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Neural control of human gait and posture

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Abstract Recent developments in neuroscience techniques such as brain imaging, functional brain imaging, and non-invasive brain stimulation, have made it possible to directly study able-bodied humans while engaged in various motor tasks. As a result of these technological advances, the last couple of decades have experienced a significant increase in new findings in the field of motor control and, more specifically, on the control of gait and posture. However, there are still a lot of difficulties and limitations in studying human neural activities during dynamic movements, like walking. In this short review, recent advances in knowledge on human gait and posture will be reviewed.

Keywords : human, gait, posture, neural control, neurorehabilitation

Introduction

Since Sherington's pioneer work on reflex studies, primarily in animals, it has been believed that experimental results obtained from human subjects provide only indirect neuroscientific evidence, requiring validation in so-called "reduced preparations" (i.e., animals with specific operations). However, recent developments in neuroscience techniques such as brain imaging, functional brain imaging, and non-invasive brain stimulation, have made it possible to directly study able-bodied humans while engaged in various motor tasks. As a result of these technological advances, the last couple of decades have experienced a significant increase in new findings in the field of motor control and, more specifically, on the control of gait and posture. In this short review, recent advances in knowledge on human gait and posture will be reviewed, which will hopefully assist readers in deepening their understanding of neural mechanisms underlying human motor control.

Neural control of human bipedal walking

Human bipedal walking in an upright posture is inherently unstable from a physical point of view, unlike physically stable quadrupedal locomotion. It may be easily claimed that, for many aspects, the neural mechanisms underlying bipedal and quadrupedal locomotion are inherently different. At the same time, the extent to which these two different locomotion styles share common neural mechanisms has remained poorly understood. In the following section, recent advances in knowledge on the contribution of the higher nervous center and of spinal neural circuits, specifically the central pattern generator (CPG) for human bipedal walking, are summarized and discussed in the current perspective of neural sciences.

Contribution of the higher nervous centers. To what extent is the central command from the higher nervous centers needed to facilitate and maintain human bipedal walk? This is a fundamental question regarding the neural mechanisms controlling human walk. Needless to say, the motor cortex is required to enable human walking, considering that pathophysiology of brain diseases - such as stroke, Parkinson's disease, and cerebral palsy - indicates that a lesion of the motor cortex or other parts of the brain can impair, to a great extent, the ability to walk independently. However, the exact roles that different parts of the brain play in, for example, the initiation, execution, and maintenance of walking are still unknown. The answer can certainly be deduced from animal studies; though, again, we should keep in mind that the underlying neural mechanisms of human bipedal walking should not necessarily be the same as those of quadrupedal locomotion.

Fig. 1 is a schematic representation of the neural mechanisms underlying human bipedal walk, which is deduced mostly from animal studies[1]. As to so-called locomotor regions in the brain, so far a few different regions in the diencephalon (SLR: subthalamic locomotor region), mesencephalon (MLR: mesencephalic locomotor region), and cerebellum (CLR: cerebellar locomotor region) have been identified. Again, it is unknown whether those locomotor regions really exist in the human brain or not; however, more or less similar regions are supposed to work for human bipedal walk as well. Actually, there is a study showing similar supraspinal locomotor regions in the human brain that are active during mental imagery of bipedal walking[2] (Fig. 2).

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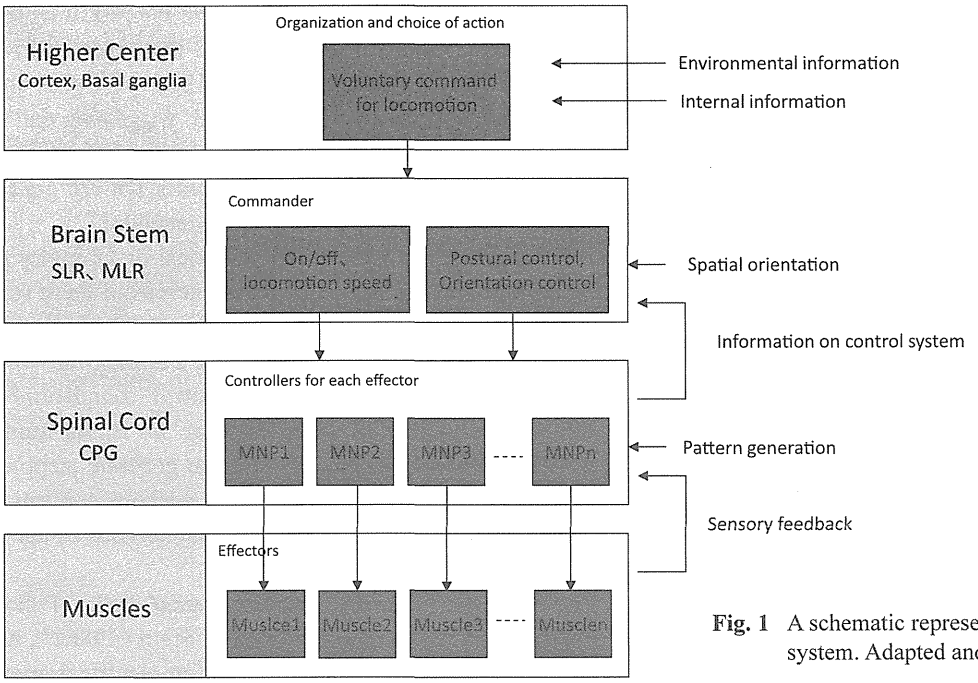

Fig. 1 A schematic representation of locomotor control system. Adapted and revised from Mori (2005).

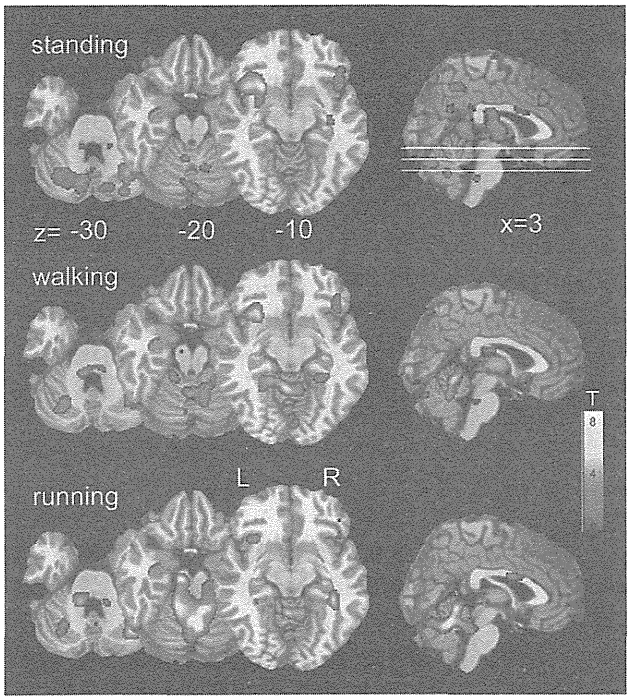

Fig. 2 Brain regions activated during mental imagery of standing, walking and running.
Cited from Jahn et al. (2008).

Evidence from transcranial magnetic stimulation. Since the noninvasive brain stimulation technique, transcranial magnetic stimulation (TMS), was developed in the late 19th century, quite a few researchers in the research area of human motor control have utilized this technique, mostly to evaluate corticospinal function or excitability in various motor tasks. During human walking, TMS can be applied if the TMS coil is adequately stabilized on the subject's head. Capaday et al. (1999) investigated the modulation of corticospinal excitability (CSE) of the human ankle muscles during treadmill walking, and found that CSE of the ankle flexor, tibialis anterior (TA), is not tuned in a parallel fashion with that of the background EMG activity[3]. They have shown that TMS induces a significantly large motor-evoked potential in the inactive TA during the stance phase of treadmill walking, suggesting that a subliminal fringe of the corticospinal tract to the TA motoneuron pool is enhanced in this phase. These observations imply that the rate of excitability in the corticospinal tract innervating the TA motoneurons is facilitated during walking compared with resting, although the EMG activity is negligible.

More recently, by using brain imaging techniques, some studies have located the brain regions that are activated during human bipedal walking. Of those studies, the technique that Hanakawa et al. (1999) used was unique in the sense that it succeeded in figuring out several brain regions activated and deactivated during normal and Parkinsonian gait, respectively[4]. The brain imaging technique they utilized was a single photon emission tomography (SPECT) scan, which is used to view how blood flows through arteries and veins in the brain. The results revealed that, during normal gait, both basal ganglia and cortical motor areas were prominently activated, which was concomitant with increased activation in the brain stem and cerebellum. Of particular interest was a notable decrease in activation in the supplementary motor area (SMA) in patients with Parkinson's disease, suggesting that the motor system, including SMA, has some relation to particular locomotor deficiencies in that particular neurological condition.

Central pattern generator (CPG). Central pattern generation is defined as the generation of oscillatory flexor and extensor ventral root outputs from the neural circuits

of the spinal cord in the absence of oscillatory input from the brain or from the periphery[5]. It has been well established that, from phylogenetically old invertebrates to mammals, central pattern generation is the common feature of the central nervous system enabling rhythmic movements or locomotion. In mammals, spinal cord neural circuitries, specifically, are known to have the ability to generate a rhythmic motor pattern. To what extent, however, the mammalian spinal cord can generate locomotion independently from the supraspinal centers has been a question that many researchers have worked on for about the last two decades. Respective insights may have significant relevance for the rehabilitation of individuals with complete and incomplete spinal cord injuries (SCI). Concerning the spinal cord of a cat, it was demonstrated, mostly in the 1990s, that the adult spinal cord can execute full weight-bearing stepping over a range of speeds, independent of supraspinal input. In humans, however, consensus is that sufficient muscular force cannot be generated by spinal neural circuits alone in order to bear body weight during stepping. At the same time, Harkema et al. (2000)reported that, "under optimal conditions of limb loading, treadmill belt speed, and appropriate kinematics, participants with clinically complete SCI could generate 3–10 consecutive steps without assistance on at least one leg" after several months of body-weight support stepping (BWSS) training. This case reported by Harkema's research group seems to be quite a rare case. In complete SCI individuals, EMG bursts of only low amplitude are known to be elicited when lower limbs are assisted in stepping by therapists or robots. Nevertheless, the finding of the patterned EMG activities induced in paralyzed human lower limb muscles was quite important, because it was regarded as the motor output generated by the interaction between spinal CPG and peripheral afferent inputs, indirectly suggesting the existence of spinal CPG in humans. Regarding human spinal CPG, several findings have been revealed, and these mostly from observations of individuals with SCI. Dietz et al. (1999)[6] have reported that the inter-muscular EMG pattern, induced in the paralyzed lower limb muscles of cervical cord-injured patients during BWSS on a treadmill, was closer to that in healthy subjects than thoracic and lumbar cord-injured patients. This observation suggests that neuronal circuits, underlying locomotor "pattern generation" in humans, are not restricted to any specific level(s) of the spinal cord; but that an intricate neuronal network contributing to bipedal locomotion extends from thoracolumbal to cervical levels. Harkema et al. (1997)[7] demonstrated in their early work that modulation of the EMG amplitude from the ankle extensors during BWSS, both across steps and within a step, was more closely associated with limb peak load than muscle-tendon stretch or its velocity. They concluded that the human spinal cord, given appropriate sensory inputs, can modulate motor pool output that may facilitate locomotion. The locomotor EMG pattern has been observed during specific gait with reciprocating long leg orthosis (Fig. 3)[8]. Modulation of the observed EMG amplitude was reported to be correlated with peak load and hip joint angular velocity as well, suggesting that afferent inputs, associated with limb load and hip joint motion, play an essential role in locomotor pattern generation from the assumed spinal pattern generator.

Using magnetic stimulation, electrical or vibratory peripheral nerve stimulation, or combinations of these stimulation modes, it has recently been demonstrated that the 'intact' human spinal cord can induce stepping-like lower limb movements in a "gravity neutral" condition[9,10]. These reports strongly suggest that the intact human spinal cord alone has the potential to generate stepping-like alternative lower limb motion without continuous descending inputs from the supraspinal nervous centers.

Reflex regulation during human bipedal walk. Following the first report of Capaday and Stein (1986)[11], amplitude modulation of the H-reflex, an electrical analog of the stretch reflex during human walking, has been extensively studied, providing evidence that the H-reflex amplitude is modulated in a phase-dependent manner. This phase-dependent modulation has been demonstrated in other reflexes, such as cutaneous and stretch reflex responses during human walking[12]. The phase-dependent nature of various reflex systems implies that the central nervous system regulates reflex excitability in a way that matches its functional requirements with respect to the walking phase. In particular regard to the stretch reflex response during human walking, Andersen and Sinkjaer (1995)[13] have developed a specific portable stretch device to induce stretches of the ankle muscles when a

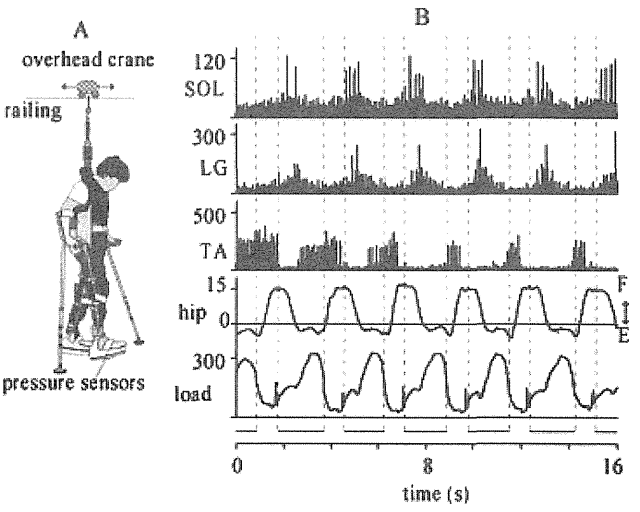

Fig. 3 A: The experimental setup to record EMG activities in lower limb muscles during the orthotic gait of a complete paraplegic subject.
B: An example of locomotor-like EMG activities, hip joint angle displacement and loading force profile under the foot during the orthotic gait. Cited from Kojima et al. (1999).

subject is walking on a treadmill. Using this device, they have demonstrated how stretch reflex EMG responses in the soleus (SOL) or TA muscles are modulated at various phases in the human walking cycle (for example see 14). Among the many findings in their series of studies, one of the noteworthy features of stretch reflex modulation was that reflexes in both the SOL and TA are facilitated at the stance phase, even though background TA activity is silent during this phase. These observations lead to the hypothesis that one of the roles of the stretch reflex function in the ankle muscles during walking would be to stiffen the ankle joint so that the joint becomes more stable. Such a stabilization would be quite important in order to ensure ankle joint support soon after the heel strike[15]. Thus, on the basis of these observations, it could be hypothesized that, when the supporting leg just after the heel strike is perturbed by removing the walkway or dropping the supportive surface, significant and sizable responses occur in both the ankle extensor and flexor muscles. To test this hypothesis, the authors developed a new experimental device that makes it possible to drop the supportive surface while a subject is walking (Fig. 4)[16]. The perturbation used in this study more closely approximated the natural disturbances occurring in everyday life than the conventional electrical or mechanical stimuli previously used to elicit reflex responses during the human walking cycle. The results showed that short-latency reflex EMG responses, after the impact of the drop (50 ms), were consistently observed in both the ankle flexor and extensor muscles in the perturbed leg (Fig. 5). Of particular interest was the distinct response that appeared in the TA muscle, although this muscle showed little background EMG activity during the stance phase. These results indicate that the reflex activities in the ankle muscles responded when the supportive surface was unexpectedly destabilized just after the heel strike while walking. These reflex responses were most probably mediated by the facilitated stretch reflex pathways of the ankle muscles at the early stance phase and were suggested to be relevant in securing stabilization around the ankle joint during human bipedal walking.

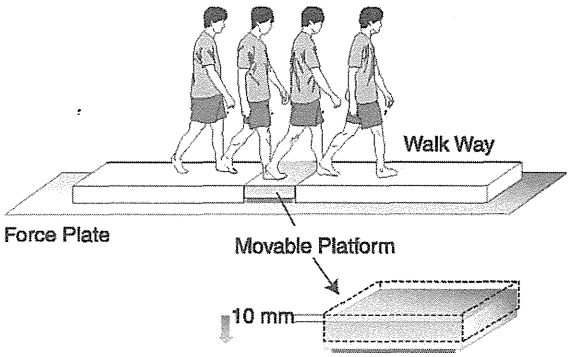

Fig. 4 The experimental setup to study EMG responses to a sudden drop of support surface during walking. The support surface of the movable platform in the middle of the walkway drops 10 mm in the early stance phase during walking. Cited from Nakazawa et al. (2004).

Neural control of human bipedal posture

Bipedal upright posture is one of the unique abilities that only human beings inherently possess. As such, the neural mechanisms of human upright posture can only be understood by studying humans, and not animals. However, it is assumed that basic neural mechanisms, for example generating postural tone in humans, are the same as those in quadruped animals. Therefore, numerous animal experiments have been conducted to reveal neural centers that play an essential role in keeping postural tone or initiating locomotion. So far, in neurophysiological experiments using cats, several nuclei in the brain stem, such as the pedunculopontine tegmental nucleus, locus coeruleus, and raphe nuclei have been found to be regions that directly increase or decrease postural tone[17]. In humans, there has been no direct evidence that the same regions in the human brain stem are active while standing, while a few brain-imaging studies have reported regions that are activated during quiet standing[18]. Novel technologies that will potentially be developed in the not too distant future may enable us to detect active regions in the human brain while maintaining upright posture.

In the following section, we will discuss studies aimed exploring the neural principle of human postural control by using biomechanical analysis, but also explore recent

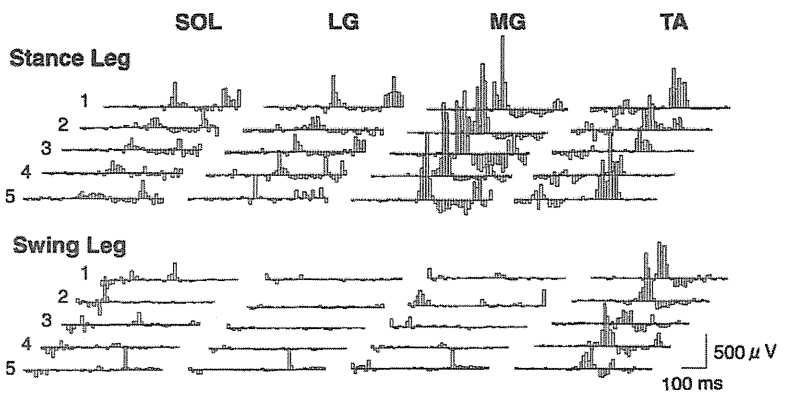

Fig. 5 Typical example of the normalized EMG responses to the drop of support surface during walking. The numbers indicate the order of perturbed trials. Cited from Nakazawa et al. (2004).

studies focusing on the involvement of the higher nervous center and modulation of local reflexes during quiet standing.

Biomechanics of human quiet standing. Human quiet standing is often approximated as a single-link inverted pendulum that pivots at the ankle joint in the sagittal plane (Fig. 6) (e.g., 19). Because the center of mass (CoM) is usually maintained in front of the ankle joints during quiet standing, gravity continuously acts on the pendulum to produce a forward toppling torque. At the same time, the ankle extensor muscles coupled to the pendulum by the series elastic elements (SEE) pull the pendulum backward to prevent it from falling. The dynamic equation of the pendulum is as follows:

$$I\ddot{\theta} = mgh\theta - T_a \quad (1)$$

where I is the moment of inertia of the body around the ankle joint; θ the CoM angle relative to the earth vertical; m the body mass (except the feet); g the gravitational acceleration; h the distance between the ankle joint and the CoM; and T_a the ankle extensor torque. *Eq. 1* indicates that disagreement between the gravitational toppling torque and the ankle extensor torque is proportional to angular acceleration of the pendulum.

Mechano-reflex hypothesis. The ankle extensor torque needed to counteract gravitational toppling torque can be evoked passively and actively[19,20]. The passive torque component arises from intrinsic mechanical properties (i.e., stiffness and/or viscosity) of muscles, aponeurosis, tendons, and other connective tissues, which act instantaneously. On the other hand, the active torque component is generated via muscle contractile elements that are regulated by neural commands.

Until the mid 1990s, it had been generally assumed, for nearly a century, that the control of human upright stance solely depended on low-level mechano-reflex mechanisms. That is, when the body swayed forward, stretched calf muscles passively generated the restoring force in a spring-like manner. If passive stiffness could not provide adequate force to counteract gravity on its own, neural reflexes provided additional force to restore the pendulum.

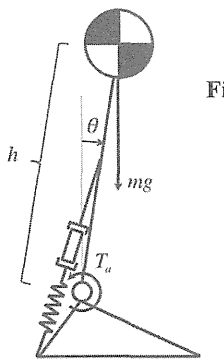

Fig. 6 Single-link inverted pendulum model of quiet standing. θ is the CoM angle relative to earth vertical; m, body mass (except the feet); g, gravitational acceleration; h, distance between the ankle joint and the CoM, and T_a, ankle extensor torque.

Stiffness control hypothesis. Winter et al. (1998)[21] argued against the above-mentioned mechano-reflex hypothesis and proposed a relatively simple control scheme for maintaining upright stance (stiffness control hypothesis). Their argument was based on the following findings: (1) the visual system does not appear to contribute to the control of upright stance; (2) the head and joint motions during quiet standing are below physiological thresholds of the vestibular and proprioceptive systems, respectively; and (3) if mechano-reflex mechanisms were present, inevitable neuromuscular transmission delays (estimated at 150 to 200 ms) would create feedback instability. The stiffness control hypothesis insists that the passive mechanical stiffness of the active calf muscles per se can provide enough force to restore the pendulum. In their theory, the intervention of the central nervous system is limited to set the appropriate tonus (elastic coefficient K) of the calf muscles. This can be possible as long as the calf muscles are stiffer than the "load stiffness" (mgh). In other words, for a given sway angle ($\Delta\theta$), the calf muscles should acquire more elastic energy by being stretched ($K\Delta\theta$) than the potential energy the pendulum loses ($mgh\Delta\theta$). Winter et al. (2001)[22] directly estimated ankle stiffness from linear regression of the ankle torque and sway angle during quiet standing; and revealed that ankle stiffness was 8.8 % larger than load stiffness.

Active, non-spring like control hypothesis. After its proposal, the stiffness control hypothesis quickly ran into problems. Criticism was initially made by Morasso and colleagues[23], who pointed out that: (1) the method of estimating ankle stiffness, proposed by Winter et al. (2001)[22], did not exclude the effect of active neural modulation; and (2) physiological values of intrinsic ankle stiffness (the word "intrinsic" means without neural modulation) were too low to prevent a forward fall of the body. Recently, two research groups investigated intrinsic ankle stiffness during quiet standing using small ankle rotations and revealed it to be 91 ± 23%[20] and 64 ± 8%[24] of load stiffness. In addition, using a system identification technique, Vette et al. (2010)[25] estimated intrinsic ankle stiffness as 83 ± 7% of load stiffness during quiet standing. Loram and Lakie (2002)[20] attributed the identified compliance to the SEE (Achilles tendon and foot) rather than the active calf muscles. When one measures the stiffness of a series arrangement of springs with different constants, the combined stiffness is smaller than the stiffness of the most compliant spring. In the situation of human quiet standing, because the compliant SEE limits the combined stiffness of the series arrangement, any constant contraction of the muscle cannot provide sufficient stiffness:

$$1/K_{total} = 1/K_{muscle} + 1/K_{SEE}\,. \quad (2)$$

In order to raise the combined stiffness (K_{total}) above the load stiffness (mgh), the muscle contractile element is predicted to behave like a "negative spring". That is,

when the body sways forward (and the muscle-tendon complex of the calf muscles, as a whole, lengthens), the muscle contractile element shortens (and vice versa when the body sways backward). Loram et al. (2005)[26] proved the validity of this prediction by tracking tiny muscular movements, occurring during unperturbed, quiet standing, with a real-time ultrasound and automated image analysis technique. Although the above-mentioned muscle movements can be produced by reflex coupling of extrafusal (EF) and intrafusal (IF) drive or the positive force feedback mechanism, in principle, Loram et al. (2005)[26] suggested that higher-level anticipatory control involving internal models is more plausible.

Involvement of the higher nervous centers in the control of human standing posture

It is technically difficult to detect specific brain regions activated while standing. However, Ouchi et al. (1999)[18] succeeded in determining the regions activated, while human subjects were keeping an upright posture, by using their mobile gantry PET (positron emission tomography) system. They reported that, as compared with the supine posture, the cerebellar anterior lobe and the right visual cortex increased cerebral blood flow levels. Jahn et al. (2008)[2] used functional magnetic resonance imaging (fMRI) to detect brain regions activated during mental imaging of standing. They reported that while imagining standing, the thalamus, basal ganglia and cerebellar vermis were activated.

There have been several studies investigating cortical involvement in the control of human standing. The excitability of the motor cortex can be investigated with transcranial magnetic stimulation (TMS). The muscular response (called the motor-evoked potential: MEP) to TMS reflects the changes in the excitability of corticospinal tract neurons (CTNs) and spinal motoneruons. In general, MEPs from TMS are compared with the responses obtained from the H-reflex or MEP from transcranial electrical stimulation (TES) in isolating the involvement of the motor cortex from the spinal and subcortical levels. TES is the method to activate the axons of corticospinal neurons directly. Using these techniques, cortical involvement in human standing posture has been investigated by some researchers. For example, Solopova et al. (2003)[27] reported an increase in SOL and TA MEP amplitude with TMS and no change in SOL H-reflex amplitude during balancing on a movable platform when compared to standing on a rigid floor. In more recent studies, Tokuno et al. (2008)[28] reported an increase in SOL and TA MEP amplitude with TMS, but no changes or decrease in SOL H-reflex amplitude or TES-evoked SOL and TA MEP amplitude during quiet standing, when compared to supported standing. Furthermore, they also reported that SOL H-reflex, SOL MEP with TMS, andSOL MEP with TES were all greater during forward sway, when compared to backward sway. These results suggest that cortical control of the ankle muscles becomes more prominent as human standing posture becomes more unstable, while postural sway is controlled at the spinal and/or subcortical levels.

Spinal reflex modulation during upright standing

The H-reflex test has been utilized as a major probe to investigate sensorimotor integration on the spinal neuronal circuits in humans while performing various motor tasks. During quiet standing, the H-reflex amplitude of the major anti-gravity muscle, soleus (SOL) is known to be suppressed compared to that while sitting, lying prone or standing with back support (e.g., 29). The decrease in SOL H-reflex was also observed when postural tasks become more challenging, such as when standing with a reduced base support or on an unstable surface[30]. It is suggested that these inhibitions during standing may help avoid excessive autogenic excitation of the SOL motoneuron and ensure receiving central descending commands. In addition, the decrease in H-reflex amplitude during standing is thought to relate to segmental and supraspinal mechanisms playing upon the SOL motoneruon. Not a few researchers suggest the involvement of descending commands as the neural origin of presynaptic inhibition. On the other hand, more recently, it has been reported that reduced SOL H-reflex in a passive standing posture is observed in patients with complete spinal cord injuries, as well as in healthy young subjects, suggesting that peripheral sensory inputs can also induce excitability changes in the SOL H-reflex without the descending command[31]. Load-related sensory information from the lower limb muscles and joints, and the sole of the foot, during standing, likely contribute to the modulation of the SOL H-reflex during standing. It has been reported that mechanical loading of the sole of the foot reduced the amplitude of the SOL H-reflex[32], whereas the SOL H-reflex was enhanced under the reduced loading condition of the ankle and knee joints[33].

Conclusion

In summary, recent advances in human gait and posture studies were summarized and discussed in this short review. Although both upright gait and posture are the most fundamental motor functions in humans, there are still many aspects that remain unanswered, especially with respect to the neural control mechanisms underlying those functions. Since studies on the neural mechanisms controlling human gait and posture are relevant to the neurorehabilitation of individuals with motor deficiencies, advances in this research field may potentially contribute to the development of novel rehabilitative interventions and assistive technologies.

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Mortality and morbidity after high-dose methylprednisolone treatment in patients with acute cervical spinal cord injury: a propensity-matched analysis using a nationwide administrative database

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ABSTRACT

Objective To examine the magnitude of the adverse impact of high-dose methylprednisolone treatment in patients with acute cervical spinal cord injury (SCI).

Methods We examined the abstracted data from the Japanese Diagnosis Procedure Combination database, and included patients with ICD-10 code S141 who were admitted on an emergency basis between 1 July and 31 December in 2007–2009. The investigation evaluated the patients' sex, age, comorbidities, Japan Coma Scale, hospital volume and the amount of methylprednisolone administered. One-to-one propensity-score matching between high-dose methylprednisolone group (>5000 mg) and control group was performed to compare the rates of in-hospital death and major complications (sepsis; pneumonia; urinary tract infection; gastrointestinal ulcer/bleeding; and pulmonary embolism).

Results We identified 3508 cervical SCI patients (2652 men and 856 women; mean age, 60.8±18.7 years) including 824 (23.5%) patients who received high-dose methylprednisolone. A propensity-matched analysis with 824 pairs of patients showed a significant increase in the occurrence of gastrointestinal ulcer/bleeding (68/812 vs 31/812; p<0.001) in the high-dose methylprednisolone group. Overall, the high-dose methylprednisolone group demonstrated a significantly higher risk of complications (144/812 vs 96/812;OR, 1.66; 95% CI 1.23 to 2.24; p=0.001) than the control group. There was no significant difference in in-hospital mortality between the high-dose methylprednisolone group and the control group (p=0.884).

Conclusions Patients receiving high-dose methylprednisolone had a significantly increased risk of major complications, in particular, gastrointestinal ulcer/bleeding. However, high-dose methylprednisolone treatment was not associated with any increase in mortality.

INTRODUCTION

Methylprednisolone is one of the most investigated agents for its neuroprotective potential, and remains the only drug used worldwide for acute spinal cord injury (SCI). The beneficial effect of high-dose methylprednisolone was initially reported in a series of National Acute Spinal Cord Injury Studies (NASCIS) in the 1990s.[1 2] Specifically, NASCIS-2 compared 24 h of high-dose methylprednisolone (given as a bolus of 30 mg/kg over 15 min followed by a continuous infusion of 5.4 mg/kg/h) with placebo in acute SCI patients.[1] Patients receiving methylprednisolone within 8 h of injury were reported to have greater neurologic improvement at 6 months. Results of NASCIS-3 further indicated slightly more recovery following 48 h of treatment than after 24 h.[2] Following publication of the NASCIS trials, the regimen of these trials was rapidly adopted worldwide; however, subsequent debate over the efficacy and safety of high-dose methylprednisolone treatment[3–5] has led to serious differences of opinion in the medical community, and considerable variations in current practice.[6–9]

According to a recent Cochrane review,[10] NASCIS-2 showed a weak trend towards an increase in complications, including wound infection (OR 2.11; 95% CI 0.81 to 5.49) and gastrointestinal haemorrhage (OR 1.48; 95% CI 0.48 to 4.56). The high-dose methylprednisolone group showed slightly lower 180-day mortality than the control group (7/162 vs 12/171; OR 0.62 95% CI 0.25 to 1.53). On the other hand, NASCIS-3, comparing 24 h and 48 h methylprednisolone administration, found a trend towards increased rates of severe pneumonia (OR 2.25; 95% CI 0.71 to 7.15) and sepsis (OR 4.00; 95% CI 0.45 to 35.38) in the 48 h treatment group. Mortality was not significantly different between the two groups.

Although many studies following the NASCIS trials reported a trend toward increased complications after high-dose methylprednisolone treatment,[11–15] the magnitude of its negative impact remains unclear. The reported incidence of complications after high-dose methylprednisolone administration varied greatly between studies, primarily because of small sample sizes and bias in selection of the study population. In addition, it is unknown whether high-dose methylprednisolone negatively affects the survival of SCI patients. Despite widespread use of this treatment, information from high-level evidence about the risks associated with high-dose methylprednisolone administration is lacking. We therefore conducted a retrospective observational study based on a propensity score-matched analysis of data from a nationwide administrative database to examine the risk of high-dose methylprednisolone treatment after acute cervical SCI.

METHODS

Diagnosis Procedure Combination database

The Diagnosis Procedure Combination (DPC) is a case-mix patient classification system which was

launched in 2002 by the Ministry of Health, Labour and Welfare of Japan, and was linked with a lump-sum payment system.[16] All 82 university teaching hospitals are obliged to adopt this system, but adoption by community hospitals is voluntary. The survey in the participating hospitals is conducted between 1 July and 31 December each year by the DPC research group, in collaboration with the Ministry of Health, Labour and Welfare. In 2009, the number of participating hospitals was 818 and the number of patients included was 2.57 million, which represented approximately 40% of all inpatient admissions to acute care hospitals in Japan. The database includes administrative claims data and the following data: unique identifiers of hospitals; patient age and sex; diagnoses, comorbidities at admission and complications after admission recorded with text data in the Japanese language and the International Classification of Diseases, 10th Revision (ICD-10) codes; consciousness level at admission measured with the Japan Coma Scale (JCS; see Appendix); discharge status; and drugs administered.[17] In the DPC database, complications that occur after admission are clearly differentiated from comorbidities that already present at admission. To optimise the accuracy of the recorded diagnoses, physicians in charge are obliged to record the diagnoses with reference to medical charts. Because of the anonymous nature of the data, informed consent was waived when this study was approved by the institutional review board at The University of Tokyo.

Patient selection and data

Using the DPC database, we identified patients who had an emergency admission to the participating hospitals with a diagnosis of cervical SCI (ICD-10 code, S141) between July and December, 2007–2009. Patients who were transferred from other hospitals were excluded. Although we were unable to confirm the presence of a neurological deficit in each patient, miscoding is relatively unlikely because the DPC data are coded by physicians and subjected to an audit. The list of drugs used during hospitalisation was reviewed for each patient, and we identified patients who started high-dose methylprednisolone treatment for acute cervical SCI at admission and received a total of ≥5000 mg methylprednisolone infusion. In Japan, many elderly patients who sustain a cervical SCI are lean. For a 40 kg person, the total dosage amounted to 6168 mg in the NASCIS-2 protocol. Therefore, we set a cut-off value of 5000 mg. As a control group, we identified cervical SCI patients who did not receive methylprednisolone, or those who received less than 500 mg methylprednisolone during hospitalisation. We selected this cut-off value according to the definition of 'high-dose' adopted by Sauerland *et al*[18] (>15 mg/kg (600 mg for a 40 kg person) or >1000 mg).

We assessed patient background, including age, sex, JCS score and Charlson Comorbidity Index (CCI). JCS 0 indicates patients with alert consciousness; JCS one-digit codes (1–3) indicate patients who are drowsy but awake without any stimuli; JCS two-digit codes (10–30) indicate patients with somnolence who can be aroused with some stimuli; JCS three-digit codes (100–300) indicate coma.[19] The JCS and the Glasgow Coma Scale assessments are well correlated. The CCI is a prognostic index as a means for quantifying the prognosis of patients enrolled in a large cohort, and is used widely to measure the case-mix with administrative data. This index is based on a point scoring system (from 0 to 40) for the presence of specific associated diseases. Quan *et al*[20] provided a validated chart showing how each comorbidity corresponds to a set of ICD-10 codes.[20] Based on Quan's protocol, each ICD-10 code of comorbidity was converted into a score, and was summed for each patient to determine CCI. Hospital volume was defined as the annual number of patients with cervical SCI at each hospital.

Clinical outcomes included in-hospital deaths and major complications (sepsis (ICD-10 codes: A40, A41), respiratory complications (pneumonia (J12-J18), postprocedural respiratory disorders (J95) or respiratory failure (J96)), pulmonary embolism (I26), gastroduodenal ulcer/bleeding (K25, K26), urinary tract infection (N10, N30, N390)).

Statistical analyses

We performed a one-to-one matching of patients in the high-dose methylprednisolone group and the control group on the basis of estimated propensity scores of each patient.[21] The propensity-score approach addresses selection bias that is inherent in retrospective observational studies, where outcomes can reflect a lack of comparability in treatment groups rather than the effects of treatment. This approach tries to construct a randomised experimental-like situation where treatment groups being contrasted are comparable for observing prognostic factors. Application of propensity-score matching involves estimation of the propensity score followed by matching of patients according to their estimated propensity score and comparison of outcomes in matched patients. To estimate the propensity score, we fitted a logistic regression model for the receipt of high-dose methylprednisolone treatment as a function of patient demographic and hospital factors, including age, sex, JCS score, CCI, receipt of cervical spinal surgery and hospital volume. The C-statistic for evaluating the goodness-of-fit was calculated. Each patient in the high-dose methylprednisolone group was matched with a patient in the control group with the closest estimated propensity on the logit scale within a specified range (≤0.6 of the pooled SD of estimated logits) to reduce differences between treatment groups by at least 90%.[21]

Descriptive statistics of the patient population included proportions to describe categorical variables and the median and IQR values to describe continuous variables. The χ^2 test was used to compare categorical data and the Wilcoxon rank sum test to compare continuous variables. Fisher's exact test was used to compare in-hospital mortality and major complication rates between the high-dose methylprednisolone group and the control group. A logistic regression analysis for major in-hospital complications was performed in the propensity score-matched patients to analyse the adjusted effects of various factors, while also adjusting for clustering of patients within hospitals using a generalised estimating equation. The threshold for significance was a p value<0.05. All statistical analyses were conducted using IBM SPSS V.19.0 (IBM SPSS, Armonk, New York, USA).

RESULTS

We identified 3508 cervical SCI patients (2652 men and 856 women; mean±SD age, 60.8±18.7 years) who had an emergency admission direct to the participating hospitals. Among them, we identified 824 (23.4%) patients who received ≥5000 mg methylprednisolone with initiation on the day of admission (high-dose methylprednisolone group). We also identified 2101 patients treated without methylprednisolone, or with <500 mg methylprednisolone during hospitalisation (the control group). By one-to-one propensity-score matching, 812 pairs of the high-dose methylprednisolone and control groups were selected. The C-statistic for goodness-of-fit was 0.630 in the propensity-score model, which suggested a moderately good fit.

Table 1 shows the patient demographics of the unmatched and propensity-matched groups. In the unmatched groups,

Table 1 Patient demographics in unmatched and propensity score-matched groups

	Unmatched group			Propensity-matched group		
	Control (n=2101)	High-dose methyl-prednisolone (n=824)	p Value	Control (n=812)	High-dose methyl-prednisolone (n=812)	p Value
Sex (males, n (%))	1570 (74.7)	645 (78.3)	0.044	650 (80.0)	634 (78.1)	0.329
Age (years, n (%))						
≤59	786 (37.4)	318 (38.6)	0.022	292 (36.0)	313 (38.5)	0.674
60–69	513 (24.4)	219 (26.6)		218 (26.8)	216 (26.6)	
70–79	456 (21.7)	198 (24.0)		213 (26.2)	195 (24.0)	
≥80	346 (16.5)	89 (10.5)		89 (11.0)	88 (10.8)	
Charlson Comorbidity Index (n (%))						
1	1414 (67.3)	456 (55.3)	<0.001	464 (57.1)	456 (56.2)	0.638
2	508 (24.2)	287 (34.8)		279 (34.4)	276 (34.0)	
≥3	179 (8.5)	81 (9.8)		69 (8.5)	80 (9.9)	
Japan Coma Scale at admission (n (%))						
0 (alert)	1811 (86.2)	689 (83.6)	0.085	692 (85.2)	681 (83.9)	0.622
1–3 (drowsy)	200 (9.5)	99 (12.0)		95 (11.7)	97 (11.9)	
10–30 (somnolence)	36 (1.7)	20 (2.4)		15 (1.8)	18 (2.2)	
100–300 (coma)	54 (2.6)	16 (1.9)		10 (1.2)	16 (2.0)	
Cervical spinal surgery	221 (10.5)	189 (22.9)	<0.001	192 (23.6)	178 (21.9)	0.408
Preoperative length of stay (days, median (IQR))	8 (1–17)	8 (1–18)	0.838	8 (2–18)	8 (1–17)	0.683
Use of tracheostomy	55 (2.6)	51 (6.2)	<0.001	38 (4.7)	48 (5.9)	0.268
Hospital volume (per year, median (IQR))	7 (4–12)	8 (4–13)	0.004	7 (4–13)	7.5 (4–13)	0.188

patients who were male, younger, or with higher CCI were more likely to receive high-dose methylprednisolone treatment. The high-dose methylprednisolone patients were admitted to hospitals of significantly higher volume than the control group. The high-dose methylprednisolone group was significantly more likely to receive cervical spinal surgery. After propensity-score matching, patient distributions were closely balanced between the high-dose methylprednisolone and the control groups.

Table 2 shows the in-hospital mortality and major complication rates in the unmatched and propensity-matched groups. Fisher's exact test in the propensity-matched groups showed no significant difference in in-hospital mortality between the high-dose methylprednisolone and control groups (2.8% vs 3.0%, p=0.884). There was a significant difference in gastrointestinal ulcer/bleeding (8.4% vs 3.8%, p=0.001) between the groups. The high-dose methylprednisolone group demonstrated a significantly higher risk of overall major complications than the control group (17.7% vs 11.8%, p=0.001). Table 3 shows the results of logistic regression analysis for the occurrence of major complications. After adjustment for the measured confounders, the high-dose methylprednisolone group was significantly more likely to have major complications than the control group (OR, 1.66; 95% CI 1.23 to 2.24; p=0.001).

DISCUSSION

In this retrospective study using a national administrative database, patients receiving high-dose methylprednisolone after cervical SCI had a significantly higher risk of complications than those without high-dose methylprednisolone treatment. A propensity score-matched analysis revealed an increased risk of gastrointestinal ulcer/bleeding and overall major complications in the high-dose methylprednisolone group. However, high-dose methylprednisolone treatment was not associated with any increase in mortality.

Strengths and weaknesses of the study

The major strength of this study is the large size of our study sample. With a study population of 3508 patients with cervical SCI, the current analysis is the largest to examine risks associated with high-dose methylprednisolone administration. Use of the

Table 2 In-hospital mortality and major complication rates in unmatched and propensity score-matched groups

	Unmatched group			Propensity-matched group		
	Control (n=2101)	High-dose methylprednisolone (n=824)	p Value	Control (n=812)	High-dose methylprednisolone (n=812)	p Value
In-hospital mortality (n (%))	71 (3.4)	23 (2.8)	0.485	24 (3.0)	23 (2.8)	0.884
Major complications (n (%))	191 (9.1)	151 (18.3)	<0.001	96 (11.8)	144 (17.7)	0.001
Respiratory complications	84 (4.0)	53 (6.4)	0.006	39 (4.8)	49 (6.0)	0.324
Urinary tract infection	52 (2.5)	29 (3.5)	0.133	32 (3.9)	29 (3.6)	0.698
Sepsis	16 (0.8)	10 (1.2)	0.273	6 (0.7)	10 (1.2)	0.330
Gastrointestinal ulcer/bleeding	66 (3.1)	71(8.6)	<0.001	31 (3.8)	68 (8.4)	<0.001
Pulmonary embolism	1 (0.05)	4 (0.5)	0.024	1 (0.1)	4 (0.5)	0.218
Length of stay (median (IQR))	16 (6–37)	27 (10–52)	<0.001	23 (8–46)	26 (10–52)	<0.001

Table 3 Logistic regression analysis of the occurrence of major complications in the propensity score-matched groups

	OR	95% CI	p
Treatment			
Control	Reference		
High-dose methylprednisolone	1.66	1.23 to 2.24	0.001
Sex			
Male	Reference		
Female	0.57	0.38 to 0.86	0.007
Age			
≤59	Reference		
60–69	1.49	1.04 to 2.12	0.029
70–79	1.81	1.26 to 2.62	0.002
≥80	2.07	1.27 to 3.39	0.004
Charlson Comorbidity Index			
1	Reference		
2	1.41	1.04 to 1.92	0.027
≥3	1.95	1.26 to 3.02	0.003
Japan Coma Scale at admission			
0 (alert)	Reference		
1–3 (drowsy)	1.51	0.99 to 2.31	0.059
10–30 (somnolence)	1.75	0.74 to 4.09	0.200
100–300 (coma)	4.55	2.06 to 10.06	<0.001
Cervical spinal surgery	1.95	1.44 to 2.64	<0.001
Hospital volume (per year)	1.01	0.99 to 1.03	0.550

DPC database, which covers approximately 40% of all acute hospitalisations in Japan, enabled us to conduct a nationwide investigation. In addition, the propensity score-matched analysis allowed us to evaluate the risks of high-dose methylprednisolone treatment while controlling for confounding variables, an assessment that prior studies have been unable to make.

Certain characteristics of the study subjects warrant mention. First, the mean age of the patients in this study was substantially higher than in other SCI studies, which may be explained by the rapid aging of our society. Currently, the geriatric population (those 65 years of age or older) accounts for approximately 23% of the Japanese population. Second, the surgery rate reported in this study was markedly lower compared with that of North American or European countries. The low surgery rate likely reflects differences in patient demographics and treatment strategy. In Japan, approximately 70% of patients sustain a cervical SCI without bone injury, such as fracture or dislocation (mostly elderly patients), and conservative treatment is recommended for these patients.

Our study has several limitations. First, as is common in studies using administrative data, coded diagnoses and outcomes are less well validated than prospective surveys. A degree of misclassification or under-reporting of outcome might have occurred in this study. Second, the DPC database does not provide important clinical data, such as severity of paralysis (ie, Frankel classification) at admission, patient disability at discharge, and cause of death. We could not confirm whether the administration of methylprednisolone conformed to the NASCIS protocol. Specifically, administrative databases such as the DPC database and National Inpatient Sample provide only limited information on the baseline neurological status, which is one of the most important factors that affect morbidity after SCI. It is possible that the high-dose methylprednisolone group included patients with more severe impairment than the control group, which would have created a bias toward overestimating the adverse effect of the high-dose methylprednisolone. Finally, although propensity-score adjustment is currently recognised as the best analytical approach for retrospective observational data, unmeasured confounders might have caused a hidden selection bias.

Comparison with other studies

Most published studies following the NASCIS trials indicated an increased overall complication rate after high-dose methylprednisolone treatment.[11–15] Regarding specific complications, pneumonia,[11–13 15] infection,[11 12] and gastrointestinal bleeding[13] are the most common complications reported in the literature, in patients receiving high-dose methylprednisolone. However, available evidence on the adverse effects of high-dose methylprednisolone is mixed, with substantial variation in reported incidences, and even conflicting results. There are several studies reporting lower complication rates in high-dose methylprednisolone groups.[22 23] Major drawbacks of these previous studies were small sample size and lack of adjustment for confounding variables, which considerably limits the validity of their conclusion.

In the present study, we first analysed the possible adverse impact of high-dose methylprednisolone treatment in SCI patients using a large nationwide database. We then performed propensity score-matched analysis to adjust for potential confounding factors. High-dose methylprednisolone was associated with a significantly higher risk of complications (17.7% vs 11.8%, p=0.001) than control after adjustment for confounding variables. Specifically, we found a significant increase in the occurrence of gastrointestinal ulcer/bleeding (8.4% vs 3.8%, p<0.001) in the high-dose methylprednisolone group.

In this study, we observed slightly lower in-hospital mortality in patients receiving high-dose methylprednisolone (2.8% in the methylprednisolone group vs 3.0% in the control group after propensity-score matching). The impact of high-dose methylprednisolone on patient survival remains unclear. The CRASH trial,[24] a randomised trial which examined the efficacy of high-dose methylprednisolone in the treatment of head injury patients, was prematurely terminated because of increased 2-week mortality in the high-dose methylprednisolone group (21.1% vs 17.9%). However, it remains to be determined whether these findings are generalisable to patients sustaining acute SCI. In fact, reported mortalities in SCI patients in the literature have been slightly more favourable in those with high-dose methylprednisolone treatment,[12 15 23] although sample bias played a substantial role. Similarly, a meta-analysis[18] of 51 randomised trials of high-dose methylprednisolone in elective and trauma surgery found reduced mortality compared with controls (1.7% vs 2.7%), although it was not statistically significant. In our propensity score-matched analysis, no significant difference in mortality was observed between the groups in spite of a significant increase in complication rate in patients receiving high-dose methylprednisolone, which may be partly attributable to advances in intensive care and increased physician awareness of steroid-related complications.

Implications for future research

We believe that the findings of our study will provide a basis for future research to re-examine the net benefit of high-dose methylprednisolone treatment described in the NASCIS trials. The main criticism of the NASCIS trials is two-fold: (1) there was no significant difference in the primary comparison; a significant but small benefit (ie, five points in motor score) was found only after posthoc subgroup analysis; (2) there was a trend toward an increase in adverse events, including

pneumonia, infection and gastrointestinal bleeding in patients receiving high-dose methylprednisolone. For the reasons stated above, current guidelines classify this treatment only as a therapeutic 'option', leaving the decision to adopt or avoid this treatment up to individual physicians. Despite the apparent need for a randomised study of better design with sufficient power to examine whether the beneficial effect of high-dose methylprednisolone is reproducible, no such study has been conducted mainly because of ethical and safety concerns. With a dearth of effective alternative therapeutic options, we believe that a strong case exists for a randomised placebo-controlled trial re-examining the potential benefit of high-dose methylprednisolone in patients sustaining SCI. The results of our study showed that high-dose methylprednisolone treatment was not associated with any increase in in-hospital mortality, despite a significant increase in complications, a finding that further justifies future randomised trials in carefully selected patient population. To minimise the heterogeneity of the study population, future trials should focus on patients with incomplete SCI, in whom a beneficial effect was observed in the NASCIS trial. According to an estimate by the International Campaign for Cures of Spinal Cord Injury Paralysis,[25] it would require about 450 subjects with incomplete motor cervical SCI in each arm of the study to show a statistically significant difference of five American Spinal Injury Association motor points between the experimental and control groups. It would clearly require a multi-institution collaboration to carry out this project.

CONCLUSION

Despite controversies lingering for more than two decades since the publication of the NASCIS trial, risks and benefits of high-dose methylprednisolone treatment remain unclear with limited high-level evidence. In this study, we focused on safety concerns of high-dose methylprednisolone treatment, and first clarified the magnitude of its adverse impact by using a large nationwide database. There was a significantly increased risk of major complications, in particular, gastrointestinal ulcer/bleeding, with high-dose methylprednisolone, but no increase in in-hospital mortality. We believe that the findings of our study provides critical information on the risks associated with high-dose methylprednisolone administration in patients with SCI, and thus, may help physicians make a more informed decision on the use of this highly controversial treatment.

Contributors HC, HY, KT, HK and ST contributed to the conception and design of the study. HH, KO, KF contributed to the analysis, and all authors contributed to the interpretation. HC drafted the article; all authors revised it critically for important intellectual content and approved the final version submitted for publication. HC is the guarantor. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) none has company support for the submitted work; (2) the authors have no relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) their spouse, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) the authors have no non-financial interests that may be relevant to the submitted work.

Ethics approval The Institutional Review Board at The University of Tokyo approved the study.

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Appendix Japan Coma Scale for grading of impaired consciousness[19]

Grade	Consciousness level
1-digit code	The patient is awake without any stimuli, and is:
1	Almost fully conscious
2	Unable to recognise time, place and person
3	Unable to recall name or date of birth
2-digit code	The patient can be aroused (then reverts to previous state after cessation of stimulation):
10	Easily by being spoken to (or is responsive with purposeful movements, phrases, or words)*
20	With loud voice or shaking of shoulders (or is almost always responsive to very simple words like yes or no, or to movements)*
30	Only by repeated mechanical stimuli
3-digit code	The patient cannot be aroused with any forceful mechanical stimuli, and:
100	Responds with movements to avoid the stimulus
200	Responds with slight movements including decerebrate and decorticate posture
300	Does not respond at all except for change of respiratory rhythm

'R' and 'I' are added to the grade to indicate restlessness and incontinence of urine and faeces, respectively: for example; 100-R and 30-RI.
*Criteria in parentheses are used in patients who cannot open their eyes for any reason.

教育総説

Review-Essentials

脊髄損傷後の歩行機能回復に向けた新しいビジョン —神経の再生・修復から機能回復まで—

A New Approach for the Restoration of Locomotor Function after Spinal Cord Injury

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歩行機能回復
脊髄 CPG

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はじめに

神経科学領域の近年の研究成果により，従来可塑的性質をもたないと考えられていた脊髄内の神経回路網がかなりの範囲でその機能を回復できることが明らかになってきた．Raineteau と Schwab[1]は，*Nature Review Neuroscience* 誌に寄せた総説論文の中で上記の脊髄可塑性に関し，受傷後の神経線維自体の可塑性（anatomical plasticity）と感覚刺激の繰り返し入力による可塑性（synaptic plasticity あるいは use-dependent plasticity）を分けて論じている（**Fig. 1**）．近年盛んに研究されている脊髄神経再生についての研究は医学的・解剖学的視座から前者を実現しようとする試みである一方で，歩行機能回復のためのリハビリテーションは機能的視座から後者を主眼に捉えた試みと位置づけることができる．本稿では，近年の神経科学・医学領域の進歩に呼応する形で今後大きな変化をみせるであろう脊髄損傷後のリハビリテーションについて，神経の再生・修復から歩行機能回復までを包括的視点から捉え，その全体像について概説する．

1．脊髄神経の再生と修復

脊髄再生研究の端緒ともいえる Aguayo ら[2]のラット脊髄切断モデルに対する肋間神経のケーブルグラフト移植の報告以来，脊髄再生の大きなテーマは皮質脊髄路の再建であった．動物実験でも再生の証明は主として皮質運動野に神経トレーサーを注入し，それが損傷部を超えて尾側で同定されるか，という組織学的検討がなされた．このような基礎研究の中で，皮質脊髄路の再生を阻害する要因の同定や，ニューロン自体を活性化する介入方法開発が進められ，中でも軸索再生阻害因子として同定された Nogo に対する抗体療法はすでにヨーロッパでの臨床治験が開始されている[3]．

また，損傷部に細胞を補うことで再生を誘導するいわゆる移植療法の研究も，iPS 細胞の発見と相まって近年目覚ましい成果を上げている．iPS 細胞の利用方法についてはいくつかの手法が考えられるが，その 1 つはあらゆる組織の細胞になりうる iPS 細胞を神経系統の幹細胞「神経幹細胞」まで誘導し，これを損傷部に移植する方法である．移植された細胞はニューロンおよびグリア（オリゴデンドロサイト・アストロサイト）に分化することで機能回復に寄与することが知られている[4]．神経線維の再構築という観点からは移植治療は 2 つの効果をもつと現時点では考えられている．1 つは移植された細胞がグリア系に分化し皮質脊髄路など long tract の再生の足場となって働く作用（**Fig. 2**①）で，もう 1 つはニューロンに分化し，これが脳からの神経線維とシナプスを形成し，そこから尾側へ新たな神経線維を伸ばし下肢機能を制御するという作用である（**Fig. 2**②）．臨床的な再生医療のトピックスとして，2012 年度から先進医療として大阪大学で開始された慢性期脊髄損傷に対する自家嗅粘膜組織移植が知られる[5]．これも嗅粘膜組織内に豊富に存在するグリア細胞を移植することで脊髄の下降路を再建することを意図したものと位置づけられる．

2．神経線維の再生と機能回復

こうした皮質脊髄路の再生誘導研究では，その多くでモデル動物において良好な後肢の運動機能回復が報告さ

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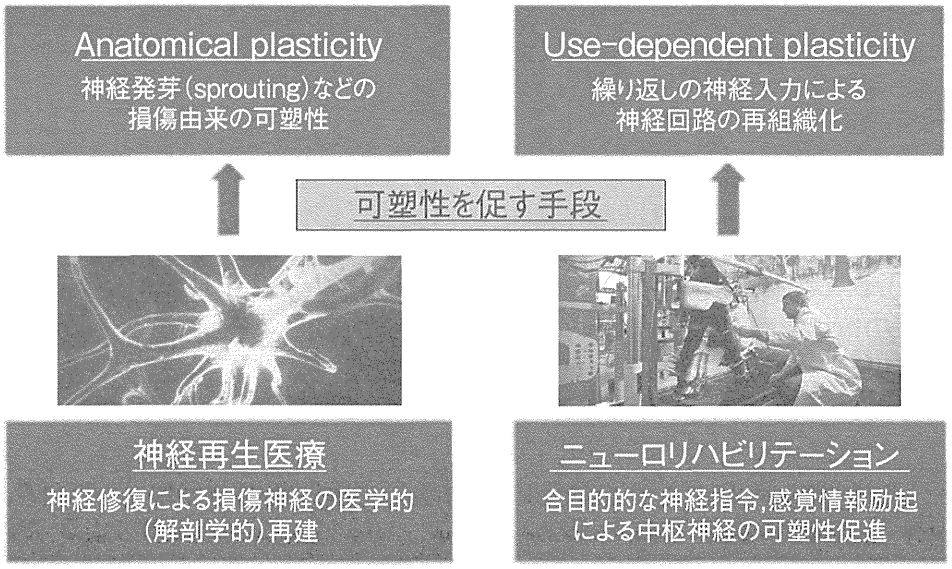

Fig. 1　2つの可塑性についての知見をベースとした歩行機能再獲得のための具体的戦略

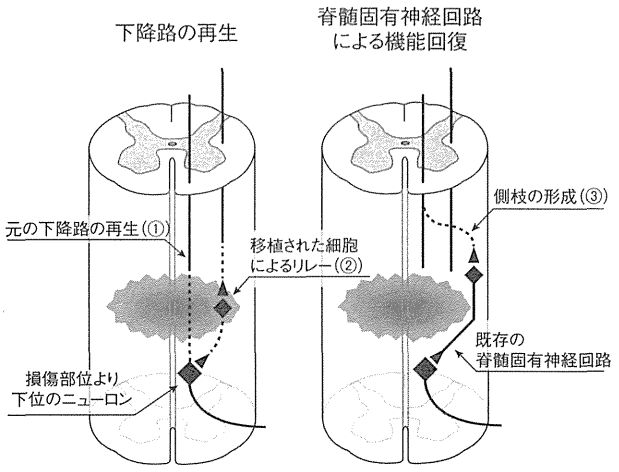

Fig. 2　脊髄再生において想定される再生パターン
脳と脊髄前角の運動ニューロンをつなぐ経路の再生には，下降路が損傷部を超えて再生するメカニズムが考えられる（①，②）．一方で，再生神経線維（点線）が損傷部を超えなくても既存の脊髄内回路とそこへの側枝形成により機能回復が得られる可能性が報告されている（③）．

れているが，その一方で実際にどのような回路形成が機能回復につながったのか，という検証はまだ十分には進んでいない．末梢神経再生の場合は損傷の遠位側に細胞外マトリックスによるチューブ状の構造が残存しており，再生線維はそれに沿って進むことで，ターゲットである神経筋接合部に到達すると考えられている．一方で，脊髄には末梢神経のようなガイドとなるマトリックス構造はないため，損傷部を超えて再生した皮質脊髄路の線維がもとのターゲットである腰膨大部の脊髄前角ニューロンまで到達するのは容易でないことが想像される．したがって，皮質脊髄路が再生した場合であっても損傷遠位部では新たな神経回路が構築される必要があり，このことは移植細胞が神経伝達を中継するニューロンとして働く場合でも同様である．

一方で，損傷部を超える軸索再生がなくても機能回復が得られるとするモデルも提唱されている．マウスの脊髄において脳からの下降路を左右異なるレベルで切断した場合，切断部における再生がなくても後肢機能が回復するという現象が報告されている[6]．この回復過程には皮質→脊髄の経路ではなく，脊髄→脊髄の経路が関与することがわかっている．すなわち，もともと損傷を逃れて残存していた脊髄→脊髄経路（脊髄固有神経：propriospinal neuron）が損傷部頭側領域で皮質脊髄路から新たな入力を受け，一方で損傷部尾側では脊髄前角ニューロンあるいは歩行に関連する神経回路に信号を伝えることとなる（**Fig. 2** ③）．この際の新しい経路は側枝の伸長（sprouting）と呼ばれ，そのメカニズムは損傷部を超える神経再生とは別個に考えられる．さらに，こうした側方向の新たな神経結合が，新たな神経線維（側枝）の形成によるものか（解剖学的な再構築），既存の結合の強化によるものか（機能的な再構築），を厳密に判定することは容易ではない．

このように，脊髄損傷後に神経線維が再生したとしても，実際の機能回復につながるためには機能を有する神経回路を形成する必要がある．そして機能的な神経回路を再組織化しようとするプロセスにおいて放出される神経栄養因子や，シナプス結合の強化といった現象自体が神経線維の再生に関与している可能性もあり，解剖学的

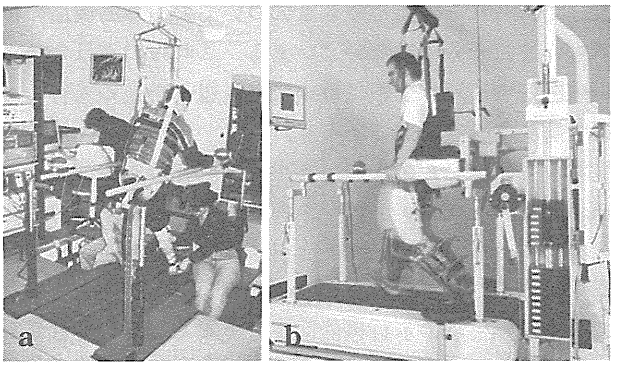

Fig. 3　理学療法士による徒手補助（a）およびロボティクス（b）による免荷歩行トレーニング

Fig. 4　脊髄 CPG の活動に影響する 2 つの求心性感覚情報

な再構築と機能的な再構築は密接な関係にあるという理解が妥当であろう．

したがって，脊髄損傷者の歩行機能回復を考える場合には，神経線維の再生誘導と神経回路再構築の誘導をバランスよく考慮する必要がある．皮質からの指令による運動が障害されている状態において神経回路の再組織化を誘導する 1 つの方法として，目的の運動に関連した感覚入力を加える手法があり，歩行機能訓練においては受動的歩行訓練（ステッピング運動）が臨床現場においても実践されてきた．次節ではこの方法について概説する．

3．脊髄神経回路の可塑性と歩行機能回復

他動的な体肢の動作（歩行を企図するならばステッピング運動）によって繰り返し生じる刺激-応答サイクルは，脊髄を中心とした歩行運動出力を発現させる神経回路を活性化し，中長期的なトレーニングの実施によって歩行能力改善の方向に誘導される，と考えられる[7]．換言すれば，免荷歩行トレッドミルトレーニングや各種ロボティクスによる歩行リハビリテーションは，繰り返しの神経入力によってもたらされる神経可塑性（use-dependent plasticity）を理論的背景とした神経リハビリテーション方法の 1 つとして位置づけることができよう．

脊髄損傷者の場合，麻痺領域への随意指令が残存している不全損傷者では脊髄より上位の中枢神経と脊髄間の連絡がわずかであっても残存しているため，歩行の基本的リズム発現を担う脊髄中枢パターン発生器（central pattern generator：CPG）の活動惹起とともに，脳と脊髄の間の機能的結合，高位中枢そのものの歩行に関連した神経活動の改善が想定できる．一方，脊髄完全損傷者に関していえば，ステッピング運動を行わせることで脊髄 CPG の活動を惹起できたとしても，現時点では歩行トレーニングを実施しても歩行機能を再獲得できる可能性は皆無に近い．しかし，動物実験において脊髄神経再生の実現可能性を膨らませるいくつかの有力な研究成果が得られている現状を考えれば，脊髄再生医療の実現を念頭に置いた先見的な研究はきわめて高い意義をもつものと考えられる．脊髄神経の再生は，神経の組織解剖学的な再建に加えて立位・歩行を含む機能面での回復を実現してこそ成功といえることから，神経修復についての研究の進歩に呼応して，修復後の効果的なリハビリテーション方法の検索に関しても多くの目が注がれるべきである．

4．免荷歩行トレーニングの理論と方法

体重を部分的に軽減したうえで補助者や装置による両脚のステッピング運動をアシストする，免荷歩行トレーニング（body weight supported treadmill training）は，歩行機能回復に有効な方法として広く認識されている．**Fig. 3 a** に示す例では，ハーネスを上方より牽引することで脊髄損傷者の体重を部分的に免荷したうえでトレッドミルに立たせ，理学療法士がベルトスピードに合わせて麻痺下肢の動作を補助し，他動的に左右交互のステッピングを行わせている．この免荷トレッドミルトレーニングは，荷重を支えるための過剰な筋活動や注意配分を免荷によって最小限に抑え，下肢のステッピング運動が表出しやすくなるようにする狙いがある．歩行中の立脚-遊脚期の切り替わりに伴う下肢への荷重，股関節の屈曲-伸展動作は，歩行機能の回復にきわめて重要である（**Fig. 4**）．なぜなら，脚全体に加わる荷重情報と股関節の伸展に関わる感覚情報は脊髄 CPG の活動を惹起するための最も重要な入力信号だと考えられているためで

ある[8~10]．受動的ステッピング運動中には多くの感覚受容器が刺激され，歩行運動の位相に応じた求心性感覚情報が，脊髄歩行中枢の活動を高めることになる[7,9,10,12,13]．脊髄不全損傷者を対象とした歩行リハビリテーションの効果を検証した大規模な無作為化比較試験（randomized controlled trial：RCT）によると，従来より行われてきた平行棒やロフストランド杖などを用いた歩行，免荷歩行という方法の違いによらず，歩行リハビリテーションを行うことで脊髄不全損傷者の多くが歩行能力改善の可能性をもつことが示されている[14~16]．

免荷歩行トレーニングでは，1人の患者に対し，2人以上の理学療法士が必要となる．さらに，ステッピング動作の補助はかなりの労力が必要であり，1人の理学療法士が続けて何人もの患者の補助をすることは現実的に不可能である．動力歩行装置 Lokomat（Hocoma 社，スイス：**Fig. 3 b**）はこれらの問題点，臨床場面での制約を克服するために，療法士によるステッピング補助を動力補助に代行させるべく開発されたものである[17]．Lokomat の基本機構は長下肢装具の膝と股関節部分に動力機構を取りつけた装具部，トレッドミル上に固定する固定部，および装具の動きを制御するコンピューターから成る．これらを免荷装置およびトレッドミルと組み合わせることで，これまで人間の手で行っていたステッピングの補助を，機械を用いて代替することが可能となった．さらに，補助者の疲労という制限因子が克服されたため，徒手では困難であった長時間のトレーニングも可能となった．Lokomat は装置自体の有用性や基本的なリハビリテーション効果についての検証段階は終えており，すでに世界数カ国の施設間ネットワークの中で臨床試験を行っている．今後テクノロジーの発達とともに，同様の機器開発がますます加速されるのは必然的流れであろう．

5．脊髄損傷者の歩行機能再獲得に向けて

再生誘導などの方法を用いて脊髄損傷により途絶されていた神経をつなげることができたとしても，無数ある，異なる特性をもった神経線維がもとのように整然とつながれることは困難である．損傷部周辺の解剖学的再建がもたらす結果は，随意指令，感覚情報の伝達といったプラスの側面だけではなく，痛みやしびれなどの感覚，交感神経系の過剰反応などが発現する可能性も孕んでいる．神経再生そのものの実現可能性に焦点が当てられている現時点では，合併症やリスクについての検証（とりわけ動物実験で検証不可能な，ヒト対象の実証研究）にまで十分な視点が注がれておらず，侵襲的治療介入によって得られる効果とリスクについての倫理的側面の検討もいまだ十分ではないといえる．これらの点は今後，再生医療の実現を念頭に置いた取り組みを進めて行くうえで解決すべき課題であろう．

本稿で概説したように，再生医療研究の成果によって anatomical plasticity が実現された後に，繰り返しの神経入力によって use-dependent plasticity（機能回復）を目指す神経リハビリテーションの取り組みが呼応することで，脊髄損傷者の歩行機能回復を実現できる可能性が高まりつつある．多くの患者さんが歩行機能の再獲得に高い願望をもっていることからうかがい知れるように，歩行能力の低下・喪失がもたらす身体的，社会的，心理的影響はきわめて大きい．それだけに，患者さん方の多くがこれまで以上に再生医療に対する期待をもつことは必然であろうし，それとともに社会全体の要請に変わっていくだろう．現状，再生医療が現実的な可能性をどの程度もっているのかということ自体，医療従事者であっても正確に判断するための情報が不足している．したがって，これまで得られている情報の集約的な整理，各分野が向かうべき指針を明確化し，anatomical plasticity を目指す立場と，use-dependent plasticity を目指す立場の双方が相互不可分な取り組みによって，患者さんの機能回復に向かって足並みをそろえることが求められる．再生医療というと兎角，次世代のものというように捉えられがちであるが，臨床現場で行われている機能回復のためのリハビリテーションは，とりもなおさず use-dependent plasticity を理論的背景としており，また，再生誘導後の機能回復の可能性を広げる意味では，合併症や二次障害を最小限に抑止するという現行のリハビリテーションアプローチそのものが，これまで以上に重要な意義をもつことが予想される．したがって，リハビリテーション現場においても，再生医療の可能性を模索しつつ，現在の治療介入，方法のもとで，機能回復が最大限にどの程度見込むことができるのかを問うような試みが必要と思われる．

再生医療による解剖学的な再構築は，現行のリハビリテーションの効果を底上げする位置づけにあり，これまで機能回復訓練の対象とならなかった患者さんを，その対象に含ませる方向に導くものとも捉えられる．したがって，再生医療が今後，現実的に歩を進めていくとすれば，リハビリテーション領域にもこれに呼応したパラダイムシフトが訪れるだろう．

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TRIALS

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Optimal treatment for Spinal Cord Injury associated with cervical canal Stenosis (OSCIS): a study protocol for a randomized controlled trial comparing early versus delayed surgery

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Abstract

Background: The optimal management of acute cervical spinal cord injury (SCI) associated with preexisting canal stenosis remains to be established. The objective of this study is to examine whether early surgical decompression (within 24 hours after admission) would result in greater improvement in motor function compared with delayed surgery (later than two weeks) in cervical SCI patients presenting with canal stenosis, but without bony injury.

Methods/design: OSCIS is a randomized, controlled, parallel-group, assessor-blinded, multicenter trial. We will recruit 100 cervical SCI patients who are admitted within 48 hours of injury (aged 20 to 79 years; without fractures or dislocations; American Spinal Injury Association (ASIA) grade C; preexisting spinal canal stenosis). Patients will be enrolled from 36 participating hospitals across Japan and randomly allocated in a 1:1 ratio to either early surgical decompression (within 24 hours after admission) or delayed surgery following at least two weeks of conservative treatment. The primary outcomes include: 1) the change from baseline to one year in the ASIA motor score; 2) the total score of the Spinal Cord Independence Measure and 3) the proportion of patients who are able to walk without human assistance. The secondary outcomes are: 1) the health-related quality of life as measured by the Medical Outcomes Study Short Form 36 and the EuroQol 5 Dimension; 2) the Neuropathic Pain Symptom Inventory and 3) the walking status as evaluated with the Walking Index for Spinal Cord Injury II. The analysis will be on an intention-to-treat basis. The primary analysis will be a comparison of the primary and secondary outcomes one year after the injury.

Discussion: The results of this study will provide evidence of the potential benefit of early surgical decompression compared to the current 'watch and wait' strategy.

Trial registration: UMIN000006780; NCT01485458

Keywords: Spinal cord injury, Surgery, Timing, Canal stenosis, Ossification of the posterior longitudinal ligament, Spondylosis, Spinal fracture, Bone injury

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Background

Acute cervical spinal cord injury (SCI) is one of the most devastating conditions, and can lead to paralysis, sensory impairment and bowel, bladder and sexual dysfunction. In addition, patients frequently suffer from intractable pain caused by neural damage. Individuals with cervical canal stenosis are known to develop cervical SCI even after minor trauma. Cervical canal stenosis may be congenital, but often results from degenerative conditions, such as spondylosis. The SCI patients with canal stenosis are mostly elderly, and usually present with incomplete SCI without bone injury, such as spinal fracture or dislocation. This subgroup of patients has been steadily increasing as the society ages and currently accounts for over 60% of cervical SCIs in Japan [1].

The clinical outcome of patients with incomplete SCI has been considered to be favorable, since patients usually show spontaneous neurologic recovery to some extent. However, the neurological prognosis varies greatly among patients; about half of ASIA C patients remain non-ambulatory six months after the injury [2]. In particular, the clinical outcomes of elderly patients are often suboptimal [3,4]. Therefore, a therapeutic option that leads to a better clinical outcome is urgently needed.

Controversy exists with regard to the efficacy of surgical decompression in the treatment of cervical SCI with preexisting canal stenosis [5,6]. The role of surgery remain unclear, especially in the absence of instability of the cervical spine [7], thus resulting in a significant difference in practice between institutions. A common approach to treating these patients has been to rule out acute instability and then observe the patients' spontaneous neurological recovery until they achieve a neurological plateau, and only then consider the possibility of surgical decompression, weeks after the initial injury [6]. Our previous retrospective multicenter study showed that the time from injury to surgery was approximately two weeks (median 13.5 days) [8].

The main drawback of this 'watch and wait' strategy is that a potential therapeutic window in the acute phase might be missed. The current concept of the pathophysiology of SCI classifies the spinal damage into two stages: primary injury and secondary injury [9]. The primary injury results from the mechanical forces delivered to the spinal cord at the time of the trauma. Secondary injury is a cascade of pathophysiological events including edema, ischemia, inflammation and apoptosis following the initial impact, which develops within minutes to hours following the trauma. There is a growing body of evidence from preclinical or animal studies that early surgical decompression alleviates 'secondary injury' and thus results in enhanced neurological and functional recovery [5].

Although numerous studies have been performed to examine the potential benefit of early surgery, the results of these prior clinical studies were mixed, and failed to provide robust support for the hypothesis that early surgery leads to improved outcomes. One small randomized trial of 42 patients showed no benefit to early (< 72 hours) decompression [10]. On the other hand, a meta-analysis of case series showed that early (< 24 hours) decompression was associated with better outcomes compared to both delayed (> 24 hours) and conservative treatment [11]. The results of STASCIS, one of the largest prospective studies of 313 patients, were also in favor of early surgery [12]. The authors of that study reported that early surgery, within 24 hours after injury, is associated with an improved neurological outcome, defined as at least a two grade ASIA Impairment Scale (AIS) improvement at the six-month follow-up examination. However, the difference in the chance of experiencing a one grade AIS improvement between early versus late surgery was not statistically significant.

With such conflicting information in the literature and a lack of high-quality evidence, it remains unclear whether early surgical decompression would result in better neurological and functional recovery. To address this issue, we launched the OSCIS study (Optimal treatment for Spinal Cord Injury associated with cervical canal Stenosis), a randomized, controlled, multicenter trial, in which we will compare the two strategies: early surgery within 24 hours after admission and delayed surgery following at least two weeks of conservative treatment.

Methods/design

Trial design

The OSCIS study is a randomized, controlled, parallel-group, assessor-blinded, multicenter study. Patients will be randomly allocated to undergo either early surgery or delayed surgery. The aim of this study is to test the hypothesis that early surgery (within 24 hours after admission) will lead to greater improvements in the motor function compared to delayed surgery (later than two weeks after injury) in patients with acute cervical SCI associated with canal stenosis. The flowchart shown in Figure 1 provides a visual description of the study.

Participants

Subjects will be recruited from 36 hospitals in Japan. The list of the participating hospitals with approval from local ethical boards is available as Additional file 1. We will screen all patients with acute traumatic cervical spinal cord injury (at C5 or below) who are admitted to one of the institutions within 48 hours after the injury. The diagnosis of cervical spinal cord injury will be made on the patient's history, including physical and neurological examinations, and the results of imaging studies,