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REVIEW ARTICLE

Spinal myoclonus following neuraxial anesthesia: a literature review

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Abstract
Spinal myoclonus (SM) is a rare neurologic movement disorder following neuraxial anesthesia (NA). SM following NA (SM-NA) has insufficient clinical information and its pathogenesis remains to be elucidated. The aim of this review article was to summarize the past cases and consider SM-NA pathophysiology. Based on our PubMed search, it was revealed that SM-NA develops within several hours after neuraxial local anesthetic (LA) administration and resolves in a day without leaving neurologic compilations. It occurs primarily in the lower extremities, but can sometimes spread upward and affect the upper extremities and trunk. Although statistical adjustments are indispensable, analysis of the previous cases provided important facts that seem to be related with the mechanism of SM-NA. The frequently used LAs for spinal anesthesia were hyperbaric. SM-NA occurrence was more frequent in women. After initiation of spinal anesthesia, intrathecal hyperbaric LA distributes cephalad. In the LA elimination process, the large concentration differences in intrathecal LA may induce the partially functioning spinal neurons, resulting in myoclonus generation. The morphological features of the lumbar spine in women can predispose to a higher LA concentration difference. SM-NA is an unpredictable and rare neural complication following NA and should be confirmed by basic experiments and large-scale researches.

Keywords Movement disorder · Involuntary movement · Myoclonus · Local anesthetic · Neuraxial anesthesia

Introduction

Neuraxial anesthesia (NA), including spinal and epidural anesthesia, is a widely used technique [1, 2]. Some large-scale clinical studies have reported severe neurologic complications following NA; these include permanent paraplegia, hematoma, infection, and cauda equina syndrome [3, 4]. However, the minor and rare neural complications associated with NA have rarely been documented, resulting in a lack of related literature. Transient myoclonic involuntary movements of the extremities and trunk, which are typically referred to as spinal myoclonus (SM), rarely develop after NA [5].

Myoclonus refers to lightning-like involuntary muscle jerks that are brought about by brief electromyographic discharges [6–8]. Myoclonus is usually classified according to either anatomic localization or etiology [6, 7]. Anatomically, myoclonus can originate from either the central or peripheral nervous system. In the central nervous system, the location of origin is further subdivided into cortical, subcortical, brain stem, and spinal cord [8]. SM is a movement disorder that arises from the spinal cord [6, 9–11] and is a rare neural complication that is infrequently encountered after NA.

The facts that are clearly known about SM following NA (SM-NA) are (1) SM-NA occurs within several hours after the initiation of NA and resolves in a day without neurologic compilations; (2) SM-NA typically develops in the lower extremities and often concurs with the myoclonus in the upper extremities; and (3) the pathophysiology of SM-NA remains speculative. We previously reported a case of SM-NA [5], but the number of past reported cases remains small [12–29] and the characteristics of the past SM-NA cases have not been described in detail. In the previous articles, NA has been considered to be directly responsible for the myoclonic involuntary movements that followed. However, SM-NA is not well recognized, probably because there is no chapter on NA-associated movement disorders in a

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major anesthesia textbook [1]. Moreover, in neurology, NA is not included in the etiologic classification of myoclonus [6, 7, 30].

For the purpose of summarizing and characterizing past SM-NA cases, case reports on SM-NA were identified through a PubMed search and were selected carefully for discussion and review. Based on the evaluated case reports, the clinical picture and course of SM-NA were summarized to provide useful information for regional anesthesia practice and research on spinal neurology. In addition, we would like to add new considerations to the conventional SM-NA pathophysiology, which was hypothesized by the previous researchers.

Past case reports related to SM-NA

We searched for the previous SM-NA-related articles in PubMed using the terms "anesthesia, spinal"; "anesthesia, epidural"; "spinal myoclonus"; "propriospinal myoclonus"; "spinal segmental myoclonus"; and "myoclonic involuntary movement". Only English articles published before July 2018 were reviewed. If an SM-NA-related article found in the reference list of the obtained articles was published on PubMed, it was also included for review.

After the first case report in 1979 [12], similar case reports have been indexed in PubMed. The criterion for SM-NA was defined as transient reversible myoclonic involuntary movements following NA. Cases suspected to have etiologies other than NA were excluded to precisely select the SM-NA cases. Those misclassified to have other etiologies were included for review if the clinical course of the movement disorder could be regarded as SM-NA. Upon searching for case reports in PubMed, we obtained 30 English case reports related to SM-NA. Eleven case reports were excluded for reasons, such as the lack of presumable clinical information at the time of SM-NA occurrence [31]; suspicion of an organic disease or iatrogenic complications of NA [32–36]; use of neuraxial opioids for the long-term pain management of the cases [37–40]; and inclusion of a neonate [41]. Some misclassified cases of sleep-related myoclonus [13, 14], clonic convulsion due to epinephrine-induced spinal ischemia [15], and opioid-induced myoclonic reaction [16] were included, because the background of the patients could be regarded as SM-NA. The 19 articles that described 23 cases with SM-NA are summarized in Tables 1 and 2 and Fig. 1a, b.

Terminology

Possibly due to the extremely low incidence of SM-NA, none of the symptoms associated with SM-NA was classified as neural complications of NA [1, 2]. The number of review articles related to SM-NA was limited [17], and there was no specified official name for a movement disorder that was described as anesthesia-related myoclonic involuntary movements following NA. Since SM-NA has no standardized symptomatic name, the symptomatic names used in the title of the SM-NA case reports varied according

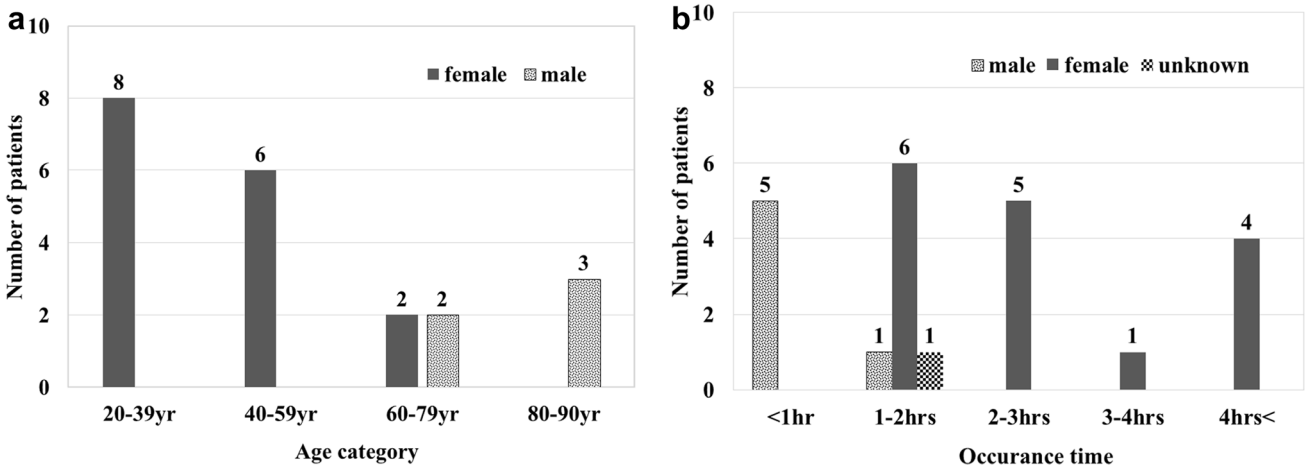

Fig. 1 **a** Age-related sex difference in patients with spinal myoclonus following neuraxial anesthesia (SM-NA). This figure shows the number of patients with SM-NA by age and sex. The vertical axis shows the number of patients. The horizontal axis shows the age. All patients younger than 60 years were women. The number of women decreased with increasing age. All men were over 60 years. One case (reference number [19]) that had no description of sex and age was excluded from this figure data. Case [14] is counted as one, and the number of patients is 21 in the graph. **b** Time of spinal myoclonus occurrence following neuraxial anesthesia, according to sex difference. This figure shows the number of patients with SM-NA according to time of occurrence and sex. The vertical axis shows the number of patients. The horizontal axis shows the SM-NA time of occurrence. All patients in whom SM-NA occurred within an hour were men. One case (reference number [19]) had no description of sex

Table 1 Summary of patients with spinal myoclonus following neuraxial anesthesia

No.	Patient		Neuraxial Anesthesia							Myoclonus Signs				Treatment		Ref
	Sex	Age	AP	PO	BA	LAs	AD	IS	MAL	MOP	LT	OT	DT	Drugs	EF	
1	M	81	Sp	Dec	Iso	DIB	none	L3/4	T6	L	BL	< 1 h	< 12 h	none	none	[13]
2	M	86	Sp	Dec	Iso	LID	none	L3/4	T6	L, U	BL	< 1 h	< 12 h	none	none	[14]
3	M	90	Sp	un	Hyper	BUP	none	L3/4	T8	L	UL	< 1 h	< 12 h	none	none	[23]-1
4	M	63	Sp	Sit	Hyper	BUP	none	L3/4	un	L	BL	< 1 h	un	DZP	−	[21]
5	M	67	Sp	un	Hyper	BUP	Diam	L4/5	T8	L	UL	1–2 h	un	MDZ	un	[23]-4
6	F	52	Sp	Sit	Hyper	PRI	none	L3/4	T8	L	BL	1–2 h	< 12 h	DZP	±	[18]
7	F	35	Sp	Dec	Hyper	BUP	Epnp	L3/4	T10	L, U	BL	1–2 h	< 12 h	MDZ CNP	±	[20]
8	F	64	Sp	un	Hyper	BUP	none	L3/4	T6	L	un	1–2 h	< 12 h	none	none	[23]-2
9	F	53	Sp	un	Hyper	BUP	Diam	L3/4	T6	L	un	1–2 h	< 12 h	MDZ	un	[23]-3
10	F	35	Sp	Dec	Hyper	BUP	Fent	L2/3	T3	U	BL	1–2 h	< 12 h	MDZ	+	[27]
11	un	un	Sp	un	Iso	BUP	none	L4/5	un	L	BL	1–2 h	< 12 h	DZP TPT	−	[19]
12	F	45	Sp	Dec	Hyper	LID	Epnp	L3/4	T6	L, T	BL	2–3 h	< 12 h	DZP	+	[15]
13	F	36	Sp	Dec	Hyper	BUP	none	L4/5	T6	L	UL	2–3 h	< 12 h	none	none	[22]
14	F	33	Sp	Dec	Hyper	BUP	none	L3/4	T2	L	BL	2–3 h	< 12 h	none	none	[5]
15	F	56	Sp	Dec	Hyper	BUP	none	L4/5	un	L	BL	2–3 h	< 12 h	none	none	[26]
16	F	28	Sp	un	Hyper	BUP	Morp	L3/4	T5	L, U, T	BL	2–3 h	6 weeks	MgS PPF	−	[17]
17	F	53	Sp	Sit	Hyper	BUP	Diam	L3/4	T6	L	BL	3–4 h	< 12 h	MDZ	+	[29]
18	F	57	Sp	Dec	Hyper	TET	Epnp	L3/4	T8	L	BL	4 h <	< 24 h	DZP	±	[12]
19	F	77	Sp	Dec	Iso	BUP	none	L2/3	un	L, U, T	BL	4 h <	4 days	CNP VP	−	[24]
20	M	86	Ep	none	none	LID	none	T8/9	T4-11	L	BL	< 1 h	< 12 h	none	none	[14]
21	F	30	Ep	none	none	LEV LID	none	L3/4	T4	L, U	BL	1–2 h	< 12 h	MDZ	±	[28]
22	F	24	Ep	none	none	LID BUP	Fent	un	un	L, U, T	BL	4 h <	< 12 h	none	none	[16]
23	F	32	Ep	none	none	LID BUP	Fent	un	un	L, U	BL	4 h <	< 24 h	none	none	[25]

In the "MOP" column, myoclonus is represented as "*L*" for the lower extremities, "*U*" for the upper extremities, and "*T*" for the muscles of the trunk

The "EF" column pertains to the corresponding treatment drug described in each article. "−" means sustained myoclonus; "±" means reduced myoclonus; and "+" means resolution of myoclonus

In case [14], the patient experienced repeated SM-NA

The numbers "1–4" following reference number [23] indicate the case number

AP approach, *PO* position at the time of puncture, *BA* baricity of intrathecal local solution, *LAs* local anesthetics, *AD* adjunct, *IS* injection site, *MAL* maximum anesthetic level, *MOP* myoclonus occurrence parts, *LT* laterality, *OT* occurrence time, *DT* disappearance time, *EF* effectiveness, *Ref* reference number, *un* not described or not inferable, *Sp* spinal anesthesia, *Ep* epidural anesthesia, *Dec* decubitus position, *Sit* sitting position, *Iso* isobaric local anesthetic (LA), *Hyper* hyperbaric LA, *DIB* dibucaine, *LID* lidocaine, *BUP* bupivacaine, *PRI* prilocaine, *TET* tetracaine, *LEV* levobupivacaine, *Diam* diamorphine, *Epnp* epinephrine, *Fent* fentanyl, *Morp* morphine, *BL* bilateral, *UL* unilateral, *DZP* diazepam, *MDZ* midazolam, *CNP* clonazepam, *TPT* thiopental, *MgS* MgSO4, *PPF* propofol, *VP* valproate

Table 2 Indications of neuraxial anesthesia in patients with a history of spinal myoclonus following neuraxial anesthesia

History	Number of cases	References
Uneventful NA	6	[5, 12, 17, 18, 27, 29]
Repeated SM-NA	3	[13, 14, 20]
Non-repeated SM-NA	2	[23]-2, [5]
Sporadic SM-NA	1	[5]

The number "2" following the reference number [23] indicates the case number

NA neuraxial anesthesia, *SM-NA* spinal myoclonus following neuraxial anesthesia

to the author. In eligible case reports, myoclonic involuntary movements were described as SM [5, 18–23], propriospinal myoclonus [17, 24, 25], segmental SM [26], myoclonus-like involuntary movement [27, 28], myoclonus [12, 29], periodic leg movement [13, 14], clonic convulsion [15], and myoclonic reaction [16].

SM-NA was first described in 1979 as myoclonus following spinal anesthesia [12]. That case report has been referenced in many subsequent case reports on SM-NA in the field of anesthesiology [5, 13, 15, 18–21, 28]. However, in recent years, it may have been appropriate to describe the myoclonic involuntary movements as SM-NA, because the origin of the myoclonus was considered to exist in the spinal

cord and the myoclonic involuntary movements occurred in patients who underwent epidural anesthesia [14, 16, 25, 28]. Although SM is neurologically classified into the segmental and propriospinal types [6], "SM", rather than "segmental SM" or "propriospinal myoclonus", seems to be a better higher level category name. In this review article, myoclonic involuntary movements following NA were comprehensively referred to as SM-NA.

Clinical signs and symptoms

Myoclonic jerks are simple and rapid and may occur singly or repetitively [8, 42]. The signs described in the previous articles were considered to be consistent with those myoclonus signs. In the SM-NA cases, the typical symptoms were initially mild myoclonic involuntary movements that changed to jerky movements with increasing frequency and amplitude [5, 12, 14, 15, 18, 19, 26, 29]. The frequency and amplitude of the myoclonus were changed regularly or irregularly. In the severe type of SM-NA, the myoclonic involuntary movements increased in frequency to over 20 times per minute and developed largely, as if dancing [12] or riding a bicycle [5]. All of the SM-NA patients had no acute or chronic underlying neurologic disease. Furthermore, the patient's consciousness remained intact during the SM-NA. SM-NA developed in the muscles innervated by the spinal nerves, and none had been observed to develop in the cranial nerve area. The signs of SM-NA developed in the extremities and trunk, especially in the lower extremities that were directly affected by local anesthetic (LA). Therefore, the generators of SM-NA likely exist in the spinal cord.

Onset and duration

In 19 of 23 cases (82.6%), the myoclonic involuntary movements started within 4 h after the injection of LA into the intrathecal or epidural space (Table 1). In the 19 patients who received spinal anesthesia, the onset of SM-NA was within 3 h in 16 cases (84.2%) and may have been related to the LA onset of action. The symptoms of SM-NA gradually resolved and the patients regained voluntary movement with the disappearance of the anesthetic effect. In 19 cases (82.6%), the patients recovered from SM-NA within a day (Table 1); whereas in two cases, minimal myoclonic involuntary movements atypically continued for longer than a day [17, 24]. The myoclonus period from the onset of symptoms to the disappearance of the symptoms overlapped with the period considered to be under NA. Intrathecal LAs have been naturally considered to be responsible for the myoclonus. Therefore, all the articles related to SM-NA speculated that intrathecal LAs might induce SM-NA. After full recovery from SM-NA, none of the patients experienced a relapse of the myoclonic involuntary movements.

Types of myoclonus: segmental and propriospinal

Myoclonic involuntary movements occurred only in the lower extremities in 14 cases (60.9%); in both the upper and lower extremities in seven cases (30.4%); in only the upper extremities in one case (4.3%); and in the trunk muscles and muscles in the extremities in four cases (17.4%) (Table 1). SM is classified into the segmental and propriospinal types [6, 7]. The segmental type of SM typically originates within a few or several adjacent spinal segments of the spinal cord, whereas the propriospinal type of SM refers to myoclonic involuntary movements that involve muscles innervated by many different segments [6, 7, 9, 11, 30]. The neural network of the propriospinal pathway localizes within the spinal cord and ascends and descends along the long axis of the spinal cord to interconnect multiple transverse and longitudinal segments, which are thought to coordinate the forelimb and hind limb movements during locomotion in quadrupeds. The propriospinal route is considered a stimulation transmission pathway among multiple spinal segments through which abnormal impulses originating from the lumbar spinal cord ascend and spread upward, resulting in myoclonic involuntary movements of the upper extremities and trunk [6, 9, 11, 30, 43]. Although the localization and function of the propriospinal pathway have yet to be elucidated in humans [6, 11], myoclonic involuntary movements in the upper extremities or trunk following NA may be an indirect evidence of the functional existence of a propriospinal pathway in humans.

NA approach: spinal and epidural

Among the 23 cases of SM-NA, 19 (82.6%) occurred following lumbar spinal anesthesia and 4 (17.4%) occurred following epidural anesthesia (Table 1). The amount of a LA used for epidural anesthesia may be higher than that used for spinal anesthesia. Although the proportion of LAs detected in cerebrospinal fluid (CSF) after epidural administration was less than 20%, a LA administered in the epidural space could penetrate the intrathecal space [1]. The LA transported from the epidural space to the intrathecal space was speculated to affect the spinal cord and result in SM-NA [12, 25, 28].

Local anesthetics

Amide-type LAs, such as dibucaine, lidocaine, bupivacaine, prilocaine, and levobupivacaine, were used in 22 cases (95.7%), whereas an ester-type LA, such as tetracaine, was

used in only one case. Although bupivacaine was used for spinal and epidural anesthesia in 16 cases (69.6%) (Table 1), there was no literature on the occurrence rate of SM-NA according to the frequency of LA use. Therefore, the specific LA and additive that were most responsible for SM-NA remain unclear. When focusing on baricity, 15 of the 19 (78.9%) patients who developed SM-NA after spinal anesthesia received intrathecal hyperbaric LAs. Furthermore, 12 of 13 (92.3%) women who developed SM-NA after spinal anesthesia received hyperbaric LAs.

Sex difference

Although statistical adjustments are necessary, a simple summary revealed that 16 of the 22 patients (72.7%) were women (Table 1). The relationship between sex differences and SM-NA occurrence has never been addressed in the previous case reports. Sorting cases by sex and age showed that age-related sex differences may also be implicated in the incidence of SM-NA (Fig. 1a). The numbers of SM-NA patients categorized by age and sex and by the time of occurrence and sex are shown in Fig. 1a, b, respectively. Based on these results, the SM-NA incidence seemed to have sex differences. The particular results include (1) of the 21 SM-NA patients, 14 (66.7%) were under the age of 60 years, and all were women (Fig. 1a); (2) 6 of the 23 (26.1%) SM-NA cases were men (Table 1), and all of male SM-NA patients were over the age of 60 years (Fig. 1a); and (3) of the 23 SM-NA cases, 5 (21.7%) developed SM-NA within an hour and all of them were men (Fig. 1b).

Examinations

No abnormal findings were confirmed in the electrophysiological examination, radiologic imaging tests, and blood examination. Furthermore, the electroencephalogram revealed no abnormal findings in the middle of the SM-NA event [16, 17, 24] and after recovery from SM-NA [13, 19, 26]. These results likely indicate that SM-NA generation is located outside of the cortex. Although the causes of SM were once considered to be tumors, infections, trauma, and degenerative disease [29], organic diseases were completely differentiated from SM-NA through clinical examination. There may be no useful clinical examinations to elucidate the underlying mechanism of SM-NA.

Hypothesis on the pathophysiology of SM-NA

In the field of anesthesiology, basic studies on the discharge generation and the spinal cord transmission pathway that elucidated the mechanism of SM-NA are few. In the field of neurology, the first case report on SM-NA in 1979 described the estimated mechanisms of SM-NA generation [12]; since then, subsequent case reports on SM-NA in the field of anesthesiology have quoted or described SM-NA mechanisms that were similar to the myoclonus mechanism initially hypothesized by Fox, based on Cohen's animal experiment results. Intrathecal LAs penetrate the spinal cord and are distributed heterogeneously in each anatomical section within the spinal cord [44]. LAs are distributed at higher concentrations in the lateral and posterior funiculi than in the CSF. On the other hand, LAs are distributed in the anterior funiculus, posterior horn, and anterior horn at lower concentrations than that in the CSF. During elimination of intrathecal LAs, anesthetic-sensitive and non-sensitive areas may coexist within the spinal cord, resulting in the generation of SM-NA. Among several authors, the common observations regarding the mechanisms of SM-NA generation include the coexistence of reduced activity in the suprasegmental descending inhibitory pathway, increased excitability of inhibitory interneurons, and the abnormal hyperexcitation produced by the recovery of α-motor neurons in the anterior horn [5, 12, 18, 20, 25, 28, 29].

Therapeutic drugs

Recovery from SM-NA was spontaneous in 10 (43.5%) cases and needed drug treatment in 13 (56.5%) cases. Table 1 shows the anticonvulsant drugs that have been used empirically for the treatment of SM-NA [6, 10]. In drug-effective cases, it is necessary to evaluate whether the medication actually resolved the SM-NA, because the resolution of SM-NA might have been spontaneous and coincided with the disappearance of the LA effects. However, some reports concluded that benzodiazepines were effective or semi-effective for rapid suppression of SM-NA (Table 1). Therefore, benzodiazepine may be considered a recommended drug for the treatment of SM-NA. However, there were SM-NA cases in which benzodiazepine was administered prior to the occurrence of SM-NA as an anesthetic premedication [18, 20, 22, 26] or as a sedative following the induction of NA [5, 12, 17]. Prior benzodiazepine administration may bring about few prophylactic effects against SM-NA [5].

Differential diagnoses

To accurately review SM-NA, the differential diagnoses are important. In particular, myoclonic involuntary movements with long-term use of neuraxial high-dose opioid therapy (NHOT) and drug-induced dystonic movements should be differentiated from SM-NA [5].

Neuraxial opioids are known to have side effects of drug-induced-myoclonus, especially when administered for a long period or at a high dose for pain control [37–40]. Because of similar movements, NHOT-associated myoclonus can be misunderstood as the same category of movement disorder. Although SM-NA was often described to manifest as large movements [5, 12, 14, 15, 18, 19, 26, 29], the myoclonus associated with NHOT seemed to be rarely described as large [37–40].

Some perioperative antiemetics act as dopamine receptor-blocking agents and possibly induce dystonic movements that are referred to as extrapyramidal syndromes, which are typically classified into three types of involuntary movements, including acute dystonia, Parkinsonism, and akathisia [45–48]. Compared with dystonia, myoclonus is faster and not complex [8]. Although the signs of SM-NA are lightning-like muscle jerks that often develop in the extremities, the symptoms of dystonic movement are characterized by sustained muscle contractions that cause abnormal twisting-like movements and postures, which may affect the facial muscles and can manifest as generalized signs involving the trunk and limbs [45–48].

Unpredictability of SM-NA occurrence and NA indications

Table 2 shows the relationship between NA history and SM-NA. According to the case reports that recorded the past histories of patients with NA, six SM-NA patients had previously undergone uneventful spinal anesthesia. Recurrent SM-NA after the next NA did not develop in two SM-NA patients, but developed in three patients. Furthermore, we previously reported a patient who sporadically encountered SM-NA only upon the second of the three series of spinal anesthesia [5]. The onset of SM-NA varied and lacked consistency among the reports. These findings suggested that SM-NA occurrence may be unpredictable. Therefore, considering the relationship between NA and SM-NA, there were three useful clinical points in considering the NA indications. First, the occurrence of SM-NA was difficult to predict [5]. Second, a history of uneventful spinal anesthesia did not guarantee normal recovery without SM-NA after the next NA [5]. Third, it is currently uncertain whether a history of SM-NA is a risk factor for repeated SM-NA. Although a history of SM-NA may not be a contraindication for a repeat NA [5], recurrence of SM-NA was considered to be within 1 year of the first episode [13, 14, 20]. When NA is planned for patients who have experienced SM-NA within the past 1 year, it is advisable to prepare for SM-NA or to choose other anesthetic methods.

Discussion

There is no fundamental research, showing that LAs act on spinal neurons and produce myoclonus, and the pathophysiology of SM-NA remains speculative until now. Although there had been no reports on the relationship between statistically adjusted SM-NA occurrence and LA use rates, three points may be highlighted from the clinical information gathered from the previous articles to discuss about the SM-NA pathophysiology. First, in women who experienced SM following spinal anesthesia, the frequently used LAs were hyperbaric. Second, the occurrence of SM-NA was more frequent in women. Third, unpredictable occurrence may be a clinical characteristic of SM-NA.

The characteristics of SM-NA clarified in this summary did not contradict and can even reinforce the conventional hypothesis on SM-NA pathophysiology. The intrathecal distribution of hyperbaric LA depends on gravity. When using a hyperbaric LA for spinal anesthesia, the intrathecal LA spreads immediately after laying a patient in a supine position. Compared with isobaric LAs, hyperbaric LAs are immediately distributed cephalad from the injection site. As a result, the drug concentration is low in the lumbar intrathecal space near the puncture site and high in the intrathecal space around the spinal cord [49]. There is a significant morphologic difference in the shape of the lumbar spine between women and men. Compared with the lumbar spine in men, the lumbar spine in women has three features that can influence the intrathecal LA distribution and concentration: (1) the lumbar spine lordosis is more curved; (2) the lumbar spine curve length is shorter from the bottom edge of the T12 vertebral body to the top edge of the sacrum; and (3) the peak of the lumbar spine lordosis is located more caudally [50]. During elimination of intrathecal LA, a large concentration difference may lead to the different spinal neural function recovery, resulting in a functional discrepancy between the thoracic and lumbar spinal neurons. This mechanism is considered to reinforce the Fox's myoclonus mechanism that had been quoted by many previous researchers. However, due to multiple factors affecting intrathecal LA distribution [1], precise prediction of intrathecal LA concentration differences is difficult. This uncertainty on the intrathecal LA concentration difference may be related to the unpredictable occurrence of SM-NA.

Even if the reinforced Fox's mechanism seemed likely feasible, the intrathecal LA concentration difference cannot be completely explained in all of the SM-NA cases, as described below. For example, some elderly men developed SM-NA relatively early, immediately after intrathecal administration [13, 23]. Moreover, there were atypical cases reported, such as a 63-year-old man with unbearable

pain in the perineal region [21] and two women with prolonged myoclonic symptoms [17, 24]. Furthermore, the relationship between SM-NA occurrence and age-related sex difference is difficult to explain. Other several experimental results on the sex differences in the human spinal cord [51–54] may elucidate other mechanisms and factors that are beyond this discussion.

To fully elucidate the details of SM-NA, a large number of patients and significant research costs will be required, potentially rendering a prospective large-scale survey on SM-NA impractical. On the other hand, a large-scale survey on SM-NA is expected in clinical anesthetic practice to specifically identify the clinical characteristics of SM-NA. Basic research in spinal anesthetic neurology may also be necessary to confirm the mechanism of SM-NA generation.

In summary, SM-NA is defined as intrathecal LA-induced transient myoclonic involuntary movements following NA and is a rare neurologic complication of NA. SM-NA may occur unpredictably and may develop more often in women who undergo spinal anesthesia with hyperbaric LA. SM-NA unexpectedly occurred within several hours after LA administration and can be expected to spontaneously resolve within a day, without paralysis sequelae. The myoclonus typically occurred in the lower extremities but sometimes in the upper extremities and trunk. The movements sometimes manifest as large in frequency and amplitude. Benzodiazepine may be a recommended drug for a patient suffering from severe SM-NA. At present, the pathophysiology of SM-NA remains speculative and needs fundamental research.

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Authors' contributions TS, KH, and MS wrote the manuscript. KH and MS revised the manuscript. KH supervised this work. TS prepared manuscript files. All authors reviewed and approved the final manuscript for submission.

References

1. Brull R, Macfarlane AJR, Chan VWS. Spinal, epidural, and caudal anesthesia. In: Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Cohen NH, Young WL, editors. Miller's anesthesia, 2-volume set. 8th ed. Philadelphia: Elsevier; 2014. pp. 1684–720.
2. Mordecai MM, Brull SJ. Spinal anesthesia. Curr Opin Anaesthesiol. 2005;18:527–33.
3. Brull R, McCartney CJL, Chan VWS, El-Beheiry H. Neurological complications after regional anesthesia: contemporary estimates of risk. Anesth Analg. 2007;104:965–74.
4. Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990–1999. Anesthesiology. 2004;101:950–9.
5. Shiratori T, Hotta K, Satoh M, Kondo N, Ikeda J, Sasao S. A case of spinal myoclonus in a patient with elective cesarean section. JA Clin Rep. 2018;4:47. https://doi.org/10.1186/s40981-018-0182-1.
6. Termsarasab P, Frucht SJ. Myoclonus. In: Louis ED, Mayer SA, Rowland LP, editors. Merritt's neurology. 13th ed. Philadelphia: Wolters Kluwer; 2016. pp. 660–5.
7. Kojovic M, Cordivari C, Bhatia K. Myoclonic disorders: a practical approach for diagnosis and treatment. Ther Adv Neurol Disord. 2011;4:47–62. https://doi.org/10.1177/1756285610395653.
8. Fahn S, Frucht S. Myoclonus. In: Rowland LP, Pedley TA, editors. Merritt's neurology. 12th ed. Philadelphia: Wolters Kluwer; 2010. pp. 732–3.
9. Rothwell JC. Pathophysiology of spinal myoclonus. Adv Neurol. 2002;89:137–44.
10. Hoehn MM, Cherington M. Spinal myoclonus. Neurology. 1977;27:942–6.
11. Termsarasab P, Thammongkolchai T, Frucht SJ. Spinal-generated movement disorders: a clinical review. J Clin Mov Disord. 2015;2:18.
12. Fox EJ, Villanueva R, Schutta HS. Myoclonus following spinal anesthesia. Neurology. 1979;29:379–80.
13. Watanabe S, Sakai K, Ono Y, Seino H, Naito H. Alternating periodic leg movement induced by spinal anesthesia in an elderly male. Anesth Analg. 1987;66:1031–2.
14. Watanabe S, Ono A, Naito H. Periodic leg movements during either epidural or spinal anesthesia in an elderly man without sleep-related (nocturnal) myoclonus. Sleep. 1990;13:262–6.
15. Nadkarni AV, Tondare AS. Localized clonic convulsions after spinal anesthesia with lidocaine and epinephrine. Anesth Analg. 1982;61:945–7.
16. Almedallah DK, Alshamlan DY, Shariff EM. Acute opioid-induced myoclonic reaction after use of fentanyl as an anesthetic drug for an emergency cesarean section. Case Rep Neurol. 2018;10:130–4. https://doi.org/10.1159/000486891.
17. Lev A, Korn-Lubezki I, Steiner-Birmanns B, Samueloff A, Gozal Y, Ioscovich A. Prolonged propriospinal myoclonus following spinal anesthesia for cesarean section: case report and literature review. Arch Gynecol Obstet. 2012;286:271–2.
18. Fores Novales B, Aguilera Celorrio L. Spinal myoclonus following intrathecal anaesthesia with prilocaine. Anaesth Intensive Care. 2009;37:498–9.
19. Lin CS, Wei-Hung C, Lee YW. Transient spinal myoclonus after spinal anaesthesia with bupivacaine in the perioperation period. Anaesthesist. 2008;57:518.
20. Lee JJ, Hwang SM, Lee JS, Jang JS, Lim S-Y, Hong SJ. Recurrent spinal myoclonus after two episodes of spinal anesthesia at a 1-year interval—a case report. Korean J Anesthesiol. 2010;59 Suppl:62–4.
21. Abrão J, Bianco MP, Roma W, Krippa JES, Hallak JE. Spinal myoclonus after subarachnoid anesthesia with bupivacaine. Rev Bras Anestesiol. 2011;61:619–23.
22. Kösem B, Kılınç H. An unusual complication of anesthesia: unilateral spinal myoclonus. Agri. 2017;29:90–1.
23. Bamgbade OA, Alfa JA, Khalaf WM, Zuokumor AP. Central neuraxial anaesthesia presenting with spinal myoclonus in the perioperative period: a case series. J Med Case Reports. 2009;3:7293.
24. Zamidei L, Bandini M, Michelagnoli G, Campostrini R, Consales G. Propriospinal myoclonus following intrathecal bupivacaine in hip surgery: a case report. Minerva Anestesiol. 2010;76:290–3.
25. Ji TT, Shih CK, Hsieh YJ, Sun WZ. Desultory propriospinal myoclonus after epidural analgesia in a healthy parturient. Int J Obstet Anesth. 2015;24:285–6.
26. Celik Y, Bekir Demirel C, Karaca S, Kose Y. Transient segmental spinal myoclonus due to spinal anaesthesia with bupivacaine. J Postgrad Med. 2003;49:286.

27. Nakamoto T, Hirota K, Iwai T, Shingu K. Complete resolution of myoclonus-like involuntary movements under subarachnoid block after midazolam administration in a patient undergoing cesarean section: a case report. Korean J Anesthesiol. 2015;68:193–5.
28. Kang HY, Lee SW, Hong EP, Sim YH, Lee S-M, Park SW, Kang J-M. Myoclonus-like involuntary movements following cesarean delivery epidural anesthesia. J Clin Anesth. 2016;34:392–4.
29. Alfa JA, Bamgbade OA. Acute myoclonus following spinal anaesthesia. Eur J Anaesthesiol. 2008;25:256–7.
30. van der Salm SMA, Erro R, Cordivari C, Edwards MJ, Koelman JHTM, van den Ende T, Bhatia KP, van Rootselaar A-F, Brown P, Tijssen MAJ. Propriospinal myoclonus: clinical reappraisal and review of literature. Neurology. 2014;83:1862–70. https://doi.org/10.1212/WNL.0000000000000982.
31. Oguri T, Hisatomi K, Kawashima S, Ueki Y, Tachibana N, Matsukawa N. Postsurgical propriospinal myoclonus emerging at wake to sleep transition. Sleep Med. 2014;15:152–4.
32. Hachisuka K, Ogata H, Kohshi K. Post-operative paraplegia with spinal myoclonus possibly caused by epidural anaesthesia: case report. Paraplegia. 1991;29:131–6.
33. Dreskin S, Bajwa ZH, Lehmann L, Warfield CA. Polymyoclonus resulting from possible accidental subdural injection of local anesthetic. Anesth Analg. 1997;84:692–3.
34. Menezes FV, Venkat N. Spinal myoclonus following combined spinal-epidural anaesthesia for caesarean section. Anaesthesia. 2006;61:597–600.
35. Ford B, Pullman SL, Khandji A, Goodman R. Spinal myoclonus induced by an intrathecal catheter. Mov Disord. 1997;12:1042–5.
36. Wong SSC, Qiu Q, Cheung CW. Segmental spinal myoclonus complicating lumbar transforaminal epidural steroid injection. Reg Anesth Pain Med. 2018;43:554–6. https://doi.org/10.1097/AAP.0000000000000742.
37. Parkinson SK, Bailey SL, Little WL, Mueller JB. Myoclonic seizure activity with chronic high-dose spinal opioid administration. Anesthesiology. 1990;72:743–5.
38. Cartwright PD, Hesse C, Jackson AO. Myoclonic spasms following intrathecal diamorphine. J Pain Symp Manage. 1993;8:492–5.
39. Kloke M, Bingel U, Seeber S. Complications of spinal opioid therapy: myoclonus, spastic muscle tone and spinal jerking. Support Care Cancer. 1994;2:249–52.
40. Jeon Y, Baek SU, Yeo JS. Spinal myoclonus developed during cervical epidural drug infusion in postherpetic neuralgia patient. Korean J Pain. 2011;24:169–71.
41. Batra YK, Rajeev S, Lokesh VC, Rao KLN. Spinal myoclonus associated with intrathecal bupivacaine and fentanyl in an infant. Can J Anaesth. 2007;54:587–8.
42. Jankovic J, Lang AE. Movement disorders: diagnosis and assessment. In: Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors. Bradley's neurology in clinical practice. 6th ed. Philadelphia: Elsevier; 2012. pp. 230–59.
43. Juvin L, Simmers J, Morin D. Propriospinal circuitry underlying interlimb coordination in mammalian quadrupedal locomotion. J Neurosci. 2005;25:6025–35.
44. Cohen EN. Distribution of local anesthetic agents in the neuraxis of the dog. Anesthesiology. 1968;29:1002–5.
45. Park CK, Choi HY, Oh IY, Kim MS. Acute dystonia by droperidol during intravenous patient-controlled analgesia in young patients. J Korean Med Sci. 2002;17:715–7.
46. Melnick BM. Extrapyramidal reactions to low-dose droperidol. Anesthesiology. 1988;69:424–6.
47. Fahn S. Dystonia. In: Louis ED, Mayer SA, Rowland LP, editors. Merritt's neurology. 13th ed. Philadelphia: Wolters Kluwer; 2016. pp. 644–56.
48. Kang UJ, Burke RE, Fahn S. Tardive dyskinesia and other neuroleptic-induced syndromes. In: Louis ED, Mayer SA, Rowland LP, editors. Merritt's neurology. 13th ed. Philadelphia: Wolters Kluwer; 2016. pp. 686–90.
49. Kitahara T, Kuri S, Yoshida J. The spread of drugs used for spinal anesthesia. Anesthesiology. 1956;17:205–8.
50. Hay O, Dar G, Abbas J, Stein D, May H, Masharawi Y, Peled N, Hershkovitz I. The lumbar lordosis in males and females, revisited. PLoS ONE. 2015;10:e0133685.
51. Schiffer E, Van Gessel E, Gamulin Z. Influence of sex on cerebrospinal fluid density in adults. Br J Anaesth. 1999;83:943–4.
52. Yuan H, Goto N, Goto J, Shiraishi N, Shimada S. Sexual dimorphism of the human spinal cord in the aging process. Okajimas Folia Anat Jpn. 1999;76:241–6.
53. Yuan H, Goto N, Akita H, Goto J, Jīn SR. Sexual dimorphism of the motoneurons in the human spinal cord. Okajimas Folia Anat Jpn. 2000;77:143–8.
54. Papinutto N, Schlaeger R, Panara V, Zhu AH, Caverzasi E, Stern WA, Hauser SL, Henry RG. Age, gender and normalization covariates for spinal cord gray matter and total cross-sectional areas at cervical and thoracic levels: a 2D phase sensitive inversion recovery imaging study. PloS One. 2015;10:e0118576.