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.

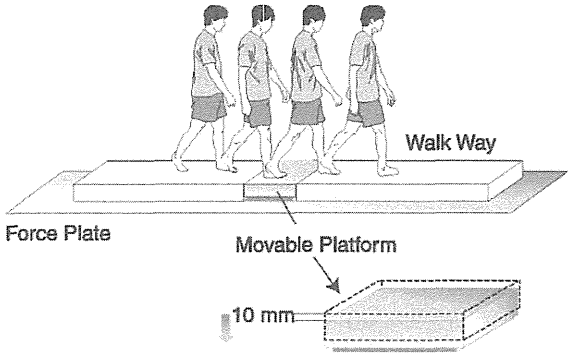

Fig. 4 The experimental setup to study EMG responses to a sudden drop of support surface during walking. The support surface of the movable platform in the middle of the walkway drops 10 mm in the early stance phase during walking. Cited from Nakazawa et al. (2004).

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

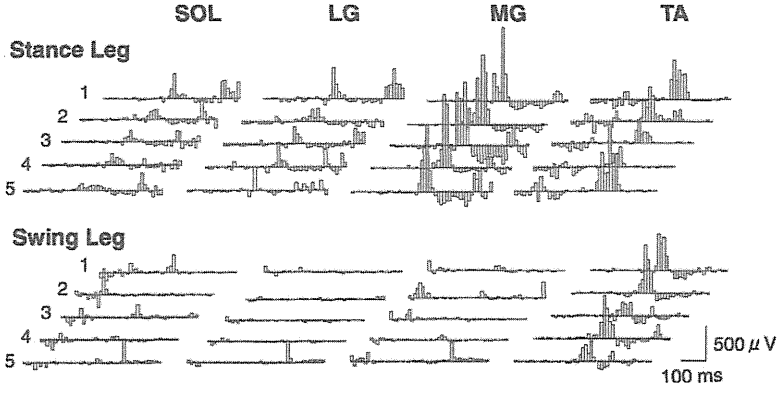

Fig. 5 Typical example of the normalized EMG responses to the drop of support surface during walking. The numbers indicate the order of perturbed trials. Cited from Nakazawa et al. (2004).

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:

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

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.

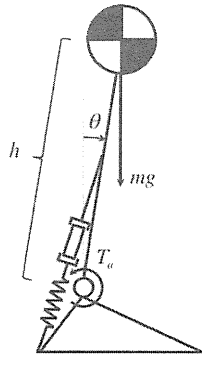

Fig. 6 Single-link inverted pendulum model of quiet standing. θ is the CoM angle relative to earth vertical; m, body mass (except the feet); g, gravitational acceleration; h, distance between the ankle joint and the CoM, and T_a, ankle extensor torque.

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:

$$1/\mathrm{K}_{total} = 1/\mathrm{K}_{muscle} + 1/K_{SEE}\,. \qquad (2)$$

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.

Acknowledgements

The authors would like to thank Dr AH Vette for his helpful comments and correcting the English.

References

1) Mori S. 2005. Mechanisms of human bipedal walk and its aging. *Geriatric Medicine* 43: 7-14 (in Japanese).
2) Jahn K, Deutschländer A, Stephan T, Kalla R, Wiesmann M, Strupp M, Brandt T. 2008. Imaging human supraspinal locomotor centers in brainstem and cerebellum. *Neuroimage* 39: 786-92.
3) Capaday C, Lavoie BA, Barbeau H, Schneider C, Bonnard M. 1999. Studies on the corticospinal control of human walking. I. Responses to focal transcranial magnetic stimulation of the motor cortex. *J Neurophysiol* 81: 129-139.
4) Hanakawa T, Katsumi Y, Fukuyama H, Honda M, Hayashi T, Kimura J, Shibasaki H. 1999. Mechanisms underlying gait disturbance in Parkison's disease: A single photon emission computed tomography study. *Brain* 122: 1271-1282.
5) Harkema SJ, Dobkin BH, Edgerton VR, Pattern. 2000. Generators in Locomotion: Implications for Recovery of Walking After Spinal Cord Injury. *Top Spinal Cord Inj Rehabil* 6: 82-96.
6) Dietz V, Nakazawa K, Wirz M, Erni T. 1999. Level of spinal cord lesion determines locomotor activity in spinal man. *Experimental Brain Research* 128, 405-4099.
7) Harkema SJ, Hurley SL, Patel UK, Requejo PS, Dobkin BH, Edgerton VR. 1997. Human lumbosacral spinal cord interprets loading during stepping. *J Neurophysiol* 77: 797-811.
8) Kojima N, Nakazawa K, Yano H. 1999. Effects of limb loading on the lower-limb electromyographic activity during orthotic locomotion in a paraplegic patient. *Neurosci Lett* 274: 211-213.
9) Gerasimenko Y, Gorodnichev R, Machueva E, Pivovarova E, Semyenov D, Savochin A, Roy R R, Edgerton V R. 2010. Novel and direct access to the human locomotor spinal circuitry. *J Neurosci*. 30: 3700-3708.
10) Courtine G, Gerasimenko Y, van den Brand R, Yew A, Musienko P, Zhong H, Song B, Ao Y, Ichiyama RM, Lavrov I, Roy RR. Sofroniew MV, Edgerton VR. 2009. Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. *Nat Neurosci*. 12: 1333-1342.
11) Capaday C and Stein RB. 1986. Amplitude modulation of the soleus H-reflex in the human during walking and standing. *J Neurosci* 6: 1308-1313.
12) Zehr EP and Stein R. 1999. What functions do reflexes serve during human locomotion? *Prog Neurobiol* 58: 185-205.
13) Andersen JB, Sinkjaer T. 1995. An actuator system for investigating electrophysiological and biomechanical features around the human ankle joint during gait. *IEEE Trans Rehabil Eng* 3: 299-306.
14) Christensen LO, Andersen JB, Sinkjaer T, and Nielsen J. 2001. Transcranial magnetic stimulation and stretch reflexes in the tibialis anterior muscle during human walking. *J Physiol* 531: 545-557.
15) Christensen LOD, Petersen N, Andersen JB, Sinkjaer T, Nielsen JB. 2000. Evidence for transcortical reflex pathways in the lower limb of man. *Prog Neurobiol* 62: 251-272.
16) Nakazawa K., Kawashima N, Akai M, Yano H. 2004. On the reflex co-activation of ankle flexor and extensor muscles induced by a sudden drop of support surface during walking in humans. *J Appl Physiol* 96: 604-611.
17) Takakusaki K, Habaguchi T, Ohinata-Sugimoto J, Saitoh K, Sakamoto T. 2003. Basal ganglia efferents to the brainstem centers controlling postural muscle tone and locomotion: a new concept for understanding motor disorders in basal ganglia dysfunction. *Neuroscience*119: 293-308.
18) Ouchi Y, Okada H, Yoshikawa E, Nobezawa S, Futatsubashi M. 1999. Brain activation during maintenance of standing postures in humans. *Brain* 122: 329-338.
19) Sasagawa S, Ushiyama J, Masani K, Kouzaki M, and Kanehisa H. 2009. Balance control under different passive contributions of the ankle extensors: quiet standing on inclined surfaces. *Exp Brain Res* 196: 537-544.
20) Loram ID, and Lakie M. 2002. Direct measurement of human ankle stiffness during quiet standing: the intrinsic mechanical stiffness is insufficient for stability. *J Physiol* 545: 1041-1053.
21) Winter DA, Patla AE, Prince F, Ishac M, and Gielo-Perczak K. 1998. Stiffness control of balance in quiet standing. *J Neurophysiol* 80: 1211-1221.
22) Winter DA, Patla AE, Rietdyk S, and Ishac MG. 2001. Ankle muscle stiffness in the control of balance during quiet standing. *J Neurophysiol* 85: 2630-2633.
23) Morasso PG, and Schieppati M. 1999. Can muscle stiffness alone stabilize upright standing? *J Neurophysiol* 82: 1622-1626.
24) Casadio M, Morasso PG, and Sanguineti V. 2005. Direct measurement of ankle stiffness during quiet standing: implications for control modeling and clinical application. *Gait Posture* 21: 410-424.
25) Vette AH, Masani K, Nakazawa K, Popovic MR. 2010. Neural-mechanical feedback control scheme generates physiological ankle torque fluctuation during quiet stance. *IEEE Trans Neural Sys Rehab Engin* 18: 86-95.
26) Loram ID, Maganaris CN, and Lakie M. 2005. Active, non-spring-like muscle movements in human postural sway: how might paradoxical changes in muscle length be produced? *J Physiol* 564: 281-293.
27) Solopova, IA, Kazennikov OV, Deniskina NB, Levik YS, Ivanenko YP. 2003. Postural instability enhances motor responses to transcranial magnetic stimulation in humans. *Neurosci Lett* 337: 25-28.
28) Tokuno CD, Taube W, Cresswell AG. 2009. An enhanced level of motor cortical excitability during the control of human standing. *Acta Physiol(Oxf)* 195: 385-395.
29) Koceja, DM, Trimble MH, Earles DR. 1993. Inhibition of the soleus H-reflex in standing man. *Brain Res* 629: 155-158.
30) Chen YS, Zhou S. 2011. Soleus H-reflex and its relation to static postural control. *Gait Posture* 33: 169-78.
31) Kawashima, N, Sekiguchi H, Miyoshi T, Nakazawa K, Akai M. 2003. Inhibition of the human soleus Hoffman reflex during standing without descending commands. *Neurosci Lett* 345: 41-44.
32) Knikou M, Conway BA. 2001. Modulation of soleus H-reflex following ipsilateral mechanical loading of the sole of the foot in normal and complete spinal cord injured humans. *Neurosci Lett* 303: 107-110.
33) Nakazawa K, Miyoshi T, Sekiguchi H, Nozaki D, Akai M, Yano H. 2004. Effects of loading and unloading of lower limb joints on the soleus H-reflex in standing humans. *Clin Neurophysiol* 115: 1296-1304.

EMJ Online First, published on February 28, 2013 as 10.1136/emermed-2012-202058

OPEN ACCESS

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

Hirotaka Chikuda,[1] Hideo Yasunaga,[2] Katsushi Takeshita,[1] Hiromasa Horiguchi,[2] Hiroshi Kawaguchi,[1] Kazuhiko Ohe,[3] Kiyohide Fushimi,[4] Sakae Tanaka[1]

[1]Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan
[2]Department of Health Management and Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[3]Department of Medical Informatics and Economics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[4]Department of Health Care Informatics, Tokyo Medical and Dental University, Tokyo, Japan

Correspondence to
Dr Hirotaka Chikuda, Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; chikuda-tky@umin.ac.jp

Received 8 October 2012
Revised 18 December 2012
Accepted 19 December 2012

To cite: Chikuda H, Yasunaga H, Takeshita K, *et al. Emerg Med J* Published Online First: [*please include* Day Month Year] doi:10.1136/emermed-2012-202058

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.

Funding This study was funded by a Grant-in-Aid for Research on Policy Planning and Evaluation from the Ministry of Health, Labour and Welfare, Japan (Grant number: H22-Policy-031), by a Grant-in-Aid for Research on Intractable Diseases from the Ministry of Health, Labour and Welfare, Japan (Grant number: H23-Nanchi-032), by a Grant-in-Aid for Scientific Research B (No. 22390131) from the Ministry of Education, Culture, Sports, Science and Technology, and by the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST programme) from the Council for Science and Technology Policy, Japan (Grant number: 0301002001001). The researchers were independent from the funders. Sponsors played no role in the study design; the collection, analysis, and interpretation of data; the writing of the article; or the decision to submit it for publication.

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.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Bracken MB, Shepard MJ, Collins WF, *et al*. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. *N Eng J Med* 1990;322:1405–11.
2 Bracken MB, Shepard MJ, Holford TR, *et al*. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *JAMA* 1997;277:1597–604.
3 Sayer FT, Kronvall E, Nilsson OG. Methylprednisolone treatment in acute spinal cord injury: the myth challenged through a structured analysis of published literature. *Spine J* 2006;6:335–43.
4 Hurlbert RJ. The role of steroids in acute spinal cord injury: an evidence-based analysis. *Spine (Phila Pa 1976)* 2001:S39–46.
5 Short DJ, El Masry WS, Jones PW. High dose methylprednisolone in the management of acute spinal cord injury—a systematic review from a clinical perspective. *Spinal Cord* 2000;38:273–86.
6 Eck JC, Nachtigall D, Humphreys SC, *et al*. Questionnaire survey of spine surgeons on the use of methylprednisolone for acute spinal cord injury. *Spine (Phila Pa 1976)* 2006;31:E250–3.
7 Frampton AE, Eynon CA. High dose methylprednisolone in the immediate management of acute, blunt spinal cord injury: what is the current practice in emergency departments, spinal units, and neurosurgical units in the UK? *Emerg Med J* 2006;23:550–3.
8 Molloy S, Price M, Casey AT. Questionnaire survey of the views of the delegates at the European Cervical Spine Research Society meeting on the administration of methylprednisolone for acute traumatic spinal cord injury. *Spine (Phila Pa 1976)* 2001;26:E562–4.
9 Rozet I. Methylprednisolone in acute spinal cord injury: is there any other ethical choice? *J Neurosurg Anesthesiol* 2008;20:137–9.
10 Bracken MB. Steroids for acute spinal cord injury. *Cochrane Database Syst Rev* 2012;1:CD001046.
11 Ito Y, Sugimoto Y, Tomioka M, *et al*. Does high dose methylprednisolone sodium succinate really improve neurological status in patient with acute cervical cord injury?: a prospective study about neurological recovery and early complications. *Spine (Phila Pa 1976)* 2009;34:2121–4.
12 Suberviola B, González-Castro A, Llorca J, *et al*. Early complications of high-dose methylprednisolone in acute spinal cord injury patients. *Injury* 2008;39:748–52.
13 Matsumoto T, Tamaki T, Kawakami M, *et al*. Early complications of high-dose methylprednisolone sodium succinate treatment in the follow-up of acute cervical spinal cord injury. *Spine (Phila Pa 1976)* 2001;26:426–30.
14 Pointillart V, Petitjean ME, Wiart L, *et al*. Pharmacological therapy of spinal cord injury during the acute phase. *Spinal Cord* 2000;38:71–6.
15 Gerndt SJ, Rodriguez JL, Pawlik JW, *et al*. Consequences of high-dose steroid therapy for acute spinal cord injury. *J Trauma* 1997;42:279–84.
16 Matsuda S, Ishikawa K, Kuwabara K, *et al*. Development and use of the Japanese case-mix system. *Eurohealth* 2008;14:27–30.
17 Chikuda H, Yasunaga H, Horiguchi H, *et al*. Mortality and morbidity in dialysis-dependent patients undergoing spinal surgery: analysis of a national administrative database in Japan. *J Bone Joint Surg Am* 2012;94:433–8.
18 Sauerland S, Nagelschmidt M, Mallmann P, *et al*. Risks and benefits of preoperative high dose methylprednisolone in surgical patients: a systematic review. *Drug Saf* 2000;23:449–61.
19 Ono K, Wada K, Takahara T, *et al*. Indications for computed tomography in patients with mild head injury. *Neurol Med-Chir* 2007;47:291–7.
20 Quan H, Sundararajan V, Halfon P, *et al*. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130–9.
21 Ayanian JZ, Landrum MB, Guadagnoli E, *et al*. Specialty of ambulatory care physicians and mortality among elderly patients after myocardial infarction. *N Engl J Med* 2002;347:1678–86.

22 Tsutsumi S, Ueta T, Shiba K, *et al*. Effects of the Second National Acute Spinal Cord Injury Study of high-dose methylprednisolone therapy on acute cervical spinal cord injury-results in spinal injuries center. *Spine (Phila Pa 1976)* 2006;31:2992–6.
23 George ER, Scholten DJ, Buechler CM, *et al*. Failure of methylprednisolone to improve the outcome of spinal cord injuries. *Am Surg* 1995;61:659–63.
24 Roberts I, Yates D, Sandercock P, *et al*. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet* 2004;364:1321–8.
25 Fawcett JW, Curt A, Steeves JD, *et al*. Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. *Spinal Cord* 2007;45:190–205.

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.