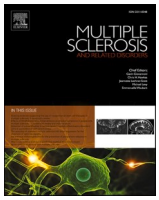
Multiple Sclerosis and Related Disorders 80 (2023) 105045

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Review article

Anaesthetic management of people with multiple sclerosis

N. Dubuisson [a,e,*], O. de Maere d'Aertrijcke [b], M. Marta [a,c], S. Gnanapavan [a,c], B. Turner [a,c], D. Baker [a], K. Schmierer [a,c], G. Giovannoni [a,c], V. Verma [d], M-A. Docquier [b]

[a] Faculty of Medicine and Dentistry, Blizard Institute (Neuroscience), Queen Mary University London, 4 Newark Street, London E1 2AT, UK
[b] Department of Anesthesia and Perioperative Medicine, Cliniques Universitaires Saint-Luc, St Luc Hospital, Avenue Hippocrate 10, Brussels 1200, Belgium
[c] Clinical Board Medicine (Neuroscience), The Royal London Hospital, Barts Health NHS Trust, London, UK
[d] Department of Anesthesia, Royal London Hospital, Barts Health NHS Trust, London, UK
[e] Neuromuscular Reference Center, Department of Neurology, Cliniques Universitaires Saint-Luc, Avenue Hippocrate 10, Brussels 1200, Belgium

ARTICLE INFO

Keywords:
Multiple sclerosis
Anaesthesia
Preoperative assessment
Peri-operative management
Pregnancy

ABSTRACT

There is a lack of published guidelines on the management of patients with multiple sclerosis (MS) undergoing procedures that require anaesthesia and respective advice is largely based on retrospective studies or case reports.

The aim of this paper is to provide recommendations for anaesthetists and neurologists for the management of patients with MS requiring anaesthesia.

This review covers issues related to the anaesthetic management of patients with MS, with a focus on pre-operative assessment, choice of anaesthetic techniques and agents, side-effects of drugs used during anaesthesia and their potential impact on the disease evolution, drug interactions that may occur, and the need to use monitoring devices. A systematic PubMed research was performed to retrieve relevant articles.

1. Introduction

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS) and the most common chronic demyelinating disease affecting approximately 2.8 million people worldwide, with females being twice more likely to suffer from MS than males. The global prevalence is estimated to be 35.9 per 100.000 inhabitants (Walton et al., 2020). A combination of genetic and environmental factors is thought to be involved in people developing MS (Dobson and Giovannoni, 2019). The symptoms people with MS (pwMS) describe are numerous and varied, depending on the region(s) of the CNS affected. Hence, there is no unique clinical phenotype. Frequently observed problems include impaired eyesight, impaired balance and coordination, motor and sensory abnormalities, fatigue, urinary and faecal incontinence and cognitive impairment. Clinically, multiple sclerosis can be divided into four different courses. The first, referred to as "Relapsing Multiple Sclerosis" (RMS) is characterised by acute episodes of neurological dysfunction, that are not triggered by infections or raised temperature or other metabolic change, with partial or complete remission. A portion of pwRMS will subsequently transition into a progressive disability phenotype - Secondary Progressive Multiple Sclerosis (SPMS), which is characterised by chronic deterioration of neurological function without remission. A third phenotype is defined by a progressive evolution from onset, ("Primary Progressive Multiple Sclerosis", PPMS). In addition, there is also a fourth course called clinically isolated syndrome (CIS) while radiologically isolated syndrome (RIS) can be considered as a MS pre-stage syndrome (Lublin et al., 2014).

Risk factors that trigger multiple sclerosis relapses include infection, fever and trauma, while surgery itself and emotional stress are more controversial (De Lott et al., 2020; Gold et al., 2005; McKay et al., 2017; Mohr et al., 2000; Xie et al., 2020).

It is of major importance that before any surgical procedure pre-existing neurological involvement is documented and assessed through a thorough preoperative evaluation, including a neurological examination and a full medical history, in order to identify the possible effects that anaesthesia may have, independently or in interaction with other concomitant medications, upon the course of the disease.

Optimal anaesthetic care also includes intraoperative and post-operative awareness of conditions that may precipitate MS relapses or exacerbate pre-existing symptoms. Currently, recommendations for

* Corresponding author at: Neuromuscular Reference Center, Department of Neurology, Cliniques Universitaires Saint-Luc, Avenue Hippocrate 10, Brussels 1200, Belgium.
E-mail address: Nicolas.j.dubuisson@uclouvain.be (N. Dubuisson).

https://doi.org/10.1016/j.msard.2023.105045
Received 9 February 2023; Received in revised form 27 August 2023; Accepted 29 September 2023
Available online 11 October 2023

management are scarce and are based on information extracted from small retrospective studies and case reports (De Lott et al., 2020; Dorotta and Schubert, 2002; Drust et al., 2016). The lack of controlled studies on the subject and the potential medico-legal issues that could occur during anaesthesia may result in anaesthetists globally preferring general instead of regional anaesthetic techniques.

The aim of this study is to clarify what is considered good anaesthetic practice in MS using up to date knowledge in this area. Therefore, we performed a systematic PubMed literature search and textbook review, and the most relevant articles were selected for analysis.

This paper covers issues related to the anaesthetic management of pwMS, with a focus on preoperative assessment, leading to the choice of the most adequate anaesthetic techniques and agents, the assessment of possible side-effects anaesthetic agents and their possible impact on disease evolution, the possible drug interactions that may occur between multiple sclerosis drugs and anaesthetic drugs, and the need to use certain monitoring devices in all circumstances. We also cover pregnancy and delivery in women with MS.

2. Methods

A systematic literature search was conducted in November 2022 using the search term 'anaesthesia' OR 'anaesthetic management' OR 'general anaesthesia' OR epidural anaesthesia' AND 'Multiple Sclerosis' applied to Pubmed (https://www.ncbi.nlm.nih.gov/pubmed/). Bibliographies and reference lists were also manually screened to identify additional papers.

3. Pre-operative assessment

3.1. Clinical presentation

The purpose of the preoperative assessment is to ensure the patient undergoes a safe and adequate anaesthetic experience by selecting the most suitable type of anaesthesia. First, this assessment must include the full documentation of the neurological deficits detailed by the neurologist in charge of the patient. The neurological assessment must cover the clinical presentation of the disease, the most recent MRI results, the duration of the disease, the presence/absence and timing of the last acute exacerbation or MS relapse, as well as a complete clinical examination evaluating the degree of neurologic impairment. The use of an established score such as the "Expanded Disability Status Scale" score or "EDSS" score should also be used in order to evaluate the degree of disability (Kurtzke, 1983; Makris et al., 2014). Second, besides neurological data, the preoperative assessment conducted by the anaesthesiologist should also document any respiratory, cardiac, renal, hepatic, autonomic or any other medical comorbidities. Based on the gathered information, additional referrals or ancillary testing might be achieved by the appropriate specialist.

3.2. Respiratory assessment

PwMS may present with respiratory impairment secondary to brainstem or cerebellar dysfunction, resulting in the lack of coordination of the respiratory muscle function (Grasso et al., 2000). Disability or the gravity of the disease (as calculated by the EDSS) rather than its duration is the principal cause of pulmonary impairment (Mutluay et al., 2005). However, the presence of pulmonary dysfunction in MS has even been reported in pwMS in the absence of any respiratory symptoms or any kind of disability (Altintas et al., 2007; Carvalho et al., 2012). The best way to assess lung function is with spirometry (Smeltzer et al., 1992). Indeed, forced vital capacity and forced expiratory volume in 1 second (FEV1) might be slightly reduced with a normal Tiffeneau index in pwMS. In addition to lung function tests and arterial blood gas determinations, simple clinical tests often allow a good assessment of the respiratory function such as their ability to breathe out deeply and to cough up (Mutluay et al., 2005). These simple measures are of clinical value as they can be easily collected during the premedication visit.

Breathing disorders that need to be identified in pwMS are obstructive sleep apnea syndrome (OSA), and more rarely central sleep apnea, insomnia or narcolepsy (Caminero and Bartolomé, 2011). OSA, which is common in patients with multiple sclerosis (Caminero and Bartolomé, 2011), also needs to be identified as it could lead to potential difficult airway access and/or a need for continuous positive airway pressure (CPAP) or bi-level positive airway pressure peri-operatively to reduce hypoxic events (De Hert et al., 2011). It must also be kept in mind that certain medications used by patients with multiple sclerosis, such as baclofen or clonazepam for example, may trigger OSA by causing excessive relaxation of the pharyngeal muscles (Brass et al., 2010), hence contributing to airway obstruction. Finally, chronic aspiration must also be expected in MS patients, especially if the pharyngeal and laryngeal muscles are severely impaired (Alali et al., 2018).

3.3. Autonomic function

Approximately 45 to 84 % of patients with multiple sclerosis suffer from autonomic nervous system dysregulation with bladder and/or bowel dysfunction (Kodounis et al., 2005; Lensch and Jost, 2011). Among them, neurocardiogenic syncope and cardiac dysrhythmias can be present in 19–42 % of pwMS (Racosta et al., 2015). The potential for haemodynamic instability should be considered likely as this may be worsened by cardiovascular side effects of pre-existing medications. Moreover, it is not uncommon that during anaesthetic induction significant hypotension with poor response to intravenous fluids and vasopressor support occurs. The need to perform baseline tests to assess autonomic dysfunction is however controversial. Flachenecker et al. (2001) monitored sympathetic and parasympathetic response in active and clinically stable MS patients. The sympathetic system was assessed by the heart rate after Valsalva manoeuvre, deep breathing and change of posture. While sympathetic dysfunction was monitored by blood pressure response to active change of position and to sustained handgrip. They concluded that sympathetic dysfunction was correlated to MS disease activity, while parasympathetic dysfunction was related to clinical disability. We would recommend a baseline autonomic assessment in patients with more advanced disease and those on a large number of medications known to affect the autonomic nervous system.

3.4. Cardiovascular and other assessments

Coronary heart disease, chronic heart failure, ischaemic stroke and peripheral arterial disease are more common in MS than in the general population (Marrie et al., 2015). PwMS seems to have worse smoking habits and suffer more frequently from obesity due to lack of exercise, both associated with subclinical atherosclerosis (Ranadive et al., 2012). Possible cardiac diseases should therefore be carefully reviewed during the preoperative assessment. In addition, cardiac evaluation (ECG and echocardiogram) and liver function tests to identify any adverse effects of treatment must be carried out when indicated.

4. MS medications and their interactions in the perioperative period

4.1. Corticosteroids

Pulsed 3–5-day steroids are typically used to treat MS relapses. The extent of a patient's steroid use must be established before surgery and if needed, supplemental steroids must be given peri-operatively in order to avoid an adrenal or Addisonian crisis (Dorotta and Schubert, 2002). It must also be kept in mind that prolonged steroid therapy, eventually used for other comorbidities, needs to be avoided since it may lead to muscle wasting and osteoporosis and hence increase the risk of injury during positioning on the operating table. Regardless of steroid use,

people with MS are at increased risk of osteopenia and osteoporosis (Åivo et al., 2017).

4.2. Baclofen

The precise mechanism of action of baclofen is not fully known. Baclofen inhibits both polysynaptic and to a lesser extent monosynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Baclofen is an analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and may exert its effects by stimulation of the GABAʙ receptor to cause muscle relaxation (Mohammed and Hussain, 2004). Baclofen is useful in the alleviation of signs and symptoms of muscle spasticity resulting from multiple sclerosis. In addition to its antispastic activity, baclofen may also cause muscle weakness and increased sensitivity to nondepolarizing muscle relaxants (Dorotta and Schubert, 2002). Therefore, if possible before a surgical procedure, oral baclofen should be gradually reduced and eventually stopped. It is mandatory that the decrease in administered doses be done gradually. Indeed, if the drug is stopped abruptly, symptoms such as agitation, delirium, and convulsions might occur. While there is no clear recommendation concerning baclofen tapering in pre-surgical patients, we recommend decreasing the doses by 5 to 10mg every 7-14 days.

Baclofen may also be administered intrathecally. Pump implantation for continuous intrathecal baclofen (ITB) administration is becoming more common for treating medically intractable spasticity of spinal cord origin.

Depending on the anaesthetic technique chosen (general versus epidural anaesthesia), specific measures must be taken. With general anaesthesia, seizures and cardiovascular disturbances resulting in the concomitant or sequential use of intrathecal baclofen and propofol have been described (Gerçek et al., 2004; Manikandan et al., 2005). However, more research must be carried out in order to understand the exact mechanisms underlying these interactions and what can be done to prevent them. A question that remains to be answered is: should intrathecal doses of baclofen be reduced in the pre-operative period and if so, when exactly?

Concerning the perioperative management of the implantable device itself, there unfortunately exists neither practice advisories nor expert consensus statements. There is also little literature to guide clinical management (Ramos and Brull, 2015). It seems reasonable to say that the perioperative goals should include a preoperative radiologic documentation of the device location, minimising electromagnetic interference, and avoiding mechanical damage to the implanted device and its components. The perioperative care of the patient should be individualised and focused on the scheduled surgical procedure. Also, the perioperative staff should discuss any safety concerns and possible surgical instrument interactions with the device. A plan to minimise the risk of damage or malfunction to the device should be developed. Strategies to minimise the risk of electrosurgery include avoiding its use altogether or using the bipolar rather than monopolar mode when necessary.

At the end of the surgery, it should be suggested that the device is checked by qualified personnel to ensure appropriate device function and if necessary, resumption of therapeutic efficacy. This should be done as soon as possible; ideally, before the patient's discharge from the hospital.

Concerning the use of epidural anaesthesia in patients with an intrathecal baclofen pump, there are no established guidelines. As a result, many clinicians are reluctant to perform spinal or epidural anaesthesia in these patients as it is commonly thought that the introduction of an epidural catheter might interfere with the intrathecal catheter by kinking or dislodging it, or even become a gateway to infection (Bojaxhi et al., 2017). Moreover, a communication between the epidural and subarachnoid spaces might exist due to the presence of the intrathecal baclofen catheter - hence, when epidural anaesthesia is the chosen technique, a reduction in the dose of local anaesthetic used is recommended.

Several cases of pregnant patients with an intrathecal baclofen pump and having epidural analgesia have however been reported (Ali Sakr Esa et al., 2009). To minimise the risk of complications it seems legitimate that before attempting any spinal anaesthesia in these patients with an intrathecal device, the clinician should obtain an X-ray or an operative record of the intrathecal device system, as the catheter may be located in the spinal needle insertion region.

4.3. Disease modifying treatments (DMT) (See Table 1)

DMTs have anti-inflammatory properties reducing the number of relapses and slowing down disability accrual. They are typically distinguished based on their efficacy. Low-efficacy (LE) DMTs include interferon (beta-1a and beta-1b) and glatiramer acetate, moderate-efficacy (ME) include teriflunomide and dimethyl fumarate, while high-efficacy (HE) DMTs are represented by fingolimod, ponesimod, ozanimod, siponimod, natalizumab, alemtuzumab, cladribine, ocrelizumab, ofatumumab, and ublituximab (Cotchett et al., 2021; Montalban et al., 2018; Rae-Grant et al., 2018). The latest having high rates of no new disease activity (NEDA); which is defined as no relapses, no sustained disability progression and no MRI activity (Havrdova et al., 2009). The products differ by their mode (subcutaneous, intramuscular injection or oral route) and frequency of administration.

Other immunosuppressive drugs either licensed by the FDA for MS (Mitoxantrone) or to treat other autoimmune diseases (cyclophosphamide or azathioprine) have been given to pwMS in the past but are seldom used now.

Discontinuation of long term DMTs in stable MS patients in preparation for surgery is not recommended. Several studies and case reports describe the potential of disease recurrence days or months after discontinuing multiple sclerosis treatment (Berkovich, 2017). Before any elective surgery, it is recommended to establish a close collaboration between the neurologist who treats the patient and the anaesthesiologist.

Table 1 summarises the important side effects of the DMTs, their possible interactions with some of the drugs used in the perioperative period and the precautions that need to be taken by the anaesthetist having taken this information into consideration.

5. Anaesthesia: techniques and anaesthetic agents

5.1. Anaesthetic medications in MS patients

There is no relationship between inhaled anaesthetic agents and the development or the aggravation of MS symptoms (Fleisher, 2012; Hedström et al., 2013). Moreover, inhalational anaesthetics do not appear to have adverse effects on nerve conduction (Fleisher, 2012). This latter statement is supported by case reports where sevoflurane (Inoue and Furuya, 2006; Yamashita et al., 2003) and desflurane, with or without nitrous oxide (Ceyhan et al., 2011; Sahin et al., 2010; Yamashita et al., 2003)bib20 were used for anaesthetic maintenance without mention of postoperative complications. The same conclusion can be drawn for intravenous hypnotic agents such as propofol (Okada et al., 2009). However, intravenous lidocaine has been associated with worsening of visual symptoms (such as acuity and colour perception) (Lirk et al., 2011; Sakurai et al., 1992). An intravenous lidocaine test has even been proposed as a diagnostic tool to detect underlying demyelination using visual evoked potentials. This is analogous to the so-called 'hot-bath' test (Malhotra, 1981) that modulates the temperature sensitivity of demyelinated axons.

Lidocaine displays sodium channel blocking properties - and this mechanism seems to be the same that reduces positive symptoms in multiple sclerosis. "Positive" symptoms refer to characteristics that are added to someone's state of being (such as spasticity or dysesthesia for

Table 1
DMTs sides effects and interactions with anaesthetic drugs.

Drugs	Possible side effects with anesthetic relevance	Perioperative considerations	Major interactions with perioperative drugs	Perioperative management
Low-efficacy DMTs				
Interferons (beta-1a and beta-1b)	*Flu-like symptoms 24-48 h after injection *Abnormal blood count tests, including thrombopenia *Elevated liver enzymes (Makris et al., 2014)	*Exclude respiratory infection or imminent disease exacerbation *Consider risks with neuraxial anaesthetic techniques *Consider anaesthetic drug metabolism and clearance (Makris et al., 2014)	Concomitant use of: -**Tramadol:** May increase the risk of seizures if combination with interferons (Gardner et al., 2000)	Use tramadol with caution
Glatiramer Acetate	*Systemic reactions (chest discomfort, palpitations, dyspnea, tachycardia, flushing) appearing immediately after SC injection *Hepatotoxicity (Makris et al., 2014)	*N/A *Consider anaesthetic drug metabolism and clearance	None described	/
Moderate-efficacy DMTs				
Teriflunomide	*Elevated liver transaminases *Hypertension *Lymphopenia *Nausea *Diarrhoea *Acute renal failure (Wingerchuk and Carter, 2014)	*Consider hepatic and renal metabolism and clearance of the anaesthetic drug *Cardiovascular investigation *Vigilance for infections *Exclude infectious pathology *Assess renal function prior to surgery	Concomitant use of: **-Aspirin, NSAIDS, Amiodarone, Clavulanate** (&na; and &NA;, 2001) may potentiate the risk of liver injury -**Corticosteroïds** may increase the risk of infections	*Caution with hepatotoxic agents. Need hepatotoxicity monitoring *Infection monitoring
Dimethyl fumarate	*Nausea, diarrhoea, abdominal pain. *Lymphopénia and leucopenia(Wingerchuk and Carter, 2014)	*Exclude infectious pathology *Vigilance for infections	None described	/
High-efficacy DMTs				
Fingolimod	*Chronic fatigue state *Cardiac conduction changes, cardiomyopathy, bradycardia, AV block *Elevated liver transaminases *Infection (Herpes Zoster) *Lymphopenia (Ziemssen et al., 2022) *Thrombocytopenia (Yuen et al., 2017)	N/A *Careful ECG evaluation/ clinical examination/ exercise tolerance *Consider hepatic metabolism and clearance of the anaesthetic drugs used. *Vigilance for infections. Careful preoperative clinical examination	Concomitant use of: -**Class Ia or class III antiarrhythmic drugs**- potentiation of the risk of torsade de pointes - **Sevoflurane, ondansetron** Risk of QT prolongation and torsade de pointes Chronic use of: **dexamethasone** - potentiates the risk of infection	Class Ia or class III antiarrhythmic drugs are contraindicated (Brown et al., 2019) Monitor cardiac rhythm closely. Monitor closely if concomitant use of fingolimod and immune-modulating therapies
Ponesimod Ozanimod	// Fingolimod Same profile than fingolimod but LESS *Cardiac conduction changes, cardiomyopathy, bradycardia, AV block *Elevated liver transaminases *Infection (Herpes Zoster) *Lymphopenia (Swallow et al., 2020)	*Careful ECG evaluation/ clinical examination/ exercise tolerance *Consider hepatic metabolism and clearance of the anaesthetic drugs used. *Vigilance for infections.	Concomitant use of: -**Class Ia or class III antiarrhythmic drugs** potentiation of the risk of torsade de pointes - **Sevoflurane, ondansetron** Risk of QT prolongation and torsade de pointes Chronic use of: **dexamethasone** - potentiates the risk of infection	**Class Ia or class III antiarrhythmic drugs** are contraindicated Monitor cardiac rhythm closely. Monitor closely if concomitant use of fingolimod and immune-modulating therapies

(*continued on next page*)

Table 1 (*continued*)

Drugs	Possible side effects with anesthetic relevance	Perioperative considerations	Major interactions with perioperative drugs	Perioperative management
Siponimod	// Fingolimod (Cree et al., 2022)			
Natalizumab	*More common infections (pharyngitis) *Progressive Multifocal Leukoencephalopathy (PML)	*Vigilance for opportunistic infections	Concomitant use of: -**Dexamethasone** may increase the risk of infections (including PML or "Progressive Multifocal Leukoencephalopathy")(Elan Pharmaceutical/Athena Neurosciences Inc, 2023)	Avoid chronic use of corticosteroïds in patients treated with natalizumab
Alemtuzumab	*Secondary auto-immune disorders (thyroid, idiopathic thrombocytopenic purpura and Goodpasture syndrome) *Prone to infections (including herpes zoster and listeria)	*Check thyroid hormones, kidney function and platelets prior to surgery *Consider risks with neuraxial anaesthetic techniques *Vigilance for infections	None described	/
Cladribine	*Nausea, fever, abdominal pain *Lymphopenia *Prone to infections (Herpes Zoster)	*Exclude digestive infectious pathology. *Exclude respiratory infection *Vigilance for infections	None described	/
Ocrelizumab	*Urinary tract and upper respiratory tract infections	*Exclude infection	None described	/
Ofatumumab	*Urinary tract and upper respiratory tract infections	*Exclude infection	None described	/
Ublituximab (FDA approved)	*Urinary tract and upper respiratory tract infections	*Exclude infection	None described	/

example). "Negative" symptoms are the contrary; they are characterised by the removal from a person's state of being (e.g: paralysis). Lidocaine may also unmask negative symptoms by provoking a further reduction of the action current in demyelinated portions of the nerve (Sakurai and Kanazawa, 1999). Hence, it should be used with caution. Continuous intravenous perioperative lidocaine infusion as used sometimes in digestive surgery for postoperative pain and recovery in adults should probably be avoided in pwMS, particularly in significantly disabled patients.

Midazolam can be used for premedication to reduce stress. The major advantage of midazolam is its minimal effect on thermoregulatory control (Honarmand and Safavi, 2008), however it should be used with caution in patients with respiratory compromise (Ceyhan et al., 2011; Sahin et al., 2010).

Dexmedetomidine at a loading dose of 1 μg/kg followed by an infusion rate of 0.2–0.5 μg/kg/h has been used in patients with multiple sclerosis for sedation, nevertheless hypotension and bradycardia was frequently observed (Anand et al., 2012).

Pain management with opioids doesn't seem to provoke any modification in the course of the disease (Barbosa et al., 2007; Inoue and Furuya, 2006; Sahin et al., 2010). However, this class of molecules should be used with caution in patients with suspected respiratory compromise, since respiratory depression is one of their common adverse effects and they may exacerbate constipation with a risk of postoperative ileus (Bragg et al., 2015).

Finally, the use of neuromuscular blocking agents should be used judiciously. In patients presenting with muscle denervation, up-regulation and spreading of Acetylcholine receptors (AChRs) well beyond the neuromuscular junction (NMJ) has been observed (Martyn et al., 1992).

Depolarising neuromuscular blocking agents such as succinylcholine, act directly on the AChRs and make them refractory to the action of ACh. However, once upregulated, supersensitivity to AChR agonists has been observed at the NMJ and also throughout the muscle (Fambrough, 1979), thereby posing the risk of hyperkalemia and ultimately cardiac arrest, linked to the release of intracellular potassium (Cooperman et al., 1970; Levine and Brown, 2012). Hence, for these reasons, succinylcholine should best be avoided in pwMS, especially with advanced disease.

Nondepolarizing muscle relaxants act by a different mechanism, they block acetylcholine from binding to the motor plate at the NMJ by competing for the binding site. They may also pose some difficulties as they have a variable pharmacodynamic effect (Dorotta and Schubert, 2002). Increased sensitivity to these molecules has been observed in patients treated by baclofen and especially in cases with muscular weakness (Brett et al., 1987; Lee et al., 2010). On the other hand, the secondary denervation which can occur in multiple sclerosis with a resulting upregulation of acetylcholine receptors may increase resistance to these agents (Brett et al., 1987; Lee et al., 2010). The same phenomenon is observed in patients treated by carbamazepine or phenytoin (Cammu, 2001).

Regarding this information, nondepolarizing neuromuscular blocking agents should therefore be used cautiously, and avoided whenever possible. The use of the lowest possible dose is recommended, by careful titration and with the use of continuous neuromuscular monitoring. The monitoring must preferentially be placed on a non-affected or the least affected limb. Theoretically, rocuronium should be preferred among other relaxants because of its pharmacokinetic profile and the existence of an antagonist in the event of an overdose (Sinikoglu et al., 2016).

5.2. *Selection of suitable anaesthetic techniques*

Once the preoperative assessment is complete, the anaesthetist must carefully choose the adequate anaesthetic technique(s): general anaesthesia, epidural, spinal techniques, or peripheral block(s), as well as the anaesthetic drugs to be used.

Based on a few case reports, *General anaesthesia* has been considered as controversial considering its potential to induce a relapse (Warren et al., 1982). However, an analysis of more recent data (Hebl et al., 2006; Martucci et al., 2011; Perlas and Chan, 2005; Vercauteren and Heytens, 2007) shows that post-operative MS relapses are not affected by the choice of the anaesthetic technique, and that all techniques,

including general anaesthesia, may be safely used (Lee et al., 2010). There is no preference as regards to the induction agents used (inhalational versus IV). Sevoflurane and desflurane are reported to be safe. Nevertheless, we recommend avoiding the use of nitrous oxide due to its potential to inhibit vitamin B_{12} metabolites, which play a role in myelin formation and maintenance (Massey et al., 2016). It is advisable to check vitamin B_{12} levels before surgery, in particular in patients who are vegan or on vegetarian diets, if nitrous oxide is used. Correcting vitamin B_{12} deficiency prior to surgery is advisable (Langan and Zawistoski, 2011). In addition, the association of general anaesthesia and epidural with low concentrations of local anaesthetic are considered safe (Dorotta and Schubert, 2002; Perlas and Chan, 2005).

Neuraxial blockade consists of local anaesthetic administration in the epidural or subarachnoid space. These procedures are also controversial in MS, as local anaesthetics used in the presence of a damaged blood-brain barrier and demyelinated axons are theoretically more likely to generate neurotoxicity (Jones and Healy 1980; Fleisher 2012; Lirk et al. 2011). However, this assertion might just be hypothetical, as neuraxial blockade has never been associated with any complications, even if there were some concerns in the past.

Moreover, the possible side effects of the technique might lead to exacerbations in MS, while the negative impact of the stress related to the procedure remains controversial (Vercauteren and Heytens 2007; Mohr et al. 2000; Kotas et al. 2021; Lovera and Reza 2013; Polick et al., 2023). Some authors reported emergence of previously silent demyelinated plaques (Levesque et al., 1988) or exacerbation of pre-existing symptoms related to subarachnoid anaesthesia (Crawford et al., 1981; Perlas and Chan, 2005) and epidural anaesthesia (Pasternak and Lanier, 2008).

However, no increase in relapse rate was reported by prospective or retrospective studies (Bornemann-Cimenti et al., 2017; Dalmas et al., 2003; Fleisher, 2012; Hebl et al., 2006; Lavie et al., 2019; Pastò et al., 2012; Perlas and Chan, 2005), or case reports (Barbosa et al., 2007; Lee et al., 2010; Martucci et al., 2011; Vercauteren and Heytens, 2007). In order to diminish the neurotoxic potential of epidural anaesthesia, two main precautions are recommended. First by using less concentrated solutions of local anaesthetic, which however leads to the risk of obtaining insufficient analgesia (Lirk et al., 2011) and second by preferring the epidural technique over spinal anaesthesia (Kulkarni et al., 2011). Indeed, the concentration of the local anaesthetic in contact with the spinal cord is 3 to 4 times lower in epidural anaesthesia than in subarachnoid anaesthesia (Finucane and Terblanche, 2005; Warren et al., 1982). The risk of hypotension is also less frequent with epidural anaesthesia. The only reports of multiple sclerosis relapses after epidural anaesthesia were related to higher concentrations of bupivacaine (>0.25 %) administered for longer periods of time (Pasternak and Lanier, 2008).

In summary, for most pwMS epidural and subarachnoid anaesthesia are not contraindicated, provided the doses of local anaesthetics used are kept to a minimum. The choice of the anaesthetic technique used should be made after careful assessment of the risks and benefits for each specific patient and his preference must also be considered.

Given MS is a disease of the CNS, *peripheral nerve blocks* should theoretically not carry any excess risk for pwMS compared to the non-MS population. Nevertheless, peripheral nervous system involvement has been reported on autopsy of pwMS (Dawson, 1916; Poser, 1987; Sakurai and Kanazawa, 1999), and in a cohort of 60 pwMS, where nerve conduction studies showed peripheral nerve demyelination in 5 % of the subjects (Misawa et al., 2008). Finucane and Terblanche (2005) reported a case of prolonged anaesthesia after a paravertebral block. However, this was probably the result of an increased sensitivity of the partially demyelinated spinal cord due to an excess of local anaesthetic, resulting in a spinal anaesthesia rather than a peripheral block. On the other hand, femoral and sciatic blocks have been achieved with no symptomatic exacerbation of MS during a 30-day follow-up period (Ingrosso et al., 2005). The addition of adrenaline as an adjuvant to the local anaesthetic leads to vasoconstriction and hence extends the duration of the block by decreasing the washout of the local anaesthetic. This may potentiate nerve toxicity, which is why some have recommended that adrenaline be avoided to minimise the risk of nerve damage (Lirk et al., 2011).

To summarise, peripheral nerve blocks performed at a certain distance from the spinal cord lesions are considered safe. Finally, ultrasound-guided blocks are recommended since by improving needle placement accuracy, this technique could reduce the onset of mechanical trauma and the dose of local anaesthetic used (Hebl, 2008).

6. Pregnancy and delivery

The positive effect of pregnancy on the course of multiple sclerosis is well established, with a reduction of the relapse rate of approximately 50 %, particularly in the second and third trimesters. In the postpartum period, it was generally accepted that the relapse rate increased up to one year after delivery (Voskuhl and Momtazee, 2017). However, a large population-based study challenged these previous results showing no increased risk of postpartum relapses (Langer-Gould et al., 2020). Finally, a systematic review reports conflicting results and couldn't conclude on this matter (Hellwig et al., 2021). Many have tried to explain the mechanism behind this potential increased relapse rate. The best explanation would be the decrease in protective oestrogen levels and the loss of the relative immunosuppressive status seen during pregnancy after delivery (Airas et al., 2008). While women with multiple sclerosis may particularly benefit from neuraxial labour analgesia, the anaesthetic procedure has once been theoretically incriminated (Jones and Healy 1980; Fleisher 2012; Lirk et al. 2011). However, the retrospective study done by Bouvet et al. (2021) was reassuring, as well as the PRIMS study, which reported no correlation between postpartum relapses and epidural analgesia. Moreover, Vukusic and al. identified three independent predictive factors of relapse in the three month period post pregnancy: (a) the number of relapses in the year before the pregnancy, (b) the number of relapses during the pregnancy, and (c) the duration of multiple sclerosis (Vukusic et al., 2004).

Concerning the delivery, neuraxial anaesthesia is preferred because it is associated with less maternal morbidity and mortality than general anaesthesia (Freedman and Lucas, 2015). For pregnant women with multiple sclerosis, there is no consensus as to which is the best technique to be used. The data available comes from case reports but also from a large prospective study where data were collected in the Pregnancy in Multiple Sclerosis (PRIMS) and Prevention Of Post-pARTtum relapses with progestin and oestradiol in MUltiple Sclerosis (POPARTMUS) studies (Bouvet et al., 2021). All of them showed good results of the subarachnoid block for caesarean section with no signs of multiple sclerosis relapse within 3 to 12 month follow-up period (Bouvet et al., 2021; Martucci et al., 2011; Oouchi et al., 2013). Epidural anaesthesia has been associated with minimal risk of postpartum multiple sclerosis relapse (Bouvet et al., 2021; Confavreux et al., 1998; Kulkarni et al., 2011).

7. Perioperative management

Specific attention is required for intraoperative hemodynamic, respiratory, neuromuscular and temperature monitoring (Kulkarni et al., 2011). Multiple sclerosis patients are at an increased risk of hypotension, with potentially a lower response to IV fluid and vasopressor administration especially with regional anaesthesia (Makris et al., 2014) due to an impaired autonomic nervous system. Hence, sufficient preloading by IV fluid is recommended in the perioperative period (Dorotta and Schubert, 2002). In addition, patients with autonomic dysfunction may show an exaggerated response to vasodilators and a-sympathomimetics.

A good preoxygenation is important during induction of anaesthesia, as multiple sclerosis lesions may affect the respiratory centres in the

medulla oblongata or the cervical or thoracic spinal cord causing diaphragmatic weakness or paralysis and therefore altering respiratory function. In these patients, total lung volume and vital capacity may be misleading with a normal result, but maximal expiratory and inspiratory efforts may be subnormal and sometimes reach only 50 % of the normal values - which implies a decreased residual functional capacity (Dorotta and Schubert, 2002). Moreover, perioperative respiratory depression, hypoventilation, atelectasis, and sleep apnea are more frequent in patients with multiple sclerosis with advanced disease (Zuccolotto et al., 2016).

Most of the time, the peri and post-operative spasticity can be easily managed with an association of preoperative oral medications such as baclofen or tizanidine, regional or neuraxial anaesthetic techniques, and intravenous muscle relaxants. However, in case of refractory patients, a case report suggests a specific anaesthetic plan starting with botulinum toxin injections 1 week before surgery, followed by diazepam which confer both preoperative anxiolysis and perioperative muscle relaxation. Then adding a dexmedetomidine infusion, which is a selective α-2 agonist, for postoperative anxiolysis and possible antispasticity effect could also be beneficial. Finally, IV dantrolene, a ryanodine receptor-1 antagonist, was used to control postoperative exacerbated spasticity if needed (Sturgill and Wittwer, 2018). However, this therapeutic plan is anecdotal and there is currently no consensus on how to cope with refractory spasticity before, during and after surgery.

In order to avoid perioperative hyperthermia responsible for recurrence of symptoms or even exacerbations (Guthrie and Nelson, 1995; Lee et al., 2010), room temperature monitoring is required combined with the use of room temperature IV fluids, cooling devices and antibiotics if an infection is suspected. Some authors recommend administering 1 g IV paracetamol to avoid pyrexia in the postoperative period, even if body temperature is normal (Sethi and Kapil, 2014). Finally, the worsening of symptoms secondary to the effect of temperature must be differentiated from real disease exacerbations. Symptom resolution is usually observed after temperature correction in the former.

8. Post-operative complications

Postoperative relapse is a common concern among pwMS and their caregivers. The evidence of relapses following surgery or anaesthesia is currently inconclusive and further investigation is needed. Indeed, while higher relapses rate has been suggested by a case series (Makris et al., 2014), a recent study has shown no increased risk of relapse following anaesthesia and surgery (De Lott et al., 2020).

A higher postoperative infection rate combined with a delayed wound healing process has been observed in MS patients after hip and knee arthroplasty. As a result, patients must be monitored closely and specific attention to the wound must be devoted in the days following surgery. This is certainly the case in people on immunosuppressive medications (Gutman et al., 2018; Hughes et al., 2016; Newman et al., 2019; Quinlan et al., 2019). On the other hand, metabolic surgery seems to be safer with a similar postoperative complications profile than controls (Stenberg et al., 2021).

Venous thrombosis is the most frequent postoperative complication in patients with multiple sclerosis after surgery. The risk factors are the following; high doses of corticosteroids and long bed stays because of the surgery, leg paralysis or ataxia. In these patients, preventive measures such as prophylactic anticoagulants, compression stockings and early perambulation after surgery must be taken (Arpaia et al., 2010; Kulkarni et al., 2011; Sethi and Kapil, 2014).

9. Conclusion

Multiple sclerosis is a demyelinating disease of the CNS that has implications for anaesthesia. Triggers of MS relapses include infections and fever of other causes, while surgical procedures and emotional stress are still controversial. The interdisciplinary management of pwMS should optimise medical follow-up and allow him/her to be fully informed. With thorough preoperative evaluation, knowledge about the disease, the medications used to treat MS and the various complications that pwMS may encounter, these patients can be managed safely.

Summary and key points

- A preoperative evaluation should comprise a detailed patient's neurological status.
- The risk of relapse in the postoperative period, should be explained to the patient during the pre-operative assessment.
- Preoperative contact between the patient's neurologist and the anaesthetist is recommended.
- Regularly administered DMTs should not be stopped in the pre-operative period.
- The use of depolarizing neuromuscular blocking agents should be avoided
- Non-depolarizing agents should be used under close monitoring.
- General anaesthesia is thought to be safe.
- There are no absolute contraindications for regional or neuraxial anaesthesia in pwMS.
- There is no consensus on optimum technique to use in pregnant women with MS.
- Both subarachnoid and epidural blocks are considered safe in pregnant women with MS.
- There is no association between the post pregnancy relapse rate and anaesthesia procedures or drugs used.
- Close perioperative monitoring of hemodynamic, respiratory function, neuromuscular and temperature is mandatory.
- Specific attention is required for post-operative complications (infection, delayed wound healing and venous thrombosis).

Declaration of Competing Interest

Oriane de Maere has no disclosure.

Nicolas Dubuisson was an ECTRIMS fellow, which is unrelated to the contents of this publication. He has received travel costs from Pfizer, Merck-Serono and Genzyme unrelated to the context of this publication.

Monica Marta has received honoraria and travel costs from Genzyme, AbbVie, Roche and Novartis, unrelated to the context of this publication.

Sharmilee Gnanapavan has received honoraria and meeting support from Biogen, Novartis, Teva, Genzyme and research funds from Genzyme, which is unrelated to the contents of this publication.

Benjamin Turner has received honoraria from Roche, Teva, Novartis, Merck-Serono, Sanofi-Genzyme and Biogen, unrelated to the context of this publication.

David Baker is a founder and consultant to Canbex therapeutics and has received research funds from Canbex therapeutics, Sanofi-Genzyme and Takeda in the past 3 years. This is unrelated to the context of this publication.

Klaus Schmierer has received research support from Biogen, Merck, and Novartis; speaking honoraria from, and/or served in an advisory role for, Amgen-Gensenta, Biogen, EMD Serono, Merck, Novartis, Roche, Sanofi, and Teva; and remuneration for teaching activities from AcadeMe, Medscape, and the Neurology Academy.This is unrelated to the context of this publication.

Gavin Giovannoni has received fees for participation in advisory board for AbbVie Biotherapeutics, Biogen, Canbex, Ironwood, Novartis, Merck, Merck Serono, Roche, Sanofi Genzyme, Synthon, Teva and Vertex; speaker fees from AbbVie, Biogen, Bayer HealthCare,Genzyme, Merck Serono, Sanofi-Aventis and Teva. Research support from Biogen, Genzyme, Ironwood, Merck, Merck Serono and Novartis. This is unrelated to the context of this publication.

Vishwajit Verma: no disclosure.

Marie-Agnès Docquier: no disclosure.

References

Airas, L., Saraste, M., Rinta, S., Elovaara, I., Huang, Y.H., Wiendl, H., Finnish Multiple Sclerosis and Pregnancy Study Group, 2008. Immunoregulatory factors in multiple sclerosis patients during and after pregnancy: relevance of natural killer cells. Clin. Exp. Immunol. 151, 235–243.

Åivo, J., Kurki, S., Sumelahti, M.L., Hänninen, K., Ruutiainen, J., Soilu-Hänninen, M., 2017. Risk of osteoporotic fractures in multiple sclerosis patients in southwest Finland. Acta Neurol. Scand. 135, 516–521.

Alali, D., Ballard, K., Bogaardt, H., 2018. The frequency of dysphagia and its impact on adults with multiple sclerosis based on patient-reported questionnaires. Mult. Scler. Relat. Disord. 25, 227–231.

Ali Sakr Esa, W., Toma, I., Tetzlaff, J.E., Barsoum, S., 2009. Epidural analgesia in labor for a woman with an intrathecal baclofen pump. Int. J. Obstet. Anesth. 18, 64–66.

Altintas, A., Demir, T., Ikitimur, H.D., Yildirim, N., 2007. Pulmonary function in multiple sclerosis without any respiratory complaints. Clin. Neurol. Neurosurg. 109, 242–246.

Anand, S., Bhatia, A., Rajkumar, Sapra, H., Gupta, V., Mehta, Y., 2012. Dexmedetomidine for monitored anesthesia care in patients undergoing liberation procedure for multiple sclerosis: an observational study. Saudi J. Anaesth. 6, 358–362.

Arpaia, G., Bavera, P.M., Caputo, D., Mendozzi, L., Cavarretta, R., Agus, G.B., Milani, M., Ippolito, E., Cimminiello, C., 2010. Risk of deep venous thrombosis (DVT) in bedridden or wheelchair-bound multiple sclerosis patients: a prospective study. Thromb. Res. 125, 315–317.

Barbosa, F.T., Bernardo, R.C., Cunha, R.M., Pedrosa, M.S.M., 2007. [Subarachnoid anesthesia for cesarean section in a patient with multiple sclerosis: case report.]. Rev. Bras. Anestesiol. 57, 301–306.

Berkovich, R., 2017. Clinical and MRI outcomes after stopping or switching disease-modifying therapy in stable MS patients: a case series report. Mult. Scler. Relat. Disord. 17, 123–127.

Bojaxhi, E., Salek, D.R., Sherman, C.E., Greengrass, R.A., 2017. Regional anesthesia for a total knee arthroplasty on an adult patient with spastic diplegia and an intrathecal baclofen pump. Rom J. Anaesth. Intensive Care 24, 69–72.

Bornemann-Cimenti, H., Sivro, N., Toft, F., Halb, L., Sandner-Kiesling, A., 2017. Anestesia neuraxial em pacientes com esclerose múltipla – uma revisão sistemática. Braz. J. Anesthesiol. https://doi.org/10.1016/j.bjan.2016.09.015.

Bouvet, L., Fontana, M., Bouthors, A.S., Bonnin, M., Storme, B., Bayoumeu, F., Corsia, G., Vukusic, S., Chassard, D., 2021. Post-partum relapse in women with multiple sclerosis after neuraxial labour analgesia or neuraxial anaesthesia: a multicentre retrospective cohort study. Anaesth. Crit. Care Pain Med. 40, 100834.

Bragg, D., El-Sharkawy, A.M., Psaltis, E., Maxwell-Armstrong, C.A., Lobo, D.N., 2015. Postoperative ileus: recent developments in pathophysiology and management. Clin. Nutr. 34, 367–376.

Brass, S.D., Duquette, P., Proulx-Therrien, J., Auerbach, S., 2010. Sleep disorders in patients with multiple sclerosis. Sleep Med. Rev. 14, 121–129.

Brett, R.S., Schmidt, J.H., Gage, J.S., Schartel, S.A., Poppers, P.J., 1987. Measurement of acetylcholine receptor concentration in skeletal muscle from a patient with multiple sclerosis and resistance to atracurium. Anesthesiology 66, 837–839.

Brown, B., Weiss, J.L., Kolodny, S., Meng, X., Williams, I.M., Osborne, J.A., 2019. Analysis of cardiac monitoring and safety data in patients initiating fingolimod treatment in the home or in clinic. BMC Neurol. 19, 287.

Caminero, A., Bartolomé, M., 2011. Sleep disturbances in multiple sclerosis. J. Neurol. Sci. 309, 86–91.

Cammu, G., 2001. Interactions of neuromuscular blocking drugs. Acta Anaesthesiol. Belg. 52, 357–363.

Carvalho, S.R.S., Alvarenga Filho, H., Papais-Alvarenga, R.M., Chacur, F.H., Dias, R.M., 2012. Is it useful to perform carbon monoxide diffusion capacity and respiratory muscle function tests in patients with multiple sclerosis without disability? Respirology 17, 869–875.

Ceyhan, A., Uyar, E.T., Gencay, I.Y., Gunal, S.E., 2011. Anesthesia in multiple sclerosis and obstructive sleep apnea: case report and literature review. J. Res. Med. Sci. 16, 828–835.

Confavreux, C., Hutchinson, M., Hours, M.M., Cortinovis-Tourniaire, P., Moreau, T., 1998. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in multiple sclerosis group. N. Engl. J. Med. 339, 285–291.

Cooperman, L.H., Strobel Jr, G.E., Kennell, E.M., 1970. Massive hyperkalemia after administration of succinylcholine. Anesthesiology 32, 161–164.

Cotchett, K.R., Dittel, B.N., Obeidat, A.Z., 2021. Comparison of the efficacy and safety of anti-CD20 B cells depleting drugs in multiple sclerosis. Mult. Scler. Relat. Disord. 49, 102787.

Crawford, J.S., Selwyn Crawford, J., Iii, F.M.J., Nolte, H., Steenberge, A., Shah, J.L., 1981. Regional analgesia for patients with chronic neurological disease aod similar conditions. Anaesthesia 36, 821.

Cree, B.A., Arnold, D.L., Fox, R.J., Gold, R., Vermersch, P., Benedict, R.H., Bar-Or, A., Piani-Meier, D., Rouyrre, N., Ritter, S., Kilaru, A., Karlsson, G., Giovannoni, G., Kappos, L., 2022. Long-term efficacy and safety of siponimod in patients with secondary progressive multiple sclerosis: Analysis of EXPAND core and extension data up to >5 years. Mult. Scler. 28, 1591–1605.

Dalmas, A.F., Texier, C., Ducloy-Bouthors, A.S., Krivosic-Horber, R., 2003. [Obstetrical analgesia and anaesthesia in multiple sclerosis]. Ann. Fr. Anesth. Reanim. 22, 861–864.

Dawson, J.W., 1916. XVIII.—the histology of disseminated sclerosis. Trans. R. Soc. Edinb. 50, 517–740.

De Hert, S., Imberger, G., Carlisle, J., Diemunsch, P., Fritsch, G., Moppett, I., Solca, M., Staender, S., Wappler, F., Smith, A., Task Force on Preoperative Evaluation of the Adult Noncardiac Surgery Patient of the European Society of Anaesthesiology, 2011. Preoperative evaluation of the adult patient undergoing non-cardiac surgery: guidelines from the European Society of Anaesthesiology. Eur. J. Anaesthesiol. 28, 684–722.

De Lott, L.B., Zerafa, S., Shedden, K., Dunietz, G.L., Earley, M., Segal, B.M., Braley, T.J., 2020. Multiple sclerosis relapse risk in the postoperative period: effects of invasive surgery and anesthesia. Mult. Scler. 26, 1437–1440.

Dobson, R., Giovannoni, G., 2019. Multiple sclerosis - a review. Eur. J. Neurol. 26, 27–40.

Dorotta, I.R., Schubert, A., 2002. Multiple sclerosis and anesthetic implications. Curr. Opin. Anaesthesiol. 15, 365–370.

Drust, A., Bartels, C., Hachenberg, T., 2016. [Anesthesia and multiple sclerosis: what needs to be considered?]. Anasthesiol. Intensivmed. Notfallmed. Schmerzther. 51, 458–467.

Elan Pharmaceutical/Athena Neurosciences Inc, South San Francisco, CA, 2023 Product Information. Tysabri (natalizumab).

Fambrough, D.M., 1979. Control of acetylcholine receptors in skeletal muscle. Physiol. Rev. 59, 165–227.

Finucane, B.T., Terblanche, O.C., 2005. Prolonged duration of anesthesia in a patient with multiple sclerosis following paravertebral block. Can. J. Anaesth. 52, 493–497.

Flachenecker, P., Reiners, K., Krauser, M., Wolf, A., Toyka, K.V., 2001. Autonomic dysfunction in multiple sclerosis is related to disease activity and progression of disability. Mult. Scler. 7, 327–334.

Fleisher, L.A., 2012. Anesthesia and Uncommon Diseases. Elsevier Health Sciences.

Freedman, R.L., Lucas, D.N., 2015. MBRRACE-UK: saving lives, improving mothers' care - implications for anaesthetists. Int. J. Obstet. Anesth. 24, 161–173.

Gardner, J.S., Blough, D., Drinkard, C.R., Shatin, D., Anderson, G., Graham, D., Alderfer, R., 2000. Tramadol and seizures: a surveillance study in a managed care population. Pharmacotherapy 20, 1423–1431.

Gerçek, A., Baykan, N., Dağçinar, A., Ozek, M.M., 2004. Does general anesthesia potentiate the GABA-ergic action of intrathecal baclofen? J. Neurosurg. Anesthesiol. 16, 323–324.

Gold, S.M., Mohr, D.C., Huitinga, I., Flachenecker, P., Sternberg, E.M., Heesen, C., 2005. The role of stress-response systems for the pathogenesis and progression of MS. Trends Immunol. 26, 644–652.

Grasso, M.G., Lubich, S., Guidi, L., Rinnenburger, D., Paolucci, S., 2000. Cerebellar deficit and respiratory impairment: a strong association in multiple sclerosis? Acta Neurol. Scand. 101, 98–103.

Guthrie, T.C., Nelson, D.A., 1995. Influence of temperature changes on multiple sclerosis: critical review of mechanisms and research potential. J. Neurol. Sci. 129, 1–8.

Gutman, J.M., Kim, K., Schwarzkopf, R., Kister, I., 2018. Total hip and knee arthroplasty in patients with multiple sclerosis. Int. J. MS Care 20, 244–250.

Havrdova, E., Galetta, S., Hutchinson, M., Stefoski, D., Bates, D., Polman, C.H., O'Connor, P.W., Giovannoni, G., Phillips, J.T., Lublin, F.D., Pace, A., Kim, R., Hyde, R., 2009. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab safety and efficacy in relapsing-remitting multiple sclerosis (AFFIRM) study. Lancet Neurol. 8, 254–260.

Hebl, J.R., 2008. Ultrasound-guided regional anesthesia and the prevention of neurologic injury. Anesthesiology 108, 186–188.

Hebl, J.R., Horlocker, T.T., Schroeder, D.R., 2006. Neuraxial anesthesia and analgesia in patients with preexisting central nervous system disorders. Anesth. Analg. 103, 223–228.

Hedström, A.K., Hillert, J., Olsson, T., Alfredsson, L., 2013. Exposure to anaesthetic agents does not affect multiple sclerosis risk. Eur. J. Neurol. 20, 735–739.

Hellwig, K., Verdun di Cantogno, E., Sabidó, M., 2021. A systematic review of relapse rates during pregnancy and postpartum in patients with relapsing multiple sclerosis. Ther. Adv. Neurol. Disord. 14, 17562864211051012.

Honarmand, A., Safavi, M.R., 2008. Comparison of prophylactic use of midazolam, ketamine, and ketamine plus midazolam for prevention of shivering during regional anaesthesia: a randomized double-blind placebo controlled trial. Br. J. Anaesth. 101, 557–562.

Hughes, K.E., Nickel, D., Gurney-Dunlop, T., Knox, K.B., 2016. Total knee arthroplasty in multiple sclerosis. Arthroplast. Today 2, 117–122.

Ingrosso, M., Cirillo, V., Papasso, A., Merolla, V., Cecere, F., 2005. Femoral and sciatic nerves block (BiBlock) in orthopedic traumatologic lower limbs surgery in patients with multiple sclerosis. Minerva Anestesiol. 71, 223–226.

Inoue, S., Furuya, H., 2006. Sevoflurane is safe for anesthetic management in patients with multiple sclerosis. Acta Anaesthesiol. Taiwan 44, 187–189.

Jones, R.M., Healy, T.E., 1980. Anaesthesia and demyelinating disease. Anaesthesia 35, 879–884.

Kodounis, A., Stamboulis, E., Constantinidis, T.S., Liolios, A., 2005. Measurement of autonomic dysregulation in multiple sclerosis. Acta Neurol. Scand. 112, 403–408.

Kotas, R., Nowakowska-Kotas, M., Budrewicz, S., Pokryszko-Dragan, A., 2021. The level of stress and coping strategies in patients with multiple sclerosis and their relationships with the disease course. J. Clin. Med. Res. 10 https://doi.org/10.3390/jcm10173916.

Kulkarni, L., Sanikop, C.S., Shilpa, H.L., Vinayan, A., 2011. Anaesthetic management in a patient with multiple sclerosis. Indian J. Anaesth. 55, 64.

Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33, 1444–1452.

Langan, R.C., Zawistoski, K.J., 2011. Update on vitamin B12 deficiency. Am. Fam. Phys. 83, 1425–1430.

Langer-Gould, A., Smith, J.B., Albers, K.B., Xiang, A.H., Wu, J., Kerezsi, E.H., McClearnen, K., Gonzales, E.G., Leimpeter, A.D., Van Den Eeden, S.K., 2020. Pregnancy-related relapses and breastfeeding in a contemporary multiple sclerosis cohort. Neurology 94, e1939–e1949.

Lavie, C., Rollot, F., Durand-Dubief, F., Marignier, R., Ionescu, I., Casey, R., Moreau, T., Tourniaire, P., Hutchinson, M., D'Hooghe, M.B., Laplaud, D.A., Clavelou, P., De

Sèze, J., Debouverie, M., Brassat, D., Pelletier, J., Lebrun-Frenay, C., Le Page, E., Castelnovo, G., Berger, E., Hautecoeur, P., Heinzlef, O., Durelli, L., Clerico, M., Trojano, M., Patti, F., Vukusic, S., PRIMS and POPARTMUS investigators, 2019. Neuraxial analgesia is not associated with an increased risk of post-partum relapses in MS. Mult. Scler. 25, 591–600.

Lee, K.H., Park, J.S., Lee, S.I., Kim, J.Y., Kim, K.T., Choi, W.J., Kim, J.W., 2010. Anesthetic management of the emergency laparotomy for a patient with multiple sclerosis -a case report. Korean J. Anesthesiol. 59, 359–362.

Lensch, E., Jost, W.H., 2011. Autonomic disorders in multiple sclerosis. Autoimmune Dis., 803841

Levesque, P., Marsepoil, T., Ho, P., Venutolo, F., Lesouef, J.M., 1988. [Multiple sclerosis disclosed by spinal anesthesia]. Ann. Fr. Anesth. Reanim. 7, 68–70.

Levine, M., Brown, D.F.M., 2012. Succinylcholine-induced hyperkalemia in a patient with multiple sclerosis. J. Emerg. Med. 43, 279–282.

Lirk, P., Birmingham, B., Hogan, Q., 2011. Regional anesthesia in patients with preexisting neuropathy. Int. Anesthesiol. Clin. 49, 144–165.

Lovera, J., Reza, T., 2013. Stress in multiple sclerosis: review of new developments and future directions. Curr. Neurol. Neurosci. Rep. 13, 398.

Lublin, F.D., Reingold, S.C., Cohen, J.A., Cutter, G.R., Sørensen, P.S., Thompson, A.J., Wolinsky, J.S., Balcer, L.J., Banwell, B., Barkhof, F., Bebo, B., Calabresi Jr, P.A., Clanet, M., Comi, G., Fox, R.J., Freedman, M.S., Goodman, A.D., Inglese, M., Kappos, L., Kieseier, B.C., Lincoln, J.A., Lubetzki, C., Miller, A.E., Montalban, X., O'Connor, P.W., Petkau, J., Pozzilli, C., Rudick, R.A., Sormani, M.P., Stüve, O., Waubant, E., Polman, C.H., 2014. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 83, 278–286.

Makris, A., Piperopoulos, A., Karmaniolou, I., 2014. Multiple sclerosis: basic knowledge and new insights in perioperative management. J. Anesth. 28, 267–278.

Malhotra, A.S., 1981. The hot bath test in the diagnosis of multiple sclerosis. JAMA. https://doi.org/10.1001/jama.246.10.1113.

Manikandan, S., Sinha, P.K., Neema, P.K., Rathod, R.C., 2005. Severe seizures during propofol induction in a patient with syringomyelia receiving baclofen. Anesth. Analg. 100, 1468–1469.

Marrie, R.A., Reider, N., Cohen, J., Stuve, O., Trojano, M., Cutter, G., Reingold, S., Sorensen, P.S., 2015. A systematic review of the incidence and prevalence of cardiac, cerebrovascular, and peripheral vascular disease in multiple sclerosis. Mult. Scler. 21, 318–331.

Martucci, G., Di Lorenzo, A., Polito, F., Acampa, L., 2011. A 12-month follow-up for neurological complication after subarachnoid anesthesia in a parturient affected by multiple sclerosis. Eur. Rev. Med. Pharmacol. Sci. 15, 458–460.

Martyn, J.A., White, D.A., Gronert, G.A., Jaffe, R.S., Ward, J.M., 1992. Up-and-down regulation of skeletal muscle acetylcholine receptors. Effects on neuromuscular blockers. Anesthesiology 76, 822–843.

Massey, T.H., Pickersgill, T.T., J Peall, K., 2016. Nitrous oxide misuse and vitamin B12 deficiency. BMJ Case Rep. https://doi.org/10.1136/bcr-2016-215728.

McKay, K.A., Jahanfar, S., Duggan, T., Tkachuk, S., Tremlett, H., 2017. Factors associated with onset, relapses or progression in multiple sclerosis: a systematic review. Neurotoxicology 61, 189–212.

Misawa, S., Kuwabara, S., Mori, M., Hayakawa, S., Sawai, S., Hattori, T., 2008. Peripheral nerve demyelination in multiple sclerosis. Clin. Neurophysiol. 119, 1829–1833.

Mohammed, I., Hussain, A., 2004. Intrathecal baclofen withdrawal syndrome- a life-threatening complication of baclofen pump: a case report. BMC Clin. Pharmacol. 4, 6.

Mohr, D.C., Goodkin, D.E., Bacchetti, P., Boudewyn, A.C., Huang, L., Marrietta, P., Cheuk, W., Dee, B., 2000. Psychological stress and the subsequent appearance of new brain MRI lesions in MS. Neurology 55, 55–61.

Montalban, X., Gold, R., Thompson, A.J., Otero-Romero, S., Amato, M.P., Chandraratna, D., Clanet, M., Comi, G., Derfuss, T., Fazekas, F., Hartung, H.P., Havrdova, E., Hemmer, B., Kappos, L., Liblau, R., Lubetzki, C., Marcus, E., Miller, D. H., Olsson, T., Pilling, S., Selmaj, K., Siva, A., Sorensen, P.S., Sormani, M.P., Thalheim, C., Wiendl, H., Zipp, F., 2018. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Mult. Scler. 24, 96–120.

Mutluay, F.K., Gürses, H.N., Saip, S., 2005. Effects of multiple sclerosis on respiratory functions. Clin. Rehabil. 19, 426–432.

&na;, &NA, 2001. EMEA Issues Public Statement on Leflunomide. Inpharma Weekly &NA, p. 20.

Newman, J.M., Sultan, A.A., Khlopas, A., Sodhi, N., Faour, M., Piuzzi, N.S., Higuera, C.A., Mont, M.A., 2019. What are the short-term outcomes in multiple sclerosis patients after total knee arthroplasty? J. Knee Surg. 32, 165–170.

Okada, A., Hirose, M., Shimizu, K., Tsugita, K., Matsuki, Y., Nobukawa, Y., Tabata, M., Ishimoto, M., Ueda, M., Shigemi, K., 2009. [Perioperative anesthetic management of a patient with multiple sclerosis]. Masui 58, 772–774.

Oouchi, S., Nagata, H., Ookawa, H., Oikawa, T., Iwabuchi, Y., Suzuki, K.S., 2013. [Spinal anesthesia for cesarean section in a patient with multiple sclerosis]. Masui 62, 474–476.

Pasternak, J.J., Lanier, W.L., 2008. Spinal Cord Disorders, in: Stoelting's Anesthesia and Co-Existing Disease. pp. 239–247.

Pastò, L., Portaccio, E., Ghezzi, A., Hakiki, B., Giannini, M., Razzolini, L., Piscolla, E., De Giglio, L., Pozzilli, C., Paolicelli, D., Trojano, M., Marrosu, M.G., Patti, F., La Mantia, L., Mancardi, G.L., Solaro, C., Totaro, R., Tola, M.R., Di Tommaso, V., Lugaresi, A., Moiola, L., Martinelli, V., Comi, G., Amato, M.P., MS Study Group of the Italian Neurological Society, 2012. Epidural analgesia and cesarean delivery in multiple sclerosis post-partum relapses: the Italian cohort study. BMC Neurol. 12, 165.

Perlas, A., Chan, V.W.S., 2005. Neuraxial anesthesia and multiple sclerosis. Can. J. Anaesth.

Polick, C.S., Ploutz-Snyder, R., Braley, T.J., Connell, C.M., Stoddard, S.A., 2023. Associations among stressors across the lifespan, disability, and relapses in adults with multiple sclerosis. Brain Behav. 13 (7), e3073.

Poser, C.M., 1987. The peripheral nervous system in multiple sclerosis. A review and pathogenetic hypothesis. J. Neurol. Sci. 79, 83–90.

Quinlan, N.D., Chen, D.Q., Werner, B.C., Lowry Barnes, C., Browne, J.A., 2019. Patients with multiple sclerosis are at increased risk for postoperative complications following total hip and knee arthroplasty. J. Arthroplasty. https://doi.org/10.1016/j.arth.2019.04.022.

Racosta, J.M., Kimpinski, K., Morrow, S.A., Kremenchutzky, M., 2015. Autonomic dysfunction in multiple sclerosis. Auton. Neurosci. 193, 1–6.

Rae-Grant, A., Day, G.S., Marrie, R.A., Rabinstein, A., Cree, B.A.C., Gronseth, G.S., Haboubi, M., Halper, J., Hosey, J.P., Jones, D.E., Lisak, R., Pelletier, D., Potrebic, S., Sitcov, C., Sommers, R., Stachowiak, J., Getchius, T.S.D., Merillat, S.A., Pringsheim, T., 2018. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the guideline development, dissemination, and implementation subcommittee of the American academy of neurology. Neurology 90, 777–788.

Ramos, J.A., Brull, S.J., 2015. Perioperative management of multiple noncardiac implantable electronic devices. A A Case Rep. 5, 189–191.

Ranadive, S.M., Yan, H., Weikert, M., Lane, A.D., Linden, M.A., Baynard, T., Motl, R.W., Fernhall, B., 2012. Vascular dysfunction and physical activity in multiple sclerosis. Med. Sci. Sports Exerc. 44, 238–243.

Sahin, L., Korkmaz, H.F., Sahin, M., Aydin, T., Toker, S., Gulcan, E., 2010. Desflurane anaesthesia in a patient with multiple sclerosis in total hip replacement. Arch. Med. Sci. 6, 984. –956.

Sakurai, M., Kanazawa, I., 1999. Positive symptoms in multiple sclerosis: their treatment with sodium channel blockers, lidocaine and mexiletine. J. Neurol. Sci. 162, 162–168.

Sakurai, M., Mannen, T., Kanazawa, I., Tanabe, H., 1992. Lidocaine unmasks silent demyelinative lesions in multiple sclerosis. Neurology 42, 2088–2093.

Sethi, S., Kapil, S., 2014. Anesthetic management of a patient with multiple sclerosis undergoing cesarean section with low dose epidural bupivacaine. Saudi J. Anaesth. 8, 402.

Sinikoglu, N., Totoz, T., Gumus, F., Karagulle, O., 2016. Repeated sugammadex usage in a patient with multiple sclerosis: a case report. Wien. Klin. Wochenschr. https://doi.org/10.1007/s00508-014-0696-0.

Smeltzer, S.C., Skurnick, J.H., Troiano, R., Cook, S.D., Duran, W., Lavietes, M.H., 1992. Respiratory function in multiple sclerosis. Utility of clinical assessment of respiratory muscle function. Chest 101, 479–484.

Stenberg, E., Forsberg, L., Hedström, A., Hillert, J., Näslund, E., 2021. Bariatric and metabolic surgery in patients with morbid obesity and multiple sclerosis - a nationwide, matched cohort study. Surg. Obes. Relat. Dis. 17, 1108–1114.

Sturgill, E.L., Wittwer, R.L., 2018. Novel treatment using intravenous dantrolene sodium for postoperative exacerbated spasticity in multiple sclerosis: a case report. A A Pract. 11 25–27.

Swallow, E., Patterson-Lomba, O., Yin, L., Mehta, R., Pelletier, C., Kao, D., Sheffield, J.K., Stonehouse, T., Signorovitch, J., 2020. Comparative safety and efficacy of ozanimod versus fingolimod for relapsing multiple sclerosis. J. Comp. Eff. Res. 9, 275–285.

Vercauteren, M., Heytens, L., 2007. Anaesthetic considerations for patients with a pre-existing neurological deficit: are neuraxial techniques safe? Acta Anaesthesiol. Scand. 51, 831–838.

Voskuhl, R., Momtazee, C., 2017. Pregnancy: effect on multiple sclerosis, treatment considerations, and breastfeeding. Neurotherapeutics. https://doi.org/10.1007/s13311-017-0562-7.

Vukusic, S., Hutchinson, M., Hours, M., Moreau, T., Cortinovis-Tourniaire, P., Adeleine, P., Confavreux, C., Pregnancy In Multiple Sclerosis Group, 2004. Pregnancy and multiple sclerosis (the PRIMS study): clinical predictors of post-partum relapse. Brain 127, 1353–1360.

Walton, C., King, R., Rechtman, L., Kaye, W., Leray, E., Marrie, R.A., Robertson, N., La Rocca, N., Uitdehaag, B., van der Mei, I., Wallin, M., Helme, A., Angood Napier, C., Rijke, N., Baneke, P., 2020. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS. third edition Mult. Scler. 26, 1816–1821.

Warren, T.M., Datta, S., Ostheimer, G.W., 1982. Lumbar epidural anesthesia in a patient with multiple sclerosis. Anesth. Analg. 61, 1022–1023.

Wingerchuk, D.M., Carter, J.L., 2014. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. Mayo Clin. Proc. 89, 225–240.

Xie, Y., Tian, Z., Han, F., Liang, S., Gao, Y., Wu, D., 2020. Factors associated with relapses in relapsing-remitting multiple sclerosis: a systematic review and meta-analysis. Medicine 99, e20885.

Yamashita, K., Yokoyama, T., Tokai, H., Imazu, Y., Lee, M., Manabe, M., 2003. [Anesthetic management for a patient with multiple sclerosis at exacerbation stage under general anesthesia]. Masui 52, 521–523.

Yuen, H.L.A., Brown, S., Chan, N., Grigoriadis, G., 2017. Immune thrombocytopenic purpura associated with fingolimod. BMJ Case Rep. https://doi.org/10.1136/bcr-2017-220590.

Ziemssen, T., Lang, M., Schmidt, S., Albrecht, H., Klotz, L., Haas, J., Lassek, C., Lang, S., Winkelmann, V.E., Ettle, B., Schulze-Topphoff, U., PANGAEA study group, 2022. Long-term real-world effectiveness and safety of fingolimod over 5 years in Germany. J. Neurol. 269, 3276–3285.

Zuccolotto, E.B., Nunes, G.C.M., Nogueira, R.S.L., Pagnussatt Neto, E., Nociti, J.R., 2016. [Anesthetic management of a patient with multiple sclerosis - case report]. Rev. Bras. Anestesiol. 66, 414–417.