an intravenous bolus at induction. After, all subjects received propofol (0.01 mg/kg), maintained by a continuous infusion (8 mg/kg/h). When anesthesia was not adequate, the infusion rate was increased and a propofol bolus given. The results showed that the infusion rates were higher in the patients with autism than in IP patients, although the difference was not significant. However, the proportion of the cases where bolus administration was needed after induction was significantly higher in the autistic patient group than in IP patients (89% vs 62%, respectively; P<0.002).

A more recent study investigated the possible relationship of three different neurological disorders, including autism, on the required propofol dose for anesthesia and the time to emergence from anesthesia, during dental treatment. They found no significant differences in the required propofol dose and time to emerge from anaesthesia among patients with different neurodevelopmental disorders, who did not receive an antiepileptic (P>0.05). Nevertheless, concerning autistic patients, the dose of propofol needed in those who received antiepileptic medications was lower than in patients not given an antiepileptic drug, though the difference was not significant (6.3 ± 1.12 vs 6.8 ± 0.46 mg/kg/h, respectively; P=0.99) [86].

Okur et al. [87] reported a case in which Bispectral Index (BIS) monitor was used to guide the intraoperative management of a 10-year-old child with ASD undergoing orchiopexy and circumcision. After premedication with midazolam and induction, the anesthesia was maintained with continuous infusions of propofol and remifentanil. The authors found BIS monitor to be useful in the management of anesthesia for a patient with ASD by optimizing doses to minimize its adverse events and to maximize its safety, and provide hemodynamic stability, easy recovery and faster discharge.

Postoperative Period

After surgery, children with ASD wake up in an unfamiliar space, which can be very stressful and lead to agitation while regaining consciousness [2,3].

To minimize this situation, many authors suggest that autistic children should recover in an isolated and quiet room with minimal surrounding noise, bright lights and unfamiliar people [1-3,6].

Besides, the presence of peripheral intravenous line may also cause distress and thus, some studies suggest to remove it as soon as possible, once there is no need for intravenous medication [6,22]. If it is not possible, assure it is well secured and camouflaged [3].

Moreover, allowing parental presence in the room as soon as possible, in some cases even before child's awakening, may be helpful in comforting and alleviating anxiety and thus, avoiding negative behaviours [1-3,21,22]. This was also found, in some case reports, to be successful [28,50].

Also, in order to minimize disruption in child's daily routines, some studies suggest physicians should discuss with parents the risks and the benefits of an early discharge, if possible and safe, in order to return patients to their normal environment, once they have regained their usual baseline, without inevitably meeting the usual discharge criteria [1,27,31].

The difficulties in communicating the presence of pain also make the postoperative period more challenging [1]. Also, the difficulty in expressing their feelings can make it harder for physicians to distinguish between pain, nausea, anxiety, confusion or ED [2]. In fact, Dubois et al. [88] studied pain expression, in daily life situations, in children with ASD (N=35) and showed that they express their pain through various behaviours, most of them similar to those exhibited in the general population, but they also exhibit behaviours more specific to the symptomology and disturbances of ASD, which are less easily identifiable as behaviours linked to pain (specific sounds, agitation, change in eyes). Also Tordjman et al. [89] measured the pain reactivity of 73 children and adolescents with ASD during venepuncture and, despite their higher rate of absent behavioral pain reactivity (41.3% vs. 8.7% in control group, $P<0.0001$), their heart rates were significantly greater than for controls (6.4 ± 2.5 vs. 1.3 ± 0.8 beats/min, $P<0.05$), as well as, plasma b-endorphin levels ($P<0.001$), which were also positively associated with autism severity ($P<0.001$). The authors suggested that these results reflect a different mode of pain expression by children with ASD, rather than a reduced pain sensitivity.

Thus, several authors suggest that using a nonverbal pain scale, such as Face, Leg, Activity, Cry, Consolability (FLACC) scale, may be helpful for pain assessment [2,3].

Ely et al. [90] conducted a qualitative, descriptive study to explore how to improve pain assessment, experienced after a surgical procedure, in children with ASD. Results included minimal time spent focusing on pain, simplistic language and actions, using familiar terms and parents' involvement to interpret child's needs and provide support.

Arnold et al. [16] conducted a retrospective cohort study and found that postoperative pain, analgesia, nausea and agitation, as well as, time in the post-anesthesia care unit and time to discharge were not significantly different between children with ASD and those without ASD. Also, according to Elliott et al. [34] no difference in posthospital negative behaviour change was shown between children with and without ASD.

DISCUSSION

Preoperative Period

Children with ASD represent a heterogeneous group of patients who have individualised needs. Although all different, they share some common features, as sensory problems and resistance to change, that can predispose them to adverse events and make their perioperative management more challenging to their parents, staff and the patients themselves [2,3].

Thus, several studies highlight the importance of an individualised approach that includes a planned, coordinated and flexible programme for the perioperative management of autistic children [6,22,23,35].

Indeed, the study conducted by Van der Walt et al. [22], one of the most cited, defends that the most important principle is to be notified in advance that an autistic child has been scheduled for a surgery, so that the parents can be contacted by the anaesthesiologist, to prepare child's plan admission and anesthetic management. Parents know their child best, so early communication between them and physicians to obtain information about child' specific needs and behavioural patterns is widely recommended, as this can have a positive impact on patient' surgical experience, staff comfort and parent satisfaction. [6,22,23,25,35]. Implementing a standardized set of questions to help individualize child's hospital stay seems to be helpful [29].

Besides, some alterations in the organization of health care delivery are defended, including a flexible admission process, scheduling autistic children first in the morning and individualised modifications in the environment to avoid child's agitation, namely providing a private room for the patient and parents and reduce the distressing sensory input (noise, movement and light) [6,22,23]. Moreover, allowing the child to have familiar and comforting objects, like a favourite toy, is suggested [24,28,29], as well as, other forms of distractions, namely games and electronic devices [26,27].

Alternative forms of communication might also be used to improve child's cooperation and decrease anxiety, including visual symbols at home before the appointments [33], electronic screen media [32], symbol timelines and social stories that explain the sequence of the expected events [31].

Improvements in systems to identify autistic children to enable advanced planning, health care delivery and staff education about this population specific needs would be beneficial [23].

Taking into account various publications, premedication is usually recommended to facilitate management of autistic children [2,3,22]. Swartz et al. [35] suggest that an individualized perioperative management plan with caregiver involvement and the knowledge of ASD severity level help determining the need for preoperative sedation.

Midazolam was found to be effective in paediatric patients, for producing sedation and anxiolysis, with minimal effects on respiration and oxygen saturation [37]. Finley et al. [38] showed that midazolam-induced decrease in anxiety during induction was greater in children with higher state anxiety level at baseline and it was contraindicated in highly impulsive children, due to probable disinhibition induction. In accordance to this, other publications showed midazolam's efficacy for milder forms of ASD [22,28]. Regarding administration, though the oral route is preferred [39-41], rectal, sublingual [42] and intranasal [42,43] midazolam are also safe and produce good levels of sedation and anxiolysis. However, intranasal administration may cause nasal irritation and limit child's cooperation [41,42].

A large dose of oral ketamine (8 mg/kg) has shown to be very effective in improving compliance during induction of anesthesia, not being associated with respiratory depression, tachycardia or ED [44]. Van der Walt et al. [22] have also proved the efficacy of this drug, suggesting its use for moderate and severe cases of autistic children. However, some adverse effects have been described in different studies, including nystagmus [44], emesis, vertigo, visual and auditory hallucinations [45] and hypersalivation [46]. The combination of ketamine with midazolam improves anxiolysis and sedation, without serious side effects [45-48] and may be helpful in extremely uncooperative children [10,36,41,50].

Both ketamine and midazolam can be administrated mixed in a flavoured drink [22,41,50].

Lubitsch et al. [53] described successful sedation for MRI in children with ASD, using dexmedetomidine, with and without midazolam, achieved with minimal side-effects. Reviewing the available studies, oral or intranasal dexmedetomidine appears to be an effective and safe alternative for premedication in children [54,56,57], though its relatively prolonged onset of action might constitute a limitation [54,55,57].

Mehta et al. [58] reported successful use of oral clonidine for sedation of autistic children undergoing EEG. It was considered well tolerated, though mild and asymptomatic reduction in blood pressure and pulse rate occurred in 4 of the 23 successfully sedated patients, requiring no intervention. No clinically significant side effects were recorded. On the other hand, one study showed that oral midazolam was superior to clonidine in relieving preoperative anxiety in children, recommending the preferential use of the first drug over clonidine. Though midazolam was superior for preanesthetic anxiolysis, greater sedative effects with clonidine could have been noted with a longer premedication period, given its long onset of action [59].

Though the goal is to avoid the intramuscular route, in the most combative or resistant children with ASD, when oral premedication is not working, intramuscular ketamine alone or in combination with midazolam has been shown to be an effective option for sedation [1,2,35,60].

There is insufficient literature to make evidence-based decisions on the ideal premedication for this population [2]. Midazolam is the most used drug [10], being ketamine a popular alternative in more severe cases [2,21]. Recently, Taghizadeh et al. [2] suggested the use of midazolam and alpha-2 agonists as first line medications, considering their many advantages, and ketamine as second-line, given its multiple side effects.

Intraoperative Period

It is advisable to consider parental presence during induction of anesthesia to help reduce child's anxiety. This must be evaluated by the anesthesiologist and agreed with the parents, on a case-by-case basis [1,26].

Taking into account the various articles analysed, it is consensual the administration of intravenous fluids and antiemetic drugs to minimize PONV and allow early removal of the intravenous cannula [2,3,8,31,40]. Both Elgueta et al. [61] and Goodarzi el al. [62] concluded that intravenous super-hydration (30 ml/kg/h lactated Ringer's solution) is an inexpensive and safe therapy for reducing PONV in children.

An adequate analgesia, using acetaminophen and anti-inflammatory medications, supplemented by regional anesthesia, if appropriate, is recommended [3,31,40].

Several studies have shown that preoperative anxiety is positively associated with EA/ED [63-66] and, thus additional medication to prevent its occurrence may be considered [2,3,40].

Propofol given by continuous administration [67,68] or as a bolus dose at the end of surgery [67] is efficient to prevent EA, whereas the administration of a bolus after induction is ineffective [67].

A 0.25 mg/kg dose of ketamine after induction [70] or before surgery end [69] is also effective, with no significant adverse effects registered.

Regarding dexmedetomidine, both continuous infusion [72] and a bolus administration at the end of surgery [73] seem to decrease the incidence of agitation, without provoking hemodynamic instability. Chen et al. [74] concluded that giving a 1 μg/kg dose after induction, plus a 1 μg/kg/hr continuous infusion reduce incidence of EA. The same pattern of administration for 1 mg/kg of ketamine was effective. No major adverse effects were reported for none of the drugs. However, dexmedetomidine also prevented PONV, leading the authors to suggest this drug over ketamine. Also dexmedetomidine was found to be superior to propofol in decreasing the incidence and severity of EA, when administered before the end of surgery [75]. A caudal injection of dexmedetomidine is another possible route of administration that is associated with lower incidence of ED [76].

A single dose of clonidine given after induction also appears to be effective in preventing agitation after sevoflurane anesthesia, without causing hemodynamic or respiratory adverse effects. [77-79]. Ghai et al. [77] compared two different doses – 1 ug/kg and 2ug/kg – and concluded that, though both effective, the higher dose is associated with a later discharge. Malviya et al. [78] also found that the higher dose is associated with sleepiness postoperatively. Caudal injection is another efficient and safe option for the anaesthesiologists [80,81]. Ghosh et al. [80] concluded that a 1 ug/kg dose is effective to prevent EA, without any significant adverse effects. Contrary to this, Bock et al. [81] found that that dose was insufficient to reduce this phenomenon. The contradiction presented in the last study is possibly explained due to the higher concentration of sevoflurane used and the difference in age of the study population. Besides, the number of children per group was only 20.

Regarding anesthetic management, the existing studies have not still found superiority of one anesthetic agent over another [3].

Ma et al. [83] found that for maintenance of general anesthesia after sevoflurane mask induction in children with ASD undergoing stem cell transplantation, both propofol and etomidate provided similar degree of sedation, surgical and recovery time, but sevoflurane-etomidate combination achieved a more stable hemodynamic response and resulted in fewer adverse effects, being therefore more suitable. Also, Li et al. [84] concluded that etomidate anesthesia achieved a stable hemodynamic response with few adverse effects. They also suggest the administration of flumazenil after the operation.

Regarding dose requirements for propofol anaesthesia, Ouchi et al. [86] concluded that the required dose for dental treatment is not affected by the type of neurological disorder, but rather by the use of antiepileptic medication, which decrease the propofol dose needed. Contrarily, Asahi et al. [85] suggested that autistic children need higher propofol doses during ordinary dental treatment, compared with IP patients. However, this last study did not take into consideration whether the patients were medicated with antiepileptic drugs or not, which may explain the differences found.

Future research is necessary to find the best anesthetic management strategy linked to lower incidence of adverse effects [3].

Postoperative Period

Waking up in PACU can be extremely stressful for this population, due to the unfamiliar and stimulating surroundings and difficulty in communicating their feelings, which can lead to increased agitation [1,3].

Reviewing the available publications, some measures appear to be widely considered beneficial to minimize this situation and, thus commonly suggested. Therefore, it is advisable to recover autistic children in an isolated room, with minimal lights and noises [1,3,6], allow the child to wake in the presence of their parents, as it can help alleviate anxiety [1-3,21,22], remove intravenous line as soon as possible, since it can cause agitation, and consider alternatives if necessary [1,3,6,22].

Regarding difficulties communicating the presence of pain, studies have concluded that children with ASD may express pain through various patterns, some of them less interpretable as pain behaviours, suggesting a different mode of pain expression [88,89]. Yet, further research in larger groups is needed to better characterize pain sensitivity and reactivity in autism and improve its communication [89].

Some authors suggest the use of a nonverbal pain scale, as FLACC scale, for a better pain evaluation [2,3].

The use of simplistic language and actions and familiar terms, as well as, early involvement of the parents also seem to help pain assessment [90].

A greater awareness of the fundamental role of stressful and painful events in the care of autistic children is recommended [89].

Minimize hospital stay, as much as possible and safe, in order to return patients to their normal environment and routines is recommended by several authors [1-3,31].

KEY LEARNING POINTS

Preoperative Period

1. It is vital an early identification of the autistic child scheduled for a surgery
2. An interview with the parents where an anesthetic questionnaire is carried out must be conducted, to collect information about children' specific needs and behavioural patterns and, thus prepare an individualised plan for admission and anesthetic management.
3. It is important to schedule autistic children as early in the day as possible and provide a flexible admission to minimize preoperative waiting time
4. It is crucial to provide a quite/private room for the child and parents with reduced distressing sensory input (noise, movement and light). It should also be used various forms of distractions, for example, child's favourite toy, games or electronic devices.
5. Alternative forms of communication might be considered, including visual symbols, electronic screen media, symbol timelines and social stories.
6. Premedication is suggested in most of the cases, to guarantee a smooth and safe pre-induction period. There is insufficient literature to determine the best premedication option.

- It is suggested the use of midazolam, dexmedetomidine and clonidine as first line medications and for milder forms of ASD, being ketamine an alternative for the more severe cases.
- The oral route is preferred and mixing the drug in a favourite drink may be considered. In the most combative children, intramuscular administration is a reliable choice.

Intraoperative Period

1. Evaluation, by the anaesthesiologist, of the possibility of parental presence during induction of anesthesia to help reduce child's anxiety is suggested.
2. It is essential an optimal intravenous hydration and the administration of antiemetic agents for PONV prophylaxis.
3. Adequate analgesia by intraoperative use of acetaminophen and anti-inflammatory medications and utilization of regional anesthesia is recommended.
4. Additional medication to prevent the occurrence of EA/ED may be required. Different drugs are efficient and can be considered.
    - Intravenous propofol given by continuous administration or as a bolus dose at the end of surgery
    - A single dose of intravenous ketamine after induction or before surgery end
    - Intravenous dexmedetomidine given by continuous infusion or as a bolus at the end of surgery, and caudal administration
    - A single dose of intravenous clonidine given after induction and caudal administration
5. Regarding anesthetic management, the existing studies have not determined the best anesthetic agent. According to the analysed bibliography, propofol and etomidate seem to be the most used agents, with similar degree of sedation and few adverse effects.

Postoperative Period

1. It is vital to provide an isolated room for recovery, with minimal light, noises and unfamiliar people.
2. Allowing parental presence in the room as early as possible, preferably even before the child's awakening, is strongly recommended, as it can reduce anxiety and negative behaviours.

3. It is suggested to remove peripheral intravenous line if possible, since the child may become distressed by its presence.
4. Regarding difficulties in communicating the presence of pain, the use of FLACC scale for pain evaluation is suggested. Moreover, using simplistic language and familiar terms and early parents' involvement also seem to help pain assessment.
5. It is suggested to minimize hospital stay, discharging children with ASD as quick as safely possible, in order to return patients to their normal environment and routines.

It is essential to develop perioperative protocols and clinical practice guidelines for the management of children with ASD, in order to integrate and improve their care and surgical outcomes.

CONCLUSION

The perioperative management of autistic children can be very challenging and, thus understanding patient's characteristics is paramount for a successful clinical care.

Preoperatively, the focus is on an early recognition of these patients, early communication with parents and advanced planning of admission process and anesthetic management.

Providing a comfortable environment during induction, as well as, an effective intraoperative analgesia, and PONV and EA/ED prophylaxis is a major goal.

Postoperatively, the aim is to provide conditions for a rapid, smooth and comfortable recovery and an early discharge.

APPENDIX

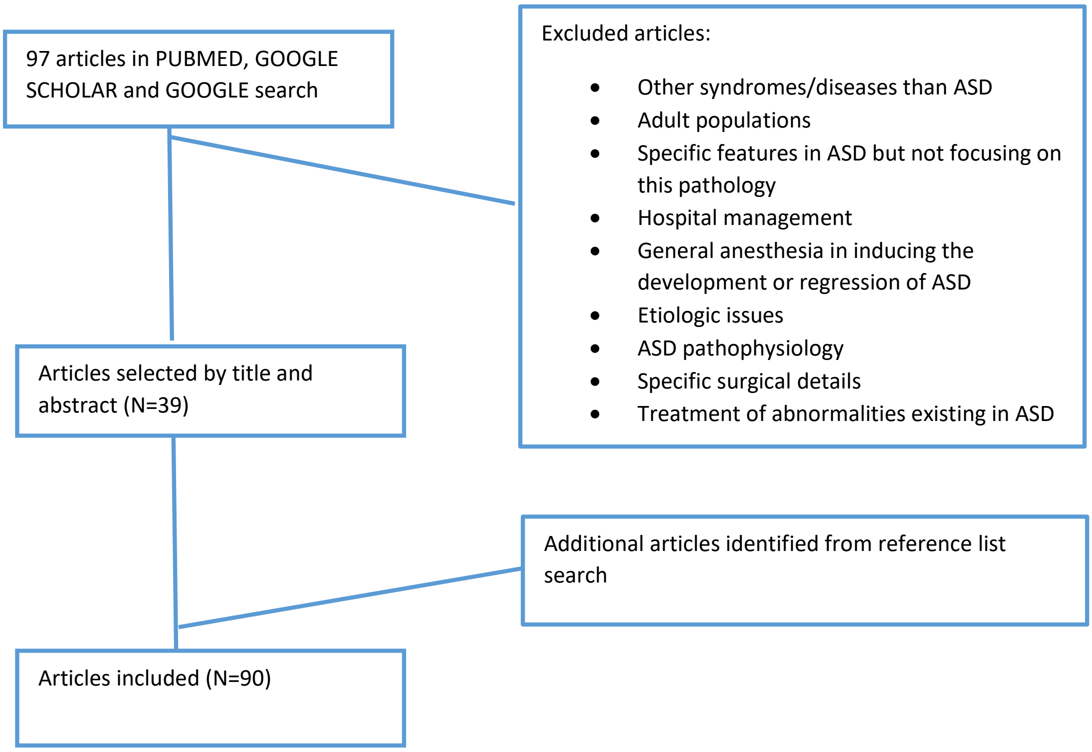

Figure 1- Articles methodology selection

REFERENCES

1. Biyani S, Morgan PS, Hotchkiss K, Cecchini M, Derkay CSJIjopo. Autism spectrum disorder 101: A primer for pediatric otolaryngologists. 2015;79(6):798-802.
2. Taghizadeh N, Davidson A, Williams K, Story DJPA. Autism spectrum disorder (ASD) and its perioperative management. 2015;25(11):1076-1084.
3. Vlassakova BG, Emmanouil DEJCoia. Perioperative considerations in children with autism spectrum disorder. 2016;29(3):359-366.
4. Gandhi RP, Klein UJJoEBDP. Autism spectrum disorders: an update on oral health management. 2014;14:115-126.
5. Delli K, Reichart PA, Bornstein MM, Livas CJMo, patologia oral y cirugia bucal. Management of children with autism spectrum disorder in the dental setting: concerns, behavioural approaches and recommendations. 2013;18(6):e862.
6. Thompson DG, Tielsch-Goddard AJJoPHC. Improving management of patients with autism spectrum disorder having scheduled surgery: optimizing practice. 2014;28(5):394-403.
7. Brown AB, Elder JHJPn. Communication in autism spectrum disorder: a guide for pediatric nurses. 2014;40(5).
8. Nelson D, Amplo KJAj. Care of the autistic patient in the perioperative area. 2009;89(2):391-397.
9. Johnson NL, Rodriguez DJPN. Children with autism spectrum disorder at a pediatric hospital: A systematic review of the literature. 2013.
10. SP S. Perioperative Management of a Patient with Autism. *Austin J Anesthesia and Analgesia.* 2014;2(2):1015.
11. Charman T, Pickles A, Simonoff E, Chandler S, Loucas T, Baird GJPm. IQ in children with autism spectrum disorders: data from the Special Needs and Autism Project (SNAP). 2011;41(3):619-627.
12. Simonoff E, Pickles A, Charman T, et al. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. 2008;47(8):921-929.
13. Bolton PF, Carcani-Rathwell I, Hutton J, Goode S, Howlin P, Rutter MJTBJoP. Epilepsy in autism: features and correlates. 2011;198(4):289-294.
14. Rada REJI, disabilities d. Treatment needs and adverse events related to dental treatment under general anesthesia for individuals with autism. 2013;51(4):246-252.
15. Oliveira G, Diogo L, Grazina M, et al. Mitochondrial dysfunction in autism spectrum disorders: a population-based study. 2005;47(3):185-189.
16. Arnold B, Elliott A, Laohamroonvorapongse D, Hanna J, Norvell D, Koh JJPA. Autistic children and anesthesia: is their perioperative experience different? 2015;25(11):1103-1110.
17. Gimbler Berglund I, Huus K, Enskär K, Faresjö M, Björkman BJJoD, Pediatrics B. Perioperative and anesthesia guidelines for children with autism: a nationwide survey from Sweden. 2016;37(6):457-464.
18. Loo CY, Graham RM, Hughes CV. Behaviour guidance in dental treatment of patients with autism spectrum disorder. *International Journal of Paediatric Dentistry.* 2009;19(6):390-398.
19. Koski S, Gabriels RL, Beresford CJAodic. Interventions for paediatric surgery patients with comorbid autism spectrum disorder: a systematic literature review. 2016:archdischild-2016-310814.
20. Muskat B, Burnham Riosa P, Nicholas DB, Roberts W, Stoddart KP, Zwaigenbaum L. Autism comes to the hospital: The experiences of patients with autism spectrum disorder, their parents and health-care providers at two Canadian paediatric hospitals. *Autism.* 2015;19(4):482-490.

21. Bagshaw M. Anaesthesia and the autistic child. *Journal of perioperative practice.* 2011;21(9):313-317.
22. Van der Walt J, Moran C. An audit of perioperative management of autistic children. *Pediatric Anesthesia.* 2001;11(4):401-408.
23. Davignon MN, Friedlaender E, Cronholm PF, Paciotti B, Levy SE. Parent and provider perspectives on procedural care for children with autism spectrum disorders. *Journal of Developmental & Behavioral Pediatrics.* 2014;35(3):207-215.
24. Berglund IG, Björkman B, Enskär K, Faresjö M, Huus K. Management of children with autism spectrum disorder in the anesthesia and radiographic context. *Journal of Developmental & Behavioral Pediatrics.* 2017;38(3):187-196.
25. Lindberg S, von Post I, Eriksson K. The experiences of parents of children with severe autism in connection with their children's anaesthetics, in the presence and absence of the perioperative dialogue: a hermeneutic study. *Scandinavian journal of caring sciences.* 2012;26(4):627-634.
26. Christiansen E, Chambers N. Induction of anesthesia in a combative child; management and issues. *Pediatric Anesthesia.* 2005;15(5):421-425.
27. Pratt K, Baird G, Gringras P. Ensuring successful admission to hospital for young people with learning difficulties, autism and challenging behaviour: a continuous quality improvement and change management programme. *Child: care, health and development.* 2012;38(6):789-797.
28. Prakash S, Pai V, Dhar M, Kumar A. Premedication in an autistic, combative child: Challenges and nuances. *Saudi journal of anaesthesia.* 2016;10(3):339.
29. Benich S, Thakur S, Schubart JR, Carr MM. Parental Perception of the Perioperative Experience for Children With Autism. *AORN journal.* 2018;108(1):34-43.
30. Scarpinato N, Bradley J, Kurbjun K, Bateman X, Holtzer B, Ely B. Caring for the child with an autism spectrum disorder in the acute care setting. *Journal for Specialists in Pediatric Nursing.* 2010;15(3):244-254.
31. Short JA, Calder A. Anaesthesia for children with special needs, including autistic spectrum disorder. *Continuing Education in Anaesthesia, Critical Care & Pain.* 2013;13(4):107-112.
32. Isong IA, Rao SR, Holifield C, et al. Addressing dental fear in children with autism spectrum disorders: a randomized controlled pilot study using electronic screen media. *Clinical pediatrics.* 2014;53(3):230-237.
33. Vaz I. Visual symbols in healthcare settings for children with learning disabilities and autism spectrum disorder. *British Journal of Nursing.* 2013;22(3):156-159.
34. Elliott AB, Holley AL, Ross AC, Soleta AO, Koh JL. A prospective study comparing perioperative anxiety and posthospital behavior in children with autism spectrum disorder vs typically developing children undergoing outpatient surgery. *Pediatric Anesthesia.* 2018;28(2):142-148.
35. Swartz JS, Amos KE, Brindas M, Girling LG, Ruth Graham M. Benefits of an individualized perioperative plan for children with autism spectrum disorder. *Pediatric Anesthesia.* 2017;27(8):856-862.
36. Bailey Jr PD, Bastien JL. Preinduction techniques for pediatric anesthesia. *Current Opinion in Anesthesiology.* 2005;18(3):265-269.
37. Coté CJ, Cohen IT, Suresh S, et al. A comparison of three doses of a commercially prepared oral midazolam syrup in children. *Anesthesia & Analgesia.* 2002;94(1):37-43.
38. Finley GA, Stewart SH, Buffett-Jerrott S, Wright KD, Millington D. High levels of impulsivity may contraindicate midazolam premedication in children. *Canadian Journal of Anesthesia.* 2006;53(1):73-78.
39. Krishnan DG. Anesthesia for the Pediatric Oral and Maxillofacial Surgery Patient. *Oral and maxillofacial surgery clinics of North America.* 2018;30(2):171-181.
40. Karam VY, Barakat H. Perioperative management of the child with behavioral disorders. *Middle East journal of anaesthesiology.* 2011;21(2):191-197.

41. Bozkurt P. Premedication of the pediatric patient–anesthesia for the uncooperative child. *Current Opinion in Anesthesiology.* 2007;20(3):211-215.
42. Kogan A, Katz J, Efrat R, Eidelman LA. Premedication with midazolam in young children: a comparison of four routes of administration. *Pediatric Anesthesia.* 2002;12(8):685-689.
43. Yildirim SV, Guc BU, Bozdogan N, Tokel K. Oral versus intranasal midazolam premedication for infants during echocardiographic study. *Advances in therapy.* 2006;23(5):719-724.
44. Turhanoğlu S, Kararmaz A, Özyilmaz M, Kaya S, Tok D. Effects of different doses of oral ketamine for premedication of children. *European journal of anaesthesiology.* 2003;20(1):56-60.
45. Funk W, Jakob W, Riedl T, Taeger K. Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone. *British journal of anaesthesia.* 2000;84(3):335-340.
46. Darlong V, Shende D, Subramanyam M, Sunder R, Naik A. Oral ketamine or midazolam or low dose combination for premedication in children. *Anaesthesia and intensive care.* 2004;32(2):246.
47. Weber F, Wulf H, El Saeidi G. Premedication with nasal s-ketamine and midazolam provides good conditions for induction of anesthesia in preschool children. *Canadian Journal of Anesthesia.* 2003;50(5):470-475.
48. Ghai B, Grandhe RP, Kumar A, Chari P. Comparative evaluation of midazolam and ketamine with midazolam alone as oral premedication. *Pediatric anesthesia.* 2005;15(7):554-559.
49. Astuto M, Disma N, Crimi E. Two doses of oral ketamine, given with midazolam, for premedication in children. *Minerva anestesiologica.* 2002;68(7-8):593-598.
50. Shah S, Shah S, Apuya J, Gopalakrishnan S, Martin T. Combination of oral ketamine and midazolam as a premedication for a severely autistic and combative patient. *Journal of anesthesia.* 2009;23(1):126-128.
51. Trabold B, Rzepecki A, Sauer K, Hobbhahn J. A comparison of two different doses of ketamine with midazolam and midazolam alone as oral preanaesthetic medication on recovery after sevoflurane anaesthesia in children. *Pediatric Anesthesia.* 2002;12(8):690-693.
52. Courtman SP, Mumby D. Children with learning disabilities. *Pediatric Anesthesia.* 2008;18(3):198-207.
53. Lubisch N, Roskos R, Berkenbosch JW. Dexmedetomidine for procedural sedation in children with autism and other behavior disorders. *Pediatric neurology.* 2009;41(2):88-94.
54. Sheta SA, Al-Sarheed MA, Abdelhalim AA. Intranasal dexmedetomidine vs midazolam for premedication in children undergoing complete dental rehabilitation: a double-blinded randomized controlled trial. *Pediatric Anesthesia.* 2014;24(2):181-189.
55. Akin A, Bayram A, Esmaoglu A, et al. Dexmedetomidine vs midazolam for premedication of pediatric patients undergoing anesthesia. *Pediatric Anesthesia.* 2012;22(9):871-876.
56. Zub D, Berkenbosch JW, Tobias JD. Preliminary experience with oral dexmedetomidine for procedural and anesthetic premedication. *Pediatric Anesthesia.* 2005;15(11):932-938.
57. Yuen VM, Hui TW, Irwin MG, Yuen MK. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: a double-blinded randomized controlled trial. *Anesthesia & Analgesia.* 2008;106(6):1715-1721.
58. Mehta UC, Patel I, Castello FV. EEG sedation for children with autism. *Journal of Developmental & Behavioral Pediatrics.* 2004;25(2):102-104.
59. Fazi L, Jantzen EC, Rose JB, Kurth CD, Watcha MF. A comparison of oral clonidine and oral midazolam as preanesthetic medications in the pediatric tonsillectomy patient. *Anesthesia & Analgesia.* 2001;92(1):56-61.
60. Verghese ST, Hannallah RS, Patel RI, Patel KM. Ketamine and midazolam is an inappropriate preinduction combination in uncooperative children undergoing brief ambulatory procedures. *Pediatric Anesthesia.* 2003;13(3):228-232.

61. Elgueta M, Echevarría G, De la Fuente N, et al. Effect of intravenous fluid therapy on postoperative vomiting in children undergoing tonsillectomy. *British journal of anaesthesia.* 2012;110(4):607-614.

62. Goodarzi M, Matar MM, Shafa M, Townsend JE, Gonzalez I. A prospective randomized blinded study of the effect of intravenous fluid therapy on postoperative nausea and vomiting in children undergoing strabismus surgery. *Pediatric Anesthesia.* 2006;16(1):49-53.

63. Tripi PA, Palermo TM, Thomas S, Goldfinger MM, Florentino-Pineda I. Assessment of risk factors for emergence distress and postoperative behavioural changes in children following general anaesthesia. *Pediatric Anesthesia.* 2004;14(3):235-240.

64. Voepel-Lewis T, Malviya S, Tait AR. A prospective cohort study of emergence agitation in the pediatric postanesthesia care unit. *Anesthesia & Analgesia.* 2003;96(6):1625-1630.

65. Kain ZN, Caldwell-Andrews AA, Maranets I, et al. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. *Anesthesia & Analgesia.* 2004;99(6):1648-1654.

66. Kain ZN, Mayes LC, Caldwell-Andrews AA, Karas DE, McClain BC. Preoperative anxiety, postoperative pain, and behavioral recovery in young children undergoing surgery. *Pediatrics.* 2006;118(2):651-658.

67. Dahmani S, Stany I, Brasher C, et al. Pharmacological prevention of sevoflurane-and desflurane-related emergence agitation in children: a meta-analysis of published studies. *British journal of anaesthesia.* 2010;104(2):216-223.

68. Kanaya A, Kuratani N, Satoh D, Kurosawa S. Lower incidence of emergence agitation in children after propofol anesthesia compared with sevoflurane: a meta-analysis of randomized controlled trials. *Journal of anesthesia.* 2014;28(1):4-11.

69. ABU-SHAHWAN I, Chowdary K. Ketamine is effective in decreasing the incidence of emergence agitation in children undergoing dental repair under sevoflurane general anesthesia. *Pediatric Anesthesia.* 2007;17(9):846-850.

70. Tsai PS, Hsu YW, Lin CS, Ko YP, Huang CJ. Ketamine but not propofol provides additional effects on attenuating sevoflurane-induced emergence agitation in midazolam premedicated pediatric patients. *Pediatric Anesthesia.* 2008;18(11):1114-1115.

71. Dalens BJ, Pinard AM, Létourneau D-R, Albert NT, Truchon RJ. Prevention of emergence agitation after sevoflurane anesthesia for pediatric cerebral magnetic resonance imaging by small doses of ketamine or nalbuphine administered just before discontinuing anesthesia. *Anesthesia & Analgesia.* 2006;102(4):1056-1061.

72. Shukry M, Clyde MC, Kalarickal PL, Ramadhyani U. Does dexmedetomidine prevent emergence delirium in children after sevoflurane-based general anesthesia? *Pediatric Anesthesia.* 2005;15(12):1098-1104.

73. Guler G, Akin A, Tosun Z, Ors S, Esmaoglu A, Boyaci A. Single-dose dexmedetomidine reduces agitation and provides smooth extubation after pediatric adenotonsillectomy. *Pediatric Anesthesia.* 2005;15(9):762-766.

74. Chen J-Y, Jia J-E, Liu T-J, Qin M-J, Li W-X. Comparison of the effects of dexmedetomidine, ketamine, and placebo on emergence agitation after strabismus surgery in children. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie.* 2013;60(4):385-392.

75. Ali MA, Abdellatif AA. Prevention of sevoflurane related emergence agitation in children undergoing adenotonsillectomy: A comparison of dexmedetomidine and propofol. *Saudi journal of anaesthesia.* 2013;7(3):296.

76. Saadawy I, Boker A, Elshahawy M, et al. Effect of dexmedetomidine on the characteristics of bupivacaine in a caudal block in pediatrics. *Acta Anaesthesiologica Scandinavica.* 2009;53(2):251-256.

77. Ghai B, Ram J, Chauhan S, Wig J. Effects of clonidine on recovery after sevoflurane anaesthesia in children undergoing cataract surgery. *Anaesthesia and intensive care.* 2010;38(3):530.

78. Malviya S, VOEPEL-LEWIS T, Ramamurthi RJ, Burke C, Tait AR. Clonidine for the prevention of emergence agitation in young children: efficacy and recovery profile. *Pediatric Anesthesia.* 2006;16(5):554-559.
79. Kulka P, Bressem M. Clonidine prevents sevoflurane-induced agitation in children. *Anesthesia & Analgesia.* 2001;93(2):335-338.
80. Ghosh SM, Agarwala RB, Pandey M, Vajifdar H. Efficacy of low-dose caudal clonidine in reduction of sevoflurane-induced agitation in children undergoing urogenital and lower limb surgery: a prospective randomised double-blind study. *European Journal of Anaesthesiology (EJA).* 2011;28(5):329-333.
81. Bock M, Kunz P, Schreckenberger R, Graf B, Martin E, Motsch J. Comparison of caudal and intravenous clonidine in the prevention of agitation after sevoflurane in children. *British journal of anaesthesia.* 2002;88(6):790-796.
82. Lankinen U, Avela R, Tarkkila P. The prevention of emergence agitation with tropisetron or clonidine after sevoflurane anesthesia in small children undergoing adenoidectomy. *Anesthesia & Analgesia.* 2006;102(5):1383-1386.
83. Ma YH, Li YW, Ma L, Cao CH, Liu XD. Anesthesia for stem cell transplantation in autistic children: A prospective, randomized, double-blind comparison of propofol and etomidate following sevoflurane inhalation. *Experimental and therapeutic medicine.* 2015;9(3):1035-1039.
84. Li Y-w, Ma L, Sui B, Cao C-h, Liu X-d. Etomidate with or without flumazenil anesthesia for stem cell transplantation in autistic children. *Drug metabolism and drug interactions.* 2014;29(1):47-51.
85. Asahi Y, Kubota K, Omichi S. Dose requirements for propofol anaesthesia for dental treatment for autistic patients compared with intellectually impaired patients. *Anaesthesia and intensive care.* 2009;37(1):70-73.
86. Ouchi K, Sugiyama K. Required propofol dose for anesthesia and time to emerge are affected by the use of antiepileptics: prospective cohort study. *BMC anesthesiology.* 2015;15(1):34.
87. Okur S, Arıkan M, Temel G, Temel V. BIS-guided total intravenous anesthesia for orchiopexy and circumcision in a child with severe autism: a case report. *Case reports in anesthesiology.* 2012;2012.
88. Dubois A, Michelon C, Rattaz C, Zabalia M, Baghdadli A. Daily living pain assessment in children with autism: Exploratory study. *Research in developmental disabilities.* 2017;62:238-246.
89. Tordjman S, Anderson GM, Botbol M, et al. Pain reactivity and plasma β-endorphin in children and adolescents with autistic disorder. *PLoS One.* 2009;4(8):e5289.
90. Ely E, Chen-Lim ML, Carpenter KM, Wallhauser E, Friedlaender E. Pain assessment of children with autism spectrum disorders. *Journal of Developmental & Behavioral Pediatrics.* 2016;37(1):53-61.