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REVIEW ARTICLE

## Neuraxial anesthesia in patients with multiple sclerosis – a systematic review

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### KEYWORDS

Multiple sclerosis;  
Neuromyelitis optica;  
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### PALAVRAS-CHAVE

Esclerose múltipla;  
Neuromielite óptica;  
Anestesia neuroaxial

### Abstract

**Background and objectives:** Current guidelines for neuraxial analgesia in patients with multiple sclerosis are ambiguous and offer the clinician only a limited basis for decision making. This systematic review examines the number of cases in which multiple sclerosis has been exacerbated after central neuraxial analgesia in order to rationally evaluate the safety of these procedures. **Methods:** A systematic literature search with the keywords “anesthesia or analgesia” and “epidural, peridural, caudal, spinal, subarachnoid or intrathecal” in combination with “multiple sclerosis” was performed in the databases PubMed and EMBASE, looking for clinical data on the effect of central neuraxial analgesia on the course of multiple sclerosis.

**Results and conclusions:** Over a period of 65 years, our search resulted in 37 reports with a total of 231 patients. In 10 patients multiple sclerosis was worsened and nine multiple sclerosis or neuromyelitis optica was first diagnosed in a timely context with central neuraxial analgesia. None of the cases showed a clear relation between cause and effect. Current clinical evidence does not support the theory that central neuraxial analgesia negatively affects the course of multiple sclerosis.

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### Anestesia neuraxial em pacientes com esclerose múltipla – uma revisão sistemática

#### Resumo

**Justificativa e objetivos:** As diretrizes atuais para analgesia neuraxial em pacientes com esclerose múltipla (EM) são ambíguas e oferecem ao clínico apenas uma base limitada para a tomada de decisão. Esta revisão sistemática examina o número de casos nos quais a EM foi exacerbada

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após analgesia neuraxial central para avaliar racionalmente a segurança desses procedimentos. *Métodos:* Uma busca sistemática da literatura usando as palavras-chave “anestesia ou analgesia” e “epidural, peridural, caudal, espinhal, subaracnoideo ou intratecal” em combinação com “multiple sclerosis” foi realizada nas bases de dados PubMed e EMBASE à procura de dados clínicos sobre a efeito da analgesia neuraxial central sobre o curso da esclerose múltipla.

*Resultados e conclusões:* Durante um período de 65 anos, nossa busca resultou em 37 relatos com um total de 231 pacientes. Em 10 pacientes, a esclerose múltipla foi agravada e, em nove pacientes, a esclerose múltipla ou neuromielite óptica foi diagnosticada pela primeira vez em momento concomitante com a analgesia neuraxial central. Nenhum dos casos apresentou uma clara relação entre causa e efeito. A evidência clínica atual não sustenta a teoria de que a analgesia neuraxial central afeta negativamente o curso da esclerose múltipla.

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## Introduction

Multiple sclerosis (MS) is a chronic autoimmune condition of the central nervous system (CNS), with diffuse and focal areas of inflammation, demyelination, gliosis, and neuronal injury. The exact mechanisms behind this disease are not completely understood, but current concepts suggest a complex multifactorial genesis with genetic, environmental, immunological, and microbiological factors.<sup>1</sup>

In 1949, Fleiss reported the appearance of MS after spinal anesthesia,<sup>2</sup> and this led to the speculation that intrathecal application of local anesthetics could precipitate or exacerbate this disease.<sup>3</sup> As a consequence, central neuraxial analgesia was regarded to be relatively contraindicated in MS.<sup>4,5</sup> Direct toxicity of local anesthetics was discussed as potentially harmful as was mechanical trauma or neural ischemia secondary to local anesthetics or additives. Oligopeptides with Na-channel blocking activities have recently been found in cerebrospinal fluid of patients suffering from MS, leading to the assumption of increased vulnerability to local anesthetics.<sup>6</sup> Despite many considerations, no commonly accepted theory exists on the particular mechanisms of how neuraxial analgesia may alter the course of MS; it also remains unclear if neuraxial techniques are actually harmful. Nevertheless, several anesthesiologists still fear the possible exacerbation of pre-existing deficits and are reluctant to offer spinal or epidural analgesia to patients with MS.<sup>7</sup>

Current guidelines for central neuraxial analgesia in patients with MS are ambiguous and offer the clinician only a limited basis for decision-making. The American Society of Regional Anesthesia and Pain Medicine (ASRA) states in its 2008 practice advisory that “the existing literature neither confirms nor refutes the safety of neuraxial anesthesia in patients with CNS or peripheral nervous system neurologic disorders, nor does it definitively address the relative safety of spinal vs. epidural anesthesia (EA) or analgesia in these patients”.<sup>8</sup> A consensus statement from 2014 recommends that the indication of spinal anesthesia in pregnant patients with MS should be discussed on a case-by-case basis.<sup>9</sup>

In the absence of sufficient high-level, large-scale, prospective studies, all these guidelines refer to cases of deterioration of MS after neuraxial anesthesia. However, until now the exact number of reported cases has not yet been investigated. This systematic review aims to determine the number of cases in which MS has been exacerbated after central neuraxial analgesia in order to rationally evaluate the safety of these procedures.

## Methods

A systematic literature search for articles reporting on the clinical course of MS after epidural, spinal, combined spinal and epidural or caudal analgesia in human subjects was carried out using the databases PubMed and EMBASE. We included all kinds of articles providing clinical data, especially case-series or case-reports. The search term included the keywords “anesthesia or analgesia” and “epidural, peridural, caudal, spinal, subarachnoid or intrathecal” in combination with “multiple sclerosis.” Language was restricted to English, German, French, Spanish and Portuguese. The Cochrane database and the clinicaltrials.gov study registry were searched to identify further ongoing or planned trials. As the distinction between neuromyelitis optica and MS was unclear until a few years ago,<sup>10</sup> we decided to include cases about both diseases.

Title, abstract, and full-text screenings were conducted consecutively by two independent reviewers (HBC and FT). If diverging appraisal of literature occurred, a third reviewer decided how to proceed. References of articles and reviews were screened further for additional publications that were not detected by our primary literature search. The manuscript was prepared according to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).<sup>11</sup>

## Results

The last literature search was conducted in May 2015. In total, 248 primary hits were identified. Thirty-seven

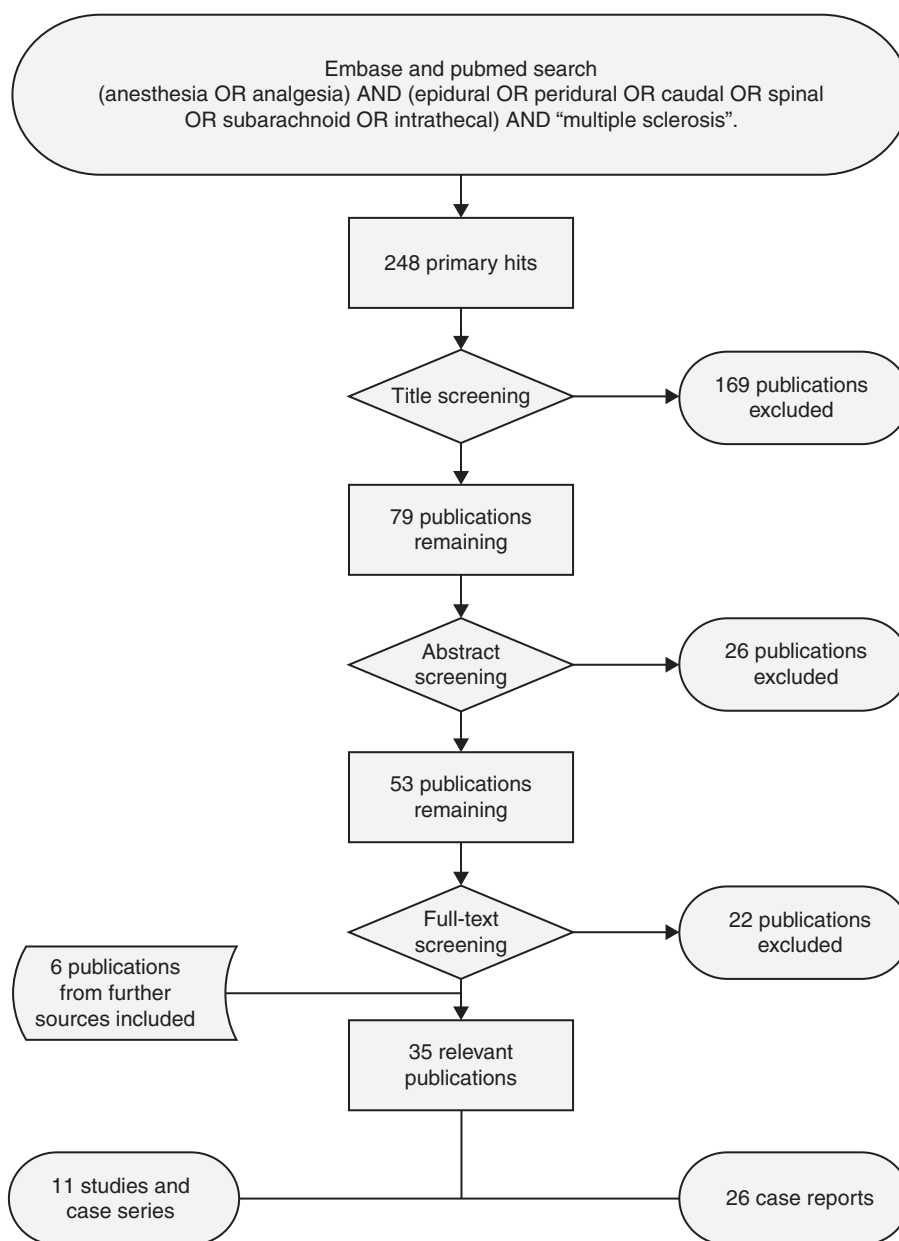


Figure 1 Flowchart.

publications were selected by title, abstract, and full-text-screening, including 11 studies and 26 case reports (Fig. 1, Tables 1 and 2).

A total of 243 interventions in 231 patients were included. EA was used in 180 cases, spinal analgesia in 59, caudal analgesia in three, and Combined Spinal and Epidural (CSE) once. In 10 patients, a deterioration of MS was observed in context with central neuraxial analgesia (three spinals, seven EAs). In six cases, MS was first diagnosed after spinal anesthesia, and in three cases neuromyelitis optica, a demyelinating disease that shares many similarities with MS, was first diagnosed after spinal analgesia. In two cases, symptoms of MS improved after EA.

## Discussion

In clinical practice, the patient with MS is a rare event. Most anesthesiologists encounter less than one of these patients per year,<sup>7</sup> and therefore, experience in perioperative management is often limited. General anesthesia is most frequently used in this population and generally regarded as safe.<sup>12,13</sup> On the other hand, neuraxial analgesia in patients with MS remains controversial. As guidelines are ambiguous or recommend a case-by-case decision,<sup>8,9</sup> their clinical applicability is limited. The question, if neuraxial techniques are safe in patients suffering from MS, has not only a medical but also a juridical dimension. In a recent legal case in Italy, the development of optical neuritis was

**Table 1** Case reports of patients with multiple sclerosis undergoing neuroaxial analgesia.

Author (reference)	Patients characteristics	Type of anesthesia	Type of surgery	Complication	Details
Fleiss <sup>2</sup>	36 years, male	Spinal	Orthopedic	Yes	Multiple sclerosis first diagnosed after spinal anesthesia
Warren <sup>24</sup>	21 years, female	EA	Vaginal delivery, CS	Yes	Hypesthesia on the thigh, restitution after 7 days (1° delivery) and 7 weeks (2° delivery)
Levesque <sup>25</sup>	33 years, female	Spinal	Plastic surgery	Yes	Multiple sclerosis first diagnosed after spinal anesthesia
Hosseini <sup>26</sup>	23 years, female	Spinal	Hallux valgus	Yes	Neuromyelitis optica first diagnosed after spinal anesthesia
Lopez Ariztegui <sup>27</sup>	32 years, female	EA	Vaginal delivery	Yes	Acute transverse disorder first diagnosed two weeks after PDA
Facco <sup>14</sup>	34 years, female	Spinal	CS	Yes	Neuromyelitis optica 6 months after spinal; conus medullaris lesion while puncturing; five years after bilateral blindness, severe tetraparesis, neurogenic bladder
Buraga <sup>28</sup>	42 years old female	Spinal	Urological	Yes	Multiple sclerosis first diagnosed after spinal anesthesia
Berger <sup>29</sup>	53 years, male	Spinal	Urological/plastic surgery	No	
Leigh <sup>30</sup>	43 years, male	Spinal	Laparotomy	No	
Wang <sup>31</sup>	45 years, female	EA	CS	No	Preexisting diseases: von Hippel Lindau disease
Kohler <sup>32</sup>	29 years, female	EA	Vaginal delivery	No	
Gunaydin <sup>21</sup>	29 years, female	EA	CS	No	Improvement of neurological symptoms postpartum
Vadalouca <sup>33</sup>	56 years, female	CSE	Hysterectomy	No	
Marshak <sup>34</sup>	61 years, female	EA	Thoracotomy	No	
Barbosa <sup>35</sup>	32 years, female	Spinal	CS	No	
Mayorga Buiza <sup>36</sup>	37 years, female	EA	CS	No	
Martucci <sup>37</sup>	29 years, female	Spinal	CS	No	
Tympa <sup>38</sup>	45 years, female	EA	Hysterectomy	No	Other pre-existing disease: ischemic brain infarct, antiphospholipid syndrome, and $\beta$ -heterozygous thalassemia
Shanmugam <sup>39</sup>	68 years, female	EA	Oesophagectomy	No	Postoperative improvement of lower limb mobility and strength
Patel <sup>40</sup>	46 years, female	EA	Cystectomy	No	Intrathecal baclofen pump implanted
Oouchi <sup>41</sup>	29 years, female	Spinal	CS	No	
Sethi <sup>42</sup>	32 years, female	EA	CS	No	
Bettencourt <sup>43</sup>	36 years, female	EA	CS	No	

EA, epidural anesthesia; CSE, combined spinal and epidural; CS, cesarean section.

regarded to be related to spinal anesthesia, resulting in financial compensation for the patient.<sup>14</sup>

In our systematic literature search, we found two prospective studies, both on epidural analgesia in an

obstetric setting. The first was the PRIMS (Pregnancy and MS) study. This European multicenter study followed 254 women with MS during pregnancy and 12 months after delivery.<sup>15</sup> Forty-two parturients had epidural analgesia for delivery.

**Table 2** Case series and studies of patients with multiple sclerosis undergoing neuroaxial analgesia.

Author (reference)	Study type	n	Type of anesthesia	Type of surgery	Check up	Complication	Art der Komplikation
Bamford <sup>44</sup>	Case series	8 patients 12 interventions	Spinal (9)	Vaginal delivery, minor surgical interventions	-	Yes	1 patient with leg weakness
Stenuit <sup>45</sup>	Case series	5	Caudal (3) Spinal	CS, urological and orthopedica	-	yes	MS first diagnosed after spinal anesthesia in 2 patients, 1 patient with exacerbation of symptoms for 1 year
Bouchard <sup>46</sup>	Case series	9 patients 14 interventions	Spinal	Urological and plastic surgery	-	Yes	1 patient with temporary exacerbation, no further description of symptoms
Bader <sup>47</sup>	Case series	20 patients 32 pregnancies	EA (14)	CS, vaginal delivery	3 month	Yes	5 patients with relapse, no further description of symptoms
Dalmas <sup>48</sup>	Case series	19	EA	CS, vaginal delivery	4 years	Yes	1 patient developed 5 month postnatal retro bulbar neuritis and dysesthesia of the extremities
Confavreux <sup>15</sup>	Prospective cohort study (PRIMS study)	42	EA	Vaginal delivery, CS	12 month	No	
Kyttä <sup>49</sup>	Case series	5	EA (3)	Urological and plastic surgery	-	No	
Vukosic <sup>16</sup>	Prospective cohort study (PRIMS Study follow-up)	42	Spinal (2) EA	Vaginal delivery, CS	2 years	No	
Hebl <sup>6</sup>	Case series	35	EA (18)	Vaginal delivery mixed surgery	46 ± 38 days	No	
May <sup>50</sup>	Case series	5	Spinal (17) EA (4)	Vaginal delivery, CS	-	No	
Pastó <sup>17</sup>	Prospective cohort study	65	Spinal (1) EA	Vaginal delivery, CS	6 month	No	

PDA, peridural anesthesia; CS, cesarean section.

When compared to 180 parturients with MS who had no epidural analgesia, no significant effect on relapse rate or severity of worsening of disabilities was found. In the follow-up analysis 2 years later, the results were confirmed.<sup>16</sup>

In 2012, Pastò et al. presented their prospective cohort study from the Italian MS Study Group.<sup>17</sup> They collected data from the gestational period until 12 months after delivery from 415 parturients with MS. Although 65 patients underwent epidural analgesia, this did not affect the relapse rate or the time-dependent profile of relapse.

This is the first systematic review which aims to include all reported cases in current literature. Although all available guidelines and recommendations refer to certain cases, the exact number was not yet investigated. We specifically decided to include these cases in our systematic review to provide an assessment of the frequency of noticeable postoperative courses. Taking the high prevalence of MS between 20 and 200/100,000<sup>18</sup> into consideration, the total number of reported cases in which symptoms deteriorated after neuraxial analgesia seems extremely low. However, this number may be highly biased, as the majority of cases are likely to be unreported. Even so, worsening of MS after neuraxial analgesia can be considered a rare event.

Over a period of 65 years, our systematic literature search resulted in 10 patients, in whom MS was worsened and nine in whom MS or neuromyelitis optica was first diagnosed in a timely context with central neuraxial analgesia. However, timely correlation does not imply causality.

The majority of cases were described in obstetric settings. This can be explained by two facts: first, due to the combined effect of sex and age, the incidence for MS is increased in the obstetric population. Second, in obstetric anesthesia and analgesia, neuraxial techniques are more commonly applied in patients with MS compared to healthy controls.<sup>19</sup> During pregnancy, symptoms of MS often improve, whereas postpartum relapse rates have been shown to increase.<sup>15</sup> Worsening of symptoms could therefore also be attributed to the normal course of disease after childbirth.

Stress is a well-known risk factor for the onset and relapse of MS.<sup>20</sup> Therefore, strategies to decrease perioperative stress help to prevent postoperative deterioration of symptoms. Optimizing pain management by EA is potentially beneficial in the postoperative course of MS; in two cases, pre-existing neurological deficits improved after EA.<sup>21,22</sup>

In some clinical recommendations, epidural is preferred to spinal analgesia in patients with MS.<sup>9,12</sup> Based on two independent prospective studies, EA in obstetric patients showed no negative outcome.<sup>15-17</sup> For spinal anesthesia, only case reports exist, and these do not show a clear relation between cause and effect. The intrathecal application of higher concentrations of local anesthetics compared with EA is discussed as possibly increasing the risk of relapse.<sup>6,13</sup> However, there is neither a clear hypothesis of the potential mechanism behind this assumption nor clinical data to support this assumption. On the other hand, spinal anesthesia is performed frequently in patients with MS.<sup>7</sup> One may argue that the number of reported cases with a deteriorated postoperative course only reflects a marginal risk, if any, for the individual patient.

For CSE and caudal analgesia, we found only one and three cases, respectively. The low number is easily explained

as caudal analgesia is a rarely used technique in adults.<sup>23</sup> CSE, on the other hand, is often omitted as most patients with MS are scheduled for elective surgery or delivery and so early placement of EA (if any) is attempted.

Our study is limited as a systematic review cannot ultimately prove the safety of a procedure, especially when the results mainly include case reports and series. Individual case cannot prove or refute a cause and effect relationship. Quantifying the number of cases, however, permits the evaluation of the scientific basis of some concerns.

Another limitation is that we cannot provide details on the material and medication used in the reported cases, as these information were not reported in the majority of publications.

Future approaches for elucidating this problem may involve prospectively collected, large, multinational databases in which postoperative courses of patients with MS are collected and risk factors may be identified.

## Conclusion

In conclusion, it is impossible to completely rule out potential risks from any procedure. Current clinical evidence does not support the theory that central neuraxial analgesia negatively affects the course of MS. Therefore, we regard this procedure as a viable option for discussion with the patient.

## Conflicts of interest

The authors declare no conflicts of interest.

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