Journal of Anesthesia & Clinical Research

Kaufman et al., J Anesth Clin Res 2016, 7:9
DOI: 10.4172/2155-6148.1000667

Research Article | Open Access

Patient Susceptibility & Technical Factors Associated with Persistent Diaphragmatic Paralysis after Interscalene Nerve Block

Matthew R Kaufman[1,2,3*], **Ryan Fields**[4], **John Cece**[2], **Catarina P Martins**[2], **Kameron Rezzadeh**[2], **Andrew I Elkwood**[1,2] **and Reza Jarrahy**[3]

[1]*The Center for Treatment of Paralysis and Reconstructive Nerve Surgery, Jersey Shore University Medical Center, Neptune, New Jersey, USA*

[2]*The Institute for Advanced Reconstruction, Shrewsbury, New Jersey, USA*

[3]*Division of Plastic and Reconstructive Surgery, David Geffen UCLA Medical Center, Los Angeles, California, USA*

[4]*Department of Anesthesiology, Jersey Shore University Medical Center, Neptune, New Jersey, USA*

*__Corresponding author__: Matthew R Kaufman, The Institute for Advanced Reconstruction, 535 Sycamore Avenue, Shrewsbury, New Jersey, USA, Tel: 2013908121; E-mail: kaufmanmatthew@hotmail.com

Received date: June 21, 2016; **Accepted date:** September 15, 2016; **Published date:** September 21, 2016

Abstract

Background and objectives: Interscalene nerve blocks (ISB) have been associated with the rare complication of persistent diaphragmatic paralysis. Little is known regarding patient susceptibility or technical factors that may contribute to the development of this debilitating adverse reaction.

Methods: An observational study was performed between 2009 and 2014 to compare two groups of patients who received ISB for upper extremity surgery. Patient demographic factors, co-morbidities, and technical aspects of the nerve block were reviewed and compared in two groups: 50 consecutive patients receiving ISB without consequence at a university-based hospital and affiliated outpatient surgery center (Group I); 29

patients with persistent diaphragmatic paralysis after ISB evaluated and treated at a tertiary referral center (Group II). We analyzed the following patient factors between groups: age, sex, BMI, laterality, history of peripheral or diabetic neuropathy, prior nerve blocks, and underlying cervical spondylosis. An assessment of technical aspects of the nerve block was also performed.

Results: In Group I there was 26 females and 24 males with an average age of 55, whereas in Group II there were 4 females and 25 males with an average age of 58. There was no significant difference between groups for BMI (mean=36 *vs.* 30) or laterality (Left=38% *vs.* 31%), however there were a significantly higher proportion of males in Group II ($p<0.01$). No difference was demonstrated between groups for peripheral or diabetic neuropathy, whereas prior ipsilateral blocks and cervical spondylosis were significantly more prevalent in Group II ($p<0.01$ & $p<0.01$, respectively). In Group I, 86% of patients received blocks performed with either nerve stimulator (64%) or ultrasound (22%) guidance, and 10% using both modalities. This contrasts to 79% of patients in Group II whose blocks were performed using either nerve stimulator (24%) or ultrasound (55%) guidance, and 6% in combination.

Conclusion: Both patient factors and technical aspects of ISB may impact occurrence of persistent diaphragmatic paralysis. Use of ultrasound and nerve stimulator guidance can improve accuracy and reduce associated tissue inflammation, and there should be a redoubling of efforts to ensure technical expertise with these modalities in clinical practice.

Keywords: Diaphragmatic paralysis; Interscalene nerve block

Introduction

The incidence of persistent diaphragmatic paralysis after ISB is not precisely known, however has been estimated to be one percent or less [1]. Alternatively, transient paralysis of the diaphragm after ISB due to the local anesthetic effect has been widely reported [1-3]. Early reports cite incidences approaching 100%, however with modified anesthetic regimens and use of ultrasound and/or nerve stimulators, the likelihood appears to be much lower [2-4]. Regional anesthesia experts have not been able to elucidate the cause(s) of persistent diaphragmatic paralysis, yet this rare, debilitating event remains a common topic of discussion. There has been much debate concerning the patient factors and technical variations that may lead to diaphragmatic paralysis, but without much supporting evidence to date.

Numerous pathogenic processes may cause an insult to a peripheral nerve resulting in segmental ischemia and muscular paralysis [5]. The inciting event may be a mechanical process (i.e. compression, traction, piercing), or pharmacologic toxicity, but the pathological result is often the same-loss of the myelin sheath and/or axons resulting in a conduction delay or block, and leading to persistent muscular paralysis. In the case of the diaphragm muscle, the insult may impact the 3rd through 5th cervical roots, and/or phrenic nerves. Although diaphragmatic paralysis is easily diagnosed on chest fluoroscopy with inspiration (sniff testing) or ultrasound, the ability to localize and quantitate injury to this neural system is not possible with any current radiographic imaging modalities. Clinicians must rely instead on electro diagnostic testing [diaphragm electromyography (EMG) and phrenic nerve conduction testing (NCS)] to confirm and quantify the extent of cervical root and/or phrenic nerve damage.

Although unilateral diaphragmatic paralysis is sometimes considered a condition that is relatively well-tolerated, there are often deficits in respiratory activity and physical functioning that have major consequences as reported on quality of life surveys [6]. The literature is vague regarding whether individuals with unilateral paralysis are more susceptible to co-morbid respiratory conditions such as pneumonia or sleep disordered breathing, however it is conceivable that diminution of lung expansion as a result of the elevated diaphragmatic position has a negative impact on overall respiratory well-being.

The aim of the current study is to investigate associations between ISB and persistent diaphragmatic paralysis. The observational study design includes careful evaluation of possible patient susceptibility factors, such as pre-existing cervical spondylosis or diabetic peripheral neuropathy, as well as technical aspects of the ISB (i.e. anesthetic agent, ultrasound guidance, and type of needle used). Our goal is to enhance current knowledge regarding susceptibility and causation of this adverse event following ISB to reduce or eliminate its occurrence for regional anesthesia practitioners.

Materials and Methods

The study design matched patients with persistent diaphragmatic paralysis after ISB to patients who had ISB without complication between 2009 and 2014. Groups were matched based upon receiving ISB for upper extremity surgery and during the same time period at accredited inpatient or outpatient surgical facilities. Patients were excluded if they had pre-existing diaphragmatic paralysis or a history of exertional dyspnea.

Group I consisted of 50 consecutive patients receiving ISB without consequence at a university-based hospital and affiliated outpatient surgery center in central New Jersey (Jersey Shore University Medical Center, Neptune, NJ). Group II was comprised of 29 patients diagnosed with persistent diaphragmatic paralysis after ISB that had been performed at various inpatient and outpatient centers throughout the United States. These patients were actively seeking specialized medical care for their symptomatic condition and travelled to one of our multidisciplinary referral centers for surgical treatment (Center for Treatment of Paralysis and Reconstructive Nerve Surgery, Neptune, NJ, and Phrenic Nerve Reconstruction Program, Division of Plastic & Reconstructive Surgery, UCLA Medical Center, Los Angeles, CA). Details of phrenic nerve reconstruction for treatment of persistent diaphragmatic after ISB can be found in prior publications [7-10].

Patients in Group I did not report any early or late respiratory symptomatology following ISB, therefore there was no indication to undergo any follow-up testing for diaphragmatic paralysis. All patients in Group II underwent an extensive diagnostic evaluation to confirm and quantitate the diaphragmatic paralysis. Diagnostic testing included: chest fluoroscopy (sniff testing), pulmonary function testing, maximal inspiratory pressure assessment, electrodiagnostic evaluation (phrenic NCS & diaphragmatic EMG), MRI cervical spine, and CT neck & chest. Diagnosis of persistent diaphragmatic paralysis was made when the patient exhibited complete paralysis (or paradoxical movement) on sniff testing, and abnormal (or absent) phrenic nerve conduction and diaphragmatic motor amplitudes on electrodiagnostic assessment. Furthermore, the injury had to be present for at least 8 months without any objective or subjective improvement.

Patient demographic factors and technical aspects of the nerve block were reviewed and compared. IRB approval was obtained at our host institution and the analysis was undertaken in accordance with study approval. We analyzed the following patient factors between groups: age, sex, BMI, laterality, history of peripheral or diabetic neuropathy, prior nerve blocks (on the same side), and underlying cervical spondylosis. A co-diagnosis of cervical spondylosis was based upon patient self-reporting, diagnostic findings on cervical spine MRI, and/or a history of prior cervical spine surgery.

An assessment of technical aspects of the nerve block was obtained from operative and anesthesia reports, and included: type of surgical procedure, use of ultrasound and/or a nerve stimulator, anesthetic agent and dosing, use of epinephrine, type of needle, and application of an indwelling catheter. During chart review there were noted to be inconsistencies in the comprehensiveness of recorded information provided in anesthesia reports from different institutions, therefore missing data points are indicated in the presentation of results.

Results

In Group I there were 26 (52%) females and 24 (48%) males with an average age of 55 ± 17, whereas in Group II there were 4 (14%) females and 25 (86%) males with an average age of 58 ± 10 (Table 1). Chi-square analysis revealed significance for male sex (48% *vs.* 86%), with a significantly higher proportion of males in Group II ($p<0.01$). There was no difference between groups for mean BMI (Group I=36 ± 8 *vs.* Group II=30 ± 4) or laterality [Left sided injury: Group I=19 (38%) *vs.* Group II=9 (31%)].

There was no statistical difference demonstrated between Groups I and II for underlying peripheral or diabetic neuropathy (14% *vs.* 31%), whereas a history of another ipsilateral nerve block prior to the ISB (0% *vs.* 21%) and cervical spondylosis (12% *vs.* 45%) were significantly more prevalent in Group II [($p<0.01$) &($p<0.01$), respectively].

Shoulder arthroplasty, arthroscopy, and rotator cuff repairs were the most common surgical procedures in both Groups I (64%) and II (89%). In Group I, 22% of patients underwent total shoulder replacement, whereas in Group II this procedure was performed in 7% of patients. The remaining procedures included various musculo-tendinous and bony repairs of the hand, forearm, and upper arm.

	Group I (n=50)	**Group II (n=29)**
Age (mean)	55.3	58.2
Sex(#) (M/F)	24/26	25/4
BMI (mean)	36.2	20
Side(#)(L/R)	19/31	9/20

Prior block (#)	0	3
Cervical Spondylosis (%)	12	45
Diabetic Neuropathy (%)	14	7
Peripheral Neuropathy (%)	0	24

Table 1: Demographic factors and co-morbid conditions in ISB cohorts.

In Group I, 86% of patients received blocks performed with either nerve stimulator (64%) or ultrasound (22%) guidance, and 10% using both modalities (Table 2). This contrasts to 79% of the 20 patients in Group II (20/29 (69%) of anesthesia reports indicated use of technological modalities) whose blocks were performed using either nerve stimulator (24%) or ultrasound (55%) guidance, and 4% in combination. A 2-sided Fisher exact test to compare Groups in the application of at least one technological modality did not demonstrate a difference (p=0.137).

In both groups the following individual or combination agents were used to perform ISB: Bupivicaine, Lidocaine, Ropivicaine, or in combination. Ropivacaine (66%) was the most common anesthetic agent used in Group I, followed by bupivacaine (34%), whereas in Group II lidocaine (45%) was used most commonly followed by ropivacaine (24%). In 70% of Group I patients and 60% of Group II patients, 30 or 40 mL anesthetic volumes were used regardless of agents(s). Epinephrine was used in 19 patients (38%) in Group I and 7 patients (24%) in Group II. In Group I all patients received ISB with a 21 or 22-gauge Tuohy needle (B. Braun, Bethlehem, PA), whereas in the 55% of Group II anesthesia reports that indicated needle size, a 22-gauge was used in 10 patients (63%), 18-gauge in 5 patients (31%), and 20-gauge in 1 patient (6%). Indwelling catheters remained in place for post-operative pain relief in 3 patients (10%) in Group II (for an average of 2.7 ± 1.5 days) and were not used in any patients (0%) in Group I.

		Group I	Group II
Technological Guidance			(69% of reports)
No guidance (%)		4 (N=2)	15 (N=3)
Ultrasound guidance (%)		22 (N=11)	55 (N=11)
Nerve Stimulator guidance (%)		64 (N=32)	24 (N=5)
Both (%)		10 (N=5)	6 (N=1)
Anesthetic agent (%)			
	Bupivicaine	34 (N=17)	4 (N=1)
	Ropivacaine	66 (N=33)	24 (N=4)
	Lidocaine	0 (N=0)	45 (N=9)
	Other	0 (N=0)	27 (N=6)
Needle gauge, (%)			(55% of reports)
	18	0 (N=0)	31 (N=5)
	20	0 (N=0)	0 (N=0)
	21	10 (N=5)	6 (N=1)
	22	90 (N=45)	63 (N=10)
Epinephrine (%)		38 (N=19)	24 (N=4)
Indwelling catheter (#)		N=0	N=3

Table 2: Technical aspects of ISB in cohorts.

Discussion

ISB is a well-established regional anesthetic technique with demonstrated value for upper extremity surgery, particularly of the shoulder [11-14]. The safety of the procedure and the extremely low risk of adverse events have been well documented in the literature [15-17]. Critical analysis of persistent diaphragmatic paralysis after ISB, a complication that occurs infrequently, can only assist in increasing the safety profile of the technique, and ensure that practitioners optimize regional anesthetic care.

There are three questions that must be addressed in analyzing the association between persistent diaphragmatic paralysis and ISB: 1. Are there patients who may be susceptible to occurrence of this adverse event?; 2. What are the technical aspects of the block that may contribute to, or prevent this from happening?; 3. What is the pathological process that leads to persistent diaphragmatic paralysis after ISB?

Although there are limitations of this observational study (i.e. non-randomized, retrospective chart review, unmatched groups), our unique position to be able to evaluate and treat relatively large numbers of patients with persistent diaphragmatic paralysis following ISB justifies assessment with the current study design. This is especially true since the literature is absent of any sort of outcomes analysis addressing this topic and the relative rarity of the disorder makes prospective analysis quite difficult.

Our observational study focused on patient demographics and co-morbid conditions that may increase susceptibility to diaphragmatic paralysis after ISB. We found there were a significantly higher proportion of males in Group II. Although it could be suggested that ISB is more technically difficult in males due to larger body habitus, we did not find an association with increased BMI. Alternatively, it could be related to the previously established notion that males have higher rates of clinical and sub-clinical nerve compression injuries due to sports and work-related trauma [16-18].

There was also a demonstrated association between cervical spondylosis and diaphragmatic paralysis after ISB. Patients deemed to have cervical spondylosis were grouped according to diagnostic MRI findings, a history of cervical spine surgery, and/or self-reported symptoms and prior treatment. The double-crush phenomenon has been widely reported in the literature for various neuropathic conditions throughout the body, but especially as it relates to a susceptibility to carpal tunnel syndrome in patients with cervical spondylosis [19-22]. Perhaps an otherwise insignificant inflammatory process occurring around the phrenic nerve during ISB in patients with cervical spondylosis is enough to result in clinical manifestation of permanent diaphragmatic paralysis. It may be suggested that clinicians consider enhanced screening and increased selectivity during pre-operative anesthesia assessment.

Previous ISB on the same side was found to be a risk factor for persistent diaphragmatic paralysis and ISB. There is the possibility of a cumulative impact on the phrenic nerve with each successive block, ultimately leading to diaphragmatic paralysis. It has been reported in the peripheral nerve literature that repetitive insults or “mini-traumas” to a nerve can be the etiology for various compression neuropathies [23-25]. Patients being considered for ISB who have had prior blocks could be sent for phrenic NCS and diaphragmatic EMG to look for sub-clinical phrenic neuropathy. A better understanding of the pathological process would assist in confirming or refuting the notion that every ISB causes at least a minimal amount of peri-neural scar following mechanical or pharmacological induced inflammation. The pathological findings observed intra-operatively during phrenic nerve reconstruction will be discussed below.

Consistent with numerous reports in the anesthesia literature, our study findings appear to support the use of ultrasound and/or nerve stimulator guidance when performing ISB [26-29]. Stundner et al. found that ultrasound-guided ISB permitted low volume injection that resulted in less central foraminal and aberrant spread, and extrapolated the possibility of a lower risk profile. The precise localization of nerves for accurate needle placement clearly reduces the chances of multiple needle sticks, repetitive needle passes, and improper distribution of the injected solution. Nerve stimulator guidance may also provide a means to co-localize appropriate needle placement, however this device may tend to be less specific when used alone [26]. Mejia-Terrazas et al. compared ultrasound versus neurostimulation for ISB in a prospective non-randomized study and concluded ultrasound-guided ISB is the technique of choice based upon a statistically significant difference in complication rates [29-31]. Current and future studies may address the value of EMG recording during ISB as a way to determine if there is diaphragmatic activity occurring concomitant with needle passage. Jeong et al. in a prospective randomized evaluation of patients undergoing ultrasound-guided ISB with nerve stimulation thresholds, found a lower rate of intramuscular spreading of local anesthetic at 0.2 mA versus 0.5 mA [27].

Although prior studies have analyzed the anesthetic agents, dosing regimens, and use of epinephrine for ISB, our results did not demonstrate any to be a particular risk factor for persistent diaphragmatic paralysis [32-34]. Alternatively, modified dosing regimens have been shown to reduce occurrence of transient diaphragmatic paralysis as part of the short-term anesthetic effect [35]. Furthermore, it has been reported that epinephrine has the potential to act as a neurotoxic agent [36]. Whether use of epinephrine for ISB may impart any negative consequences is unclear, however surgical practitioners use local anesthesia and epinephrine routinely in proximity to peripheral nerves without impactful clinical evidence to support otherwise [37].

Additional technical factors that were analyzed for possible association with diaphragmatic paralysis included, needle size and use of indwelling catheters. Although we did not find a significant association for either, it is reasonable to consider options expected to create the least amount of peri-neural inflammation. This may include smaller needle gauges and being very selective in whom post-operative catheters are placed.

It is most difficult to address the third question regarding the exact pathological process following ISB that results in persistent diaphragmatic paralysis. Many theories abound, everything from the phrenic nerve being “pierced” by the needle, to inflammation in adjacent tissues that leads to phrenic nerve compression, and even that paralysis occurs not from ISB at all, but rather from patient positioning or a traction injury during the surgical procedure [38].

Although we may never completely know the exact mechanism, it is possible to comment on the intra-operative findings from performing phrenic nerve reconstruction on numerous patients with this condition. In the majority of patients treated, there has been a consistent finding of nerve degeneration at the C5 root contribution to the phrenic nerve along the posterior portion of the anterior scalene muscle (Figure 1).

Whereas both the proximal and distal portions along this neuraxis typically appear to be of good integrity, the involved segment is narrowed in caliber and exhibits an orange hue, a clear indication of myelin sheath loss and axonal degeneration. Commonly, there are dense fascial and vascular adhesions in the region that encompass the phrenic nerve, findings that also support a compression neuropathy (Figure 2).

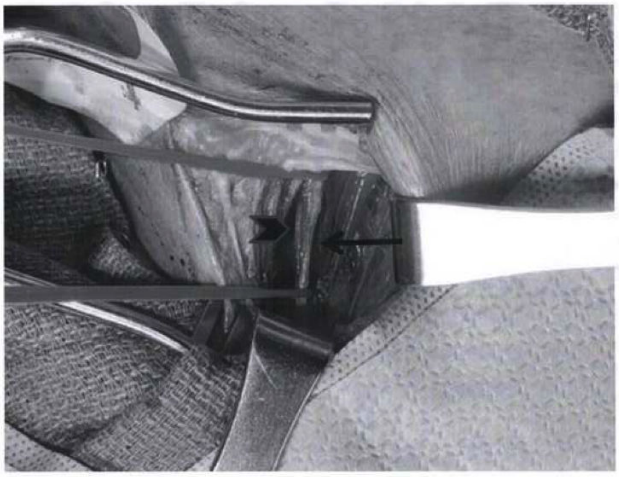

Figure 1: Atrophic segment of the phrenic nerve (arrow) at the C5 root (arrowhead) contribution along the posterior portion of the anterior scalene muscle. The proximal and distal loops are on relatively normal appearing phrenic nerve.

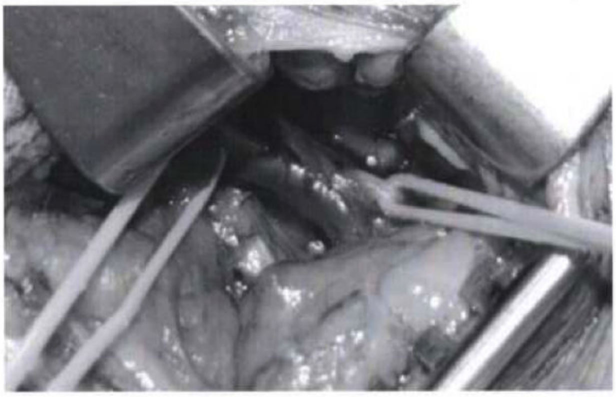

Figure 2: Perineural fibrosis and adhesions encompassing the phrenic nerve (loops proximal and distal to adhesions).

Given these findings, it certainly appears that inflammation plays a role in the nerve pathology, especially in susceptible patients. Thus, every effort should be made to limit the inflammatory process during ISB. This may include any or all of the following: ultrasound and/or nerve stimulator guidance, smaller gauge needle, maximum number of allowed needle sticks or passes, limited use of indwelling catheters, and pre-operative steroids. Future studies should compare the possible clinical benefits (versus cost) of implementing additional screening measures (i.e. MRI cervical spine, phrenic NCS & diaphragmatic EMG) for "at risk" patients.

References

1. [No authors listed] (1992) American Academy of Pediatrics Committee on Drugs: Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures. Pediatrics 89: 1110-1115.
2. Asahi Y, Kubota K, Omichi S (2009) Dose requirements for propofol anaesthesia for dental treatment for autistic patients compared with intellectually impaired patients. Anaesth Intensive Care 37: 70-73.
3. Buggy DJ, Nicol B, Rowbotham DJ, Lambert DG (2000) Effects of intravenous anesthetic agents on glutamate release: a role for GABAA receptor-mediated inhibition. Anesthesiology 92: 1067-1073.
4. Cressey DM, Claydon P, Bhaskaran NC, Reilly CS (2001) Effect of midazolam pretreatment on induction dose requirements of propofol in combination with fentanyl in younger and older adults. Anaesthesia 56: 108-113.
5. Dalal PG, Murray D, Cox T, McAllister J, Snider R (2006) Sedation and anesthesia protocols used for magnetic resonance imaging studies in infants: provider and pharmacologic considerations. Anesth Analg 103: 863-888.
6. Daskalopoulos R, Korcok J, Farhangkhgoee P, Karmazyn M, Gelb AW, et al. (2001) Propofol protection of sodium-hydrogen exchange activity sustains glutamate uptake during oxidative stress. Anesth Analg 93: 1199-1204.
7. Eaves RC, Milner B (1993) The criterion-related validity of the Childhood Autism Rating Scale and the Autism Behavior Checklist. J Abnorm Child Psychol 21: 481-491.
8. Eggermont JJ, Don M (1986) Mechanisms of central conduction time prolongation in brain-stem auditory evoked potentials. Arch Neurol 43: 116-120.
9. Fein D, Skoff B, Mirsky AF (1981) Clinical correlates of brainstem dysfunction in autistic children. J Autism Dev Disord 11: 303-315.
10. Fodale V, Pratico C, Santamaria LB (2004) Coadministration of propofol and midazolam decreases bispectral index value as a result of synergic muscle relaxant action on the motor system. Anesthesiology 101: 799.
11. Gillberg C, Rosenhall U, Johansson E (1983) Auditory brainstem responses in childhood psychosis. J Autism Dev Disord 13: 181-195.
12. Gomot M, Giard MH, Adrien JL, Barthelemy C, Bruneau N (2002) Hypersensitivity to acoustic change in children with autism: electrophysiological evidence of left frontal cortex dysfunctioning. Psychophysiology 39: 577-584.
13. Hadjikhani N, Joseph RM, Snyder J, Tager-Flusberg H (2006) Anatomical differences in the mirror neuron system and social cognition network in autism. Cereb Cortex 16: 1276-1282.
14. Herbert MR (2005) Large brains in autism: the challenge of pervasive abnormality. Neuroscientist 11: 417-440.
15. Hosey MT, Makin A, Jones RM, Gilchrist F, Carruthers M (2004) Propofol intravenous conscious sedation for anxious children in a specialist paediatric dentistry unit. Int J Paediatr Dent 14: 2-8.
16. Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ (2007) Functional and anatomical cortical underconnectivity in autism: evidence from an FMRI study of an executive function task and corpus callosum morphometry. Cereb Cortex 17: 951-961.
17. Kitt E Friderici J, Kleppel R, Canarie M (2015) Procedural sedation for MRI in children with ADHD. Paediatr Anaesth 25: 1026-1032.
18. Klin A, Pauls D, Schultz R, Volkmar F (2005) Three diagnostic approaches to Asperger syndrome: implications for research. J Autism Dev Disord 35: 221-234.
19. Leitch JA, Anderson K, Gambhir S, Millar K, Robb ND, et al. (2004) A partially blinded randomised controlled trial of patient-maintained propofol sedation and operator controlled midazolam sedation in third molar extractions. Anaesthesia 59: 853-860.
20. Leung AK, Kao CP (1999) Evaluation and management of the child with speech delay. Am Fam Physician 59: 3121-3128.
21. Ma DQ, Whitehead PL, Menold MM, Martin ER, Ashley-Koch AE, et al. (2005) Identification of significant association and gene-gene interaction of GABA receptor subunit genes in autism. Am J Hum Genet 77: 377-388.
22. Matschke RG, Stenzel C, Plath P, Zilles K (1994) Maturational aspects of the human auditory pathway: anatomical and electrophysiological findings. ORL J Otorhinolaryngol Relat Spec 56: 68-72.

23. McClelland RJ, Eyre DG, Watson D, Calvert GJ, Sherrard E (1992) Central conduction time in childhood autism. Br J Psychiatry 160: 659-663.
24. Miyawaki T, Kohjitani A, Maeda S, Egusa M, Mori T, et al. (2004) Intravenous sedation for dental patients with intellectual disability. J Intellect Disabil Res 48: 764-768.
25. Norrix LW, Trepanier S, Atlas M, Kim D (2012) The auditory brainstem response: latencies obtained in children while under general anesthesia. J Am Acad Audiol 23: 57-63.
26. Paspatis GA, Charoniti I, Manolaraki M, Vardas E, Papanikolaou N, et al. (2006) Synergistic sedation with oral midazolam as a premedication and intravenous propofol versus intravenous propofol alone in upper gastrointestinal endoscopies in children: a prospective, randomized study. J Pediatr Gastroenterol Nutr 43: 195-199.
27. Rainey L, van der Walt JH (1998) The anaesthetic management of autistic children. Anaesth Intensive Care 26: 682-686.
28. Ramsay MA, Savege TM, Simpson BR, Goodwin R (1974) Controlled sedation with alphaxalone-alphadolone. Br Med J 2: 656-659.
29. Schopler E, Reichler RJ, DeVellis RF, Daly K (1980) Toward objective classification of childhood autism: Childhood Autism Rating Scale (CARS). J Autism Dev Disord 10: 91-103.
30. Sebel LE, Richardson JE, Singh SP, Bell SV, Jenkins A (2006) Additive effects of sevoflurane and propofol on gamma-aminobutyric acid receptor function. Anesthesiology 104: 1176-1183.
31. Shinohe A, Hashimoto K, Nakamura K, Tsujii M, Iwata Y, et al. (2006) Increased serum levels of glutamate in adult patients with autism. Prog Neuropsychopharmacol Biol Psychiatry 30: 1472-1477.
32. Sitar SM, Hanifi-Moghaddam P, Gelb A, Cechetto DF, Siushansian R, et al. (1999) Propofol prevents peroxide-induced inhibition of glutamate transport in cultured astrocytes. Anesthesiology 90: 1446-1453.
33. Stephens AJ, Sapsford DJ, Curzon ME (1993) Intravenous sedation for handicapped dental patients: a clinical trial of midazolam and propofol. Br Dent J 175: 20-25.
34. Wakasugi M, Hirota K, Roth SH, Ito Y (1999) The effects of general anesthetics on excitatory and inhibitory synaptic transmission in area CA1 of the rat hippocampus in vitro. Anesth Analg 88: 676-680.
35. Westphalen RI, Hemmings HC (2003) Selective depression by general anesthetics of glutamate versus GABA release from isolated cortical nerve terminals. J Pharmacol Exp Ther 304: 1188-1196.
36. Yu ZY, Wang W, Fritschy JM, Witte OW, Redecker C (2006) Changes in neocortical and hippocampal GABAA receptor subunit distribution during brain maturation and aging. Brain Res 1099: 73-81.