Central Poststroke Pain: A Review of Pathophysiology and Treatment

Bishwanath Kumar, MD

Jayantee Kalita, DM

Gyanendra Kumar, MD

Usha K. Misra, DM

BACKGROUND: Central poststroke pain (CPSP) is a disabling morbidity occurring in 8%–14% of patients with stroke. It is infrequently recognized and difficult to manage.
OBJECTIVE: We systematically reviewed the pathophysiology and treatment of CPSP.
METHODS: We conducted a Medline search using the key words "central post-stroke pain," "post-stroke pain," "CPSP and basic studies," "CPSP and clinical features," "CPSP and pharmacological treatment," "CPSP and nonpharmacological treatment" and "CPSP and treatment guideline." The articles related to CPSP were categorized into clinical features, pathophysiology and treatment, and then systematically reviewed.
RESULTS: Stroke along the spinothalamocortical pathway may result in CPSP after a variable period, usually after 1–2 mo. CPSP may be spontaneous or evoked, variable in intensity and quality. It tends to improve with time. CPSP is associated with mild motor symptoms with relative sparing of joint position and vibration sensations. The pathophysiology of CPSP is not well understood, but central disinhibition, imbalance of stimuli and central sensitization have been suggested. There are few class I and class II studies regarding its management. Amitriptyline and lamotrigine (class IIB) are recommended as first-line and mexiletine, fluvoxamine and gabapentin as second-line drugs. In pharmacoresistant patients, repetitive transcranial magnetic stimulation and deep brain stimulation have been beneficial.
CONCLUSIONS: CPSP patients present with diverse sensory symptoms and its pathophysiology is still poorly understood. Amitriptyline and lamotrigine are effective treatments. Further studies are needed to understand the pathophysiology and investigate newer therapeutic modalities.
(Anesth Analg 2009;108:1645–57)

Stroke is a leading cause of death and disability in low and middle income countries.[1] Central poststroke pain (CPSP) refers to pain resulting from a primary lesion or dysfunction of the central nervous system after a stroke. In the past, CPSP was attributed to a thalamic lesion but is now also associated with extrathalamic lesions.[2–4] It is probably the least recognized complication of stroke.[5] Most CPSP studies are based on patients from the general ward or stroke unit and rarely from population based surveys.[5–8] The prevalence of shoulder pain in stroke patients has ranged between 11% and 14%[9–11] and for CPSP between 8% and 35%.[4,12,13] The difference in the prevalence of CPSP is due to variations in inclusion criteria, the definition of CPSP and timing of the study. A prospective population-based study on 297 patients who had ischemic and hemorrhagic strokes revealed moderate to severe pain in 32% of patients after 4 mo and 21% after 16 mo. These patients were evaluated by a neurologist and the diagnosis of CPSP was considered if pain occurred after an obvious stroke, and when pain due to peripheral neuropathy, psychological cause, bedsore, pericapsulitis, and deep venous thrombosis was unlikely. At 16 mo, the higher pain intensity correlated with female sex, worse Geriatric Depression Scale score, better Mini Mental State Examination score, and increased glycosylated hemoglobin.[5] In another prospective hospital-based study including all type of strokes, pain onset was within 1 mo in 63%, between 1 and 6 mo in 19% and after 6 mo in 19% of patients.[12]

CPSP is unique because of its diversity, which is reflected in its clinical picture, latency from the onset of stroke, pathophysiological mechanisms, and treatment options. CPSP can result in disability, interfere with rehabilitation and adversely affect quality of life. With the recent advances in imaging technique, neurophysiology, molecular biology and various pharmacological and nonpharmacological treatment options, a comprehensive review of CPSP with

From the Department of Neurology Sanjay Gandhi PGIMS, Lucknow, India.

Accepted for publication November 18, 2008.

Address correspondence and reprint requests to Usha K. Misra, DM, Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raebareily Rd., Lucknow 226014. Address e-mail to ukmisra@sgpgi.ac.in or drukmisra@rediffmail.com.

DOI: 10.1213/ane.0b013e31819d644c

Table 1. Evidence Classification Scheme for Therapeutic Interventions

Class 1:
An adequately powered randomized controlled trial with measured outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled trials (RCTs) with masked outcome assessment in representative populations. The following are required:
(a) Randomization concealment.
(b) Primary outcome (s) are clearly defined.
(c) Exclusion/inclusion criteria are clearly defined.
(d) Accurate accounting for dropout and crossovers with numbers sufficiently low to have minimal potential for bias
(e) Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate adjustment for differences.

Class II:
Prospective matched group cohort study in a representative population with masked outcome assessment that meets a-c, above or RCT in a representative population that lacks one criteria.

Class III:
All other controlled trials (including well defined natural history controls or patients serves as own controls) in a representative population where outcome assessment is independent of patient treatment.

Class IV:
Evidence from uncontrolled studies, case series or case report or expert opinion.

Rating of recommendation:
Level A: Established as effective, ineffective or harmful; requires at least one class I study or 2 consistent convincing class II studies.
Level B: Probably requires at least 1 convincing class II in overwhelming class III evidence.
Level C: Probably requires at least 2 class III studies.

Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces–revised recommendations 2004. Eur J Neurol 2004;11:577–81.

emphasis on its management is important to the pain medicine practitioner.

Search Methodology and Classification of Levels of Evidence

On September 1, 2008, a MEDLINE search using the key words "central post-stroke pain" yielded 45 articles, "post-stroke pain" 72 articles, "CPSP AND Basic studies" no articles, "CPSP AND Clinical feature" no articles, "CPSP AND Pharmacological treatment" 9 articles, "CPSP AND Nonpharmacological treatment" no articles and "Post-stroke pain AND Animal studies" 7 articles. These articles form the basis of the present review which addresses clinical features, clinicoradiological correlation, pathophysiology, and treatment of CPSP. The therapeutic studies and level of recommendations are categorized according to the European Federation of Neurological Society and are described in Table 1.[14]

Clinical Picture

Central pain may be spontaneous or evoked. Spontaneous pain may be continuous or paroxysmal.

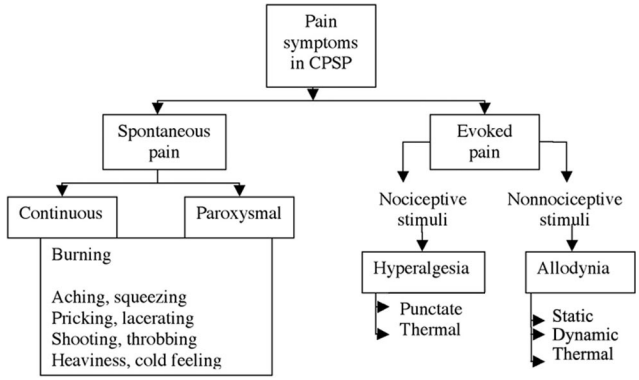

Figure 1. Pain symptoms in central poststroke pain (CPSP).

Evoked pain may be precipitated by nonnociceptive or nociceptive stimuli (Fig. 1). Most CPSP patients complain of burning and other symptoms, including aching, pricking, lacerating, shooting, squeezing, and throbbing in isolation or in various combinations. These symptoms may be continuous or intermittent. The pain may be aggravated by several stimuli, such as movement, touch, temperature, or stress. Allodynia, dysaesthesia and hyperalgesia are commonly associated with most patients with CPSP. A simple bedside test may elicit allodynia or dysaesthesia by touch or temperature stimuli in 33%–86% patients with CPSP,[2,3] but these conditions are rarely found in pain-free stroke patients with similar somatosensory deficit. Hyperalgesia or allodynia therefore are important and perhaps essential parts of CPSP syndrome.[2,15]

The term "CPSP" implies the occurrence of pain after a variable period after stroke. In most patients, CPSP develops within 6 mo of stroke onset and its incidence decreases thereafter. In a review of patients with CPSP after thalamic stroke, 36% of patients developed pain within 1 and 3 mo, 12% between 3 and 6 mo, 6% between 6 and 12 mo, and 11% after 12 mo.[2] Two-thirds of patients with CPSP have impaired pinprick, temperature and touch sensation, whereas impairment of vibration and joint position occur less frequently. The distributions of pain, in terms of frequency, are arm, leg, trunk, and face. The most common pattern is hemibody. CPSP may occur in the absence of weakness; however, various neurological deficits, such as hemiparesis, ataxia and choreoathetosis on the affected side, may be present in 60% of patients.

The sensory symptoms of CPSP are usually contralateral to the stroke. Recently, CPSP on the ipsilateral and contralateral side has also been reported in 6 patients: 2 with thalamic, 1 with pontine, 2 with medullary infarctions, and 1 with capsular hemorrhage. In these patients, ipsilateral CPSP developed 6 to 24 mo after the stroke, which was associated with the worsening of contralateral pain. The ipsilateral symptoms were mild, and without objective sensory deficit and developed in the body part mirroring the greatest pain on the contralateral side.[16] The reported clinical features of various studies on CPSP are summarized in Table 2.

Table 2. Percentages of the Quality, Onset, and Durations of the Signs and Symptoms of Central Poststroke Pain (CPSP)

Pain quality		Symptom onset		Location of stroke (%)	
Leijon et al.[33] 1989 (n = 27)					
Burning	59%	Immediate	15%	Thalamus	33.33%
Aching	30%	Within 1st month	37%	Brainstem	29.63%
Pricking	30%	1–3 mo	26%	Supratentorial	22.22%
Lacerating	26%	5–12 mo	11%	Not located	14.81%
Shooting	11%	24–34 mo	11%		
Squeezing	11%				
Throbbing	11%				
Other	19%				
Andersen et al.[12] 1995 (n = 207, CPSP = 16)					
Lacerating	50%	Within 1st month	63%	Thalamus	25%
Aching	25%	1–6 mo	19%	Extrathalamic	75%
Burning	19%	>6 mo	19%		
Freezing	19%				
Squeezing	19%				
Other	13%				
Widar et al.[13] 2002 (n = 43)					
Stabbing		Within 1st week	33%	Brainstem	11.62%
Aching		Within 1st month	20%	Thalamus	11.62
Dull aching		2–6 mo	47%	Supratentorial	62.79%
Burning				Not located	13.59%
Bowsher et al.[17] 1998 (n = 73)					
Burning	43.8%			Infratentorial	16.43%
Aching and throbbing and cramps	41%			Thalamic + capsular	36.98%
Electrical	10.9%			Supratentorial	28.76%
				Multiple	17.80%

Pain quality		Symptom onset		Pain distribution	
MacGowan et al.[18] 1997 (n = 63, CPSP 16) Lateral medullary infarction					
Burning	87.5%	2 wk	18.6%	I/L cheek	31.25%
Add. electrical	37.5%	1 mo	51.36%	C/L arm leg	18.7%
Only electrical	12.5%	6 mo	All	C/L arm	12.5%
Cold	75%			I/L cheek, C/L arm leg	37.5%
Mechanical	27.5%				
Kim[72] 2003 (n = 20, Capsular hemorrhage)					
Cold	50%	Simultaneous	15%	Leg	45%
Numb	95%	Within 1 mo	25%	Foot	5%
Aching	20%	2–3 mo	45%	Leg, arm	20%
Swollen	95%	4–6 mo	10%	Leg, trunk	5%
Squeezing	10%	>6 mo	5%	Leg, arm, face	25%

Kim[19] 1999

Pain characters and percentage Lateral medullary syndrome (n = 41)		Pain characters and percentage Medial medullary syndrome (n = 1 4)	
Cold	17%	Numb	7.1%
Burning	7.3%	Numb, cold	28.5%
Burning, cold	12.2%	Cold, numb, pricky	7.1%
Burning, numb	7.3%	Squeezing, numb, heavy	14.2%
Squeezing	2.4%	Numb and heavy	14.2%
Burning, numb, cold	4.8%		
Burning, numb, pricky	2.4%		
Cold, numb	2.4%		
Cold, numb, pricky	2.4%		
Distributions			
Face	4.8%	Body limb	64.4%
Body limb	29.2%	Face (C/L), Body limb	14.2%
I/L face, body limb	34.1%		
C/L face, body and limb	12.2%		

I/L = Ipsilateral; CL = contralateral; CPSP = central poststroke pain.

Clinical and Radiological Correlation

Stroke anywhere in the spinothalamic pathway and its cortical projection may result in CPSP, although in the past, thalamic pain was synonymous with thalamic stroke (Fig. 2). Most CPSP patients have multiple lesions on their magnetic resonance imaging (MRI), and many of these are unrelated to pain. Ventroposterolateral (VPL) thalamic nuclear lesions are more likely to produce hemibody (Fig. 3) pain than lesions elsewhere. The most severe pain is more likely in an extremity in

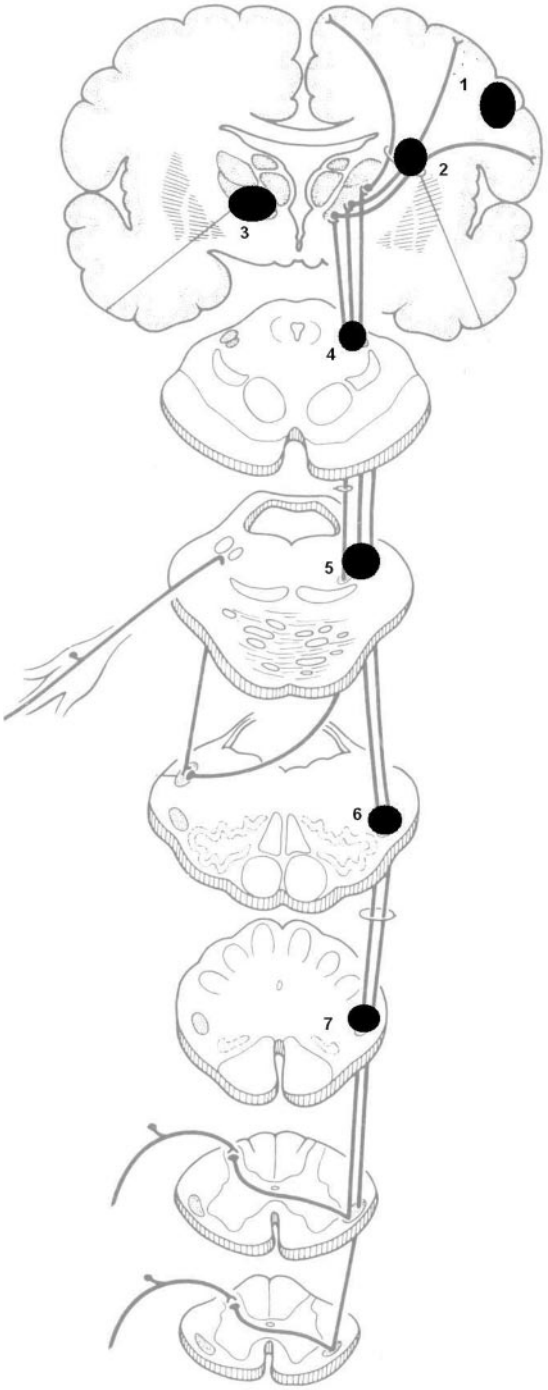

Figure 2. Schematic diagram shows the various locations of stroke producing central poststroke pain. 1 = sensory cortex; 2 = thalamocortical projection of spinothalamic sensations; 3 = ventral posterolateral nucleus of thalamus; 4 = Midbrain; 5 = Pons and 6 and 7 = Medulla.

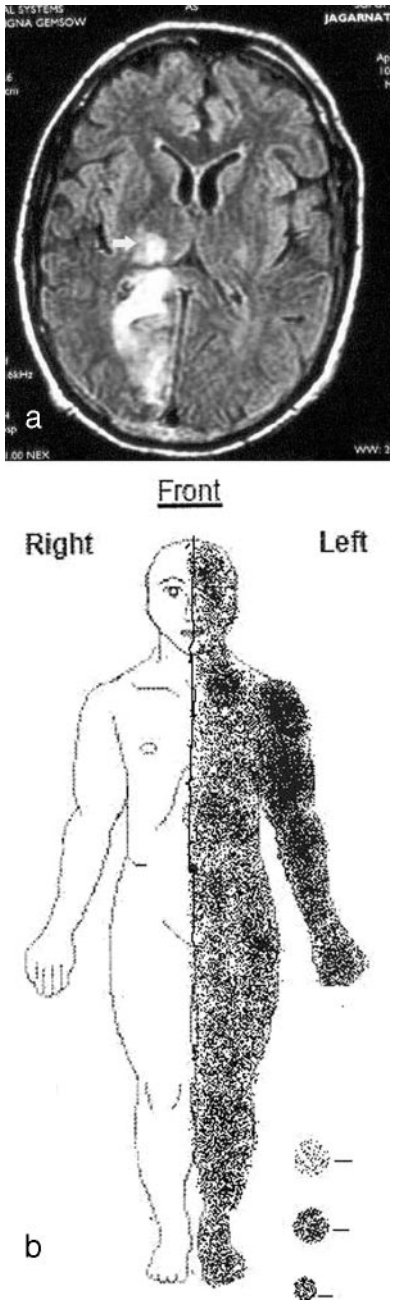

Figure 3. a, Cranial MRI, FLAIR sequence showing infarction of right thalamic and occipital region. b, Schematic diagram of the same patient showing areas of central poststroke pain with different severity which is depicted by density of black dots.

supratentorial lesions and on the face in infratentorial lesions. Unlike pain-free stroke patients, patients with CPSP due to supratentorial lesions have a deficit of sensation to sharpness or cold (predominantly mediated by A δ fibers) than pain free stroke patients, whereas patients with infratentorial CPSP have a deficit of C fiber-mediated temperature sensation and heat pain. Burning pain is more common than nonburning pain in younger patients.[17] CPSP usually occurs from where the lesion is in the sensory pathways, but CPSP resulting from capsular hemorrhage (Fig. 4), Wallenberg syndrome (lateral medullary wedge infarction with characteristic clinical features) and cortical infarctions has also been reported. CPSP occurred in 20 patients after capsular hemorrhage. Sensory symptoms appeared 0–24 mo after the stroke involving mainly the leg. The symptoms were attributed to the medio-lateral orientation of sensory pathways in the VPL nucleus of the thalamus. Lateral medullary syndrome involves spinothalamic and trigeminothalamic pathways, and medial medullary syndrome involves lemniscal pathways. In a study of 63 patients with

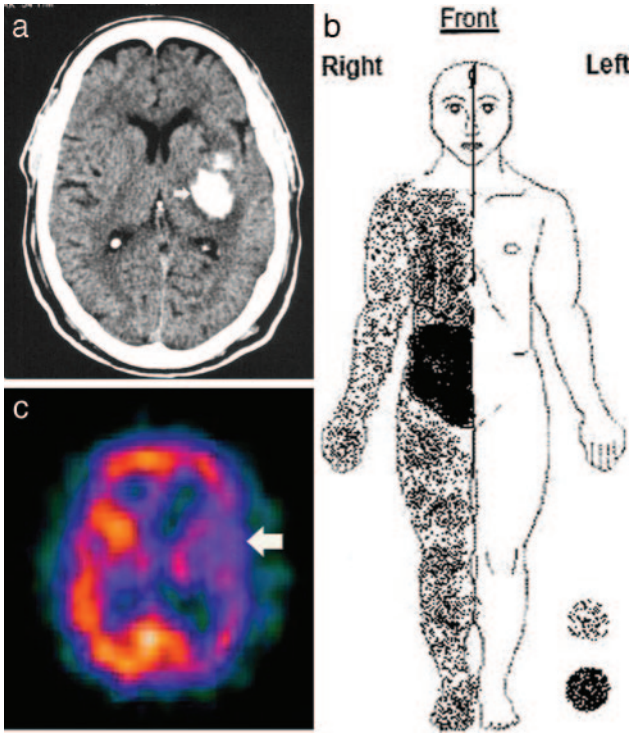

Figure 4. a, Cranial computed tomography (CT) scan of a patient with central poststroke pain showing left putaminal hemorrhage with capsular extension. b, Schematic diagram of the same patient showing area pain, the density of darkness depicts the intensity of pain. c, Tc^{99}ECD SPECT of the same patient showing hypoperfusion of left fronto-parietal and ganglionic region.

Wallenberg syndrome, 25% developed CPSP within 6 mo of the onset of stroke. The pain was constant and severe, with frequent allodynia. CPSP was associated with ipsilateral periorbital pain, with or without contralateral limb pain, and was correlated with sensory loss, but not with the size of infarction on MRI.[18] A comparative study of lateral (41 patients) and medial (14 patients) medullary infarctions revealed that lateral medullary infarctions were associated with numbness, burning, and cold on the face, with or without trunk and limb involvement. In medial medullary infarctions, symptoms included numbness, squeezing, and cold sensation but rarely burning. The patients with lateral medullary infarcts more frequently cited a cold environment as an aggravating factor for sensory symptoms.[19]

Cortical stroke involving insular and opercular areas was related to primitive sensory impairment and to CPSP, whereas involvement of post central gyrus was related to cortical sensory loss without CPSP.[20] The insular and opercular regions roughly correspond to secondary sensory areas and seem to modulate pain and thermal sensation.[21]

Pathophysiology

In 1906, Dejerine and Roussy[22] first described the thalamic syndrome, a condition which follows a thalamic stroke, with severe pain in the contralateral side. The pathophysiology of CPSP is not well understood but central disinhibition, imbalance of stimuli and central sensitization have been suggested. Head and Holmes,[23] in 1911, proposed the disinhibition theory, according to which injury to the lateral thalamus sets the medial thalamus free from its control. Later it was found that the lesions anywhere in the spinothalamocortical pathway lead to prominent over-activity of the lateral thalamus. In either situation, CPSP is associated with impaired sensation evoked by cotton whisp, vibration, roughness, heat and cold.[23] The essential component of this hypothesis is that discriminative sensory deficit in CPSP results in disinhibition, which gives rise to spontaneous pain or allodynia. Hyperalgesia or allodynia are probably an integral component of CPSP. In earlier studies, partial sensory loss of spinothalamic modalities was considered necessary for the development of CPSP.[22,24] This, however, is not sufficient, as spinothalamic deficit, manifested by loss of thermal sensation but without pain, is found in more than half of patients.[12] It is therefore not possible to predict the development of CPSP by documenting sensory loss. The most likely mechanism for hyperalgesia and partial sensory loss in a body part with normal somatosensory function in a nonpainful body territory is central sensitization of the third order neurons that have been partially deafferented.[25] In the clinical setting, central sensitization can be assessed by mapping the hypersensitive areas, psychophysiological measurement of different thresholds, and response to various stimuli.[25] The specific neuronal populations which are sensitized in CPSP are not well known, but certain thalamic nuclei are likely to be responsible. Thalamic neurons may be divided into two main groups:

1. Relay cells that project to cerebral cortex and
2. GABAergic inter-neurons that produce local inhibition.

These cell types have two firing patterns: (a) bursting when the neuronal cell membrane is hyperpolarized and (b) single-spike activity when the neuron is depolarized.[26] Reticular nucleus surrounding the dorsal and lateral aspect of thalamus produces GABAergic inhibition of relay cells. Groups of deafferented cells in the reticular formation are capable of generating intrinsic bursting activity, which results in a vicious cycle. The corticothalamic axons traverse through the reticular nucleus and innervate these cells by collaterals; hence, cortical lesions may also influence the firing pattern of reticular neurons. In neuropathic pain, spontaneous neuronal activity is found in the mediodorsal, centrolateral, centromedian, and parafascicular nuclei as well as principal sensory nuclei (ventralis caudalis).[27]

A positron emission tomography (PET) study in volunteers also confirms the role of the thalamus in normal nociceptive processing. Thalamic metabolic

Table 3. Drugs Studied in Central Poststroke Pain and Their Mechanism of Action

Drugs	Mechanism
Antidepressants Amitriptyline	Balanced monoamine reuptake inhibition
Anticonvulsants	
Phenytoin	Voltage-gated sodium-channel blockade
Carbamazepine	Voltage-gated sodium-channel blockade
Lamotrigine	Presynaptic voltage-gated sodium-channel inhibition thus reduced release of presynaptic transmitters
Topiramate	Voltage-gated sodium-channel block and inhibition of glutamate release by an action on AMPA/kainase receptors
Gabapentine	Binding to $\alpha_{2\delta}$ subunit of presynaptic voltage-dependent calcium channels with reduced release of presynaptic transmitters
Zonisamide	Voltage-gated sodium-channel block
Anesthetics	
Lidocain	Blockade of sodium channels thus preventing ectopic discharges
Mexiletine	Same as lidocain
NMDA receptor antagonist	
Ketamine	NMDA receptor antagonist
Analgesics	
Tramadol	μ opioid-receptor agonist and monoamine
Morphine	Reuptake inhibitor

activity increases after noxious stimuli. In CPSP, thalamic hypoperfusion in single photon emission computerized tomography and hypometabolism in PET studies have been reported. In one patient, the PET scan revealed hypometabolism of the thalamus on the corresponding side.[28] Single photon emission computerized tomography studies in CPSP patients with allodynia have revealed hypoperfusion in the contralateral thalamus.[29] Metabolic activity in the thalamus improves with pain-relieving procedures. Spatial resolution of PET does not differentiate various nuclei, but this limitation is overcome by functional MRI studies. In a patient with CPSP with right thalamic VPL nucleus and adjacent posterior limb internal capsule infarction, functional MRI revealed pain-specific signal changes in the anterior cingulate gyrus and association parietal cortex. The damage to the lateral nociceptive thalamoparietal fibers, together with release of activity of the anterior cingulate and posterior parietal regions, have been suggested as a mechanism of CPSP.[30]

Neurotransmitters and Their Modulation

The shift of thalamic neuronal activity from rhythmic burst firing to single-spike activity is determined by serotonergic, noradrenergic, and cholinergic input of thalamic neurons. Noradrenaline originating from the locus ceruleus and serotonergic pathway from dorsal Raphe nuclei mediate thalamic burst firing by acting through reticular and relay nuclei.[31] The beneficial effect of amitriptyline and duloxetine may be mediated through the above-mentioned mechanisms. Excitatory aminoacids, such as *N*-methyl-D-aspartate, may mediate nociceptive or nonnociceptive inputs to the thalamic nuclei. ^{11}C-diprenorphine PET studies in CPSP have been used to evaluate the distribution of opioid receptors; these studies have demonstrated a significant decrease in opioid receptor binding, not only in thalamus contralateral to pain, but also in insula, anterior cingulate and secondary sensory cortex. The decrease in opioid receptor binding may be due to an increase in endogenous release, internalization or dysregulation of receptors and loss of neurons carrying these receptors.[32]

Treatment

The pharmacological and nonpharmacological treatment of CPSP is challenging, and MEDLINE search results on this subject highlight the inadequacy and limitation of the present therapies. The drugs used for CPSP are listed in Table 3.

Antidepressants

Amitriptyline

There is only one class II, three-phase, placebo-controlled, crossover study comparing amitriptyline, carbamazepine, and placebo. The study involved 15 patients with CPSP without depression. The patients were randomly given amitriptyline up to 75 mg daily, carbamazepine up to 800 mg daily or placebo for 4 wk followed by 1 wk washout and then were crossed-over to the alternate treatment (without placebo). Amitriptyline was significantly better than placebo in relieving pain at 2 wk, 3 wk, and 4 wk. Carbamazepine was better at 3 wk only, compared with placebo, and at other time points it was no more effective than placebo in reducing pain. Patients taking amitriptyline complained of fatigue and dry mouth more frequently, though no dose modification or drug withdrawal was needed. Patients receiving carbamazepine experienced vertigo, tiredness/gait disturbance. A dose reduction was required for four patients.[33]

Conclusion

Amitriptyline is effective, safe, and well tolerated compared with placebo for treatment of CPSP (class II, level B evidence).

The role of amitriptyline in preventing CPSP in thalamic stroke has also been evaluated in a double-blind, placebo-controlled study. Extended release amitriptyline (titrated from 10 to 75 mg) and placebo were randomly assigned in 39 and 20 patients for 365 days. CPSP developed in 21% of patients in the placebo compared with 17% in the amitriptyline group. Amitriptyline was not effective for preventing CPSP in patients with thalamic stroke.[34]

Conclusion

Amitriptyline is not effective for preventing CPSP in thalamic stroke (class II, level B).

Fluvoxamine

The selective serotonin reuptake inhibitor fluvoxamine up to 125 mg showed some efficacy in an open-labeled study of 31 patients with CPSP. The average pain was reduced from 7.7 to 6.0 on a visual analog scale. It was effective in those patients who had stroke within 1 yr and its effect was not related to its antidepressant action.

Conclusion

Fluvoxamine at least 125 mg daily is effective (class II, level B) in CPSP patients who had a stroke within 1 yr.

In an open-level study of five patients with CPSP, clomipramine resulted in mild and moderate improvement in two patients each and excellent in one.[35] Citalopram and reboxetine have been tried in a small number of CPSP patients and were not found to be effective.[35,36]

Anticonvulsants

Carbamazepine

The study on carbamazepine has been described in the previous section on amitriptyline. On the basis of this study, we conclude that carbamazepine is minimally effective (better than placebo only) at the 3-wk assessment period—class II level B.[33]

Lamotrigine

In a class I, randomized, double-blind, placebo-controlled, crossover study, 30 patients with CPSP received lamotrigine or placebo. The study consisted of two 8-wk treatment periods separated by 2 wk of washout. Lamotrigine was started at 50 mg/d and escalated up to 200 mg/d. The primary end-point was the median value of the mean daily pain score during the last week of treatment although receiving 200 mg of lamotrigine. Lamotrigine 200 mg/d reduced the median pain score to five compared to seven with placebo in the intention-to-treat population of 27 patients ($P = 0.01$). Twelve patients in the lamotrigine group responded with a pain reduction of more than two points, whereas only three patients in the placebo group responded. The secondary end-points, such as global pain score, assessment of evoked pain, duration of spontaneous pain, allodynia and dysesthesia tended to improve insignificantly in the lamotrigine group compared with placebo. Side effects were reported in 57% of patients in the lamotrigine group (control 60%); the main side effects requiring withdrawal of lamotrigine in three patients included skin rash, headache, and pain.[37]

Conclusion

Lamotrigine is a moderately effective and well tolerated drug for CPSP (class I level B evidence).

Gabapentin

Gabapentin has been tried in a randomized, placebo-controlled trial of 305 patients with chronic pain, 9 of whom had CPSP.[38] The starting dose of gabapentin was 300 mg 3 times daily for 3 days, gradually increasing to 1800 or 2400 mg daily for 8 wk. Gabapentin administration resulted in improvement of pain score in 21% of patients compared with 14% of controls which is not significant ($P = 0.48$). Gabapentin was well tolerated and the majority of patients completed the study (79% vs 73%). The most common adverse events were mild to moderate dizziness and somnolence which were transient and occurred during the titration phase.[38] Usefulness of gabapentin, however, has been reported in a 45-yr old man with CPSP who was refractory to phenytoin, carbamazepine, and sodium valproate.[39]

Conclusion

Gabapentin is well tolerated but not effective in CPSP (class III).

Phenytoin, zonisamide, and topiramate have been tried in a small number of patients with CPSP. In an open-labeled study, phenytoin was tried in eight patients with thalamic pain. The dose of phenytoin increased until the side effects appeared. Three patients improved markedly, two minimally and three worsened.[40] Zonisamide, in a dose of 200 mg daily, was found to be effective in two patients with CPSP after right thalamic infarction. One of these patients was refractory to carbamazepine 300 mg daily. The second patient responded to amitriptyline 20 mg as well. There were no side effects.[41] Topiramate has been studied in seven patients with central pain; three of whom had CPSP. All patients were refractory to carbamazepine, amitriptyline, lamotrigine, gabapentin, and mexiletine. The patients were prescribed topiramate 25 mg twice daily, increased by 50 mg weekly up to a maximum of 200 mg 3 times daily or until toxicity or adequate relief. None of the patients had meaningful CPSP relief. The side effects included urinary sludge or lethargy.[42]

Conclusion

There is inconclusive evidence for phenytoin, zonisamide, and topiramate in CPSP.

N-methyl-D-aspartate Antagonist

Ketamine

In an uncontrolled trial, 23 patients with CPSP were given ketamine in a dose of 5 mg every 5 min to a total

dose 25 mg. More than 40% pain relief was observed in 11 patients, which lasted less than an hour. Pain worsened in two patients.[43]

Dextromethorphan

In a placebo-controlled trail of 21 patients with neuropathic pain, including nine patients with CPSP, dextromethorphan in a dose of 81 mg/d did not have any effect compared with placebo.[44]

Conclusion

Ketamine may be tried in refractory patients with CPSP as a short-term measure (class IV) and dextromethorphan is not effective (class III).

Opioids

Morphine

Morphine was evaluated in a double-blind, placebo-controlled, crossover study in 15 patients with central pain (CPSP 6, spinal cord injury 9). The double-blind phase was performed 3 wk after the open-label titration phase. In an open-label phase, 2 mg morphine IV was administered every 10 min until the maximum tolerated dose (when there were side effects in the form of nausea, vomiting, somnolence, or O_2 saturation $<75\%$). In the double-blind phase, a predetermined dose of IM morphine (9–30 mg, mean 16 ± 6.1 mg) or the same volume of saline was infused over 20 min. The treatment protocol was reversed after 2 wk. Morphine significantly reduced brush-induced allodynia but had no effect on other evoked pain e.g., static, mechanical and thermal allodynia/hyperalgesia. The effect of morphine on continuing pain was not significantly different compared with placebo (46% vs 13% in placebo). Forty-six percent of patients in the morphine group responded. Fourteen of these patients were prescribed oral morphine but 10 were withdrawn from the study before 12 weeks due to the side effects. Morphine caused significant side effects compared with placebo (60%vs 40%, $P = 0.005$) which included somnolence, headache, and nausea.[45]

Conclusion

Morphine is ineffective in CPSP and side effects are frequent; class II level B evidence.

Naloxone

In a randomized, placebo-controlled, crossover trial of 20 patients with CPSP, the efficacy and safety of naloxone was evaluated. Naloxone 8 mg or less was infused in 11 patients and those patients were compared with 9 patients who received normal saline. After 2–3 wk, the treatment protocol was reversed. Transient pain relief was reported in three patients receiving naloxone, four patients receiving saline and four taking both; these differences were not significant. Adverse effects of naloxone included increased heart rate, sweating, tremor, salivation and increase in pain in two patients. One patient had to withdraw from therapy in the naloxone group.[46]

Conclusion

Naloxone is ineffective in CPSP and causes more side effects (class II, level B).

Levorphanol

Levorphanol which is an μ-opioid agonist was used in 81 patients with refractory neuropathic pain; 10 of them had CPSP or focal brain lesion. The patients were randomly assigned high (8.9 mg/d) and low dose (2.7 mg/d) levorphanol. The percentage of pain reduction in the high dose group was 23% compared with 14% in the low dose group. Because of the frequency of side effects, 7 of 10 patients with CPSP could not complete the study.[47]

Conclusion

Oral levorphanol is not effective (class III, level C).

Tramadol

Tramadol has been tried in 1 patient with CPSP; 50 mg tramadol IV was given over 5 min after which oral codeine phosphate 20 mg and milnacepram 25 mg twice daily were given. After injection of tramadol, complete pain relief was achieved for 5 h; the patient was asymptomatic for 10 mo with codeine phosphate and milnacepram.[48] There were no side effects.

Conclusion

Only one class IV study showed tramadol to be beneficial.

Anesthetics

Lidocaine

The effect of lidocaine was evaluated in a randomized, double-blind, placebo-controlled trial of 16 patients with neuropathic pain, 60% of whom had CPSP. Lidocaine was administered in a dose of 5 mg/kg IV over 30 min and compared with saline. The treatment protocol was reversed after 3 wk. Lidocaine was significantly superior to placebo in relieving spontaneous continuing pain up to 45 min after infusion. A majority of patients (62.5%) had significant relief of spontaneous pain after receiving lidocaine, whereas 37.5% achieved pain relief with placebo. The effect of lidocaine began after infusion and declined to a negligible level by 2–6 h. Lidocaine also significantly reduced the intensity of brush allodynia and mechanical hyperalgesia but was not better than placebo. All patients completed treatment except for one in whom infusion had to be stopped because of somnolence and light-headedness. Mild to moderate side effects were noted in 11 patients in the lidocaine and 5 in the placebo group. Light-headedness was noted only in the lidocaine group. Lidocaine significantly reduced spontaneous pain in CPSP.[49]

Three weeks after completion of this study, 12 subjects were prescribed mexiletine, starting 200 mg

Table 4. Important Studies on Pharmacological Treatment of Central Poststroke Pain (CPSP)

Author	Class	Level	No. of pts	Drugs, dose, duration	Efficacy	Adverse effects
Vestergard et al.[38] 2001	I	B	30	Lamotrigine 25 mg/d increased to 200 mg/day or placebo × 8 wk, followed by 2 wk wash out then crossed over	Median pain score at last week of treatment ↓ to 5 in lamotrigine 200 mg/d and to 7 in placebo ($P = 0.01$)	Lamotrigine 57% vs Placebo 60%. 5 patients developed rash in lamotrigine vs 2 patients in placebo. 3 patients withdrawn from lamotrigine due to rash, headache and pain
Serpell et al.[39] 2002	I for pain III for CPSP	—	Pain ($n = 307$) CPSP (9/307)	Gabapentin: 900 mg/d increased to 1800 or 2400 mg mg/day × 8 wk, gabapentin ($n = 153$), Placebo ($n = 152$)	Improvement in pain score, gabapentin (21%) vs placebo (14%), $P = 0.48$	Dizziness (24% vs 8%) and somnolence (14% vs 5%) Were common in gabapentin compare with placebo
Leijon, Boivie.[33] 1989	II	B	($n = 15$)	Carbamazepine upto 800 mg/d or placebo × 4 wk then 1 wk washout period followed cross over	Carbamazepine better than placebo in relieving pain at 3 wk ($P < 0.05$) over the course of but not at other time points	CBZ resulted vertigo, tiredness, dry mouth, GI disturbance resulting in dose reduction in 4 patients
Leijon et al.[33] 1989	II	B	15	CBZ 800 mg/d vs amitriptyline 75 mg/d or placebo × 4 wk then wash out 1 wk followed by crossover	Pain relief was significantly better in amitriptyline than placebo at 2 wk ($P < 0.01$), 3 wk ($P < 0.05$), and 4 wk ($P < 0.05$)	Tiredness, dry month
Attal et al.[50] 2000	II	B	Central pain (16) CPSP (6/16)	Lidocain 5 mg/kg over 30 min vs saline; after 3 wk oral mexiletine 200 mg/d ↑ to 800 mg/d × 4–12 wk in 12 patients	Moderate to complete pain relief in 69% in lidocain vs 38% in placebo. Oral mexiletine not effective	11 patients in lidocain had side effect (1 withdrawn), vs 5 in placebo. Major side effect light headedness
Bainton et al.[47] 1992	II	B	20	Naloxone 8 mg IV vs normal saline then crossover	Pain relief in naloxone 27.2% vs placebo 44% (nonsignificant) group	Sweating, tremor, salivation, increased, abdominal pain in naloxone group
Attal et al.[46] 2002	II	B	15 pts, CPSP-6	IV morphine mean 16 mg (9–13 mg) vs saline infusion over 30 min. Switched over to oral morphine	Pain relief 46% in morphine 13.6% in placebo group (insignificant)	Higher side effects in morphine 60% vs 40%); somnolence, nausea and vomiting

CPSP = central poststroke pain.

daily which was increased weekly up to 400–800 mg and the effect was evaluated after 4–12 mo. Twenty-five percent of patients experienced moderate pain relief (visual analog scale score reduced by 30%–50%), 1 patient reported slight pain relief (8.7%) and 8 (66.3%) patients did not have any relief. Side effects were reported by 10, leading to drug withdrawal in 2 patients. The side effects included nausea, hypotonia, somnolence, and drowsiness.[49]

Conclusion

IV lidocaine may be effective for a short period in CPSP (class II level B).

Propofol

In a placebo-controlled study, a subhypnotic dose of IV propofol was tried in seven patients with CPSP which resulted in relief of both spontaneous and evoked pain in five patients.[50]

Pentothal

Pentothal was used in a subanesthetic dose IV (maximum 250 mg) in 39 patients with CPSP. It resulted in pain reduction up to 40% in 22 patients. The effect lasted for at least 1 h.[42]

Conclusion

IV propofol and pentothal (class III) may be effective for a short period in CPSP. Mexiletine is not effective in CPSP and has a high side effect profile (class III).

Some important studies on various pharmacological treatments are summarized in Table 4.

Guidelines

A number of academic bodies have issued guidelines for treatment of neuropathic pain but there are few guidelines for CPSP. The Western Australian Therapeutic Advisory Group[51] recommends tricyclic antidepressants as a first-line and lamotrigine as a second-line drug for treatment of CPSP. In a systematic review of pharmacological treatment of CPSP, amitriptyline and lamotrigine have been recommended as first-line and mexiletine, fluvoxamine, and gabapentin as second-line drugs. For short-term pain relief in intractable pain patients with CPSP, lidocaine and propofol have been recommended.[52]

Table 5. Important Studies on Invasive Motor Cortex Stimulation in Central Poststroke Pain (CPSP)

Author	Class	No. of patients	Response	Adverse effect
Tsubokawa et al.[56] 1993	III	11	Pain improved in 73% at 1 wk; 45% at 2 yr	Not available
Hosobuchi[73] 1993	III	6	Short-term complete relief 2–3 mo 4 excellent 1:30%	Not significant
Yamamoto et al.[44] 1997	III	28	>12 mo follow up: 36/26 had pain relief	Not significant
Katayama et al.[62] 1998	III	31	Short-term 74% excellent to good response Long-term: good relief in 13/18 (72.2%) without weakness and 2/13 (15.4%) with weakness	Not significant
Nguyen et al.[74] 1999	III	32 (13 CPSP)	Short-term: pain relief in 10; same relief up to 27.3 mo	Not significant
Mertens et al.[75] 1999	III	23 (16 CPSP)	At mean 23 mo follow up pain relief was excellent 25% Good 35% Fair 15%	Method failure 25%
Nuti et al.[76]2005	III	31 (22 CPSP)	Long-term pain relief was excellent 10% Good 42% Poor 35% Negligible 13% Reduced analgesic intake 52% Withdrawal analgesic in 42% Subjective improvement 72%	Not significant

Nonpharmacological Treatment

Invasive motor cortex simulation, deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), and vestibulocochlear stimulation have been tried in patients with CPSP refractory to pharmacotherapy. Cortical simulation for relieving chronic pain was noted during epilepsy surgery by Penfield and Jasper (appearing in Lende et al.) who observed relief of burning pain after resection of the contralateral postcentral gyrus. Recurrence of pain subsided after resection of the contralateral precentral gyrus.[53] Electrical stimulation of the prefrontal cortex resulted in significant alleviation of nociceptive response latency in experimental animals.[54] Epidural motor cortex stimulation is a less invasive method for central deafferentation pain.[55] Motor cortex stimulation activates the intercortical interneurons rather than the corticospinal axons. Stimulation of these neurons affects different areas such as thalamocortical projections from ventrolateral and ventroanterior thalamus, collaterals of corticocortical projections, especially in premotor and post central cortex, and local cortical connections parallel to cortical layers. Both orthodromic and antidromic propagation of these stimuli result in a cascade of events which modulate neuronal networks of the limbic system, thalamus, and brainstem.[56–59] Motor cortex stimulation has also been shown to increase noradrenergic activity and increased release of endogenous morphine.[60,61]

Invasive Motor Cortex Stimulation

In a review, 31 patients undergoing motor cortex stimulation were prospectively followed for 2 yr. Excellent or good (>60%) pain relief was noted in 48% of patients. The pain relief was significantly better in the patients who did not have a motor deficit compared with those who did (73% vs 9%, $P = 0.001$). It seems that an intact corticospinal system is necessary for pain relief.[62] In a study of 15 patients with chronic pain (8 patients with CPSP) motor cortex stimulation devices were implanted in the subdural space for stimulation. Pain relief was good to excellent in 2 patients only. Thirty minute stimulation was associated with pain relief for 1–24 h. One patient developed subdural effusion.[63] Some class III studies on invasive motor cortex stimulation are summarized in Table 5.

Conclusion

In the absence of randomized, controlled trials, motor cortex stimulation should be considered in drug-resistant CPSP patients only.

DBS

DBS is a tool for chronic pain refractory to drug treatment and is less invasive compared with epidural stimulation. The exact mechanism by which DBS results in pain relief is yet to be fully understood. The advantages of DBS are that it is reversible, nondestructive and can be modified by adjustment of the stimulator settings after implantation. The role of DBS in chronic intractable pain has been reported in a meta analysis evaluating six qualified studies. DBS was found to be more effective in nociceptive pain (60%) compared with deafferentation pain (47%). Fifty-eight percent CPSP patients achieved pain relief after permanent implantation of DBS. Pain relief was greater after stimulation of the periventricular or periaqueductal gray area with or without thalamic stimulation compared with thalamic stimulation alone. The authors concluded that DBS is well tolerated and effective in properly selected patients with neuropathic pain.[64] In a later study of 56 patients with different types of neuropathic pain, the best long-term results were obtained in patients with chronic low back and

leg pain (failed back surgery syndrome). The patients with neuropathic pain of peripheral origin also responded well to DBS but results were disappointing in patients with central pain syndrome, such as spinal cord injury (12 patients) and poststroke pain (11 patients). In CPSP, only 2 of 11 patients had mild to moderate relief.[65] In another study on a small number of patients with CPSP, pain relief was achieved in 70% of patients after permanent DBS implantation.[66]

Conclusion

DBS can be used in pharmaco-resistant, well selected patients with CPSP.

rTMS

There are two randomized controlled studies on rTMS. In one, there were 48 patients with neuropathic pain, 24 of whom had CPSP. In the CPSP group rTMS was performed in 14 and sham stimulation in 10 patients. The stimulation intensity was 80% of motor threshold and trains were delivered at 20 Hz, 10 trains of 10 s each given daily for 5 days to the hand area of the motor cortex. Sham stimulation was given holding the real TMS coil elevated and angled 45° away from the skull. Patients were unaware of the type of stimulation. After rTMS there was significant reduction in pain compared with controls ($P = 0.025$) and it was maintained at all time points after the first, 4th and 5th day and 2 wk after the last session. There were no significant side effects.[67] Another randomized controlled study evaluated 60 patients with neuropathic pain for possible surgery. Twenty-four of these patients had CPSP, which was restricted to the face in 2, upper limb in 15, and lower limb in 7 patients. The patients were subjected to sham or real rTMS sessions 3 wk apart for 20 min sessions of 10 Hz rTMS over the motor cortex corresponding to the hand area. The outcome was assessed after each session. The percentage of pain reduction was larger after real stimulation compared with sham stimulation (22.9% vs 7.8%, $P = 0.0002$). Pain relief was not as successful in brainstem stroke.[68]

Conclusion

rTMS is effective and safe in CPSP (class II, level A evidence).

Comparison of Invasive and Noninvasive Motor Cortex Stimulation

The role of motor cortex stimulation in chronic pain has been evaluated in a meta analysis. This analysis was based on 22 invasive and 11 noninvasive (9 rTMS and 2 DBS) motor cortex stimulation studies. Three-hundred-twenty-seven patients received invasive stimulation, of whom 196 had CPSP, whereas in the noninvasive group there were 274 patients with chronic pain, of whom 114 had CPSP. The mean responders in the invasive studies were 64% (95% CI, 58.7–69.2) and in the noninvasive studies 40% (95% CI, 33.9–46). Comparing the invasive and noninvasive cortical stimulation studies, epidural motor cortex stimulation resulted in significantly more pain reduction ($P < 0.0001$). The response in the real rTMS group was also significantly higher compared with sham rTMS (risk ratio of 2.64, 95% CI, 1.63–4.30).[69]

Vestibular Caloric Stimulation

Vestibular caloric stimulation activates the posterior insula which, in turn, inhibits the generation of pain in the anterior cingulate gyrus. In initial studies on two patients with CPSP, vestibular caloric stimulation relieved central pain whereas placebo did not.[70] A recent single-blind, placebo-controlled trial of 9 patients with CPSP found reduction of pain by 2.58 points on a 10 point scale after cold caloric vestibular stimulation compared with 0.54 in the placebo group.[71]

Conclusion

Based on our evaluation of the published literature on the management of CPSP and a review of two guidelines,[51,52] we conclude that amitriptyline and lamotrigine are the first-line drugs. For resistant cases, fluvoxamine, gabapentin, and mexiletine may be used as second-line drugs. A large multicenter, double-blind, placebo-controlled trial of pregabalin is underway and its results may be important. In intractable cases, short-term pain relief may be achieved by IV lidocaine, propofol, or pentothal. DBS and rTMS may be tried in pharmacoresistant CPSP patients. The role of newer drugs and combination therapy in CPSP needs further exploration.

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