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Incidence of acute spinal cord injury and associated complications of methylprednisolone therapy: a national population-based study in South Korea

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Abstract

Study design Retrospective population-based cohort study

Objectives To evaluate the incidence of acute spinal cord injury (SCI) in South Korea, and the prescription rates and complications related to high dose methylprednisolone therapy.

Setting Health Insurance Review and Assessment Service (HIRA) data

Methods National database of the Korean HIRA between 2007 and 2017 was reviewed. To identify patients with acute SCI and the use of high dose methylprednisolone, International Classification of Disease revision codes, medical behavior codes and examination codes were used. Patients were grouped according to whether or not they received methylprednisolone therapy (MP group vs non-MP group).

Results The average age-adjusted incidence of acute SCI per 1,000,000 persons was 26.4 and the peak incidence was in the 50s overall. The methylprednisolone prescription rate was highest in 2012 (76%) and continued to decrease thereafter, being lowest in 2017 (41%). The MP group showed higher complication rates in terms of pneumonia (OR 1.8, 95% CI, 1.62–2.0), GI bleeding (OR 1.2, 95% CI, 1.05–1.38), and UTI (OR 1.68, 95% CI, 1.53–1.84). The average length of hospitalization was longer in patients who received methylprednisolone (26.5 days vs. 24.4 days, $p < 0.05$).

Conclusions The average age-adjusted incidence of acute SCI for 11 years was 26.4 per 1,000,000 persons and highest in 50s. Strategies should be established, and national health resources should be allocated to prevent acute SCI from occurring in older people. The prescription rate of high dose methylprednisolone for acute SCI is decreasing in South Korea but it is still high.

Introduction

Acute spinal cord injury (SCI) is a catastrophic traumatic event that affects the physical and psychological wellbeing of individuals, and results in considerable socio-economic losses [1, 2]. The high treatment costs and extended hospitalization have a tremendous impact on the individual and their family and are a substantial financial burden on the

health care system. Therefore, identifying the epidemiology of acute SCI is essential for health care providers to establish policies for preventing the disease and redistributing resources.

Several studies have compared the prevalence and incidence rates of acute SCI in different geographical and economic conditions [3, 4]. In particular, the reported incidence rates of acute SCI differ widely according to research method, date, and region; in developed nations, it has been reported variously as 11.5–53.4 persons per million persons [5, 6] and 13.0–220.0 persons per million in developing countries [7, 8]. Acute SCI patients have been reported to account for 2.6% of the patients in major trauma centers in North America [5], and not only are there more than 10,000 new patients every year, but this number would be much higher if individuals who expire before arriving at the hospital were included [6, 9, 10]. However, most data on acute SCI are based on developed nations such as the US

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and Spain, and data for developing nations such as Africa, South America and Asia are limited [11].

After the report on the effect of high dose methylprednisolone treatment for acute SCI by Bracken et al. [12], a number of studies were conducted to examine the efficacy of methylprednisolone [13, 14]. According to recent studies, the use of methylprednisolone for acute SCI patients leads to increased numbers of complications, without having any beneficial effect on neurological symptoms, and therefore, methylprednisolone is not recommended as first line treatment [15, 16]. Although the Food and Drug Administration (FDA) no longer recommends methylprednisolone for treating acute SCI [15, 16], many countries including South Korea still use it [17].

Therefore, in this study we assessed the incidence of acute SCI in South Korea and investigated the prescription rate of methylprednisolone for acute SCI over the years, and the acute complications following its use in a population-based study using a national database.

Methods

Data source and study population

This was a retrospective population-based cohort study using the database of the Health Insurance Review and Assessment Service (HIRA). Korea's national health insurance system, which began in 1989, is operated by the government and covers medical expenses for outpatient, inpatient, and emergency medical services. Apart from cosmetic services such as plastic surgery, almost all medical services are covered by the system. All citizens are required to subscribe to it, and it covers over 98% of the Korean population, working with all hospitals and clinics. As a result, the system boasts of high accessibility, low cost, and short waiting times, and it is easy to collect data for planning, researching, monitoring, and evaluating the various medical services. All hospitals and clinics in Korea must provide the HIRA with information on

the diagnosis, treatment, and clinical behavior, etc. of outpatients and inpatients in order to invoice it for costs. Therefore, in addition to personal information such as age and gender of patients, all information on diagnoses, examinations performed, and treatment can be acquired through the data of the HIRA. When the HIRA provides such information, however, all of it including personal identities is encrypted in order to protect the personal information and data of patients. There has recently been a surge in epidemiological research using HIRA's data [18].

The participants for this study were acute SCI patients registered in the HIRA data between January 1, 2007 and December 31, 2017. The patients were identified using the International Classification of Disease (ICD-10) codes (Table 1), and 12,137 patients categorized in this way were classified according to gender and 10-year age groups.

Assessment of high dose methylprednisolone prescription and related complication rate

Patients that received high dose methylprednisolone (National Acute Spinal Cord Injury Study (NASCIS) 3 protocol: methylprednisolone 30 mg/kg bolus over 15 min, followed by 45 min of rest period, then 5.4 mg/kg/h for 23 h if they were within 3 h of injury. If treatment started between 3 and 8 h after injury, methylprednisolone 30 mg/kg bolus over 15 min, followed by 45 min of rest period, then 5.4 mg/kg/h for 48 h) were identified by the medical behavior code (193604BIJ) for prescriptions to acute SCI patients categorized by the ICD-10 code. In order to exclude uses of methylprednisolone to treat other diseases, patients who attended outpatient clinics and received low dose methylprednisolone were excluded. Annual prescription rate of high dose methylprednisolone was investigated to assess its trend. Patients were divided into an MP group and a non-MP group for analyses of pneumonia, urinary tract infections, gastrointestinal tract hemorrhage, and wound infections in order to investigate the complication rate following high dose methylprednisolone treatment.

Table 1 ICD-10 codes for searching cohorts

Parameters	Codes	Description
ICD-10 code	S14	Injury of nerves and spinal cord at neck level
	S14.0	Concussion and edema of cervical spinal cord
	S14.1	Other and unspecified injuries of cervical spinal cord
	S24	Injury of nerves and spinal cord at thorax level
	S24.0	Concussion and edema of thoracic spinal cord
	S24.1	Other and unspecified injuries of thoracic spinal cord
	S34	Injury of lumbar and sacral spinal cord and nerves at abdomen, lower back and pelvis level
	S34.0	Concussion and edema of lumbar and sacral spinal cord
	S34.1	Other and unspecified injury of lumbar and sacral spinal cord

Table 2 ICD-10 codes for searching cohorts

Parameters	Description	Codes
ICD-10 code	Pneumonia	J12 ^a , J13, J14, J15 ^a , J16 ^a , J17 ^a , J18 ^a
	Gastrointestinal bleeding	K25 ^a , K26 ^a , K27 ^a , K28 ^a , K29, K92 ^a
	Urinary tract infection	N30 ^a , N34 ^a , N41 ^a
	Wound infection	M46 ^a , T81 ^a

^aMeans that all sub-codes of the respective code are included

Complications were defined when pneumonia, urinary tract infection, gastrointestinal tract hemorrhage or wound infection occurred within three months of MP administration. In order to assess whether complications occurred due to the use of methylprednisolone, patients were categorized using the ICD-10 codes related to each complication (Table 2).

Statistical analysis

SPSS 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Student's *t*-test was used for continuous variables, and the chi square test was used to analyze classification variables. The Joinpoint Regression Program version 4.3.1.0 (National Cancer Institute, Bethesda, MD, USA) was also used. Age-adjusted incidences were calculated employing the standard population of the Republic of Korea according to age and gender registered on the Korean Statistical Information Service website (<http://www.kosis.kr>) and the 2000 US Standard Population (<https://seer.cancer.gov>), and annual percentage changes were calculated. Odds ratio and 95% confidence interval of each complications were calculated. Statistically significance was defined as $P < 0.05$.

Results

A total of 12,137 (M:F = 3.4:1) patients were identified with acute SCI over 11 years from 2007 to 2017. The age-adjusted average incidence of acute SCI was 26.4 ± 0.9 persons per million persons (Table 3). The annual percentage change for age-adjusted average incidence has increased by 2% for men and 2% for women ($p < 0.001$ respectively). However, while the overall trend towards an increase was 1%, it was not statistically significant ($p = 0.2$). The mean age for men was 59.5 ± 14.4 years (range 6–94 years) and for women 54.9 ± 15.4 years (range 4–95 years), and the incidence was highest in men in their 50s and in women in their 70s. Overall, the highest incidence occurred in individuals in their 50s (Fig. 1).

Methylprednisolone was prescribed to 59% of all acute SCI patients over the past 11 years. The prescription rate

Table 3 Number of cases, and age-adjusted rates of spinal cord injury, from 2007 to 2017

Year	No. of cases			Age-adjusted rate per 100,000 persons		
	Total	Men	Women	Total	Men	Women
2007	1156	856	300	25.07	36.48	11.31
2008	905	654	251	25.33	37.2	11.54
2009	967	718	249	25.6	37.92	11.77
2010	1101	776	325	25.86	38.67	12.01
2011	1061	795	266	26.13	39.42	12.25
2012	1004	742	262	26.4	40.2	12.49
2013	1104	810	294	26.68	40.98	12.74
2014	1231	848	383	26.95	41.78	13
2015	1164	872	292	27.23	42.6	13.26
2016	1285	940	345	27.52	43.44	13.53
2017	1159	852	307	27.8	44.29	13.8
Overall	12137	8863	3274	26.4	40.3	12.5
APC		1.0	2.0	2.0		

APC annual percentage change

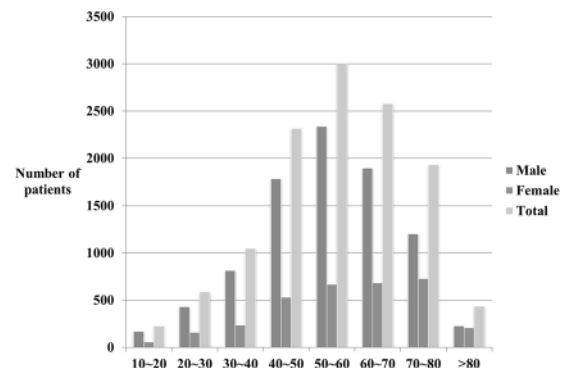


Fig. 1 Numbers of spinal cord injury patients over 11 years according to age

was highest in 2012 at 76% and decreased gradually to a low of 41% in 2017 (Table 4) (Fig. 2). Compared with the non-MP group, the MP group had increased risks of pneumonia (OR 1.8, 95% CI, 1.62–2.0), gastrointestinal tract hemorrhage (OR 1.2, 95% CI, 1.05–1.38) and urinary tract infections (OR 1.68, 95% CI, 1.53–1.84). The risk of wound infection (OR 0.98, 95% CI, 0.77–1.25) did not differ between the two groups (Fig. 3). The mean hospitalization period was 26.5 ± 19.2 days for the MP group, and 24.4 ± 16.5 for the non-MP group ($p = 0.002$).

Discussion

The incidence of acute SCI per million persons was reported as 39 in North America, 15 in Australia, and 16 in

Table 4 Methylprednisolone treatment of acute spinal cord injury patients

Year	Number of cases of acute spinal cord injury	No. of cases receiving methylprednisolone	Prescription rate (%)
2007	1156	789	68.3
2008	905	600	66.3
2009	967	619	64.0
2010	1101	750	68.1
2011	1061	726	68.4
2012	1004	760	75.7
2013	1104	719	65.1
2014	1231	702	57.0
2015	1164	658	56.5
2016	1285	598	46.5
2017	1159	472	40.7
Total	12,137	7183	61.5

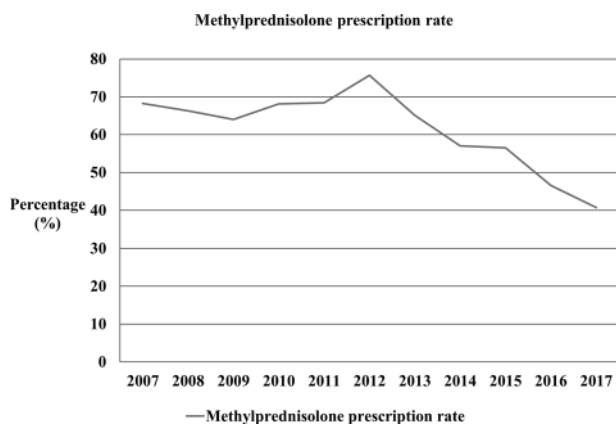


Fig. 2 High dose methylprednisolone prescription rate over the years

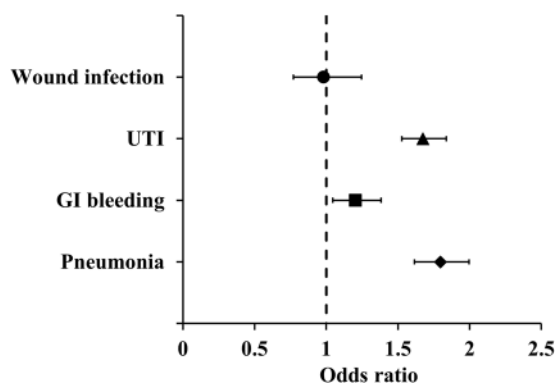


Fig. 3 The risk of complications in the methylprednisolone group compared with non-methylprednisolone group

Western Europe [3], while in Asia, it was reported as 40.2 in Japan [19], and 18.8 in Taiwan [20]. However, studies on the epidemiology of acute SCI per country or region have focused mainly on developed countries. There have been a few reports comparing the worldwide prevalence and incidence of acute SCI, but because there have been no studies of the epidemiology of acute SCI in many developing countries including South Korea it is difficult to assess global epidemiology [3, 4, 11]. In most studies, male patients accounted for the majority and incidence was highest in those under 30. In this study, the age-adjusted average incidence per million persons was 26.4, and the male-to-female ratio was 3.41:1. This incidence and male-to-female ratio were similar to those of other developed nations. However, the age of peak incidence in South Korea was highest in the 50s which was older than in other countries. This may have been associated with the fact that there is a higher incidence of ossified posterior longitudinal ligament (OPLL) in the older age groups of South Korea, as well as that the degenerative spondyloses in the rapidly aging South Korean society escalates the risk of posttraumatic acute SCI. Between 2002 and 2013, annual incidence of OPLL was ~199–371 per million persons in South Korea and the peak age of annual incidence was 60–75 years [21]. The incidence of acute SCI in Japan was also highest in people in their 50s [19] and it has been reported that Japan’s OPLL incidence is also higher than in other countries [22]. Therefore, as the population of Korea is aging, there is an increasing possibility of acute SCI in older patients, and this should be reflected in planning out how to prevent acute SCI and how to allocate medical resources.

The apparent incidence of acute SCI differs by region, and even in the same region, it can vary with the study period [11]. While this may be the result of demographical or geographical characteristics, it may also be due to the use of different research modalities. For example, hospital-based studies tend to undervalue specific disease incidences compared with population-based studies [23]. Therefore, in order to make international comparisons or to accurately estimate global incidence, the data collection method needs to be standardized.

High dose methylprednisolone has been recommended for use as it is the only drug with proven effectiveness on neural protection for acute SCI patients based on the results of the NASCIS [24]. However, many studies have questioned the quality of the data of the NASCIS research, its statistical analysis method, interpretation, and conclusions. Furthermore, there is no Class I or Class II evidence for the beneficial effect of methylprednisolone, and the FDA no longer recommends its use for treating acute SCI [15, 16]. Despite this, many clinicians still prescribe methylprednisolone. According to one study, some clinicians believe that it is effective for acute SCI, while others know that it is

ineffective, but think that they have to do something for the patient; some clinicians prescribe it to avoid medical litigation for not using the drug [17].

Worldwide, methylprednisolone is prescribed in 53% of cases, and in Canada, its use dropped from 76% in 2001 to 24% in 2006, and in England, from 68% in 2004 to 19% in 2012 [25, 26], apparently as the effect of studies on the side effects and inefficacy of methylprednisolone [24, 27]. In this study, South Korea had the highest prescription rate in 2012 (76%) and then declined to 41% in 2017. However, South Korea still has a high prescription rate compared with North America and Europe, and education and notification is needed especially for spine surgeons to ensure that they do not use methylprednisolone inappropriately.

Early studies reported that treatment of acute SCI patients with methylprednisolone increased the risk of complications such as pneumonia, gastrointestinal hemorrhage, urinary tract infection, wound infection, hyperglycemia, myopathy, and sepsis [28–30]. In this study we found that when compared with the non-MP group, the MP group showed a higher correlation with pneumonia, gastrointestinal hemorrhage and urinary tract infections, but there was no difference between the two groups in terms of wound infection. According to research by Suberviola et al. [30], the incidence of pneumonia was significantly higher in the methylprednisolone user group, but again no substantial difference in wound infections. Matsumoto et al. [29] reported a higher incidence of pneumonia and gastrointestinal hemorrhage in the group using methylprednisolone, but no difference in urinary tract infection incidence. However, Ito et al. [28] reported an increased incidence of pneumonia, urinary tract infections, and wound infections. The differences among these studies may have been due to variation in the severity and extent of neurologic deficits as well as in the definitions of complications. It is likely that our MP group had a longer hospitalization period than the non-MP group due to the difference in complication rates (26.5 vs. 24.4).

This is the first study of the incidence of acute SCI in South Korea using a population-based database, and it is significant in that it analyzed the methylprednisolone prescription rate and the incidence of complications based on a large sample size. However, it has a few limitations. First, it is a retrospective study. Second, the HIRA database is constructed for the purpose of invoicing, and data may have been omitted or entered erroneously in the event that South Korean hospitals or clinics failed to enter the correct ICD-10 codes or medical practice codes during examinations and treatments. This might affect the overall results on the incidence of acute SCI and the occurrence of complications. But it was a large population-based study, we believe such errors had little effect on our results. Third, only four complications which were known to be common complication of high dose

methylprednisolone therapy were evaluated. There usually were other complications such as decubital wounds and deep vein thrombosis, but we focused on major complications [28–30]. Fourth, because we just used a simple comparison of those that did and did not receive methylprednisolone to assess complications, it is difficult to suggest a causation. However, this study could show some correlation between two variables by analyzing large size sample. Fifth, because it is not possible to conduct surveys on whether methylprednisolone improves neurological symptoms in acute SCI patients, only the use of methylprednisolone and the resulting complications were investigated.

This is the first epidemiological study of acute SCI in South Korea. Its average incidence in the past 11 years was 26.4 per 1 million persons, and peak incidence occurred in the 50 s age group. This should be reflected in policies for preventing the occurrence of acute SCI and distributing medical resources. Despite the doubts over the efficacy of methylprednisolone treatment and the known complications, it is still frequently prescribed for acute SCI in Korea.

Data archiving

All data generated or analyzed during this study are included in this published article and its supplementary material file. They are also available from the HIRA website (<https://www.hira.or.kr>) on reasonable request.

Author contributions SHC and CNK were responsible for designing the cohort study. CS was responsible for preparing the manuscript content. DRH and SYJ contributed on revising the manuscript content.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics statement This study was approved according to the standards of the Hanyang University Hospital institutional review board (HYUH 2018-06-037).

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