

## Management of Pain after Spinal Cord Injury

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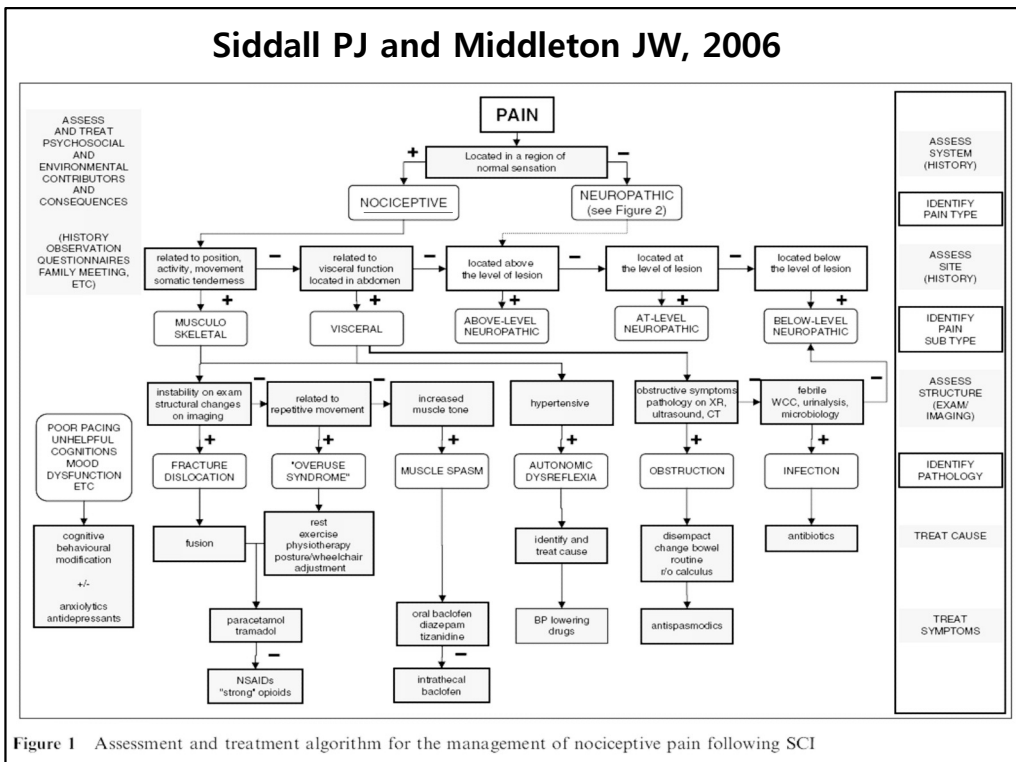
### Paraplegic Pain



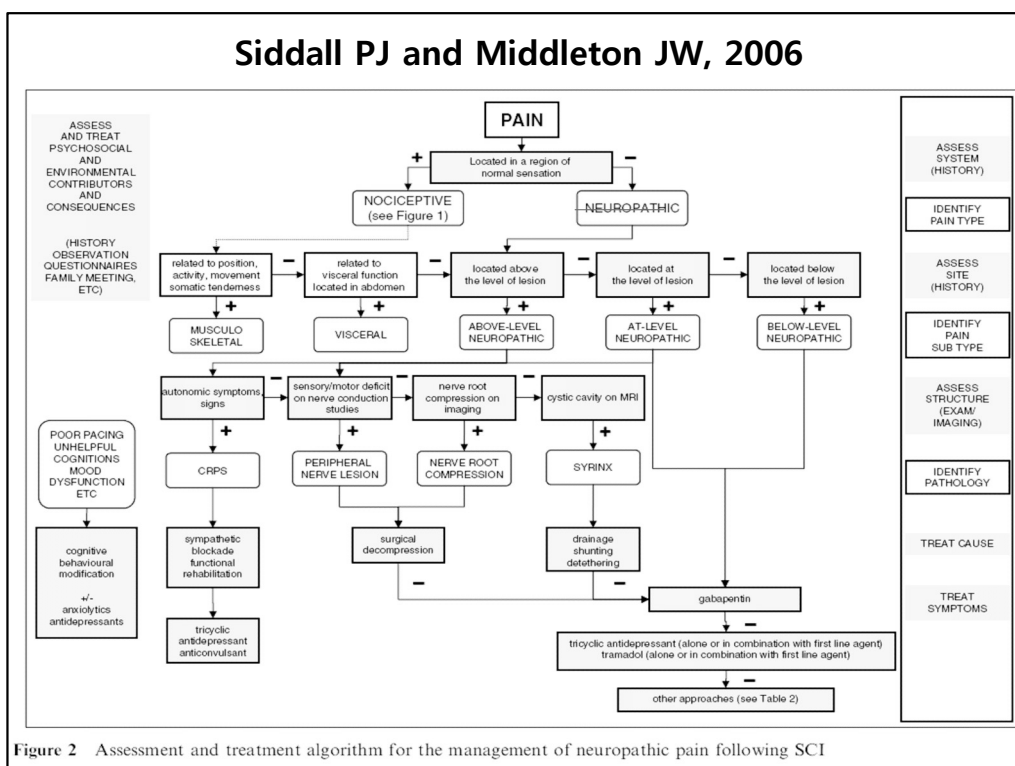
- Two thirds of patients with SCI; pain
- One thirds of pain; severe & debilitating

**Table 1. Proposed IASP Classification of Pain Related to SCI**

Broad Type (Tier 1)	Broad System (Tier 2)	Specific Structures/Pathology (Tier 3)
Nociceptive	Musculoskeletal	Bone, joint, muscle trauma, or inflammation
		Mechanical instability
		Muscle spasm
		Secondary overuse syndromes
		Renal calculus, bowel, sphincter dysfunction, etc.
Neuropathic	Visceral	Dysreflexic headache
	Above level	Compressive mononeuropathies
		Complex regional pain syndromes
	At level	Nerve root compression(including cauda equina)
		Syringomyelia
	Below level	Spinal cord trauma/ischemia(transitional zone, etc.)
		Dual-level cord and root trauma(double lesion syndrome)
		Spinal cord trauma/ischemia(central dysesthesia syndrome, etc)



# Siddall PJ and Middleton JW, 2006



## Siddall PJ and Middleton JW, 2006

Table 2 Evidence, limitations and specific indications of third-line treatments

Treatment	Level of evidence	Disadvantages or side effects <sup>a</sup>	Specific indications
Pregabalin	Unpublished RCT	Somnolence, dizziness, asthenia, dry mouth, oedema, constipation	
Opioids	+ve cases	Constipation, drowsiness, tolerance, dependence	
Mixed serotonin/noradrenaline reuptake inhibitors	+ve cases	Hypertensive effects, gastrointestinal disturbance, dry mouth, reduced appetite, sweating	
Mexiletine	-ve RCT	Gastrointestinal upset, cardiovascular, haematological disturbance, skin reactions	
Topiramate	+ve RCT	Drowsiness, dizziness, ataxia, anorexia, fatigue, gastrointestinal upset	
Lamotrigine	-ve RCT	Potentially life-threatening skin rash, hepatic effects, diplopia, blurred vision, dizziness	
Dronabinol	+ve cases	Dizziness, drowsiness, irritability	
Older anticonvulsants	-ve RCT (valproate)	Drowsiness, dizziness, liver dysfunction, haematological effects	
Acupuncture	+ve cases	Invasive	Effectiveness for below-level neuropathic pain uncertain
Intravenous ketamine	+ve RCT	Short-term relief, invasive, dysphoria	
Intravenous propofol	+ve RCT	Short-term relief, invasive, hypotension, arrhythmias, bradycardia	
Intravenous alfentanil	+ve RCT	Short-term relief, invasive, respiratory depression, bradycardia, sedation, hypotension, nausea, vomiting	
Intravenous morphine	+ve RCT	Short-term relief, invasive, respiratory depression, sedation, hypotension, nausea, vomiting	Effectiveness demonstrated for mechanical allodynia
Intrathecal baclofen	+ve RCT	Invasive, reports of increased or 'unmasked' neuropathic pain	Stronger evidence for spasm-related pain
Intrathecal morphine and clonidine	+ve RCT	Invasive, tolerance, hypotension, respiratory depression, drowsiness	
Subarachnoid lignocaine	+ve RCT	Invasive, central nervous system disturbance	
Spinal cord stimulation	+ve cases	Invasive	At-level neuropathic pain, incomplete injuries
Deep brain stimulation	+ve cases	Invasive, intracranial haemorrhage	
Motor cortex stimulation (transcranial)	+ve cases	Short-term effect	
Motor cortex stimulation (epidural)	+ve cases	Invasive	
DREZ	+ve cases	Invasive, risk of further deficits	At-level neuropathic pain
Cordotomy	+ve cases	Invasive, risk of further deficits	

<sup>a</sup>Commonly listed side effects. For further details, consult prescribing information  
 RCT, randomised controlled trial; -ve or +ve, evidence indicates drug superior (+ve) or no more effective (-ve) when compared with placebo (RCT) or reported as beneficial (+ve cases)

**Table 7. Treatment Effectiveness Summary**

Treatment	Type of Pain	Effectiveness	Level of Evidence
Gabapentin	Neuropathic	+	1
Pregabalin	Neuropathic	+	1
Lamotrigine	Neuropathic	+*	2
Valproic acid	Neuropathic	-	1
Levetiracetam	Neuropathic	-	1
Trazodone	Neuropathic	-	1
Amitriptyline	Neuropathic	+†	1
Lidocaine	Neuropathic	+‡	1
Intravenous ketamine	Neuropathic	+	1
Intravenous alfentanil	Neuropathic	+	1
Intrathecal morphine/ clonidine	Neuropathic/ Mixed	+	1/2
Intravenous morphine	Mixed	+	1
Tramadol	Neuropathic	+	1
Mexilitene	Neuropathic	-	1
Capsaicin	Mixed	+	5
Cannabinoids	Spastic	+/-	2/4
Intrathecal baclofen	Neuropathic	+/-	1/4
Intrathecal baclofen	Musculoskeletal/ Spastic	+	4
Botulinum toxin	Spastic	+	4

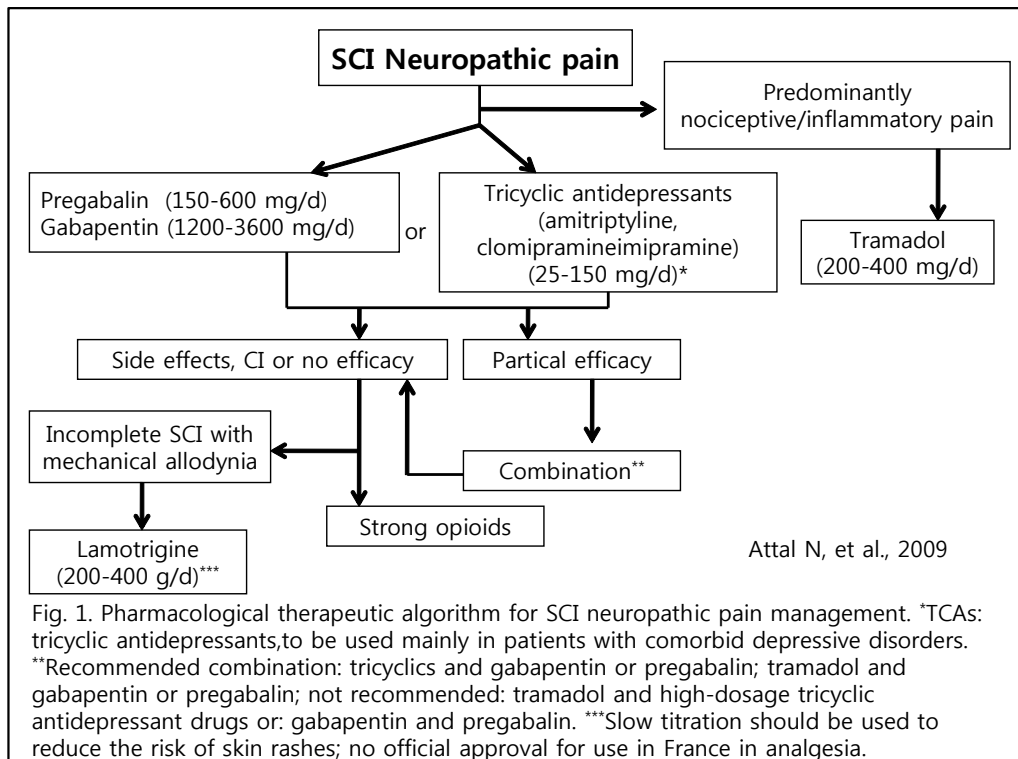
Abbreviation : +, effective; -, not effective; +/-, conflicting.

\* Only in persons with incomplete SCI.

† Only in depressed persons.

‡ Short-term.

Teasell RW, et al., 2010



**Table 2 Level of evidence and grade of commendation for the pharmacological treatments evaluated in SCI pain (based on the classification of the French Authority of Health, HAS)**

Pharmacological treatments	Level of scientific evidence	Grade of recommendation for SCI pain
<b>Antiepileptic drugs</b>		
Gabapentin	2	B (discrepant results) <sup>a</sup>
Pregabalin	1	A (scientific evidence for efficacy)
Lamotrigine	2	B (presumed inefficacy <sup>b</sup> )
Valproate	2	B (presumed inefficacy )
Clonazepam	4	C (low level of evidence)
Carbamazepine	3	C (low level of evidence)
<b>Tricyclic antidepressant drugs</b>		
Amitriptyline	2	B (presumed efficacy in a subgroup of depressed patients)
<b>Opioids</b>		
Levorphanol <sup>c</sup>	2	B (presumed efficacy)
IV Morphine	2	B (presumed inefficacy <sup>d</sup> )
IV Alfentanil	2	B (presumed efficacy)
<b>Local anesthetic drugs/equivalent</b>		
IV lidocaine	2	B (presumed inefficacy)
Mexiletine	2	B (presumed efficacy)
<b>GABAergic agonists</b>		
IV Propofol	2	B (presumed efficacy)

<sup>a</sup> One positive study(20 patients) and one negative study (22 patients).

<sup>b</sup> Efficacy on the basis of one study on a small sub-group of patients with incomplete SCI and allodynia.

<sup>c</sup> Treatment not available in France.

<sup>d</sup> Except on allodynia (brushing).

Attal N, et al., 2009

## Pregabalin in central neuropathic pain associated with spinal cord injury

### A placebo-controlled trial

P.J. Siddall, MBBS, PhD; M.J. Cousins, MD, DSc; A. Otte, MD, PhD; T. Griesing, PhD;  
R. Chambers, MSPH; and T.K. Murphy, PhD

#### • Method

- 12 week, multi-center, double-blind, randomized clinical trial comparing pregabalin 150 mg to 600 mg/day (n=70) vs placebo (n=67)

#### • Patients

- Patients with central neuropathic pain associated with spinal cord injury

#### • End Point

- Primary: End Mean Pain Score
- Secondary: Pain Responder Rates, SF-MPQ, Sleep Interference, Mood and the Patients Global Measure of Change

Neurology 2006;67:1729-1800

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R. Chambers, MSPH; and T.K. Murphy, PhD

**RESULTS:** The mean baseline pain score was 6.54 in the pregabalin group and 6.73 in the placebo group. The mean endpoint pain score was lower in the pregabalin group (4.62) than the placebo group (6.27;  $p < 0.001$ ), with efficacy observed as early as week 1 and maintained for the duration of the study. The average pregabalin dose after the 3-week stabilization phase was 460 mg/day. Pregabalin was significantly superior to placebo in endpoint assessments on the SF-MPQ. The  $>$  or  $\geq 30\%$  and  $>$  or  $\geq 50\%$  pain responder rates were higher with pregabalin than placebo ( $p < 0.05$ ). Pregabalin was associated with improvements in disturbed sleep ( $p < 0.001$ ) and anxiety ( $p < 0.05$ ), and more patients reported global improvement at endpoint in the pregabalin group ( $p < 0.001$ ). Mild or moderate, typically transient, somnolence and dizziness were the most common adverse events.

**CONCLUSIONS:** Pregabalin 150 to 600 mg/day was effective in relieving central neuropathic pain, improving sleep, anxiety, and overall patient status in patients with spinal cord injury.

Neurology 2006;67:1729-1800

## Pregabalin in patients with central neuropathic pain: A randomized, double-blind, placebo-controlled trial of a flexible-dose regimen

J.H. Vranken <sup>a,\*</sup>, M.G.W. Dijkgraaf <sup>b</sup>, M.R. Kruis <sup>a</sup>, M.H. van der Vegt <sup>a</sup>,  
M.W. Hollmann <sup>a</sup>, M. Heesen <sup>c</sup>

### • Method

- 4 week, double-blind, randomized, placebo-controlled trial of a flexible-dose regimen pregabalin 150, 300, 600 mg/day (n=20) vs placebo (n=20)

### • Patients

- Patients with central neuropathic pain

### • Efficacy parameter

- Pain Intensity Score (at baseline, end of each week, and 4 weeks following) using VAS
- Health status (Pain Disability Index and EQ-5D) and Quality of Life(SF-36)

Pain 136 (2008) 150-157

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- Forty patients received escalating doses of either pregabalin (150, 300, and 600 mg/day) or matching placebo capsules. In both groups, patients started with 1 capsule per day (either 150mg of pregabalin or placebo). If pain relief was insufficient, patients were titrated to a higher dose.
- There was a statistically significant decrease in mean pain score at endpoint for pregabalin treatment, compared with placebo ( $p=0.016$ ). Follow-up observation showed no significant difference in Pain Disability Index scores between the two groups.
- The pregabalin group, however, showed a statistically significant improvement for the EQ-5D. Pregabalin treatment led to a significant improvement in the bodily pain domain of the SF36. In the other domains, more favorable scores were reported without reaching statistical significance.
- Pregabalin, in a flexible-dose regime, produced clinically significant reductions in pain, as well as improvements in health status in patients suffering from severe central neuropathic pain.

Pain 136 (2008) 150-157

## Pregabalin for Central Cord Pain

- Pregabalin is effective in relieving central neuropathic pain and mean global pain score in patients with spinal cord injury
- Pregabalin is effective in improving sleep, anxiety and overall patients status in patients with spinal cord injury
- Pregabalin efficacy observed as early as week 1 and maintained for the duration of the study

## Pregabalin의 장점

1. 투여 후 이틀째부터 신속한 작용 발현
2. Gabapentine, TCA, SSNRIs에 불응성인 환자에서 강력한 통증 감소 효과
3. 1주 이내의 탁월한 수면장애 개선 효과
4. 우수한 내약성과 안전성
5. Titration이 필요 없는 1일 2회 복용의 편리성
6. 신경병증 통증 환자의 삶의 질 개선

## Cord Central Pain

- 치료가 매우 어렵다.
- DBS & MCS: 별 효과가 없다.
- SCS (Kim, et al, Neurosurgery 48:1056-1065, 2001)

7/20 – successful trial stimulation

5/7 – successful pain control for at least 1 year after permanent  
insertion

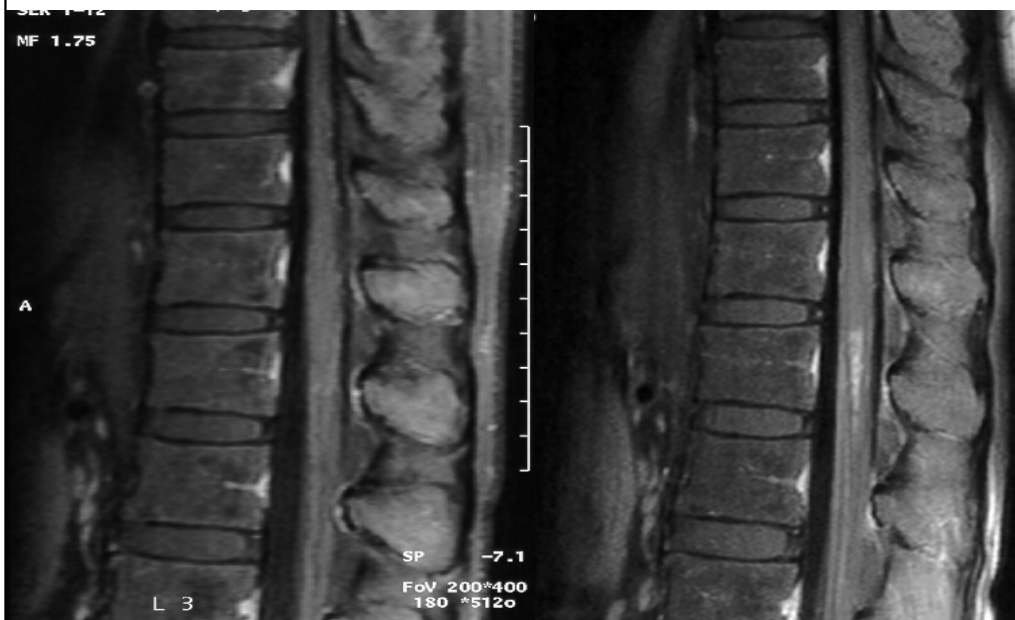


## Failed Trial Stimulation

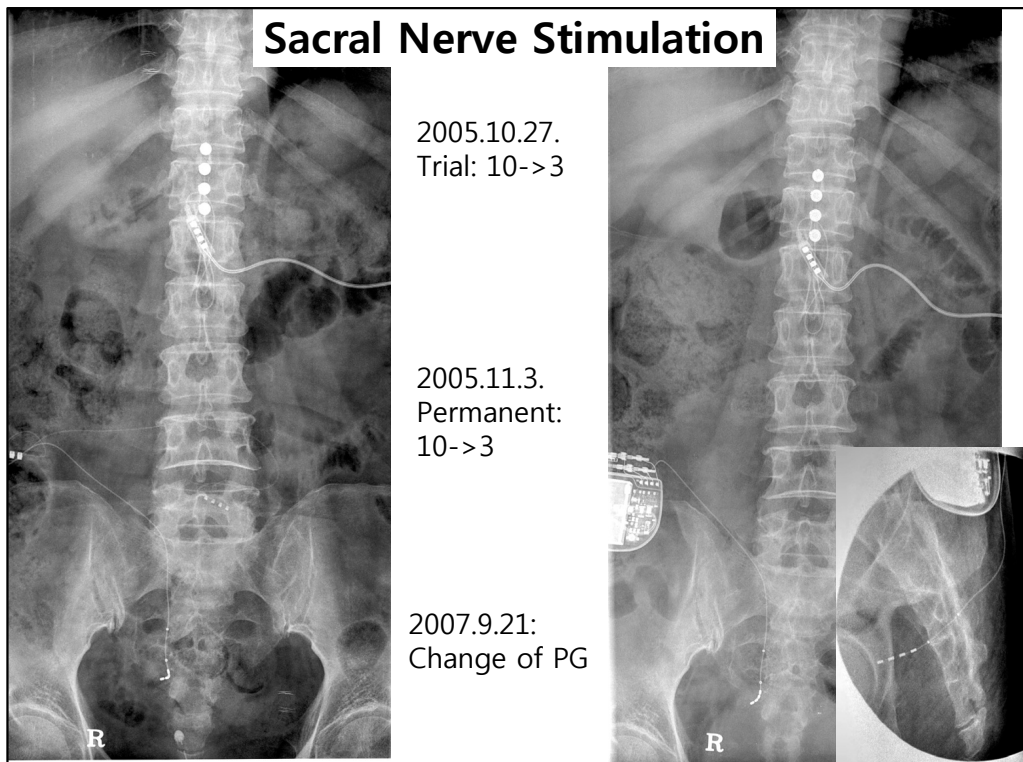
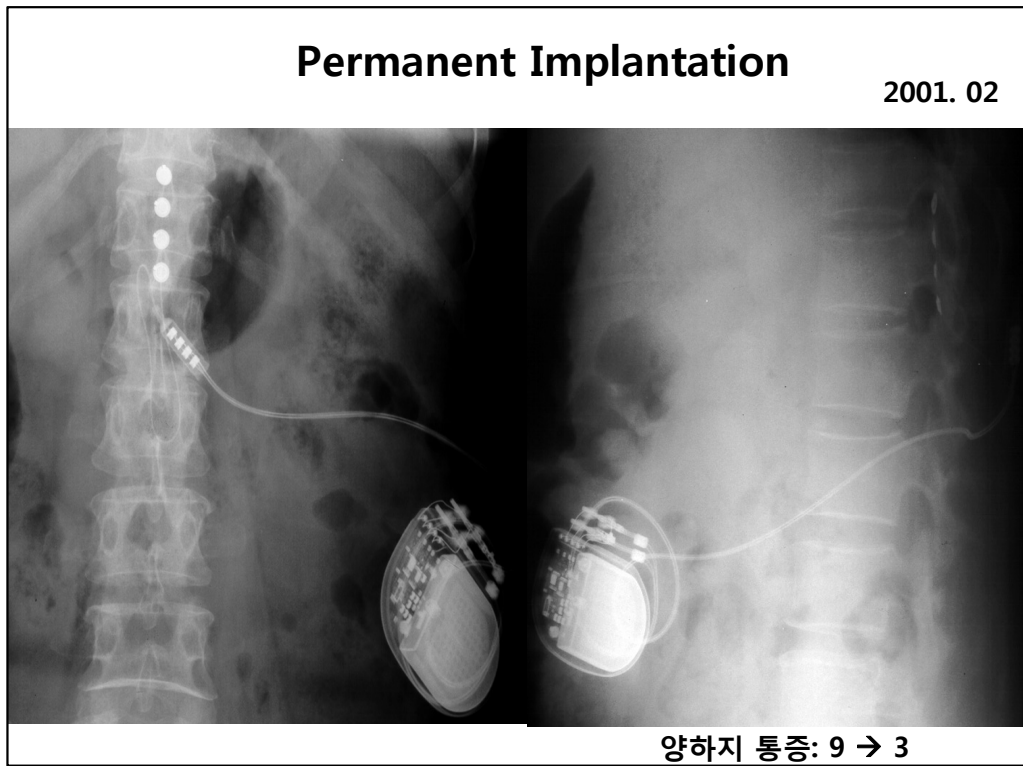
(cord central pain)

Failed trial	44/122	13/20
Paresthesia, but no pain relief	29	05
Insufficient paresthesia	06	04
Painful or unpleasant sense	08	04
Failure of procedure	01	0
(Kim et al, Neurosurgery, 2001)		

## Spinal Cord Infarction (여/56)



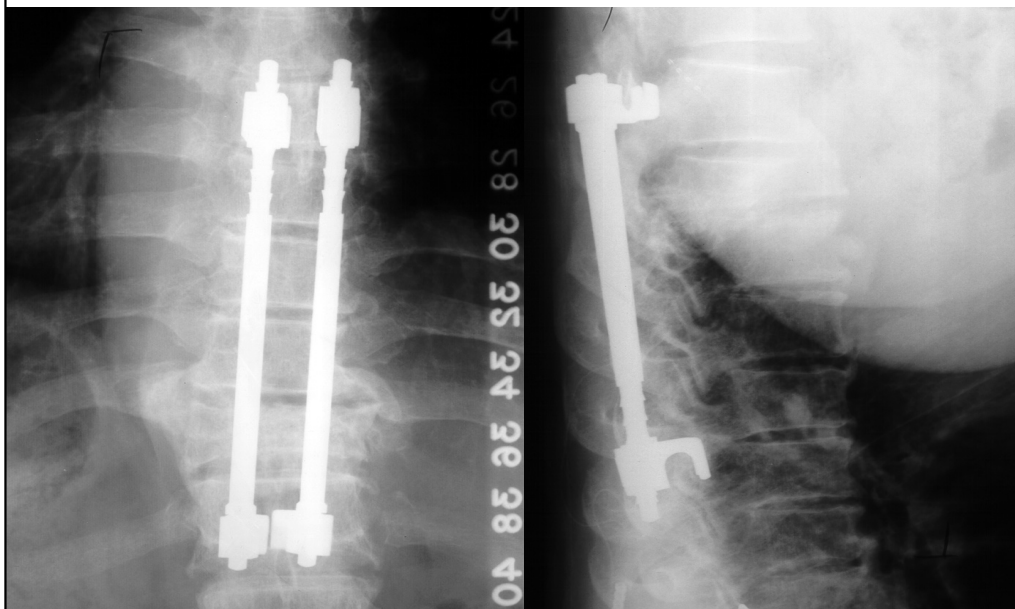
2001. 2. 13.



## ORIGINAL ARTICLE

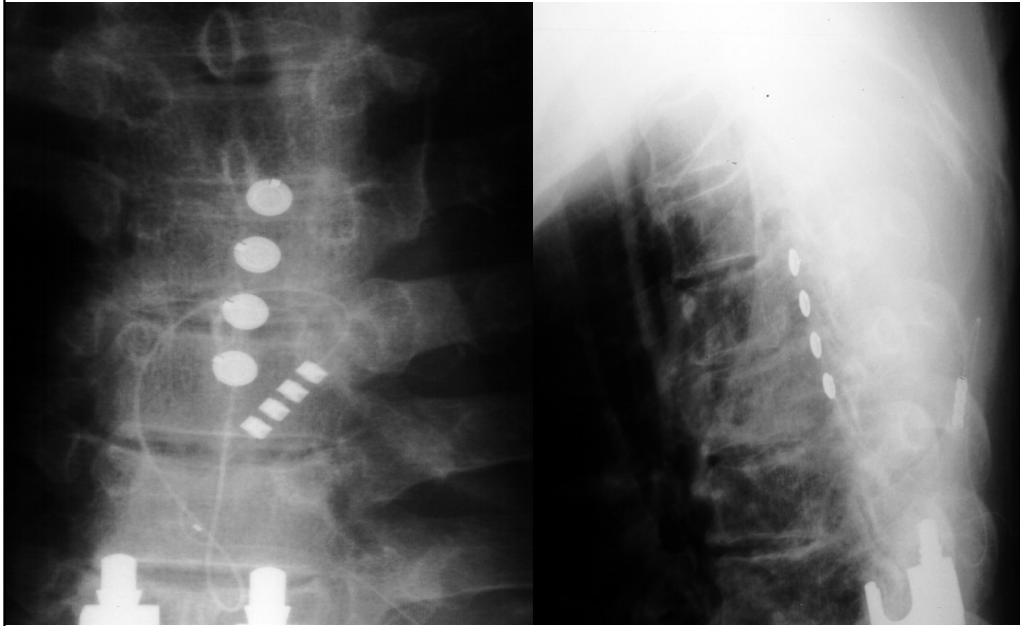
**Sacral Nerve and Spinal Cord Stimulation for Intractable Neuropathic Pain Caused by Spinal Cord Infarction**Sung Ho Kim, MD\* • Seong Ho Kim, MD\* • Sang Woo Kim, MD\* •  
Sung Ho Jang, MD†*Departments of \*Neurosurgery and †Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, Daegu, South Korea***ABSTRACT**

Central cord pain is very difficult to relieve, even with the many kinds of medical and surgical treatments available. Following spinal cord infarctions, central cord pain can develop. The problems that may arise could include limb pain, pelvic pain, difficulties voiding, and difficulties defecating. We are reporting a case of central cord pain caused by a spinal cord infarction of the conus medullaris. Limb pain was reduced by spinal cord stimulation. Voiding and defecation difficulties and pelvic pain were reduced by sacral nerve stimulation. Thus, in a case involving both intractable limb and pelvic pain, a combination therapy of these two stimulations might be an effective treatment modality.

**KEY WORDS:** *Bladder-bowel dysfunction, intractable pain, sacral nerve stimulation, spinal cord infarction, spinal cord stimulation.***Spinal Cord Injury (남/62)**

2001. 8. 10.

### Trial Stimulation (T 4-5)



### Spinal Cord Injury (34/M)

- Onset; 2007.02

Vector; 스노우보드 타다가 추락

- T12 burst fracture, complete cord injury

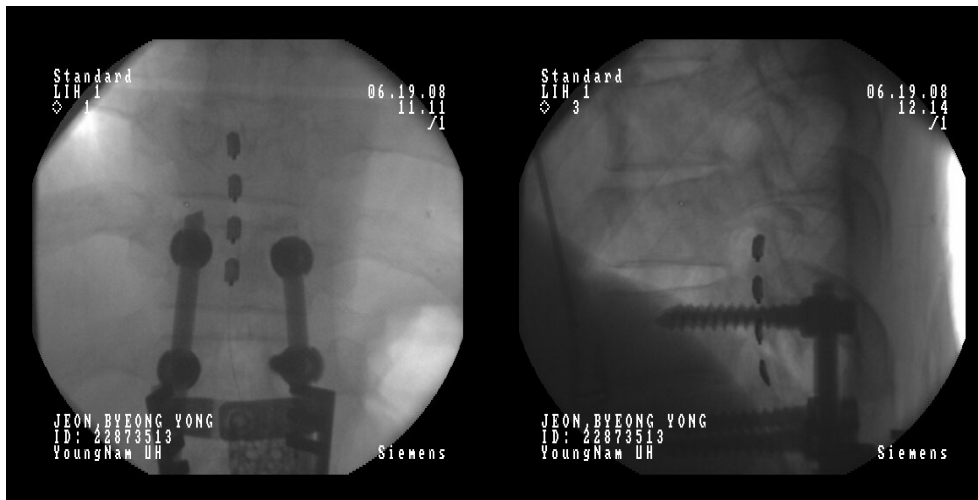
(T12 이하)로 기구고정술 받았으며, 수술 후부터 지속적인 배꼽주위의 band like pain (Rt. T9-T12, Lt. T7-T8) (Continuous pain + paroxysmal pain)

- Insomnia



## Progress

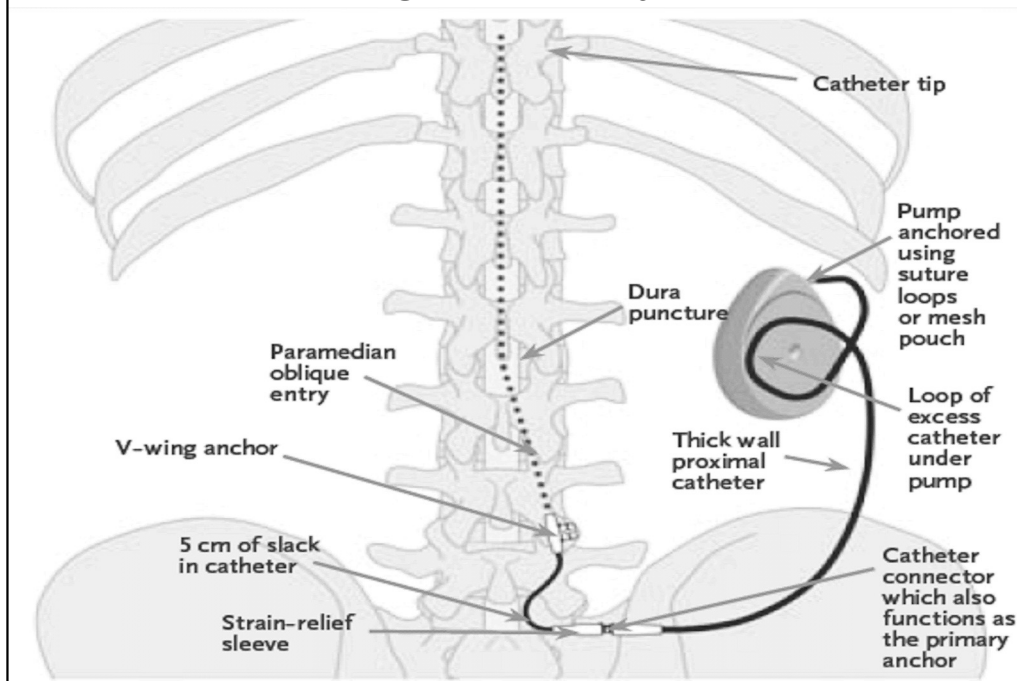
- 2008.05.26-06.19 : adm. & medication에도 VAS 9 → 8
- 2008.06. : nerve blocks → no effect
- 2008.06. : 임상심리 검사
- 2008.06.20 : trial, SCS → postop. wound site pain(+)
- 2008.06.22 : trial 2일째부터 pain 감소됨(Rt. side로 좀더 호전됨).  
VAS score 8-→3  
Rt. T9 - T12(VAS 8-→3)  
Lt. T7 - T8(VAS 8-→7)
- 2008.06.26 : Pulse generator insertion op. 함.  
(wire형 전극 추가 삽입 실시)
- 2008.10.20 : pain 호전 상태(VAS 8-→3)
- 2009.02.17 : pain 악화(VAS 8) MDT 시행(VAS 8)
- 2009.11.02 : 많이 호전됨(VAS 3-4)



## SCS for Pain with SCI

- Op procedure
  - Plate type (trial & permanent)
  - Trial: Laminotomy under LA or SA
- Successful trial stimulation
  - Sufficient dorsal column fibers
  - No allodynia
  - Segmental pain (complete)
  - Limb pain > perineal pain (incomplete)

## Drug Infusion System



## Intrathecal Therapy for Pain

- Opiates
- Non-opiate analgesics

Clonidine, octreotide, ziconotide(neuronal specific Ca- channel blocker), NMDA antagonists, benzodiazepines, butamin, bioactive implants(matrix adrenal medullary cells), tricyclic antidepressants, NO synthetase inhibitors

### The Efficacy of Intrathecal Morphine and Clonidine in the Treatment of Pain After Spinal Cord Injury

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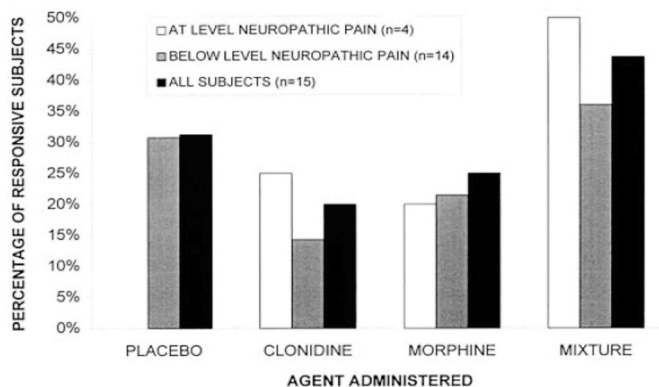


Figure 1. Percentage of people in each group (at-level neuropathic pain, below-level neuropathic pain) who obtained 50% or greater pain relief after the administration of intrathecal saline (placebo), morphine, clonidine, or a mixture of morphine and clonidine.

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Anesth Analg. 2000 Dec;91(6):1493-8.

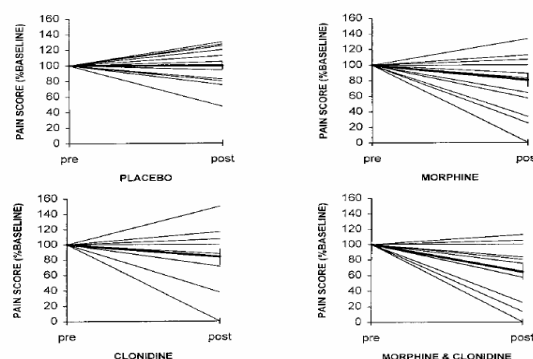


Figure 2. Pain relief (expressed as a percentage of the pretest baseline numerical pain rating score) after the administration of saline (placebo), morphine, clonidine, and a mixture of morphine and clonidine in the group of subjects with spinal cord injury. Lines represent the change in individual subjects and the heavy lines represent the means for the group with the vertical line indicating SEM. Pre, pretest; post, end of test.

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Table 1. Incidence of Side Effects

	Pruritus	Hypotension	Nausea	Sedation	Dry mouth	Oxygen desaturation
Saline	0	0	0	2 (13%)	0	2 (13%)
Morphine	6 (38%)	1 (6%)	2 (13%)	8 (50%)	0	8 (50%)
Clonidine	0	8 (53%)	6 (40%)	5 (33%)	3 (20%)	5 (33%)
Morphine/clonidine	4 (25%)	9 (56%)	0	3 (19%)	4 (25%)	7 (44%)



### **Combined intrathecal baclofen & morphine infusion for the tx. of spasticity related pain and central deafferentiation pain.**

- 5 patients with severe spasticity related pain.
- Patients with spasticity treated with intrathecal application of baclofen and morphine were pain free for a mean period of 2 years.

Acta Neurochir Suppl. 2002;79:75-6.

### **Intrathecal clonidine and baclofen in the management of spasticity and neuropathic pain following spinal cord injury: a case study**

- (F/32) incomplete C5 tetraplegia (anterior cord syndrome)
- Severe, intractable anal spasm following a hemorrhoidectomy, which persisted despite very good healing. (This prevented evacuation of her bowels and resulted in severe rectal pain and episodes of autonomic dysreflexia.)
- Intrathecal baclofen through an existing programmable infusion pump failed to reduce anal sphincter spasm or improve symptoms. A right-sided pudendal block with lignocaine provided some relief.
- Clonidine was added to baclofen in the pump reservoir and both drugs were administered intrathecally in combination.
- An immediate improvement in anal sphincter spasm and pain relief, allowing rapid reestablishment of her normal bowel pattern without need for any supplemental analgesia.

Arch Phys Med Rehabil. 1996 Aug;77(8):824-6

## Treatment of SCI Pain

	Evidence Required	Evidence Available
Standards	I	Intrathecal: morphine + clonidine
Guidelines	II,III	Intrathecal: alfentanil + ketamine Epidural: morphine; clonidine Intrathecal: baclofen
Options	III	Oral: tricyclic antidepressants; carbamazepine; gabapentin Intrathecal: morphine Ablative surgery: DREZ lesions, cordectomy, cordotomy, myelotomy

Burchiel KJ, et al, 2001

## Treatment of SCI Pain

### 비수술적 치료

- 약물치료  
Anticonvulsants, Antidepressants,  
Na channel blockers, Opioids,  
Clonidine, K channel blockers,  
NMDA receptor antagonists,  
GABA-B receptor agonist
- 물리치료(TENS)

### 수술적 치료

- 척수자극술(SCS)
- 뇌심부자극술(DBS)
- 운동피질자극술(MCS)
- 신경차단술
- 약물주입술 (ITD)