

Iranian specialists' approach to surgery in patients with multiple sclerosis

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Keywords

Infections; Multiple Sclerosis; Postoperative Complications; Surgery

Abstract

Background: Data on perioperative risk stratification in patients with multiple sclerosis (MS) are limited. In this regard, the present study was conducted to investigate Iranian specialists' approach to surgical counseling for patients with MS (PwMS).

Methods: 21 MS specialists were asked about 11 case scenarios with different MS disease statuses, disease-

modifying therapies (DMTs), and urgency of the operation. The reasons for refusing surgery or factors that have to be considered before surgery were studied.

Results: Overall, Fleiss Kappa was estimated to be 0.091 [95% confidence interval (CI): 0.090-0.093, $P < 0.001$] indicating a very poor level of agreement among responders.

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Conclusion: PwMS face surgery for various reasons. Risk assessment of surgery, the effect of various drugs such as anesthetics and DMT on patients, as well as many other aspects of MS are issues challenging the practitioners. Clarifying the various dimensions of these issues requires further research.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory illness characterized by demyelination of the central nervous system (CNS), which results in the loss of saltatory conduction and conduction velocity in axonal pathways.¹ The condition mostly happens among women, and it is most commonly reported between the ages of 25 and 40.² MS often takes a relapsing-remitting (RR) course in the early stages, with symptomatic bouts or exacerbations that recover wholly or partly. After ten years, nearly half of patients enter the secondary progressive (SP) phase, which is characterized by a slow increase of impairment with or without exacerbations.³

Patients with MS (PwMS) may need surgery for various reasons. The main concern is disease exacerbation following the surgery. The disease itself, as well as the medication used, may have various implications in anesthetic practice. Furthermore, PwMS may be anxious that surgery or anesthesia would trigger a flare-up.⁴ The belief that PwMS are more likely to relapse after anesthesia and surgery might influence clinical decision-making, culminating in the postponement of essential operation and neurological review for preoperative clearance.⁵

Prior data guiding perioperative risk stratification in PwMS are limited. Decision on surgery should be based on the presence of side effects and how these could complicate anesthesia. Consultation with a neurologist should be sought in difficult cases. If medication is discontinued, it should be restarted as soon as possible.⁶

Although there are some studies addressing past surgery as a risk factor for MS, they are mainly small-scale observational studies of varying methodological quality with a wide range of contradicting positive and negative outcomes. In this regard, the present study was conducted to investigate Iranian specialists' approach to surgical counseling for PwMS.

Materials and Methods

To investigate the experts' opinions about the best decision for a patient with MS requiring surgery, we designed 11 case scenarios with different MS

disease statuses, disease-modifying therapies (DMTs), and urgency of the operation (Table 1). The participants were 21 MS specialists from different regions of Iran. They were asked to determine if they would permit the surgery without any further consideration, would permit if some criteria were met, or would not permit it. The reasons for disallowance or factors that have to be considered before surgery were also studied.

Tabulations were made for the basic characteristics of the enrolled experts and their response patterns. To test the level of agreement among responders, Fleiss Kappa was adopted.⁷ According to Altman, Kappa value of less than 0.2 is considered an indicator of poor agreement while 0.2-0.4 shows fair, 0.4-0.6 moderate, 0.6-0.8 good, and 0.8-1 very good strength of agreement.⁸

Results

Of 21 participants, 11 (52.4%) were women. The experts were 33 to 52 years old (mean: 43.0 ± 5.9). Their mean experience in the field of MS was 7.8 ± 5.8 years. The pattern of participants' preferred approaches is illustrated in figure 1.

Overall Fleiss Kappa was estimated to be 0.091 [95% confidence interval (CI): 0.090-0.093, $P < 0.001$] indicating a very poor level of agreement among responders.

Regarding case 1, a stable patient with MS on interferon (IFN)-beta was referred for an elective nonessential operation; two responders mentioned lab data [complete blood count (CBC) and liver enzymes] to be checked before surgery. Two others suggested a new magnetic resonance imaging (MRI). The remaining three (out of seven who chose the "permit with some consideration") preferred to explain the risk of relapse to the patient.

The most frequent approach to case 2, a patient recently diagnosed with MS who was candidate for elective essential surgery, was to wait for a period of time after the attack and/or fingolimod start (including those who chose "do not permit"). There was no final agreement on the exact needed time, ranging from two weeks to 12 months. However, the most frequently suggested period was one month (suggested by six experts). Seven participants recommended checking for lab data (CBC including absolute lymphocyte count and liver enzymes) before surgery.

Case 3 was a patient with RRMS who became unstable after delivery and was treated with rituximab. She was referred for a pre-operative consult for elective essential surgery.

Table 1. Details of clinical scenarios to investigate specialists' approach to surgery in patients with multiple sclerosis (MS)

Case number	Demographics (gender, age)	MS disease status	DMT	Surgery
1	Woman, 35	RRMS for 4 years, clinically and radiologically stable (last MRI: one year ago)	Platform injectable (IFN beta-1b)	Abdominoplasty
2	Woman, 18	Recently diagnosed with RRMS, an attack of hemiparesis two weeks ago, received IVMP with full recovery	Fingolimod started	Thyroid lobectomy due to a cold thyroid nodule
3	Woman, 38	RRMS for 8 years, was on GA, unplanned pregnancy 1 year ago (third pregnancy), 2 attacks since delivery (last attack 1.5 months ago)	Rituximab started	Hysterectomy due to a large fibromyoma
4	Man, 25	RRMS for 4 years, stable	Fingolimod	Sleeve gastrectomy for morbid obesity
5	Woman, 32	RRMS for 5 years, severe attack of myelitis 2 years ago, stable since then	Ocrelizumab	Cholecystectomy after cholangitis due to gallstone
6	Man, 38	RRMS stable for 5 years, diagnosed with thyroid cancer recently, afterward had a brainstem attack with compatible MRI activity, the attack responded to IVMP and PLEX	DMF	Total thyroidectomy and radical neck dissection
7	Man, 40	RRMS for 3 years, progressed to SPMS since last year, clinically and radiologically stable (last MRI: one year ago)	Ocrelizumab (last dose: 3 months ago)	Total colectomy due to colon cancer
8	Man, 45	RRMS for 12 years, progressed to SPMS since 5 years ago, an attack of hemiparesis one month ago that led to falling, the attack responded relatively to IVMP	Ocrelizumab	Humerus fracture & dislocation
9	Woman, 30	RRMS for 6 years, progressed to SPMS since 4 years ago, clinically and radiologically stable (last MRI: one year ago)	Rituximab	Sleeve gastrectomy for morbid obesity
10	Woman, 38	PPMS for 7 years, radiologically stable (last MRI: one year ago), EDSS: 5 since last year	None	Breast reconstruction and abdominal liposuction
11	Man, 28	RRMS for 7 years, had two attacks during the last year (mild right-hand weakness 3 months ago, right side hemiparesis and ataxia 2 weeks ago with gadolinium-enhancing lesions in the right cerebellar peduncle and periventricular regions), the recent attack responded to IVMP	DMF switched to ocrelizumab	Emergent appendectomy

MS: Multiple sclerosis; DMF: Dimethyl fumarate; DMT: Disease-modifying therapy; IFN: Interferon; IVMP: Intravenous methylprednisolone; PLEX: Plasma exchange; PPMS: Primary progressive multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; EDSS: Expanded Disability Status Scale; MRI: Magnetic resonance imaging; GA: Glatiramer acetate

Out of four responders who believed that surgery could be done without any extra evaluation, one thought that this was an emergent situation. Eleven experts preferred to wait for some time (ranging from one month to one year) to assure MS disease stability. Six believed lab data (CBC differential and liver enzymes) were needed before surgery.

Considering the best approach to the fourth case (stable RRMS on fingolimod), four specialists agreed with surgery without any concern. One expert mentioned that as the surgery might interfere with the successful absorption of fingolimod, the gastrectomy should not be performed. 12 others believed that checking for absolute lymph count was needed before surgery.

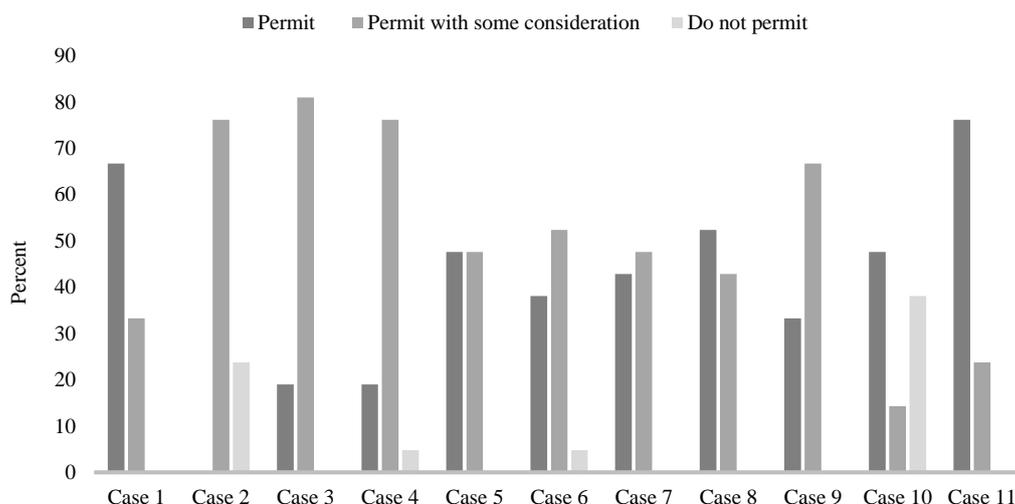


Figure 1. The response pattern of the participants regarding the selected approach to each case

One expert expressed concerns about abrupt weight loss that could lead to MS exacerbation. Three would warn the surgeon about the risk of infection. For one of the participants, the duration of the surgery was important.

The fifth scenario was a stable patient with RRMS on ocrelizumab who was a candidate for elective essential surgery. Ten responders stated that they would let the surgery without any additional information. Others declared they needed more information, especially CBC to rule out leukopenia.

A patient with RRMS on dimethyl fumarate (DMF) who experienced a severe brainstem attack after being informed about his thyroid cancer was a candidate for an essential surgery which was urgent (not emergent). Only one participant would be hesitant to surgery and preferred to escalate the DMT and postpone the surgery. Seven declared that they would not wait for any additional data. The remaining experts recommended either waiting for about one month after the relapse or checking lab data.

Case scenario 7 was a case of SPMS on ocrelizumab who had to undergo total colectomy due to colon cancer. Two participants did not answer this question. Ten experts recommended a check for CBC or immunoglobulin G (IgG) and/or being cautious about the risk of infection. The remaining specialists did not recommend any additional study regarding MS before the surgery.

The approach to the eighth case was similar to case number 7. Eight responders would agree with sleeve gastrectomy for a stable patient with SPMS on rituximab, without any extra data. Others

would be more conservative and asked for lab data to decrease the risk of post-operative infection.

The heterogeneity of answers to case number 10 [primary progressive MS (PPMS) case demanding abdominal and breast plastic surgery] was notable. Ten experts chose the first option “permit without any further consideration”. Eight participants thought that the patient should not go under such unnecessary surgery as this could impose considerable stress on the patient. Of three specialists who would consider some data before allowing the operation, one would discourage the patient but not forbid the surgery. Two others would recommend a time limit for the surgeries and recommended dividing abdominal and breast surgeries into two sessions.

Most of the participants (16/21) agreed that the emergent case of appendectomy should not be delayed. The remaining would check lab data (especially CBC differential) before the operation.

Discussion

Surgical management and its complications in PwMS are controversial. This controversy can be observed in different aspects of MS.

This study appraises the pliancy of MS experts' opinions about pre and post-operation considerations in PwMS. The differences among opinions on this issue are obvious and significant. On the other hand, there is no definitive guideline around making it difficult for physicians to choose the best approach.

We designed scenarios based on MS cases to gauge the perspectives of different professionals and evaluate how much consensus there is among

physicians who specifically visit PwMS.

Studies on this issue are limited and many aspects have not been considered. One of the concerns about surgical complications in these patients who undergo invasive surgical procedures requiring anesthesia is the occurrence of an attack.

A study reported that the relapse risk among patients who experienced invasive surgery with anesthesia did not increase within a 90-day window.⁵ In this study, the type of DMT was not considered.

There is no evidence about the discontinuation of DMT before surgery. On the other hand, numerous data and studies caution disease reactivation sometime after cessation.^{9,10} Siger et al. studied 43 PwMS whose DMT, IFN beta, was interrupted. They reported 20% reactivation of MS especially in highly active MS cases.¹¹

Makris et al. provided a brief overview of different preoperative recommendations on DMT in their review article. The authors mentioned that it was important to check liver function tests, active infection before surgery in IFN beta users, respiratory infection, and risk of an early flare-up. In addition to the above considerations, it was emphasized to take an electrocardiography (ECG) in patients taking fingolimod.¹²

In our study, about case 1 who was a patient on IFN beta requiring an elective surgery, most commentators believed that no further investigation was needed and none of them intended to discontinue the drug. Only two doctors asked for blood and liver tests before surgery. In Makris et al. review, the authors advised checking respiratory infection, risk of relapse, and the risk of neuraxial anesthetic techniques.¹² Besides, IFN beta is the first-line medication in MS prescribed for less serious cases.¹³ The rate of infection or other complications after taking this drug is low and it is considered a safe drug.¹⁴ Therefore, it does not appear to increase surgical complications such as infection.

There was no consensus among physicians about the second patient. Given that the case has recently experienced an attack and the patient's surgery was elective, it is important to consider a period to stabilize the immune system and then perform surgery. There was no argument on the duration from attack to surgery. Most of the participants considered a month to be the right time.

The third patient has just started treatment with rituximab and the last attack was a month and a half ago. There are three points that should be considered. First, the patient has had an attack

almost recently and had major stress conditions due to the recent delivery and a recent attack. Secondly, rituximab is a highly potent B cell-depleting drug. Third, the patient's surgery, although elective, was necessary due to a large fibromyoma.

Stress has a significant effect on the immune system and CNS inflammation.¹⁵⁻¹⁷ A meta-analysis of 14 reports confirmed the association between stressful situations and MS relapse.¹⁸ In this patient, as more than a month has passed since the attack, it seems that the conditions caused by the attack have been minimized. However, there is no consensus on how long it takes for the immune system to stabilize. Moreover, it is necessary to involve the patient and a gynecologist in the decision-making and discuss the importance of surgery and its risks and benefits.

Rituximab reduces B-cell for about 2-6 months before B-cell repopulation; therefore, the rate of infections is high.¹⁹ The other complication of rituximab is hypogammaglobulinemia; however, it usually occurs after a long time of its consumption.²⁰⁻²² Thus, as the drug has been started recently, the risk of infection does not seem to be high in this patient. However, it is recommended to check for infection before surgery.

The main concerns about case 4 were the risk of infection due to the consumption of fingolimod after surgery and the risk of MS exacerbation after sleeve gastrectomy for morbid obesity. Fingolimod traps lymphocytes in lymph node tissue and reduces the peripheral lymphocyte count but not total lymphocyte, yet increasing the overall infection risk.^{23,24} Another important point is the risk of rebound after stopping this drug; therefore, it is recommended to continue it.^{25,26}

Stenberg et al.'s study compared 196 PwMS with healthy control who underwent gastric bypass or sleeve surgery. This matched cohort study revealed that postoperative complications did not differ between the two groups and the surgery was safe and improved quality of life in PwMS.²⁷

One of the problems of PwMS is gait difficulty. Obesity can exacerbate this problem. Therefore, obese PwMS are advised to lose weight through different methods.²⁸ Thus, it seems that in case of severe obesity, the patient will benefit from surgery.

Patient 9 had a similar surgery ahead; however, her disease was progressive although it was currently stable. To our knowledge, there has been no study on the effect of surgery or anesthesia on the progression of MS so far. However, if we

consider the negative effects of obesity on gait mentioned earlier, it seems that the patient would benefit from surgery. The fifth scenario addressed a stable patient with MS using ocrelizumab and waiting for an elective but essential surgery. He suffered from active infection (cholangitis) which could be the result of ocrelizumab consumption. In phase III clinical trials of ocrelizumab²⁹ and the study by Seery *et al.*,³⁰ a lower IgG level was associated with a higher risk of serious infection; therefore, it is reasonable to check the immune level for evaluating hypogammaglobulinemia.

Patient 6 represented an urgent case. The patient has had a severe attack recently. Most experts suggested a short time delay after the attack and before the surgery. Consulting with an oncologist to assess the patient's cancer condition and the risk and benefit of waiting for the surgery seemed to be helpful. The patient was faced with a threatening situation. Delay in surgery could have irreparable consequences for the patient's life; thereafter, it seemed more reasonable for the majority of the physicians to wait for an escalation DMT than to delay surgery for a long time. Cases 7 and 8 were patients with SPMS (case 7 with stable and case 8 with active SPMS) who underwent treatment with ocrelizumab. Due to cancer, decision-making in case 7 was a life-threatening issue, like case 6. Cancer management is the most important issue in these cases as the short treatment window outweighs the potential risks of surgical complications. In both cases, most specialists allowed surgery without any specific piece of advice. The opinions of the experts about patient 10, a case of PPMS without specific treatment, were very different making it difficult to interpret. As there are no studies on the effects of surgery on progressive conditions, it is not possible to give a definite opinion.

In patient 11, like case 2, the patient suffered from a recent attack. However, emergent appendectomy was an emergency in this case, the delay of which could have serious complications.³¹ Therefore, the majority of participants agreed not to delay surgery. Since infection is a complication of an appendectomy,³² in cases like this who are treated with ocrelizumab, it is not in vain if one examines the immune system through CBC and the level of immunoglobulin (Ig).

In case of a patient with MS who intends to have surgery, it is important to prioritize the

surgery; is the surgery emergency or elective? If elective, determine what side effects may occur after surgery and whether these side effects interfere with the MS disease or the medications the patient is taking. What is the patient's status in terms of MS disease? If the disease is mild without a recent attack and the patient is being treated with first-line injections, there is less concern about the complications of surgery.

If the patient is taking oral medications such as DMF and fingolimod, we should consider the risk of lymphopenia and infection. It is reasonable to check for infection through a CBC and other measurements to prevent postoperative infection. In cases of taking fingolimod and natalizumab, it is better not to stop the drugs due to the risk of rebound. In a patient with highly active MS or a patient who has had a recent attack, it is important to evaluate the likelihood of a postoperative recurrence as well as the increased risk of surgical complications. If the surgery is not a life-threatening emergency, it is safer to delay the surgery to return the person's immune system to normal. Regarding anti-B cell drugs, due to hypogammaglobulinemia, which can increase the risk of infections, it is suggested to check the level of Igs. There are limited data on the effect of anesthesia on the progressive nature of the disease in patients with progressive MS. If the patient is stable, necessary surgery is allowed but if the progressive phase is active, the physician should consider the effect of surgery on the neurodegenerative nature of the disease.

Conclusion

The purpose of describing these scenarios was to examine different views in the field of MS and surgery. PwMS face surgery for various reasons. Risk assessment of surgery, the effect of various drugs such as anesthetics and DMTs on patients, as well as many other aspects of MS are issues challenging the practitioners. Clarifying the various dimensions of these issues requires further research.

Conflict of Interests

The authors declare no conflict of interest in this study.

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