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FRONTIER

Immunomodulatory effects of dexmedetomidine: From bench to clinic

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Abstract

Dexmedetomidine is a central alpha2-adrenergic receptor agonist with sedative and analgesic properties that has a proven safety profile. It has several beneficial effects such as decreasing sympathetic tone, leading to reduced opiate use and anxiolysis, making it an attractive option for sedation in the perioperative and intensive care unit setting. These effects also modify favorably the time spent on a ventilator, intensive care unit length of stay and development of delirium. Recent studies also suggest that dexmedetomidine possesses wide-ranging immunomodulating properties. It has been associated with reduced inflammatory cytokine release, modulation of inflammatory transcription factors, oxidative stress and inflammatory cells. These properties could be beneficial in the context of inflammatory conditions that require sedation, such as sepsis, ischemia-reperfusion injury and ventilator-associated lung injury, among many others. In this review, we propose specific clinical scenarios where these properties could turn out to be clinically relevant.

Key words: Dexmedetomidine; Immunomodulation; Inflammation; Sepsis; Anesthesia

Core tip: Dexmedetomdine is a sedative-analgesic agent widely used in intensive-care units. It has favorable hemodynamic, opioid-sparing and delirium-preventive properties. In addition, experimental evidence suggests it has immunomodulating effects, including reduction of inflammatory cytokine release and oxidative stress. Future studies should address the question of whether these properties can be used to alter the course of devastating conditions such as ischemia-reperfusion injury and sepsis.

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INTRODUCTION

The introduction of clonidine as an antihypertensive drug in 1966 gave rise to the clinical application of sympatholytics acting on the alpha2A-adrenoceptor. Dexmedetomidine, developed in 1980, is the dextro enantiomer of medetomidine (an agent used in veterinary medicine), the methylated derivative of detomidine. It is a highly selective alpha2 adrenoreceptor agonist, with an alpha2 to alpha1 adrenoreceptor ratio considerably higher than other agonists such as clonidine[1]. This favors its sedative/anxiolytic actions rather than hemodynamic effects. After its approval by the Food and Drug Administration

in 1999, its viability as a non-benzodiazepine option in the intensive-care unit as a light sedative, in ventilator weaning, and in the management of delirium and agitation has become well established[2]. Current indications have been expanded to include peri-operative and procedural sedation. Recent experimental and clinical evidence also suggests that dexmedetomidine could have wide ranging and potent immunomodulating effects. We review this evidence and propose specific clinical scenarios where these properties could turn out to be clinically relevant.

PHARMACOKINETICS AND PHARMACODYNAMICS

Onset of sedation with dexmedetomidine occurs within 15 min and peak sedation occurs within 1 h of starting an Ⅳ infusion. Dexmedetomidine is mostly bound with protein and rapidly redistributed into peripheral tissues and is metabolized by the liver (direct glucuronidation and cytochrome P450 metabolism), with elimination half-life of approximately 3 h in normal subjects[3]. Although dexmedetomidine has only been approved in the United States for short-term sedation of intensive care unit (ICU) patients (< 24 h) at a maximal dose of 0.7 μg/kg per hour (up to 1.0 μg/kg per hour for procedural sedation), several studies demonstrate the safety and efficacy of dexmedetomidine infusions administered for greater than 24 h and at higher doses up to 1.5 μg/kg per hour[4-6] . Long-term sedation is safe even in the context of critically ill patients[7]. Dexmedetomidine does not significantly affect respiratory drive or gas exchange, which makes it attractive for use in non-intubated patients[4,6]. There is evidence that dexmedetomidine sedation causes suppression of autonomic activity to a similar extent as propofol[8]. The most common side effects of dexmedetomidine are hypotension and bradycardia. These occur most commonly in the loading phase, and omitting a loading dose can reduce the incidence of adverse events.

PLEIOTROPIC EFFECTS AND SPECIAL SITUATIONS

Alpha2 adrenoreceptors are present in both pre-synaptic and post-synaptic sites, and at least three alpha2 isoreceptors have been described. All alpha2 receptor subtypes are modulated by dexmedetomidine (Table 1). Agonism at the alpha2A receptor promotes sedation, hypnosis, analgesia, sympatholysis, neuroprotection and inhibition of insulin secretion. Agonism at the alpha2B receptor centrally suppresses shivering, promotes analgesia at spinal cord sites, and induces vasoconstriction in peripheral arteries. The alpha2C receptor is associated with modulation of cognition, sensory processing, mood- and stimulant-induced locomotor activity, and regulation of epinephrine outflow from the adrenal medulla[9]

Pathways other than that of alpha2-adrenoceptor G-protein and adenylate cyclase, such as inhibition of neuronal sodium and potassium currents, extracellular signal regulated kinases (ERK)1/2 phosphorylation and protein kinase C, could account for dexmedetomidine´s effects on neuronal function[10,11]. Dexmedetomidine also increases the expression of growth factors such as epidermal growth factor and brain-derived neurotropic factors, which could participate in neuroprotection[10,11].

Table 1 Alpha2-adrenoreceptor subtypes

Receptor	Action	Dexmedetomdine	Effect
Alpha2A	Reduced sympathetic tone	Hypotension, bradycardia	Sedation, neuroprotection
Alpha2B	Increases blood pressure	Biphasic blood pressure	Vasoconstriction response, analgesia
Alpha2C	Modulates neurotransmitter release	Analgesia, sedation from adrenergic nerves	Increases stimulant induced locomotor activity

Dexmedetomidine has analgesic properties. In the locus coeruleus of the brain stem, it has been shown to inhibit the firing of nociceptive neurons by stimulation of alpha2 adrenoreceptors. In the substantia gelatinosa of the dorsal horn it can inhibit the firing of nociceptive neurons stimulated by peripheral Aδ and C fibers, as well as reducing the release of the nociceptive neurotransmitter substance P[12]. When compared to conventional sedatives it has been demonstrated to possess opiate sparing effects and to reduce delirium, agitation and time spent on a ventilator[7,13,14]. Dexmedetomidine has been compared with benzodiazepines and propofol, consistently showing lower probability of precipitating delirium, being currently approved specifically for this indication[15]. In the MENDS trial, a double-blind, randomized controlled trial of 106 adult mechanically ventilated medical and surgical ICU patients, dexmedetomidine was associated with reduced delirium and a trend towards decreased mortality when compared with lorazepam[16]. Considering the detrimental effects of delirium over ICU mortality, these findings could be of great clinical significance[13].

Dexmedetomidine has been extensively studied in the context of prolonged mechanical intubation. In a prospective, double-blind, randomized trial (SEDCOM) comparing dexmedetomidine to midazolam in 375 ICU patients requiring more than 24 h of sedation in ICU, dexmedetomidine reduced time spent on a ventilator under equal sedation indices[7]. Two phase 3 multicenter, randomized, double-blind trials carried out from 2007 to 2010 including close to 500 patients each, the MIDEX trial and the PRODEX trial, compared dexmedetomidine with midazolam or propofol in ICU patients receiving mechanical ventilation who needed light to moderate sedation for more than 24 h[17]. These trials showed non-inferiority in achieving light sedation as well as reduced time spent on ventilator, in support of the SEDCOM trial. In a recent meta-analysis of ten randomized controlled trials, involving 1202 patients, dexmedetomidine was shown to be associated with reduced time spent in ICU when compared to propofol[18]. These results suggest that ventilator weaning and reduction in time spent

in the ICU could be some of the primary indications for dexmedetomidine.

Dexmedetomidine has a biphasic response in the cardiovascular system, the first leading to a mild and transient (10 min) increase in heart rate and blood pressure, followed by an equally mild reduction in both parameters[1,2]. In the context of cardiac surgery dexmedetomidine reduces pulmonary vascular pressure, pulmonary vascular resistance, decreases capillary wedge pressure, and some studies suggest it could accelerate extubation times[19,20]. A recent clinical trial involving over 1000 patients undergoing coronary artery bypass surgery showed that perioperative dexmedetomidine infusion reduced complications and 1-year mortality[21]. In Neurosurgical patients dexmedetomidine sedation can allow for awake craniotomy and avoid sudden increases in intracranial pressure (ICP) during intubation and surgery attenuating agitation and delirium[15]. Observational studies and clinical trials have shown that dexmedetomidine can reduce ICP, increase hemodynamic stability, accelerate extubation and improve outcomes in major neurosurgical procedures[22,23].

Dexmedetomidine use is safe and could have beneficial effects in other special situations such as in transplant surgery, pregnancy and in both very elderly and pediatric populations[24-27].

Although dexmedetomidine at clinically relevant doses does not affect adrenocorticotropic hormone secretion[28], it has been shown to possess immunomodulating effects by direct stimulation of alpha- and beta-adrenoreceptors on immune effectors, through stimulation of cAMP formation that in turn triggers signaling cascades[29]. In addition Dexmedetomidine improves macrophage function and has antiapoptotic activity. It is these properties that will mainly concern us in this review.

EXPERIMENTAL STUDIES OF SEPSIS

Animal models of sepsis, such as the cecal ligation and puncture model (CLP) or the injection of lipopolysaccharide, are useful tools in the investigation of its pathophysiological mechanisms and in the search for novel treatments. These models replicate both the acute phase of immune overstimulation and the late phase of immunoparalysis. In experimental studies, alpha2A-adrenoceptors have been implicated in the development of the inflammatory response and end-organ injury in sepsis. Using the models of CLP-induced sepsis and endotoxin injection, it has been shown that during sepsis the gene expression of alpha2A-adrenoceptor is increased[30]. Additionally, administration of norepinephrine led to increased tumor necrosis factor-alpha (TNF-α) production and expression in blood and cultured Kupffer cells, an effect abrogated by co-administration of an alpha2A-adrenoceptor antagonist[30]. Alpha2A-adrenoceptor antagonists were then shown to reduce mortality, systemic inflammation and end organ damage using a model CLP-induced sepsis[31]. Dexmedetomidine has shown immunomodulating properties in experimental models of sepsis as well.

In a rat model of endotoxemia, the administration of dexmedetomidine reduced the serum elevations of both TNF-α and interleukin (IL)-6, as well as histopathologic evidence of lung endothelial injury[32]. These effects were also accompanied by a reduction in endotoxemia-induced mortality. In later studies, the same group showed that these effects were dose dependent[33]. Other studies have confirmed survival benefits in rats subjected to CLP-induced sepsis by the administration of either dexmedetomidine or clonidine, another central sympatholytic[34]. In rats with endotoxin-induced septic shock, alpha2A-adrenoceptor agonists (dexmedetomidine and clonidine) preserved pressor responses to norepinephrine[35]. Another study involving CLP-induced sepsis in rats compared dexmedetomidine with midazolam sedation. Dexmedetomidine had a greater effect over mortality, reduced TNF-α and IL-6, and could also reduce evidence of abdominal organ apoptosis[36]. Virtually identical results were obtained when using a model of CLP-induced sepsis in mice[37].

Recent studies suggest that reduction of sepsis-induced lung injury could be a central mediator of dexmedetomidine's beneficial effects over survival. Dexmedetomidine reduced lung injury and mortality associated with CLP-induced sepsis by modulating the TLR4/nuclear factor (NF)-κB pathway, resulting in decreased lung inflammation and expression of TNF-α and IL-6[38]. Using endotoxin injection to induce lung injury, dexmedetomidine was able to reduce lung edema and decrease lung tissue expression of NF-κB, TLR4 and levels of IL-1, IL-6 and TNF-α[39]. In endotoxemic rats subjected to high tidal volume ventilation for induction of ventilator-induced acute lung injury, a combination of dexmedetomidine and ketamine led to reductions in macrophage inflammatory protein-2 and IL-1b release, as well as reduced lung edema, inflammatory cell infiltration and nitric oxide (NO) levels[40]. This dexmedetomidine-ketamine combination could also mitigate the acute lung injury in hemorrhagic shock model in rats[41]. Dexmedetomidine alone was also effective in reducing lung injury and inflammation in models of ventilator-induced acute lung injury[42]. However, the protective effects of dexmedetomidine in the setting of CLP-induced sepsis are not limited to the lungs, and studies have also found reduced kidney injury and of apoptosis markers in both lung and renal tissue[43]. The mechanisms involved in nephroprotection were elucidated in a study involving CLP-induced sepsis. Dexmedetomidine reduced sepsis-induced acute kidney injury by decreasing TNF-α, monocyte chemotactic protein-1, and increasing acetyl histone H3 and bone morphogenetic protein-7[44].

In vitro studies of macrophages have shown that dexmedetomidine could inhibit the endotoxin-mediated production of TNF-α, IL-6, inducible-NO synthase (iNOs) and other inflammatory mediators, although at higher that clinically-relevant doses[45].

These effects were in part mediated by adrenergic receptors. Similar findings were obtained in cultured

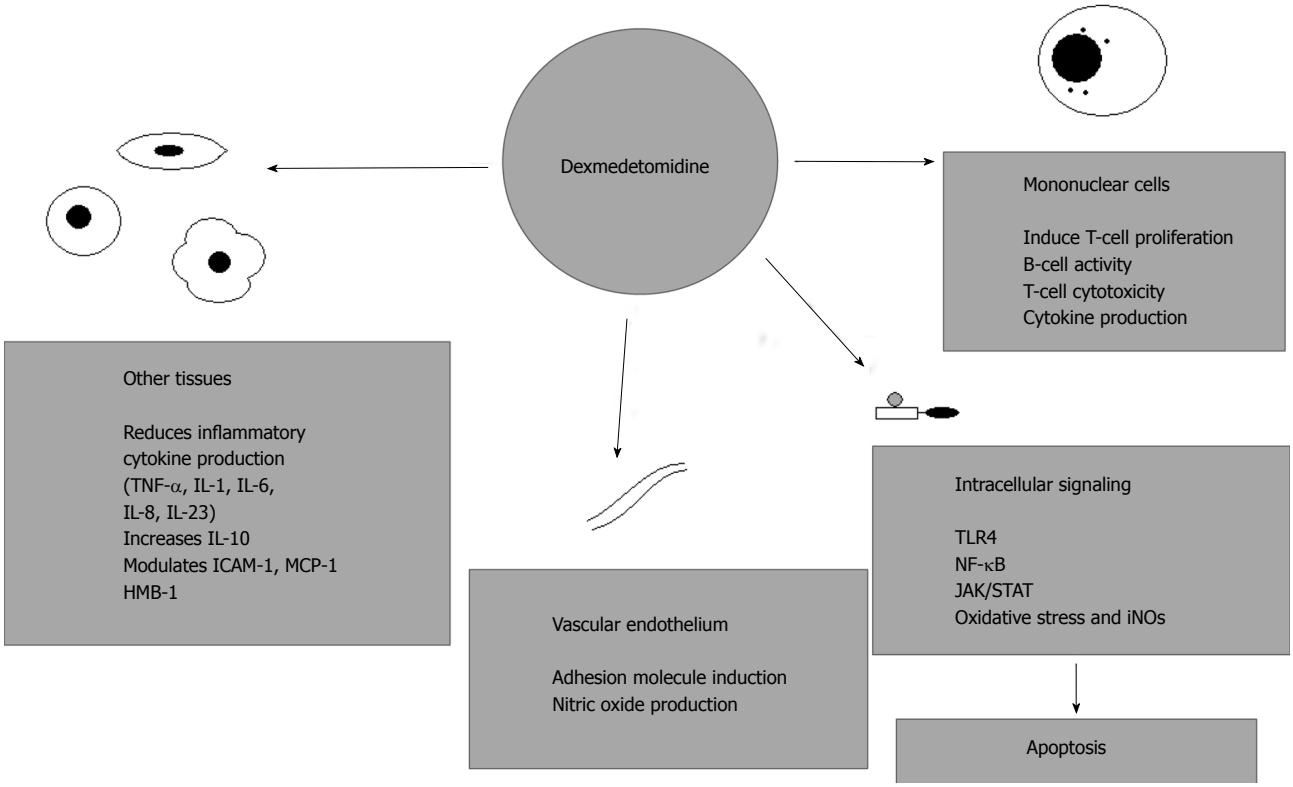

Figure 1 Immunomodulating effects of dexmedetomidine. TNF-α: Tumor necrosis factor alpha; IL: Interleukin; TLR4: Toll-like receptor 4; iNOs: Inducible nitric Oxide synthase; ICAM-1: Intercellular adhesion molecule 1; MCP-1: Monocyte chemoattractant protein 1; NFκB: Nuclear factor kappa B.

microglia stimulated by lipopolysaccharide, where dexmedetomidine could inhibit the production of TNF-α, IL-1b, prostaglandins and iNOs[46]. In studies of human whole blood incubated with endotoxin, dexmedetomidine also led to reduced production of TNF-α, IL-6, IL-8, and high-mobility group box 1 protein, possibly trough inhibition of NF-κB[47]. Dexmedetomidine could also inhibit the translocation of high-mobility group box 1 (a central regulator of sepsis) and NF-κB from the nucleus to the cytoplasm in LPS-activated macrophages in a dose-dependent manner[48]. Yohimbine eliminated these effects, suggesting that they may be mediated by alpha2A-adrenoceptors.

These studies highlight some of the networks involved in the immunopathology of sepsis capable of being modulated by dexmedetomidine, as well as effects over end-organ damage and mortality (Figure 1). Although this evidence comes from animal and basic science studies, their combined results suggest that dexmedetomidine could be beneficial in the clinical setting. Ideally, candidates for a clinical trial would be constituted by patients with established sepsis in need for sedation in an intensive-care unit. It is true that other intravenous sedative or anesthetic agents such as ketamine or propofol show similar effects[49], and comparative studies would be needed.

EXPERIMENTAL STUDIES OF ISCHEMIA-REPERFUSION INJURY

Ischemia-reperfusion (IR) injury occurs when an organ or tissue is deprived of blood flow, followed by its restoration, either spontaneous or therapeutic. It is a common condition in the settings of transplantation, vascular surgery, low-flow states such as sepsis or shock, and arterial or venous embolism or atherosclerosis. The initial phase of ischemia leads to depletion of energy stores in the involved cells, leading to calcium influx, necrosis and apoptosis. Reperfusion leads to the generation of a severe local and systemic inflammatory response, involving the release of proinflammatory cytokines and reactive oxygen species, inflammatory cell infiltration and other immune mediators, responsible for local and remote organ injury[50,51]. Recent studies have found that dexmedetomidine can also affect the immune response associated with IR-injury.

The earlier reports of a beneficial effect of dexmedetomidine in IR-injury were seen in the central nervous system, probably given its effects on central adrenergic receptors. Dexmedetomidine was able to reduce the severity of brain infarction trough the modulation of pro-apoptoic and anti-apoptoic signals[52]. Dexmedetomidine could also reduce hippocampal IR-injury, as well as reduce TNF-α, oxidative stress and neuronal apoptosis[53]. Another study showed that dexmedetomidine administration led to improved neurological outcome in rats subjected to aortic occlusion (spinal IR-injury), and to reduced levels of IL-6 and microglial production of TNF-α[54]. Anti-inflammatory effects do not account for all of dexmedetomidine's neuroprotective properties. In a model of middle cerebral artery occlusion, dexmedetomidine reduced infarct severity trough the up-regulation

Table 2 Effects of dexmedetomdine on pro-apoptoic and anti-apoptoic signals

Signal	Effect
Anti-apoptoic	
Bcl-2	Increased expression
Mdm-2	Increased expression
pERK	Increased expression
RTP801	Increased expression
Pro-apoptoic	
Bax	Reduced expression
Caspase-3	Reduced expression
JAK/STAT	Reduced expression
NF-κB	Reduced expression

pERK: Pxtracellular signal-regulated kinase; JAK/STAT: Janus kinase/signal transducers and activators of transcription; NF-κB: Nuclear factor kappa B.

of pro-survival kinases[55].

Recently, these findings have been expanded to include other organs. In a study of liver IR-injury, dexmedetomidine could reduce hepatic injury as well as the associated oxidative stress response, also preserving endogenous levels of antioxidants[56,57]. Similar effects were observed in tissue flap studies, along with improved flap survival after IR[58]. Dexmedetomidine could also reduce lipid peroxidation, iNOs, apoptosis and injury severity in models of testicular and ovarian IR-injury[59,60]. In the gut, intestinal IR-injury and epithelial cell apoptosis was also reduced by dexmedetomidine, and TNF-α levels were reduced as well[61]. These effects were abolished by yohimbine, directly involving the alpha2A-adrenoceptor as well. An infusion of dexmedetomidine reduced renal dysfunction and the mRNA expression of IL-6, ICAM-1 and iNOs following renal IR[62]. Additionally, during renal IR-injury dexmedetomidine can also modulate the JAK/STAT signaling pathway and down-regulate of Monocyte chemoattractant protein-1 and pro-apoptoic signals[63]. The detrimental effects of bilateral renal IR over the lungs were also ameliorated by dexmedetomidine administration[64]. These effects were associated to reduced lung myeloperoxidase, TNF-α and adhesion molecule expression in the lung, and partly reversed by yohimbine. Dexmedetomidine has also been shown to reduce infarct size in a model of myocardial IR-injury in rats, partly through the alpha2A-adrenoceptor[65]. These immunomodulatory effects seem to confer a protective effect of dexmedetomidine over IR-injury in a variety of organs.

Other animal models of inflammatory conditions have contributed to our knowledge of dexmedetomidine's immunomodulating and organ-protective effects. In a model of experimental spinal cord injury, dexmedetomidine was able to reduce neutrophil infiltration and the levels of TNF-α and IL-6, with effects similar in magnitude to methylprednisolone[66]. In a model of trinitrobenzene sulfonic acid-induced experimental colitis, dexmedetomidine was able to down-regulate the production of IL-23 and up-regulate the anti-inflammatory cytokine IL-10, as well as reducing tissue injury[67]. The lung injury induced by blunt-chest trauma is partly mediated by NF-κB signaling and by increased TNF-α and IL-1beta production; dexmedetomidine could ameliorate all of these changes in an experimental model[68]. These effects could be mediated by alpha2A-adrenoceptors as well, as they were reversed by yohimbine.

OTHER IMMUNOMODULATING EFFECTS

Other immune cell functions are also altered by alpha2A-adrenoceptor signaling. Alpha2A-adrenoceptors are present in T lymphocytes, and agonists to this receptor decrease lymphocyte proliferation and both interferon-gamma and IL-4 production[69]. Dexmedetomidine could reduce IL-2 production in macrophages and led to a decreased ratio of helper T lymphocytes subsets, Th1 to Th[70]. Natural killer cells also show increased cytotoxic activity in response to alpha2A-adrenoceptor agonists[71]. In human volunteers, clonidine, another alpha2A-adrenoceptor agonist, led to improved endothelial function and decreased cytokine production in a model of brachial artery flow-mediated dilatation[72]. Dexmedetomidine could modulate endothelial function and most inflammatory cell subtypes trough a alpha2A-adrenoceptor mechanism.

Besides a direct immunomodulating effect of dexmedetomidine, mediated by alpha2A-adrenoceptor signaling, a possible role has been suggested for the vagal-cholinergic anti-inflammatory pathway[34]. In recent years, it has been established that efferent vagus nerve activity inhibits pro-inflammatory cytokine release, inflammatory cell activation and protects against systemic inflammation in various experimental models, an effect termed "the cholinergic anti-inflammatory pathway"[73,74]. Dexmedetomidine could alter the sympathetic/parasympathetic pathway by its central adrenergic effect, leading to increased vagal activity[34]. In animal studies, a direct positive effect of dexmedetomidine over vagal activity has been demonstrated, leading to increased vagal tone, decreased adrenergic-induced arrhymogenesis and reduced heart rate[75,76]. At least some of dexmedetomidine's immunomodulating properties could be mediated by the activation of the cholinergic anti-inflammatory pathway.

Dexmedetomidine is able to modulate apoptosis signaling in several models (Table 2), such as neurons, renal, intestinal and testicular cells subjected to ischemia as well as spleen, lungs and kidneys subjected to sepsis-induced injury, and through a variety of mechanisms[31,36,43,59,63]. In brain cells, dexmedetomidine is able to reduce Bax protein and to increase the anti-apoptosis proteins Bcl-2 and Mdm-2 after ischemic injury[52], as well as reducing caspase-3 and increasing pERK after anesthetic-induced injury[77,78]. Dexmedetomidine administration was also shown to be able to suppress apoptosis and enhance brain-derived neurotrophic factor and tyrosine kinase B expression in a model of cerebral hemorrhage-induced injury[79]. In renal cells, dexmedetomidine could also reduce apoptosis through its inhibitory effects on injury-induced activation of the JAK/STAT signaling pathway[63]. Dexmedetomidine activated the I2 imidazoline receptor-

PI3K/AKT pathway, and up-regulated hypoxia-inducible factor-1α, vascular endothelial growth factor and the stress-related protein RTP801 expression to protect against oxygen-glucose deprivation-induced apoptosis in cultured glioblastoma cells[68]. Considering the importance of apoptosis in regulating end-organ damage in sepsis, among other conditions[80], as well as the therapeutic potential of negative regulators of apoptosis[81], this evidence strengthens the case for dexmedetomidine as a protecting agent.

POSSIBLE CLINICAL APPLICABILITY

The previous considerations suggest that the clinical applicability of dexmedetomidine can be widened. Conditions involving hypovolemic or septic shock, both commonly encountered in emergency departments and ICUs, constitute the most obvious candidates, and there is some clinical evidence supporting its utility. In a-prioiri analysis of only septic patients involved in the aforementioned MENDS trial, dexmedetomidine sedation was associated with reduced mortality compared to lorazepam, showing a greater effect than in non-septic patients[82]. Further prospective clinical trials will be required to establish this issue. However, many other diseases and procedures requiring sedation or analgesia, where the inflammatory response plays a central pathophysiological role, could also be relevant. Dexmedetomidine could prove of use in acute pancreatitis, endoscopic procedures, both cardiological and neurological endovascular procedures, transplantation surgery among many others.

Transplantation of solid organs always involves ischemia-reperfusion injury, a thoroughly inflammatory condition, where many mediators modulated by dexmedetomidine play important roles[50,51]. Dexmedetomidine could be used both as an anesthetic adjunct during harvesting or in the recipient, and a post-transplantation analgesic and sedative. Case reports suggest dexmedetomidine is safe in transplantation recipients, and could be used as an opiate sparing drug[83,24]. Analgesia is essential in the management of acute pancreatitis, a condition associated with a systemic inflammatory response where cytokines such as TNF-α, IL-6 and oxidative stress play central regulatory roles[84]. To the best of our knowledge, the analgesic properties of dexmedetomidine have not been studied in this context. Some endoscopic procedures that require mild sedation, such as endoscopic retrograde cholangiopancreatography (ERCP), are also associated with the induction of a pro-inflammatory state that could be associated with the development of complications such as post-ERCP-pancreatitis[85]. Acute respiratory distress syndorme is another serious and common condition in the ICU whose physiopathology is characterized by disruption of the alveolar lining and capillary endothelium, coupled with a marked inflammatory response[86], where the use of dexmedetomidine remains to be evaluated[87].

It is worth mentioning some shortcommings associated with dexmedetomidine before any formal proposal of widening its applicability. Dexmedetomidine is also much more expensive compared to either propofol or midazolam, but increased costs could potentially be offset by reductions in time spent on a ventilator and delirium incidence[88]. Changes in usual sedation strategies could also potentially lead to unplanned or self-extubations, although a recent meta-analysis did not find this unwanted effect[89]. Considering the short clinical experience with dexmedetomidine use compared to traditional sedatives, it is also plausible that undesirable side effects could begin to be uncovered. For example, a recent study found reduced fluid responsiveness in patients with circulatory failure with dexmedetomidine infusion compared to propofol infusion[90]. There is also a distinct lack of evidence of improved long-term outcomes with dexmedetomidine use in the intensive-care setting.

CONCLUSION

Dexmedetomidine is a tolerable and safe sedative/analgesic for use in various populations and clinical scenarios. It has shown some remarkable properties, such as a neutral effect over respiratory drive, prevention of delirium in the ICU, opiate sparing, and in some circumstances it has led to improved clinical outcomes, when compared to other agents such as benzodiazepines and propofol, but these issues are far from settled. We also reviewed considerable evidence that suggests that dexmedetomidine can favorably modulate the immunological response, reducing the expression and release of a variety of pro-inflammatory cytokines and mediators. This has led to the investigation of the possible therapeutic uses of dexmedetomidine in conditions such as sepsis and ventilator-induced lung injury, with encouraging results. It should be mentioned that there are no clinical trials supporting these off-label indications. On a more speculative side, dexmedetomidine's pleiotropic effects could widen its applicability to other conditions such as acute pancreatitis, transplantation surgery, endoscopic procedures among many others. Large clinical trials will be needed to establish the full potential of this exciting drug.

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REVIEW

Phantom limb pain: A review of evidence-based treatment options

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Abstract

Phantom limb pain (PLP) is not uncommon after amputation. PLP is described as a painful sensation perceived in the missing limb. Despite of its complicated pathophysiology, high prevalence of PLP has been associated with poor health-related quality of life, low daily activity and short walking distances. A prompt and effective management of PLP is essential in caring for the amputee population. Current treatments including physical therapy, psychotherapy, medications, and interventions have been used with limited success. In this review, we provided an updated and evidence-based review of treatment options for PLP.

Key words: Phantom limb pain; Rehabilitation; Drug therapy; Anesthesia

Core tip: An evidence-based review of treatment options for phantom limb pain.

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INTRODUCTION

Post-amputation phenomena include phantom limb sensation (PLS), phantom limb pain (PLP) and residual limb pain (RLP). PLS refers to the persistent perception of a body part even after it has been removed by amputation or trauma, whereas PLP refers to the perception of pain experienced in the missing body part. The term RLP refers to pain in the remaining limb.

PLS and PLP can occur after the amputation of any part of the body, but are most often described in the limbs[1,2]. The incidence of PLP varies from 0% to 88% after lower extremity amputations, 51% to 72% after upper extremity amputations with increase seen in more proximal amputations. The reports of PLP after hemipelvectomy range from 68% to 88%; the incidence reported is 40% to 88% following hip disarticulation[3,4].

The etiology and pathophysiologic mechanisms of PLP are not clearly defined. However, both peripheral and central neuronal mechanisms are likely involved. In addition, psychological mechanisms have been proposed. Several investigators have considered pre-amputation pain as a risk factor for PLP[5]. Independently, none of the theories fully explains the clinical characteristics of this condition.

PLP is generally located in the distal parts of the missing limb, and is usually intermittent. The intervals of pain typically range from days to weeks, but rarely interval over months or years. Each pain attack may take from a few seconds to a few hours, sometimes days. Patients with PLP often have poor health-related quality of life, low daily activity and short walking distances[6]. Therefore, a prompt and effective treatment of PLP is essential

Table 1 Treatment options for phantom limb pain

Physical therapies	Desensitization
	Prosthesis use
	Stump stocking,
	Transcutaneous electrical nerve stimulation
	Repetitive transcranial magnetic stimulation
	Mirror therapy
Behavioral and psychological therapies	Stress-relaxation Techniques
	Hypnosis
	Electroconvulsive therapy
Antidepressants	Tricyclic antidepressants
	Sodium channel blockers
	Amitriptyline and tramadol
Anticonvulsants	Carbamazepine, chlorpromazine, gabapentin,
	Combined duloxetine and pregabalin
Opioids	Methadone
	Morphine
NMDA receptor antagonists	Ketamine, dextromethorphan
Others	Beta-adrenergic blockers
	Benzodiazepines: Clonazepam
	Capsaicin cream
	Salmon-calcitonin
Central nervous system	Deep brain stimulation
	Motor cortex stimulation
	Stereotactaxis lesions,
	Spinal cord stimulation
	Intrathecal implantable devices
	Cordotomy
Peripheral nervous system	Bupivacaine blocks
	Brachial plexus analgesia
	Nerve sheath catheter analgesia,
	Contralateral Bupivacaine Injection
	Neuroablative procedures
Musculoskeletal system	Neurosclerosis
	Acupuncture,
	Neurotoxin
	Lidocaine/depomedrol injection

in caring for the amputee population. In this review we have included the treatment options that are currently available for PLP.

TREATMENT OF PLP

Treatment of PLP continues to be difficult and mostly unsuccessful. Studies pertaining to the treatment of PLP do not contain large controlled clinical trials that provide definitive evidence of treatment options.

This article will review the most commonly used, evidence-based practices in treating PLP, as available through literature review. Management options for PLP fall into three general categories: Physical, Behavioral and Psychological Therapies, Pharmacotherapy, and Surgery/Interventional Management summarized in Table 1.

Physical, behavioral and psychological therapies

PLP is most commonly seen in patients who are unable to use prosthesis within the first 6 mo following amputation[4]. Physical therapy in preparation for the use of prosthesis has been shown successful in decreasing the patient's PLP[7].

Desensitization techniques including massaging, tapping, slapping, wrapping, and friction rubbing of the residual limb are often used to treat bothersome PLS, PLP and RLP[8]. Anecdotally, many patients find that for a phantom itch, scratching the remaining leg in the same spot is helpful. However no evidence-based studies to date have supported the above treatment options. Patients frequently find that their PLP diminishes with the stimulation of using prosthesis. Kern *et al*[9] researched the effect of using an electromagnetically shielding stump stocking interwoven with metal lining on PLP. The influence of a silicon liner with electromagnetically protecting properties on PLP was highly significant.

Other physical therapies commonly used for the treatment of PLP are: transcutaneous electrical nerve stimulation (TENS), repetitive transcranial magnetic stimulation (rTMS), Electroconvulsive Therapy, Stress-relaxation techniques and Biofeedback.

TENS has been shown to give temporary relief to PLP[10]. Finsen *et al*[11] studied the effect of TENS on stump healing, and postoperative and late PLP after major amputations of the lower limb. The prevalence of PLP after active TENS was significantly decreased after 4 mo, but not after more than one year.

Ahmed *et al*[12] studied the long-term analgesic effect of rTMS on chronic PLP. This clinical trial confirmed that five consecutive days of rTMS (20 Hz, 10 s trains, intensity 80% of motor threshold) over the motor cortex could produce long lasting pain relief in patients with PLP. The significant increase of beta-endorphin was noted in these PLP patients as a result of the treatment. On the other hand, Irlbacher *et al*[13] did not observe any significant long-term effects of rTMS on pain intensity or mood compared with sham stimulation recipients. Using low-frequency and intensity electromagnetic fields, Bókkon *et al*[14] reported majority (10/15) of the patients with PLP had a marked reduction in the frequency and intensity of PLP and improvement in sleep and mood.

The effect of stress-relaxation training with or without biofeedback or hypnosis has been studied on PLP[15]. Investigators[16] reported that in 12 of 14 patients with chronic PLP, significant improvement was noted with muscular relaxation training to disrupt the pain-anxiety-tension cycle. In this study, patients required an average of 6 treatments to produce therapeutic effect. This approach was also associated with decreased anxiety levels and increased pain relief.

Multiple psychological modalities have been attempted in managing PLP.

Mirror therapy is one of the most extensively studied techniques used to treat PLP. During mirror therapy, the patient is allowed to feel the imaginary movement of the removed body part behaving as normal bodily movement through a mirror. The mirror image of the normal body part helps reorganize and integrate the mismatch between proprioception and visual feedback of the removed body[17]. Mirror therapy has primarily been used with upper limb amputations with clinically proven effect in PLP

and functional improvement[18], but has been attempted in patients with lower limb loss as well[19,20]. Chan *et al*[19] conducted a randomized, sham-controlled trial of mirror therapy *vs* imagery therapy involving patients with PLP after the amputation of a leg or foot where 22 patients were randomly assigned to one of three groups: one that viewed a reflected image of their intact foot in a mirror (mirror group), one that viewed a covered mirror, and one that was trained in mental visualization. Their findings showed that mirror therapy reduced PLP in patients who had undergone amputation of lower limbs. Such pain was not reduced by either covered-mirror or mental-visualization treatment.

Psychotherapy was reported to yield good results. Hypnotic suggestion of stocking-glove anesthesia may lead to a reduction in PLP[21]. Investigators showed that 45% of patients were successfully hypnotized, and 35% had successful improvement in PLP. Relapses occurred soon after the discontinuation of the treatment in 34% of the patients. For cramped or mal-positioned limb sensations, hypnosis can be helpful. Under hypnosis, the patient might be able to alleviate a cramped phantom hand or move an awkwardly phantom positioned limb to a more comfortable position.

Pharmacotherapy

Antidepressants: Many randomized, controlled clinical trials have shown a beneficial effect of tricyclic antidepressants and sodium channel blockers on different neuropathic pain conditions and denervation syndromes, such as post herpetic neuralgia and diabetic neuropathy. These medications are generally considered to be effective on PLP, at least for some patients[22,23]. Wilder-Smith *et al*[22] studied 94 treatment-naïve posttraumatic limb amputees with PLP who were randomly assigned to receive individually titrated doses of tramadol, placebo (double-blind comparison), or amitriptyline (open comparison) for 1 mo. Both amitriptyline and tramadol provided excellent control of PLP and RLP for the treatment- naïve patients. In contrast, another study conducted by Robinson *et al*[23] evaluated 39 persons with amputation-related pain lasting more than 6 mo in a 6-wk randomized, controlled trial of amitriptyline (titrated up to 125 mg per day) or an active placebo. No significant difference was noticed between the treatment groups, thus their findings did not support the use of amitriptyline in the treatment of post amputation pain.

Anticonvulsants: Among anticonvulsants, carbamazepine is the most commonly used medication. Elliott *et al*[24] and Patterson[25] reported cases of lancinating PLP that improved with oral carbamazepine. Logan[26] reported incomplete relief with carbamazepine but complete relief with chlorpromazine in longstanding PLP. However, there is no evidence suggesting that carbamazepine is effective for pain that is not of the intense, brief, lancinating type. Gabapentin is another commonly used anticonvulsant for PLP. Other than sedation, the side effects are rare. Because gabapentin has no known long-term toxicity, blood level monitoring as associated with other anticonvulsants is not required. However, the results of clinical studies on the use of gabapentin to treat PLP are conflicting. For example, Bone *et al*[27] concluded that a daily treatment of gabapentin, titrated in increments of 300 to 2400 mg of the maximum tolerated dose is better than placebo in relieving PLP. No significant differences in mood sleep interference, or activities of daily living were reported. Nikolajsen *et al*[28], on the other hand, found that gabapentin administered in the first 30 post-operative days, with a daily dosage gradually increasing to 2400 mg/d, does not reduce the incidence or intensity of post amputation pain. Pregablin has been rarely studied in this manner, rather in one case report indicating that duloxetine and pregabalin combined effectively controlled PLP from a below knee amputation[29].

Opioids: Opioid analgesics are not the primary options for the treatment of PLP. However, Methadone has been reported to provide effective relief from PLP at 10-20 mg per day. Multiple lines of evidence have demonstrated that opioids can be used safely for years with a limited risk of drug dependence[30,31]. Patients undergoing amputation related to systemic medical diseases have a 42% 5-year survival rate; thus, the risk of opioid addiction may be weighed against quality-of-life issues[32]. In a study by Wu *et al*[31] therapy with morphine, but not mexiletine, resulted in a decrease of post amputation pain intensity. This treatment resulted in a higher rate of side effects, with no improvement in self-reported levels of overall functional activity and pain-related interference in daily activities.

N-Methyl-D-Aspartate receptor antagonists: The effects of N-Methyl-D-Aspartate (NMDA) receptor antagonists on PLP have been examined in different studies[33,34]. Experimental and clinical literature supports the effectiveness of ketamine in blocking central sensitization via affecting the NMDA receptor[35,36]. Studies have reported low-dose ketamine infusion to be effective in the treatment of complex regional pain syndrome (CRPS). However the effectiveness of ketamine was controversial in relieving PLP in one randomized clinical trial[37]. Nikolajsen *et al*[38] researched on the effects of ketamine on persistent RLP and PLP in a double blind, placebo-controlled study. In this study, Ketamine (bolus at 0.1 mg/kg per 5 min followed by an infusion of 7 micrograms/kg per min) was administered intravenously to 11 patients with established RLP and PLP. All 11 patients responded with a decrease in the rating of RLP and PLP assessed by VAS and McGill Pain Questionnaire (MPQ). Ketamine increased pressure-pain thresholds significantly. Wind-up like pain (pain evoked by repeatedly tapping the dysaesthetic skin area) was reduced significantly by ketamine. In contrast, no effect was seen on pain evoked by repeated thermal stimuli. In another study by Nikolajsen[33], 19 patients received memantine, an NMDA

receptor antagonist available for oral use, in a blinded, placebo-controlled, crossover fashion. Memantine failed to have any effect on spontaneous pain, allodynia, or hyperalgesia. Similar results were also found by a different study group[34]. Oral dextromethorphan, another NMDA receptor antagonist, was found to effectively reduce PLP in a cancer-related amputation group[20].

Beta-adrenergic blockers: Beta-adrenergic blockers have also been suggested for treatment of PLP, based on three cases studies[39]. However, in a double-blind crossover trial of propranolol dosed up to 240 mg daily, the investigators were unable to show significant improvement in post-traumatic neuralgias[40].

Benzodiazepines: The general impression is that benzodiazepines do not produce substantial pain relief, but Bartusch *et al*[41] have reported that Clonazepam did provide effective pain relief when used on two patients with lancating PLP after total hip disarticulation.

Capsaicin: Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the pungent component of red peppers. Studies indicate that capsaicin, when applied topically to skin, depletes substance P from peripheral nociceptive C fiber nerve terminals, thereby increasing the threshold for, and rendering the skin area relatively insensitive to chemical and thermal stimuli. The effect of capsaicin as an alternative treatment on RLP was also tested in a case study to be effective[42].

Intravenous and epidural therapy: A few studies were found to use intravenous therapy for PLP, although the clinical use of such treatments is not widely accepted. Ina study by Simanski *et al*[43], six of eight patients (75%) had no phantom limb pain after 10 d of intravenous treatment with salmon-calcitonin (maximum of five cycles of calcitonin infusion). Patient satisfaction was examined with a numeric rating scale (NRS 1-6) between the single infusion cycles. Modifications were done to the time period or drug dosage between infusions as the result of patient satisfaction rates. This study shows good or excellent results in patient satisfaction for six of eight patients (75%) in systematic follow-up examinations after 3, 6 and 12 mo. Authors recommend a prospective randomized trial to verify the results of intravenous salmon-calcitonin in a larger population. However, in another study[44], intravenous calcitonin reduced PLP in the early postoperative period, but PLP on longer-term follow-up was not adequately controlled.

Karanikolas *et al*[45] used a randomized clinical trial to assess the effectiveness of optimized perioperative analgesia on PLP, as measured at 1 and 6 mo postoperatively, using the visual analog scale (VAS) and the McGill Pain Questionnaire (MPQ). In this study, patients received epidural analgesia or intravenous PCA starting from 48 h preoperatively and continuing 48 h postoperatively. The study concluded that using optimized epidural analgesia or intravenous PCA, starting 48 hours preoperatively and continuing for 48 h postoperatively, decreases PLP at 6 mo. Gehling *et al*[46] showed that preoperative, intraoperative, and postoperative epidural anesthesia were associated with a significant reduction of PLP, 12 mo after amputation. This technique does not completely abolish PLP, but rather increases the number of patients with a milder form of PLP.

Interventional therapy

Central nervous system: Several neurosurgical procedures, including deep brain stimulation (DBS), and motor cortex stimulation (MCS) have been used to treat refractory PLP. Intracranial neurostimulation caused initial pain relief in 80% of patients with sensory thalamic stimulation[47] and 86% of patients had significant relief with DBS. Thalamic stimulation may block spontaneous neuronal discharge in the brain which has been proposed to mediate phantom sensation in some models[48].

Bittar *et al*[49] concluded from his research that DBS has been used successfully for the treatment of PLP, with results of decreased pain, decreased opiate intake, and improved quality of life.

Yamamoto *et al*[48] concluded that inhibition of spinothalamic tract neurons, restoration of the original receptive field representation and modulation of thalamocortical rhythmic oscillations are possible mechanisms of Vc-DBS for the treatment of deafferentation pain, including PLP. Roux *et al*[50] and Sol *et al*[51] used long-term MCS in three patients with intractable pain after upper limb amputation. Functional magnetic resonance imaging (fMRI) correlated with anatomic MRI permitted frameless image guidance for electrode placement. Pain control was obtained for all patients initially, and relief was stable for two of the three patients at 2-year follow-up. Percutaneous stimulation of the periosteum has been used, even though it has not been well studied[52].

SCS could produce increased inhibition in the dorsal column of the spinal cord and result in relief from PLP[53]. Evaluations of SCS have shown encouraging results in neuropathic pain, including reflex sympathetic dystrophy[54]. Thus, spinal cord posterior column stimulation is the most common neurosurgical technique used for the treatment of PLP. The selection process is very crucial. Response to TENS or percutaneous electrical stimulation may predict a response to dorsal column stimulation[55]. Even with appropriate patient selection, investigators have reported that only 65% of patients receive a greater than 25% reduction in pain immediately after surgical implantation[56]. Further, the success rate of dorsal column stimulation steadily declines over time, and a greater than 50% long-term pain reduction is present in only one third of patients who originally showed improvement. SCS may not provide any improvement in patients with severe pain and PLS.

Some investigators have reported multiple neurosurgical techniques apart from electrical stimulation, including intrathecal implantable devices, stereotactic

thermocoagulation lesions, and cordotomy. Some of these treatments may have more serious complications than benefits[4].

Peripheral nervous system: Neural Blocks or neuroablative procedures are commonly used in the treatment of PLP. These procedures range from lumbar sympathetic trunk block, peripheral nerve block, epidural and subarachnoid blocks, to radiofrequency ablation or chemo- or neurolytic ablation of peripheral nerves. Overall the efficacy of these procedure has not been substantiated[8].

Multiple trials assessed perineural[57] and intraneural[58] bupivacaine blocks, either at the time of surgery or immediately postoperatively. Despite some early benefits, no difference in pain was reported between the intervention and control groups in the postoperative period[59]. Perineural block was similar to infusion of local anesthetic through epidural catheter[57]. Evaluation of continuous brachial plexus analgesia showed prevention of the establishment of PLP, which did not reappear during follow-up of 1 year[60]. Nerve sheath catheter analgesia also showed reduced prevalence[61].

In a study by Casale *et al*[62], contralateral injections of 1 mL 0.25% bupivacaine in myofascial hyperalgesic areas attenuated phantom limb pain and affected phantom limb sensation. Sixty minutes after bupivacaine injection, a statistically significant relief of phantom limb pain was observed. Bupivacaine consistently reduced/abolished the phantom sensation in 6 out of 8 patients. The clinical importance of this treatment method requires further investigation

Musculoskeletal system: Neuromas develop in a large number of patients and not only cause RLP, but are also involved in the generation of PLP. Gruber *et al*[63] studied the effects of a procedure for sclerosis of painful stump neuromas under real-time high-resolution sonographic guidance. In this study, neurosclerosis was performed on 82 patients by means of high-resolution sonographically guided injection of up to 0.8 mL of 80% phenol solution. During treatment all patients had marked improvement in terms of reduction of pain measured by VAS. Twelve (15%) of the subjects were pain free after one to three treatments, 9 of the 12 achieving relief after the initial instillation. At 6-mo follow-up evaluation, 52 patients assessed their present pain quantity with a simplified three-step score. Twenty (38%) of the 52 patients reported almost unnoticeable pain, 33 of the 52 patients (64%) reported pain equal to the minimum reached during therapy, and 18 (35%) of the 52 patients had markedly decreased incidences of painful periods. The neurosclerosis procedure had a low complication rate (5% rate of minor complications, 1.3% rate of major complications). The study concluded that high-resolution sonographically guided neurosclerosis should be included in the list of recommended procedures to manage chronic PLP and RLP.

ACUPUNCTURE

Electroacupuncture has been shown to provide relief from PLP in the arm[64]. Recently Davies[65] reported that a series of seven weekly sessions of acupuncture carried out on a patient's left intact arm, provided complete relief of PLP and a considerable improvement of PLS in the patient's above-elbow amputated right arm.

Although short-term relief has been reported with several acupuncture studies, no long-term improvement in patients with a history of nerve damage, Including PLP, has been reported[66].

NEUROTOXIN INJECTION

Botulinum toxin injections have commonly been used to treat spasticity and other hypertonic muscular diseases by selectively preventing the release of acetylcholine at the nerve-muscle junction. Recently, such injections have been used for the treatment of RLP and PLP[67-70]. Kern *et al*[68,69] injected 100 IU of botulinum toxin A in four muscle trigger points of an amputation stump and reported that the injection reduced PLP by approximately 60% to 80%. In a subsequent study, patients who had undergone amputation of the arm (n = 2) or leg (n = 2) were treated with botulinum toxin type B injections at several trigger points of their stump musculature. As a result, all patients experienced a reduction in RLP that lasted for many weeks. Wu *et al*[67] conducted a prospective randomized double-blinded pilot study to examine the effect of botulinum toxin type A injection *vs* the combination of Lidocaine and Depomedrol injection. The study consisted of 14 amputees with intractable, refractory RLP and/or PLP. Each patient was evaluated at baseline and every month after injection for 6 mo. The study found that both botulinum toxin type A and Lidocaine/Depomedrol combination injections resulted in immediate improvement of RLP (but not PLP) and pain tolerance. The treatment effect lasted for 6 mo after the injection in both groups. Another case study by Jin *et al*[70] have also reported significant relief in both RLP and PLP from intramuscular and/or cutaneous injections of botulinum toxin type A.

FUTURE DIRECTIONS OF PLP TREATMENT

PLP is a common consequence of the removal of a limb or organ. The understanding of PLP has improved substantially since the 1990s as a result of experimental studies that showed a series of morphologic, physiologic, and biologic changes resulting in hyper-excitability in the nervous system. At present, no evidence-based clinical guidelines to manage PLP are available. As we summarized above, many options were reported to manage PLP. It is important to treat each PLP patient with a tailored, individualized and sequential protocol. A multidisciplinary approach may achieve the best result. It is also advised that initial treatment should be low cost, and less invasive. The invasive treatment options should be reserved until non-invasive attempts fail.

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REVIEW

Preeclampsia and eclampsia: Etiopathogenesis and perioperative management

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Abstract

Preeclampsia is a pregnancy specific syndrome of elusive etiology, developing in 2nd trimester and associated with high maternal and perinatal morbidity and mortality. The spectrum ranges from mild preeclampsia with no systemic involvement to multi-system involvement. The course is unpredictable and delivery is the only curative treatment. Elevated blood pressure (> 160/110 mmHg) should be reduced gradually to a safe level (140/90) using antihypertensive drugs. Prophylaxis and treatment of convulsions using $MgSO_4$ is indicated for severe preeclampsia. Fluid therapy is controversial due to potential delicate balance between constricted plasma volume and risk of fluid overload and pulmonary oedema secondary to increased capillary permeability and reduced colloid osmotic pressure. Single shot spinal anaesthesia is the technique of choice for caesarean delivery unless contraindicated. General anaesthesia is indicated in patients with coagulopathy or eclampsia but is associated with risk of difficult airway and exaggerated sympathetic response during laryngoscopy. Epidural analgesia and anaesthesia is safe in absence of coagulopathy.

Key words: Preeclampsia; Eclampsia; Regional anaesthesia; Caesarean section; Fluid therapy

Core tip: Preeclampsia and eclampsia constitute the commonest life-threatening complications of pregnancy characterized by hypertension and proteinuria presenting after 20 wk of gestation. In the severe form the condition is challenging for anaesthetists due to involvement of almost every system. The chief problems include hypertension, thrombocytopaenia, renal dysfunction, contracted plasma volume, reduced colloid osmotic pressure, leaky capillaries, oedema of airway and larynx, *etc*. Fluid management is complex and carries risk of pulmonary oedema. Haemolysis elevated liver enzymes low platelets syndrome and eclampsia are associated with high maternal mortality. For caesarean section spinal anaesthesia is technique of choice unless contraindicated. Epidural analgesia is good for labor pain.

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INTRODUCTION

Preeclampsia is a multisystem disorder affecting 5%-10% women during 2nd trimester of pregnancy. It is characterized by hypertension and proteinuria and affects 3%-7% primiparas and 1%-5% multiparas. It is a principal cause of maternal mortality and morbidity worldwide constituting about 16% of peripartum deaths[1]. The condition is life threatening to foetus in addition to mother. Although the exact etio-pathogenesis remains to be determined, the placenta is undoubtedly involved, as termination of pregnancy is the only curative treatment. The preeclamp-

sia may increase the risk of premature cardio-vascular disease such as hypertension, ischemic heart disease and stroke is later life[2,3]. Multidisciplinary team approach involving obstetrician, anaesthetist and pediatricians is required for management[4-6].

CLASSIFICATION OF HYPERTENSIVE DISEASES OF PREGNANCY

The National High Blood Pressure Education Programme Working group (2000)[7] classified hypertensive disorders as follows.

Gestational hypertension

Systolic BP ⩾ 140 or Diastolic BP ⩾ 90 mmHg for 1st time during pregnancy; No Proteinuria; BP returns to normal within 12 wk post partum; Final diagnosis only post partum; May have some features of preeclampsia for example epigastric pain or thrombocytopaenia.

Preeclampsia

BP ⩾ 140/90 mmHg after 20 wk of gestation; Proteinuria ⩾ 300 mg/24 h or ⩾ 1 + dipstick in a random urine sample.

Eclampsia

Seizures that cannot be attributed to any other cause in a woman with preeclampsia.

Superimposed preeclampsia on chronic hypertension

New onset proteinuria ⩾ 300 mg/d in hypertensive women but no proteinuria before 20 wk of gestation; Sudden increase in proteinuria or BP or decrease in platelet count to < 100000/mm^3 in women with hypertension and proteinuria before 20 wk of gestation.

Chronic hypertension

BP > 140/90 before pregnancy or diagnosed before 20 wk of gestation not attributable to gestational trophoblastic disease or hypertension first diagnosed after 20 wk of gestation and persistent after 12 wk postpartum.

Preeclampsia is denoted as mild when only hypertension and proteinuria are present. Oedema is no longer considered to be diagnostic criteria. Severe preeclampsia is defined as the one of the following features in presence of preeclampsia: Systolic BP of 160 mmHg or higher, diastolic BP of 110 mmHg or higher on two occasions at least six hours apart; Proteinuria of more than 5 g in 24 h; headache; visual disturbances; oliguria; pulmonary oedema; upper abdominal pain; thrombocytopaenia; convulsions; serum creatinine level raised; impaired liver functions; intrauterine growth retardation of foetus.

RISK FACTORS FOR DEVELOPMENT OF PREECLAMPSIA

Young and nulliparas; genetic predisposition; multifoetal pregnancy; history of preeclampsia in previous pregnancy; family history of preeclampsia; obesity, diabetes; afro-American race

PATHOGENESIS OF PREECLAMPSIA

The pathogenesis of preeclampsia involves a number of maternal, placental and foetal factors, the exact mechanism of which is still not clearly known. These include[8]: (1) placental implantation with abnormal trophoblastic invasion of uterine vessels; (2) immunological factors; (3) maternal maladaptation to cardio-vascular or inflammatory changes of normal pregnancy; and (4) genetic factors.

During normal trophoblastic invasion in normal pregnancy spiral arteries of uterus are transformed from high resistance vessels into low resistance vessels and stop responding to vasoconstrictors. Abnormal trophoblastic invasion in preeclampsia results in failure of spiral vessels to dilate. These vessels became more responsive to vasoconstrictors. This results in chronic placental ischemia and oxidative stress[9]. Placental ischaemia causes fetal complications like intra uterine growth retardation (IUGR) and death. Oxidative stress leads to endothelial cell activation with secretion of free radicals, oxidized lipids and cytokines which causes wide spread endothetial dysfunction[10,11]. Four fold increase of circulating endothetial cells has been reported in preeclampsia patients[12]. Endothelial dysfunction causes: (1) vascular hyperpermeability[13,14] resulting in oedema, proteinuria; (2) vasospasm resulting in hypertension, oliguria, seizures, liver ischaemia, abruption; and (3) activation of coagulation resulting in thrombocytopaenia. Endothetial dysfunction is main factor responsible for clinical effects on various organ systems like liver, brain and kidney. It also promotes microangiopathic haemolytic anaemia.

There is also increased secretion of thromboxane (vasoconstrictor) and reduced secretion of prostacyclines (vasodilator). The imbalance in normal ratio of thrombaxane and prostacycline[15] coupled with reduced production of nitric oxide, which is a potent dilator favours increased sensitivity to angiotensin II and ultimately leads to widespread vasoconstriction[16] and endothelial injury and platelet activation and consumption[14].

PHYSIOLOGIC DERANGEMENTS IN VARIOUS SYSTEMS

The effects are variable and depend upon the duration and severity.

Cardio-vascular system and plasma volume

Chief effects are hypertension, increased systemic vascular resistance, hyperdynamic circulation with low or normal cardiac output and hyperdynamic left ventricular function. Contracted plasma volume together with incompetent endothelial barrier, hypoalbuminemia and low colloid osmotic pressure lead to peripheral oedema. Despite water and sodium retention, hypovolaemia is

present because of loss of fluids and proteins in the extra vascular compartment. Haemocencentration is the hallmark of preeclampsia.

Maternal plasma volume expansion which accompanies normal pregnancy is attenuated in preeclampsia. Deficit of 600-800/m^2 has been reported[17]. Colloidal osmotic pressure is significantly reduced in preeclampsia due to reduced proteins levels compared to normal pregnancy being 14 mmHg (22 mmHg in normal pregnancy and 25-28 in nonpregnant population)[18,19].

Central nervous system

Hyperreflexia, irritability, headache, visual disturbances, altered mental status may be present in severe preeclampsia. Encephalopathy, convulsions, raised intracranial tension and even post seizure coma may be seen. Pathogenesis of convulsions is disputed but it possibly occurs as a result of cerebral vasospasm, oedema, encephalopathy, microinfarcts or haemorrhage[20]. Intracranial hemorrhage is commonest cause of maternal mortality[21].

Respiratory system

Mucosal and airway oedema, along with laryngeal oedema is common in severe preeclampsia. Pulmonary oedema can occur in about 3% of patient[22] and is common after delivery. It is multifactorial; due to left ventricular dysfunction or failure, pulmonary capillary leak and due to reduced colloid osmotic pressure gradient.

Kidneys

Swelling of capillary endothelial cells is hallmark of renal pathology. GFR is reduced and serum creatinine and uric acid are raised. Oliguria and acute tubular necrosis may occur but renal failure is rare except in Haemolysis Elevated Live enzymes Low Platelets (HELLP) syndrome.

Liver

Involvement of liver is mild except in severe preeclampsia complicated by HELLP syndrome. Ischemic lesions, raised liver enzymes, hypo-albuminaemia and subcapsular hepatic hematoma may be seen.

Coagulation

Thrombocytopaenia (Platelet count < 100000/mm^3) may be present in 18% of cases with severe preeclampsia. Platelet function may also be affected. Platelet aggregation is reduced compared to normally present finding of increased aggregation in pregnancy.

Uterine activity and foetus

Uterine activity is increased resulting in premature labor. Because of reduction in intervillous blood flow, increased vascular resistance and increased viscosity of blood secondary to haemoconcentration, placenta may show early aging, calcification, infarcts and abruption. Chronic placental hypoperfusion with loss of autoregulation is also seen[23]. There may be intrauterine growth retardation, death and premature delivery.

COMPLICATIONS OF SEVERE PREECLAMPSIA

Eclampsia is defined as the development of convulsions and/or unexplained coma during pregnancy or postpartum in patients of preeclampsia. The convulsions may occur during ante-partum period, during labor or postdelivery[20]. The overall incidence is 1-2000 deliveries in developed countries and 1-200-1600 in developing countries[8].

The convulsions are generalized and there are no reliable symptoms (except symptom of preeclampsia) or tests that can predict development of convulsions. Eclampsia is associated with risk of maternal death in 0%-1.8% parturients in developed countries[24-26]. Risk of maternal death is higher in developing countries primarily due to recurrent seizures, lack of proper antenatal[27] or ICU care[26]. Eclamptic convulsions should be immediately controlled with thiopental (50-100 mg), diazepam (2.5-5 mg), midazolam (1-2 mg) or $MgSO_4$ (2-4 g) intravenously. Airway support, oxygenation and protection from aspiration pneumonites should also be done[28-30]. Recurrence of convulsions should be prevented by infusion of $MgSO_4$.

HELLP syndrome

Usually develops after 36 wk of gestation in women with severe preeclampsia. The incidence may be as high as 20%[28]. The symptoms are vague and patient may present with malaise, epigastric pain, nausea, vomiting and jaundice. Its severity ranges from a mild self limiting condition to a multi-organ involvement (DIC, liver and renal failure, pulmonary and cerebral oedema) with high foetal and maternal mortality[29,30]. The diagnostic criteria[31] are haemolysis (defined by abnormal peripheral blood smear and increased serum bilirubin), increased liver enzymes (aspartate aminotransferase level $\geq$ 70 U/L, LDH > 600 U/L) and a low platelet count (< 100000/mm^3. It's diagnosis calls for immediate delivery[8,29]. Administration of systemic steroids has been shown to reduce the risk of neonatal respiratory distress syndrome.

MANAGEMENT OF PREECLAMPSIA

The definite treatment is delivery of foetus and placenta. Until this can be accomplished, the main objective is to control the disease process, treat hypertension and prevent convulsions[8,28,29,32]. Early hospitalization with bed rest and regular clinical, cardio-tochographic study and lab investigations are useful to tailor the management of severe preeclampsia.

INDICATIONS FOR EXPEDITED DELIVERY

Uncontrolled severe hypertension not responding to treatment; eclampsia; HELLP syndrome; acute pulmonary oedema; abruptio placentae; foetal distress.

CONTROL OF BLOOD PRESSURE

Antihypertensive treatment is not indicated for mild preeclampsia as prolonged treatment with antihypertensive drugs may be associated with foetal growth retardation particularly in women with mild or moderate preeclampsia[33]. But if BP is persistently elevated, risk of hemorrhagic stroke increases. Most guidelines recommend antihypertensive medication when systolic BP is > 160 mmHg and diastolic > 110 mmHg and lowering of systolic BP to 140-150 mmHg and diastolic BP to 90-100 mmHg is desirable. A gradual reduction in BP is recommended at the rate of 10-20 mmHg every 10-20 min[34] as sudden precipitous fall may result in maternal and foetal complications. The aim is not to normalize the BP but to reduce to a safe level. However, there is no international consensus regarding choice of drug[5]. The choice is usually made depending upon experience of clinician with the particular drug[35]. Most commonly used drugs are labetalol (oral or IV), oral nifedipine and intravenous hydrallazine. Currently labetalol is most frequently used drug. Hydrallzine is frequently used by obstetricians but side effects like tachycardia, headache, postural hypotension and vomiting limits it use[6]. Nifedipine is also used but should be avoided where $MgSO_4$ has been used as profound hypotension may occur.

Dosage schedule of anti-hypertensive drugs

Hydralazine 5-10 mg IV every 20-30 min or 5-20 mg per hour as continuous infusion following 5 mg IV bolus; labetalol 10-20 mg IV or 20-60 mg per hour as continuous infusion 50-100 mg per oral; nitroglycerine 10 μg per minute IV titrated to response.

MANAGEMENT AND PROPHYLAXIS FOR CONVULSIONS

$MgSO_4$ is the drug of choice for both control and prophylaxis of convulsions[36]. $MgSO_4$ is a tocolytic, anticonvulsant and mild generalized vasodilator. Its mode of action is not clearly known but is thought to act by releasing spasm of cerebral vasculature and by blocking calcium influx through NMDA subtype of glutamate channel. Whether or not all patients require prophylactic $MgSO_4$, is debated. However most obstetricians use in severe preeclampsia when there is evidence of involvement of CNS, as evidenced by presence of severe persistent headache, visual disturbances, hyperreflexia and following a convulsion. It reduces risk of convulsions in 58% of patients[36]. But it should only be used in hospitalized women[18]. The dose is 4-6 g IV given slowly over 10-20 min followed by continuous infusion of 1-2 g/h. Monitoring during magnesium therapy includes: urine output (> 30 mL/h), deep tendon reflex, respiration and level of consciousness. Chances of toxicity increase with impaired renal functions, so doses should be reduced. Magnesium has low therapeutic index (Table 1). Early signs of toxicity are nausea, feeling of warmth, somnolence, double vision slurred speech and weakness. In case of any manifestation of toxicity, the infusion should be stopped and calcium gluconate (10 mL, 10%) should be given if needed along with supportive treatment.

Table 1 Effects of increasing plasma magnesium level

Plasma Mg level (mEq/L)	Clinical effects
1.5-2.0	Normal level
4.0-4.8	Therapeutic range
5.0-10.0	Prolong P-Q interval, wide QRS
⩾ 10.0	Loss of deep tendon reflex
⩾ 15.0	Respiratory paralysis
25	Cardiac arrest

Role of anaesthetist in management of pre-eclampsia and eclampsia

Chief role of anesthetist is to provide safe labor analgesia and anesthesia for caesarean delivery. Other roles are in resuscitation, ICU management including invasive monitoring and limitation of complications[6,29,30,34].

ANALGESIA FOR LABOR AND DELIVERY

Use of lumbar epidural analgesia for the severely preeclamptic or eclamptic patients when convulsions are under control is recommended both by obstetricians and anesthetist. Several advantages offered by this technique[29] include: (1) complete relief from labor pain without any neonatal depression; (2) ideal obstetric conditions for vaginal delivery especially for preterm babies; (3) suitable for operative vaginal delivery; (4) decreases circulating levels of catecholamine's; (5) improves intervillous blood flow; (6) stabilizes BP to a modest level; (7) attenuates hypertensive response to pain; and (8) anesthesia can be extended for caesarean delivery.

The concerns for epidural analgesia include possibility of hypotension and rarely epidural haematoma. With judicious hydration and gradual induction of block, hypotension may be minimized[6,29]. Hydration must be done with great caution and 500-1000 mL of crystalloid is usually adequate[28,29]. In patients with mild preeclampsia 1-1.5 liters of balanced salt solution can be used. The block may be initiated with 6-10 mL of dilute local anesthetic with opioid. Bolus may be repeated if no hypotension noted. Combined spinal epidural has also been shown to be safe in severely preeclamptic patients[37].

ANAESTHESIA FOR CAESAREAN SECTION

Management of anaesthesia in patients with severe preeclampsia or eclampsia is challenging for anaesthetists. Emergency caesarean section is often required due to worsening of mother's condition or due to foetal distress with limited time for optimization. But BP must be controlled and fluid volume must be optimized before proceeding for anaesthesia. It is important to have a flexible

anaesthetic plan with more than two options as condition may change rapidly[38]. Detailed preanaesthetic evaluation including severity of condition, systemic involvement, fluid status and airway assessment should be done. Use of prior pharmacological therapy must be enquired. Complete blood count, blood urea nitrogen, creatinine and liver functions tests should be obtained especially if HELLP syndrome is suspected. Routine coagulation screening is not necessary[39]. But if coagulopathy is suspected clinically by history of easy bruising ecchymoses or petechial haemorrhage, coagulation studies should be done. Platelet count should be available before neuraxial analgesia or anesthesia in severe preeclampsia.

REGIONAL ANAESTHESIA

Choice of anesthesia should be individualized depending upon patient's condition. Single shot spinal, combined spinal epidural or epidural anesthesia, all may be utilized[34] provided meticulous attention is paid to fluid management, hypotension and prevention of aorto-caval compression. Traditionally spinal anaesthesia was not employed for caesarean section in severely preeclamptic parturients. It was considered unsafe due to fear of severe hypotension induced by sympathetic block risking fetal safely. Another concern was development of pulmonary oedema following prophylactic IV fluids or fluids given to treat hypotension[40]. Therefore obstetric anaesthetist preferred epidural over spinal with the view that slow incremental doses of local anesthetic through epidural catheter would result in slow ascent of block and thus minimize the risk of sudden hypotension. However, retrospective analysis[41], prospective studies[42-45] and some editorials[46,47] strongly supported the use of spinal anesthesia in severe preeclampsia in absence of any contraindication and if epidural catheter had not already been placed for labor analgesia. The studies demonstrated lesser degree of hypotension when compared with healthy parturient receiving spinal for caesarean section[42-45]. Spinal anaesthesia with usual doses of local anaesthetic is now recommended as anaesthetic technique of choice for parturients with severe preeclampsia unless contraindicated[23,34,48,49]. Fast onset of block combined with certainty are critical advantages in emergency situation. Although spinal anesthesia can cause greater degree of hypotension than epidural anesthesia, the hypotension is short lived and can be easily treated with vasoactive drugs[23,50]. In addition, requirement of vasopressors was not found to be increased after spinal, epidural[51] or combined spinal epidural anaesthesia[52]. Before institution of block, patients with mild preeclampsia tolerate prehydration (10-15 mL/kg of crystalloid) well[28-30,38]. Most patients with severe pre-eclampsia can be prehydrated with 500-1000 mL of crystalloid if urine output is adequate[29].

Spinal anaesthesia is controversial in the setting of eclampsia[6] due to risk of convulsions[53] although has been used in a patient with difficult airway[54]. Some advocate use of epidural or general anaesthesia[55] for eclampsia. Epidural anaesthesia is indicated if woman is haemodynamically stable, is fully conscious, convulsions are controlled, has no neurological deficit and has no contraindication[29].

Regional analgesia/anesthesia and risk of haemorrhage

There is no absolute platelet count below which neuraxial analgesia or anaesthesia is contraindicated. But it is generally agreed that platelet count above 75000/mm^3 in absence of other coagulation abnormality would not be associated with problems of haemorrhage with neuraxial technique[45,56]. Rate of fall of platelet count is also important and neuraxial block may be contraindicated if the count falls rapidly over a short period[29,30]. Decision to place epidural catheter must be individualized, but catheter should be removed only when platelet count has normalized.

Intravenous volume and fluid management

The vasculature in preeclampsia has been described as 'constricted and porous'. Volume expansion although is advocated on the rationale that it is contracted, however there is no evidence to support the notion that it will be effective in presence of raised afterload[57]. There may be advantage in expanding maternal circulating volume, but there can be potential hazard of development of pulmonary oedema especially when renal function is impaired[19,40]. Therefore fluid administration should be done carefully utilizing clinical and urine output monitoring with invasive monitoring only in certain cases. Severe preeclampsia is associated with complex set of haemodynamic changes[38] central venous pressure (CVP) may not correlate well with pulmonary capillary wedge pressure (PCWP). Often CVP may be low but PCWP may be quite high. In addition with fluid infusion, rise in PCWP may be earlier than that of CVP, and may remain disproportionately high[58,59]. Hence fluid management against CVP measurement is not recommended as it may lead to overhydration in most cases[60]. If CVP alone is monitored, volume expansion of CVP up to 5 mmHg or less is sufficient[38], because CVP- PCWP gradient can be as high as 8-10. The higher CVP may result in overload[61].

In patients with oliguria (urine output < 300-500 mL/d), after excluding hypovolaemia as a cause, fluid challenge with 250-500 mL of crystalloid is given over 20 min. If patient responds by increase in urine output, additional fluid bolus may be repeated cautiously before regional block. If no response to initial fluid bolus, CVP/PCWP monitoring is recommended[60].

Consensus is that, invasive monitoring is not essential for safe fluid management in all patients of preeclampsia[38]. PCWP monitoring is recommended in patients with hypertension refractory to treatment, pulmonary oedema and oliguria not responding to modest fluid load[29,60,62].

There is no clear data regarding ideal volume and type of fluid[40,38,60]. Use of crystalloid may further reduce colloid osmotic pressure whereas colloids may lead to

volume overload after delivery due to fluid mobilization owing to their longer half life[19]. Colloids may be preferred when there is cardio-respiratory or renal compromise.

General anaesthesia

General anesthesia is indicated in severe preeclampsia with HELLP syndrome, eclampsia, coagulopathy, cerebral oedema and in patients who refuse regional anaesthesia. The risks include: (1) potentially difficult airway due to airway and laryngeal oedema; (2) exaggerated sympathetic response to laryngoscopy and intubation and also during extubation; (3) Aspiration of gastric contents; (4) potentiation of neuromuscular block especially non-depolarizer block owing to prior use of $MgSO_4$; and (5) impaired placental blood flow.

Before induction of anesthesia, BP must be controlled because untreated hypertension increases risk of cerebral haemorrhage, pulmonary congestion, hepatic and renal dysfunction and reduction in placental perfusion. Thiopental and succinylcholine are most frequently used and usually a smaller endotracheal tube is required. Presser response to laryngoscope may be attenuated using lignocaine, fentanyl, labetalol, nitroglycerine or magnesium sulphate. Laryngeal oedema resulting in failed intubation is fortunately rare but well described in preeclampsia[63]. The duration of single dose of succinyl choline is usually not affected by previous use of $MgSO_4$[29], but doses of non-depolarizing muscle relaxants must be reduced. Use of peripheral nerve stimulator is recommended[29]. Atracurium is a preferred agent[64]. Ergotamine should be avoided and if required oxytocin infusion should be used[34].

POSTOPERATIVE MANAGEMENT

Management should be done in high dependency unit or transferred to ICU if required. The patients with severe preeclampsia are prone to convulse or develop pulmonary oedema within 24 h of delivery. If $MgSO_4$ was given, it should be continued for 24-48 h. If required oral antihypertensive medication should also be given. Pain must be controlled by epidural or other route. Strict intake output chart should be maintained for at least 24 h or until diuresis develops.

CONCLUSION

Despite advancement in understanding of etiopathogenesis and management, preeclampsia and eclampsia still remain a leading cause of maternal mortality. Multidisciplinary care with early reference to anaesthesiologists who have clear knowledge of pathophysiology and are well trained in resuscitation and monitoring and critical care management may help in limiting complications and improve outcome.

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REVIEW

Lumbar radiculopathy and its neurobiological basis

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Abstract

Lumbar radiculopathy, a group of diseases in which the dorsal root ganglia (DRG) or dorsal roots are adversely affected by herniated discs or spinal stenosis, are clinically characterized by spontaneous and evoked types of pain. The pain is underpinned by various distinct pathophysiological mechanisms in the peripheral and central nervous systems. However, the diagnosis of lumbar radiculopathy is still unsatisfactory, because the association of the pain with the neurobiological basis of radiculopathy is largely unknown. Several animal models used to explore the underlying neurobiological basis of lumbar radiculopathy could be classified as mechanical, chemical, or both based on the component of injury. Mechanical injury elevates the intraneural pressure, reduces blood flow, and eventually establishes ischemia in the dorsal root and the DRG. Ischemia may induce ischemic pain and cause nerve damage or death, and the subsequent nerve damage or death may induce neuropathic pain. Chemical injury predominately induces inflammation surrounding the dorsal roots or DRG and consequent inflammatory mediators cause inflammatory pain. Furthermore, DRG neurons sensitized by inflammatory mediators are hypersensitive to innocuous mechanical force (stretch or compression) and responsible for mechanical allodynia in radiculopathy. As well, central sensitization in the spinal cord may play an important role in pain generation in lumbar radiculopathy. Increasing knowledge of pain-generating mechanisms and their translation into clinical symptoms and signs might allow for dissecting the mechanisms that operate in each patient. With precise clinical phenotypic characterization of lumbar radiculopathy and its connection to a specific underlying mechanism, we should be able to design optimal treatments for individuals. This review discusses the present knowledge of lumbar radiculopathy and proposes a novel mechanism-based classification.

Key words: Low back pain; Acid-sensing ion channel; Dorsal root; Dorsal root ganglia; Disc herniation; Lumbar spine

Core tip: Lumbar radiculopathy is the most common form of neuropathic pain. However, the diagnosis of lumbar radiculopathy is still not satisfactory because of the largely unknown neurobiological basis of neuropathic pain and paresthesia. Accumulating evidence has shown that lumbar radiculopathy is a multi-factor disease and may involve almost all types of pain, including ischemic, inflammatory, mechanical, and neuropathic pain. Ion channels such as Acid-sensing ion channel 3, Piezo2 and transient receptor potential vanilloid receptor 1 responding to tissue acidosis, mechanical force, and inflammatory mediators may be the pathways transducing the pain.

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INTRODUCTION

Demographics

Lumbar radiculopathy or nerve root pain represents one distinct presentation of low back-related leg pain, which is generally characterized by pain radiating to below the knee and into the foot and toes. The annual prevalence of low back pain, varies from 9.9% to 25%. The point prevalence (4.6% to 13.4%) and lifetime prevalence (1.2% to 43%) are high[1], so lumbosacral radicular pain may be the most commonly occurring form of neuropathic pain[2,3].

Definition

The terms radicular pain and radiculopathy are sometimes used interchangeably, although they are not synonymous. With radicular pain, only radiating pain is present, whereas with radiculopathy, sensory and/or motor loss can be objectified. Both syndromes frequently occur together and radiculopathy can be a continuum of radicular pain.

Symptoms and signs

Patients with lumbar radiculopathy typically present a chief complaint of pain. The patient may experience the radiating pain as sharp, dull, piercing, throbbing, or burning. Pain caused by a herniated disc classically increases with bending forward, sitting, coughing, or (excessive) stress on the lumbar discs and can be avoided by lying down or sometimes by walking[4]. Conversely, pain due to lumbar spinal-canal stenosis can typically increase during walking and improve immediately with bending forward[5]. In addition to the pain, patients often report paresthesia in affected dermatomes. Although the distribution of pain along a dermatome can determine the affected levels of dorsal roots, the variation in radiation pattern is large. The S1 dermatome seems the most reliable[6]. If present, the dermatomal distribution of paresthesia is more specific[5]. Among the symptoms, pain and paresthesia are often referred to as positive symptoms of radiculopathy, whereas weakness and numbness are considered negative symptoms. Positive symptoms are believed to reflect neuronal hyperactivity, and negative symptoms may stem from diminished neural firing occurring with axonal loss or conduction block[7]. Commonly used physical tests include the straight-leg raise test, Lasègue's crossed straight-leg raise test, tendon reflexes, and signs of weakness, atrophy or sensory deficits[8-11].

CLINICAL SCENARIOS IN ANIMAL MODELS OF RADICULOPATHY

Mechanical and chemical injury

The investigation of the pathway for lumbar radiculopathy in a number of animal models has included mechanical constriction of a nerve root via suture ligation, application of exogenous pro-inflammatory mediators to a nerve root, and application of autologous nucleus pulpous (NP) tissue to a nerve root[12-32]. According to the component of primary injury, these animal models are classified as mechanical or chemical injury or both (Table 1). Mechanical compressors that do not directly produce biochemical effects include silk ligation[26], ameroid constrictors[24], and stainless rods[25,32]; the chemical factors that produce direct biochemical effects include autologous NP application[16,28-30], chromic gut ligatures[27], and Surgiflo[31]. Evidence of mechanical allodynia and thermal hyperalgesia is commonly identified, occurring as early as 2 d post-procedure and persisting for 2 to 6 wk[14,16-23,33,34]. The structural changes in nerve fibers include edema and demyelination, deposition and engulfment of inflammatory cells, and Wallerian degeneration of nerve fibers[29,35]. Mechanical and chemical injury do not differ in pain behaviors or histopathological changes; however, they could have different effects on gene expression in the dorsal root ganglia (DRG) at 7 d after surgery, which suggests that the underlying mechanisms of the 2 types of nerve injury differ[32].

Nerve root and DRG

The anatomical structure of the nerve root differs from that of DRG. The spinal nerve roots and their nutrient vessels lack a perineurium and feature a poorly developed epineurium. In contrast, DRG, where the soma of sensory neurons reside, feature dense perineurium vascular supply. The blood flow supply is greater in the nerve root proximal than distal to the DRG[36]. Spinal nerve roots are surrounded by cerebrospinal fluid and receive 58% of their nutritional supply from cerebrospinal fluid and 38% from intramural blood vessels, whereas peripheral nerves receive 95% of their nutritional supply from intramural blood vessels[37]. Accordingly, DRG are more sensitive to mechanical compression and consequent ischemia changes than nerve roots and are considered a key player in lumbar radiculopathy. In addition, the direction of information flow from the periphery to DRG to the spinal cord itself is a main factor in the distal lesion inducing strong neuropathic signs. After spinal nerve injury distal to the DRG, the sensory neurons are excited and exhibit ectopic firing. Takiguchi *et al*[38] observed more severe radiculopathy and more microglia activation in the spinal dorsal horn in rats with injury distal than proximal to the DRG. Another study suggested that spinal-nerve crush injuries produce a greater degree of DRG apoptosis than do corresponding nerve-root crush injuries and that the former injuries are associated with longer-lasting mechanical allodynia[39].

Gait analysis and motor function

Behavioral changes observed in pre-clinical models of lumbar radicular pain may be similar to painful symptoms observed in human subjects. Patients with low back pain and sciatica report fear of movement and substan-

Table 1 Animal models of lumbar radiculopathy

Injury component	Model	Species	Injury site	Pain behaviors	Motor function
Mechanical	Chronic gradual nerve root compression (Cornefjord *et al*[24])	Porcine	Preganglion	NA	NA
	chronic compression of dorsal root ganglion produced by intervertebral foramen stenosis (Hu *et al*[25])	Rat (SD)	Dorsal root ganglion	Heat hyperalgesia 5-35 d after surgery	NA
	Compression strain of nerve root (Winkelstein *et al*[26])	Holtzman rats	Preganglion	Mechanical allodynia	NA
	Stainless rod -induced lumbar radiculopathy(Takayama *et al*[32])	Rat (SD)	Preganglion	NA	NA
Chemical	Autologus nucleus pulposus-induced lumbar radiculopathy (Olmarker *et al*[28])	Porcine	Preganglion	NA	NA
	Autologus nucleus pulposus-induced lumbar radiculopathy (Yabuki *et al*[29])	Rat (SD)	Preganglion	NA	NA
	Autologus nucleus pulposus-induced lumbar radiculopathy (Otani *et al*[30])	Dog	Preganglion	NA	NA
	Autologus nucleus pulposus-induced lumbar radiculopathy (Shamji *et al*[16])	Rat (SD)	Dorsal root ganglion	Mechanical allodynia	Marked gait asymmetry, preference to bear weight on the contralateral limb
Mechanical + chemical	Spinal nerve root irritation with chromic gut ligatures (Kawakami *et al*[27])	Rat(SD)	Preganglion	Prolonged thermal hyperalgesia 2 to 12 wk	Immeditaely paresis resolved in 2 wk, totally recovered in 6 wk
	Chronic compression of lumbar dorsal root ganglion with SURGIFLO™(Gu *et al*[31])	Rat(SD)	Dorsal root ganglion	Mechanical allodynia and thermal hyperalgesia up to 4 or 5 postoperative week	NA

NA: Not available.

tial decreases in activity levels[40], and recently, patients with lumbar spinal stenosis reported significantly lower activity levels than both control subjects and patients with knee or hip osteoarthritis[41]. Patients with lumbar radiculopathy have been found with reduced walking velocities, short stride lengths, and increased periods of double limb support[42]. In a rat model of non-compressive disc herniation with autologous NP application, animals exhibited behavioral changes such as heightened behavioral mechanical sensitivity, stance asymmetry, and disturbed gait parameters including symmetry and force analysis[16,43,44]. In animal models of lumbar radiculopathy, motor weakness developed immediately after the injury and pain behaviors developed at the same time. Motor functions recovered gradually within 1 or 2 wk, whereas pain behaviors persisted for at least 6 wk to 3 mo. During the acute or subacute post-injury period, motor weakness is seldom observed in humans but is the predominant symptom in rats. This contradiction may be related to the times of the observations or differences between animal models and humans. Further studies are needed for clarification.

Contralateral and ipsilateral sides

Clinically, in the common lateral type of lumbar disc herniation, radiculopathy is usually ipsilateral, but contralateral radiculopathy exists in some patients[45-48]. Contralateral mechanical allodynia has been shown in some animal models of neuropathic pain[49,50]. In addition, unilateral nerve injuries or inflammation induces molecular changes in the contralateral DRG, which have been demonstrated to contribute to the induction of neuropathic pain[49,51,52]. A previous study suggested that NP application to the unilateral DRG could induce nerve injury, satellite cell activation and upregulation of tumor necrosis factor α (TNF-α) expression in the contralateral DRG[53]. Furthermore, injury of motor neurons might have a significant role in contralateral changes.

NEUROBIOLOGY BASIS

Mechanical injury and ischemia

Tissue acidosis and involvement of acid-sensing ion channels: The most pertinent mechanical effect of herniated disc material or degenerative stenosis on neural tissue is likely the result of increased intraneural pressure[7]. With increasing intraneural pressure, mechanical compression of the nerve root induces a decrease in intraradicular blood flow, histological changes such as intramural edema, eletrophysiological changes such as reduced nerve conduction velocity and enhanced excitability of DRG neurons, and reduced mechanical and thermal withdrawal thresholds[54-56] (Figure 1). In addition, compression of the periradicular venous plexus within the foramen and resulting blood stasis can lead to congestion, ischemia, intraneural edema, and increased intraneural pressure[57]. The resulting hypoxia causes tissue acidosis and damage or even death of DRG sensory neurons. Acid-sensing ion channel 3 (ASIC3) is a member of the proton-gated ion channels of the DEG/ENaC/ASIC superfamily, which are two-transmembrane proteins assembling as a trimeric sodium channel that is amiloride-sensitive and voltage-

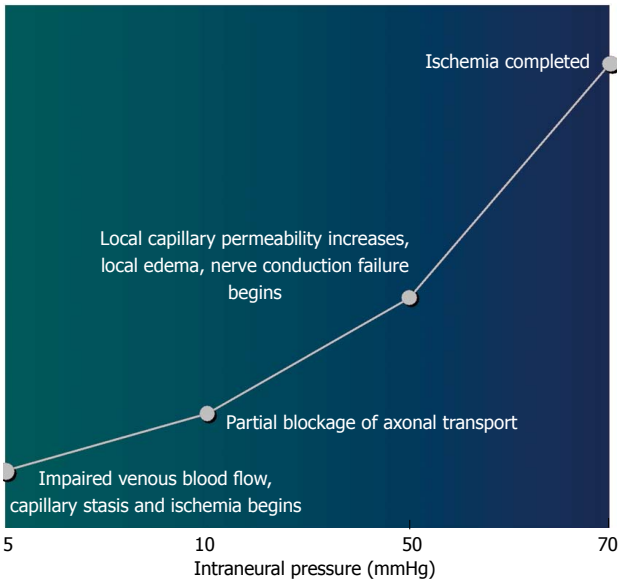

Figure 1 Ischemia changes in the nerve root with increasing intraneural pressure.

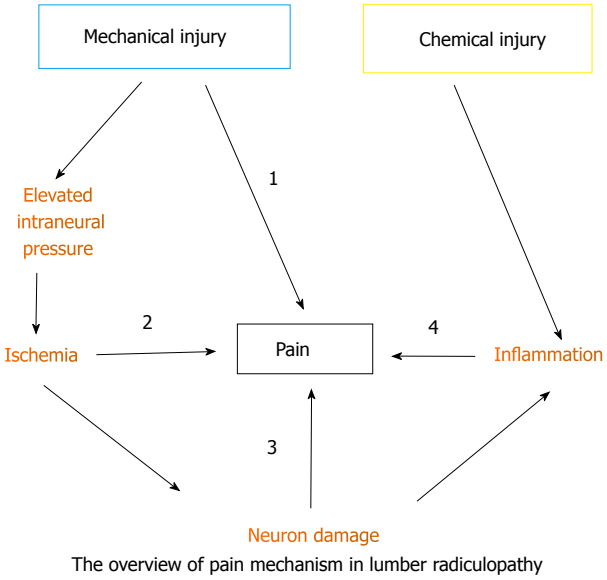

Figure 2 The overview of the pain mechanism in lumbar radiculopathy. 1: Mechanical pain, 2: Ischemic pain, 3: Neuropathic pain, 4: Inflammatory pain.

independent[58]. Tissue acidosis activates ASIC3 on DRG sensory neurons and the activation has been reported to be sufficient to cause pain[59]. However, the P2X3 receptor has been demonstrated to mediate nociceptive information of cell damage and inflammation, with activation dependent on peripheral ATP released from the damaged cells. The expression of P2X3 in DRG can be induced by local NP application[60]. Also, ATP may be involved in inducing mechanical and thermal hyperalgesia in experimental animal models. Finally, ATP works together with acid to increase the pH sensitivity of ASIC3 and may enhance the pain caused by acidosis[61].

Neuron damage or death: After damage to the DRG and the dorsal nerve root, primary afferent fibers often show aberrant "ectopic" activity, with an altered pattern of neuronal excitability and conduction causing spontaneous pain and hyperalgesia. The accumulation of sodium channels at or around the site of injury is thought to be responsible for the ectopic activity[62,63] Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels located within the DRG are thought to generate spontaneous rhythmic activity and contribute to neuronal excitability and plasticity[64]. In particular, increased expression of HCN1 channels in large-diameter afferents is responsible for evoking spontaneous pacemaker-driven action potentials in the damaged nerve[65]. In addition, damage to peripheral nerves upregulates vanilloid receptors (TRPV1), which are only marginally expressed under physiological conditions at the membrane of primary afferents[66]. TRPV1 is essential for selective modalities of pain sensation and for tissue injury-induced thermal hyperalgesia[67]. Two studies demonstrated that nerve injury triggers downregulated TRPV1 in damaged afferents but upregulated TRPV1 in uninjured C- and A-fibers[66,68].

Role of mechanosensitive channels: In physiological status, nerve roots and spinal nerves typically demonstrate 2 to 8 mm of glide within their neural foramen depending on the model and measurement technique[69-76]. In compression injury, the presence of periradicular fibrosis will compound the nerve root pain by fixing the nerve in one position, thereby increasing the susceptibility of the nerve root to tension or compression[77-80]. Use of the intraoperative straight-leg raise test in humans has shown that hernia compresses the nerve roots and increases their flatness, thus resulting in a clear disturbance with gliding distance reduced to only a few millimeters, reduced intraradicular blood flow, and significantly deteriorated amplitude of the nerve root action potential after 30 s of the test[79,80]. This transient conduction disturbance probably results from temporary ischemic changes in the nerve root, which suggests that the primary cause of radicular pain is mechanical force of the nerve root induced by periradicular adhesive tissue around the herniated disc[79,80]. However, radicular pain can be produced *via* stimulation of a swollen or stretched nerve root alone. A normal or uncompressed nerve root could be manipulated, with associated paresthesia but without significant pain[81-83].

Although some intimate contact between the herniated disc material and the nerve root is required for the pain, neither the size of the disc herniation seen on MRI nor the amount of thecal sac deformation is necessarily related to the degree of pain experienced. A common assumption is that some portion of the inflammatory cascade is responsible. Thus, the potentiation or sensitization of the nerve roots or DRG is required for a stretch or tension force on the nerve root to cause radicular pain or ectopic spontaneous activity. The underlying mechanisms of the radicular pain or ectopic spontaneous activity are not clear, and the mechanosensitive channels that allow sensory neurons to transmit noxious mechanical stimuli when the nerve root is under stretch or tension force are

still unknown. ASIC3, Piezo2, and channels of transient receptor potential C (TRPC) family have been reported to be essential for a neuron to sense the mechanical force[84-88]. Among these candidate channels, ASIC3 is upregulated in DRG neurons with application of NP[89] or a mixed inflammatory soup[90,91] containing serotonin, bradykinin, interleukins 1 and 6 (IL-1 and IL-6), and TNF-α. Moreover, serotonin potentiates the proton-evoked sustained current of ASIC3[92]. Thereafter, ASIC3, which is upregulated and potentiated in DRG neurons under an inflammatory condition, may be responsible for the neuron to sense the noxious mechanical stimuli.

Chemical injury

The application of autologous NP induces electrophysiological changes and similarly enhances DRG neuron excitability, reduces mechanical and thermal withdrawal threshold and nerve blood flow, and causes histological changes such as axonal degeneration, intramural edema, and Schwann cell edema in the nerve root and DRG[28-30,93-99]. Indeed, upon systemic exposure, the NP component of intervertebral disc tissue initiates a specific immune response, likely a consequence of its immune privileged avascular location bounded by the annulus fibrosus[97,100]. In an *in vitro* canine model, prostaglandin E2, a chemical mediator of inflammation, could provoke an ectopic eruption of impulses from the nerve roots[101]. Leakage of chemical mediators or inflammatory cytokines, which are produced in the painful disk, into the epidural space through anular tears could lead to injury to adjacent nerve roots and the leakage might be the primary pathophysiological mechanism of radiating leg pain without disk herniation[102,103].

Cytokines: TNF-α, IL-1, IL-6: Accumulating evidence shows that sciatica due to disc herniation and low back pain may be related to activation and sensitization of intraspinal nervous structures by disc-derived substances; one key substance for inducing such irritation is TNF-α[12,14,20,35,104-106]. In a rat model of lumbar disc herniation, endoneural macrophages (macrophages infiltrating the DRG), neurons, and activated satellite cells in DRG are the sources of TNF-α[34,51,105,107]. TNF-α can induce neuropathological damage, or neuropathic pain states, which can be prevented by selective TNF-α inhibitors[107,108]. However, initial clinical trials of TNF-α blockers for treating sciatica have shown good[109-112] or inconclusive results[113-116]. Therefore, blockage of other cytokines along with TNF-α may enhance the therapeutic effects because the cytokine network would be inhibited at multiple levels. In fact, cytokines such as IL-1 and IL-6 are strongly linked to radicular pain[21,28,117]. IL-1, IL-6, and TNF-α are activated in the spinal cord, DRG, and Schwann cells in the spinal nerve roots after lumbar spinal stenosis, and their expression is closely related to pain as well as motor nerve dysfunction and degeneration[118].

Glutamate: Discs are avascular and have low rates of cellular metabolism. Because of no reuptake systems for extracellular glutamate in and around cartilage, free glutamate may be cleared quite slowly and much less rapidly in discs than in neural tissue, which contain avid reuptake systems for glutamate[119]. A rat model showed that epidural glutamate infusion at several concentrations created dose-related focal hyperesthesia as measured by von Frey fiber testing[120]. The finding suggests a change in sensory neurotransmission through primary afferents if glutamate cleaved from disc matrix were to diffuse in high enough concentration to the DRG[119], where ionotropic and metabotropic glutamate receptors are found in high densities on cell bodies[121,122].

Protease-activated protein receptor 2: Protease-activated protein receptor 2 (PAR2) is a G-protein–coupled receptor that functions in hemostasis and thrombosis and in the inflammatory and proliferative response triggered by tissue injury[123]. PAR2 is expressed by a subset of sensory neurons and PAR2 agonists to elicit neurogenic inflammation by release of substance P and calcitonin gene-related peptide[124]. PAR2 activation could lower the pain threshold to thermal stimuli *via* an afferent pathway that involves the activation of spinal neurokinin 1 receptors and prostaglandins[125]. In an animal model of chronic compression of DRG, PAR2 activation was critical for induction of neuronal hyperexcitability induced by nerve injury[126].

Neurotrophic factor and brain-derived trophic factor: Neurotrophic factor (NGF) concentration is increased in response to tissue injury[127,128] and leads to increased brain-derived trophic factor (*BDNF*) gene expression, mainly in trkA-expressing small- and medium-sized neurons[129-131]. BDNF, a neuromodulator of nociceptive information in the spinal dorsal horn, causes the N-methyl-D-aspartate-mediated depolarization responsible for synaptic plasticity related to central sensitization[132-135]. In a rat model of lumbar disc herniation, Obata *et al*[34] demonstrated increased NGF-immunoreactive cells and BDNF-immunoreactive neurons within the DRG, which was closely related to pain behaviors, and endoneural injection of NGF led to the same findings in the DRG and in pain behaviors. Thus, increased NGF level in response to tissue or nerve injury upregulates BDNF level in primary sensory afferents, then BDNF causes synaptic plasticity related to central sensitization.

Microgliosis in the spinal dorsal horn

Microgliosis (accumulation of activated microglia) around degenerative neurons is a common pathological feature of various neurological disorders including radiculopathy. Microglia activation in the spinal cord progresses through a hypertrophic morphology, with thickened and retracted processes and an increase in cell number. Peripheral nerve injury leads to marked activation of microglia within the spinal dorsal horn[136] and increases the number of dorsal horn microglia by two- to fourfold[137-141].

Table 2 Hypothetic mechanisms of neuropathic pain and target molecules involved in radiculopathy

Symptoms/signs	Type of pain	Mechanism	Molecules/channels
Spontaneous shooting pain	neuropathic	Spontaneous ectopic DRG neuron activity	Na channels
Spontaneous ongoing pain	Inflammatory	Inflammation surrounding or within DRG	TNF-α, IL-1/6
Positive straight-leg raise test	Inflammatory, mechanical, ischemic	Induction of ectopic neuron activity or ischemia when a sensitized and constricted nerve root stretches	ASIC3, Piezo2, 5-HTR
Sensory deficit	Neuropathic	Apoptosis or phenotype shift of DRG neurons	?
Heat allodynia	Neuropathic	Reduced threshold to heat	TRPV1
Cold allodynia	Neuropathic	Reduced threshold to cold	TRPM8
Static Mechanical allodynia	neuropathic	Reduced threshold to mechanical	ASIC3?, Piezo2?
Dynamic Mechanical allodynia	neuropathic	Reduced threshold to mechanical	ASIC3?, Piezo2?
Soreness	Inflammatory, ischemic	Increased protons	ASIC3, TNF-α, IL-1, IL-6

TNF-α: Tumor necrosis factor α; DRG: Dorsal root ganglia; ASIC: Acid-sensing ion channel; IL: Interleukin.

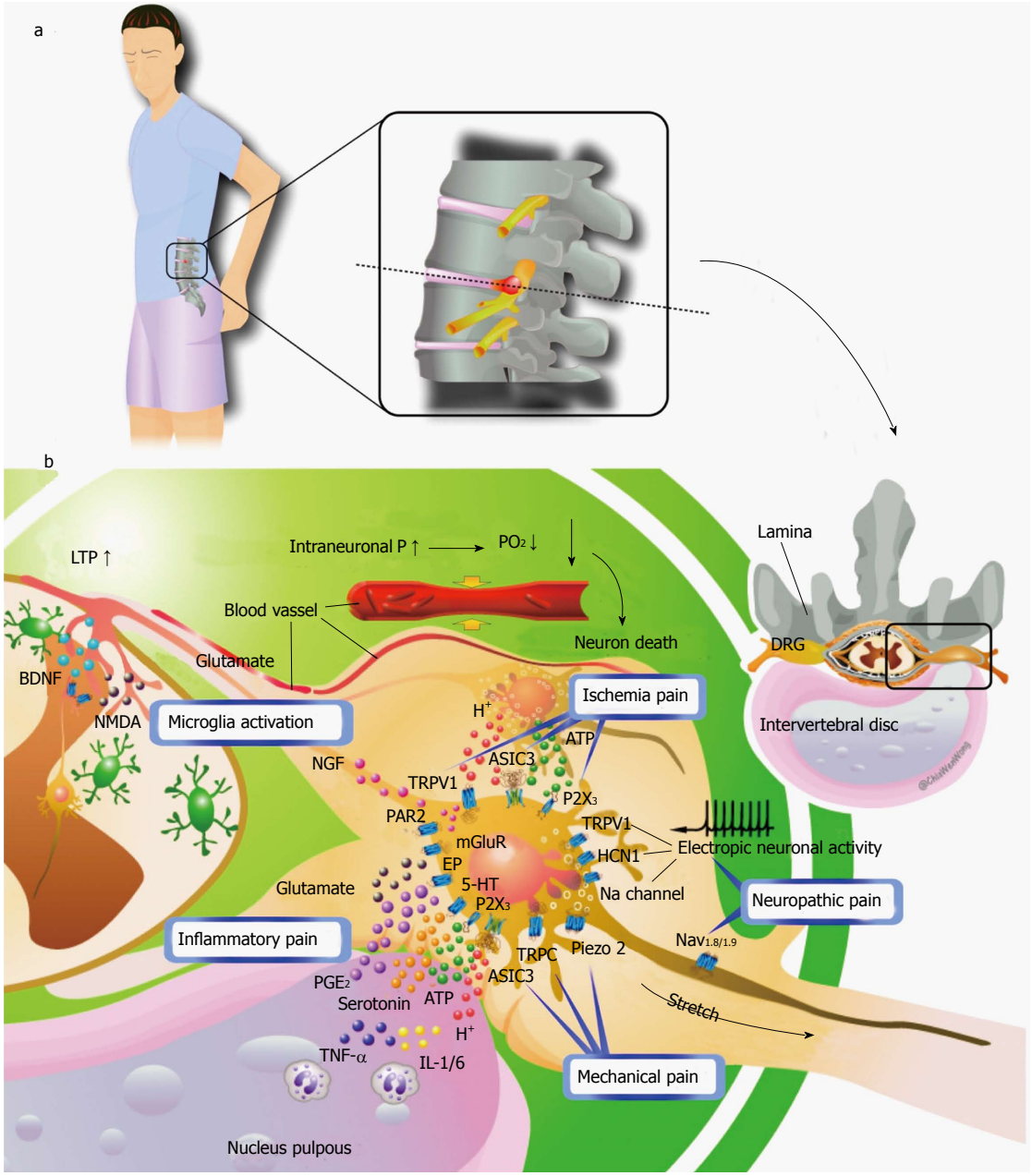

Figure 3 A hypothetical mechanism of lumbar radiculopathy. (a) The clinical scenario of lumbar radiculopathy in which a lumbar DRG is compressed by a lumbar herniated disc. (b) Lumbar radiculopathy includes multiple pain problems caused by mechanical stress, ischemia, inflammation, and nerve damage. Receptors or ion channels involved in neurosensory mechanotransduction (ASIC3, Piezo2, TRPC), acid chemosensation (ASIC3, TRPV1), inflammation responses (HTR2B, mGluR, P2X3, TRPV1, *etc.*), and ectopic neuronal activity (HCN1, Nav1.8) may be the key players in transducing the pain. DRG: Dorsal root ganglia; LTP: Long-term potentiation; BDNF: Brain-derived neurotrophic factor; NMDA: N-methyl-D-aspartate receptor; PGE_2: Prostaglandin E2; TRPC: Transient receptor potential C; ASIC3: Acid-sensing ion channel 3; ATP: Adenosine triphosphate.

Animal models based on compression injury of the DRG demonstrate resultant allodynia and functional deficits associated with increased microglial activation in the spinal cord[105,142-145]. Peripheral nerve injury increases the release of neurotransmitters such as glutamate, substance P, and ATP from primary afferent neurons activating both secondary neurons and surrounding glial cells. These changes appear to be crucial to the ability of glial cells to produce cytokines and other inflammatory agents. The release of inflammatory mediators including TNF-α, IL-1b, IL-6, nitric oxide (NO), and prostaglandins initiates self-propagating enhanced cytokine expression in glial cells. These agents are then capable of sensitizing primary afferent and dorsal horn neurons thereby contributing to neuropathic pain after nerve injury. Therefore, in contrast to behavioral findings, microglia were activated before pain-related behavior and returned to a normal state despite persistent mechanical and thermal hypersensitivity. Increasing evidence shows that microglia cells are involved in the initiation of chronic pain in neuropathic pain models, although no role for microglia in ongoing maintenance of pain has been reported[146].

THE WHOLE PICTURE OF LUMBAR RADICULOPATHY

Lumbar radiculopathy is no doubt a multi-factor disease and may involve almost all types of pain, such as ischemic, inflammatory, mechanical, and neuropathic pain (Figure 2). Mechanical injury elevates the intraneural pressure of the dorsal roots and the DRG, reduces blood flow, and eventually establishes ischemia. Ischemia may trigger ischemic pain and cause nerve damage or death. The subsequent nerve damage or death may further induce neuropathic pain. In contrast, chemical injury predominately induces inflammation surrounding the dorsal roots or DRG and the consequent inflammatory mediators cause inflammatory pain. Furthermore, DRG neurons sensitized by inflammatory mediators will produce a nociceptive signal with application of a mechanical force (stretch or compression). As well, central sensitization in the spinal-cord dorsal horn plays an important role in pain generation of lumbar radiculopathy. Here, we propose an overall picture of lumbar radiculopathy and attempt to translate the clinical symptoms and signs based on the present knowledge of the neurobiological basis of pain. (Table 2 and Figure 3)

CONCLUSION

Lumbar radiculopathy remains an important and largely unresolved medical problem that requires further research into the etiological factors to determine the correct diagnosis, despite pronounced advances in the knowledge of the neurological basis of pain in the past decade. There is clear interest in identifying the cell populations affected by disc herniation-induced radiculopathy, and the role of neurotransmitters and their receptors that mediate the symptomatic and functional deficits of radiculopathy. However, our ability to translate pain complaints and sensory abnormalities into specific pathophysiological mechanisms that have treatment implications is in its infancy. Whether different underlying mechanisms cause different symptoms and signs in patients is unknown. Improvement in the animal models of lumbar radiculopathy and the methods of pain-behaviors is warranted.

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MINIREVIEWS

Intraoperative magnetic resonance imaging in neurosurgery and anesthetic considerations

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Abstract

Currently, magnetic resonance imaging (MRI) is the only imaging modality available which is capable of acquiring intra-operative images frequently with acceptable spatial and contrast resolution. However, the incorporation of MRI technology into the operating room requires special anesthetic considerations. It may include various aspects such as transport, remote location anesthesia, strong electromagnetic field, use of approved items, equipment counts, possible emergencies, and surgery in awake patients. The patient safety may be compromised by health-related, equipment-related, and procedure-related risks. Direct patient observation may be compromised by acoustic noise, darkened environment, obstructed line of sight, and distractions along with difficult access to the patient for airway management. Most often, the patient's head will be 180° away from the anesthesiologist during the procedure. Several monitors exist that are designed for conditional use in a MR environment. The general design criterion in these monitors is to eliminate conductors that carry electrical signals for monitoring physiologic parameters of the patient. General anesthesia requires an extended anesthetic circuit for ventilation maintenance and drug administration because the patient is located farther from the anesthesia machine than in traditional operating room settings. Dead space creates a time delay before the volatile anesthetic and drugs are administered and when expected effects can be observed. Therefore, the attending anaesthesiologists must understand the above aspects for safe conduct of neurosurgical procedures by minimizing MRI associated accidents while assuring optimal patient vigilance.

Key words: Intraoperative magnetic resonance imaging; Electromagnetic field; Safety; Anesthesia; Neurosurgery

Core tip: Intraoperative magnetic resonance imaging (MRI) has been used for the identification of eloquent brain areas. However, the incorporation of MRI technology into the operating room requires special anesthetic and procedural considerations. This review article focussed on these aspects.

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INTRODUCTION

Successful neurosurgical procedures rely on the accurate targeting of regions of interest along with preservation of eloquent cortex such as motor, speech, and visual areas during the procedure. This helps the neurosurgeons achieving maximal resection of the lesion with minimal untoward neurologic sequelae. The development of magnetic resonance imaging (MRI)-guided navigation sys-

tems represents a significant improvement in the surgical treatment of various intracranial lesions. At present, MRI is the only imaging modality available which is capable of acquiring intra-operative images frequently with acceptable spatial and contrast resolution.

BENEFITS AND USE OF INTRA-OPERATIVE MRI IN NEUROSURGERY

Intraoperative MRI (iMRI) has been used for the identification of eloquent brain areas. It is also known as functional MRI (fMRI) during intraoperative period, thus help in reducing postoperative morbidity after excision of lesions in eloquent areas of brain[1]. Intracranial anatomy undergoes dynamic changes after the opening of the dura (known as "brain shift"), thereby compromising the localization of neural structures in space relative to their preoperative location on imaging. The brain shift occurs up to one centimeter in most of the cranial neurosurgeries due to drainage of cerebrospinal fluid (CSF), brain edema, and tumor resection[2-4]. This is most likely to occur in patients with large tumors (> 3 cm diameter) or tumors adjacent to the ventricles[5]. Only serial intraoperative imaging with high spatial resolution allows the distinction of deformation patterns and reveals brain compartments with differing reactions to surgical manipulations[2].

Among intracranial tumors, gliomas pose technical challenges to the neurosurgeon as many of these tumors (particularly low-grade gliomas) do not possess distinct capsules, thus causing an uncertainty as to where the border of the lesion ends and viable brain begins.This may lead to either inadequate resection if surgeon limits the resection within the boundaries of abnormal tissue (to avoid neurologic damage). Abundant evidence indicates that a more complete resection under the guidance of iMRI directly impacts the survival time and quality of life of patients with low-grade gliomas and glioblastoma multiforme[6-8].

During trans-sphenoidal microsurgical resection of pituitary adenomas, the extent of resection may be difficult to assess, especially when extensive suprasellar and parasellar growth has occurred. iMRI is particularly useful in guiding resection safely, aiding in clinical decision making, allowing identification and preservation of the pituitary stalk and normal pituitary gland with good postoperative outcomes[9,10]. Temporal lobe resection or selective amygdalo-hippocampectomy to remove an epileptogenic focus can be performed much more accurately under iMRI[11]. Its application in spine surgeries, particularly those involving critical regions like cervical and craniocervical junctions may increase the surgical accuracy and safety[12,13].

Subthalamic nucleus deep brain stimulator (DBS) placement using high-field interventional magnetic resonance imaging and a skull-mounted aiming device simplifies DBS implantation by eliminating the use of the traditional stereotactic frame and the subsequent requirement for registration of the brain in stereotactic space[14].

In case of an intraoperative complication, global status of the brain can be checked such as intracerebral hemorrhage, diffuse cerebral edema, hydrocephalus, *etc*. Auxillary adjuncts of iMRI such as diffusion-weighted images, MR-angiography and MR-venography could clearly demonstrate vascular complications like ischemia[15]. It also helps to reduce the need for further surgeries, as scans done after the process can help doctors identify and remove any residual tumor that may have been missed[16]. It also avoids the transfer of the critically ill patient to another suite should urgent imaging be needed be needed during or after operation.

ORIGIN OF IMRI

It has been almost three decades since the introduction of iMRI into the field of neurosurgery. Collaboration between the Brigham and Women's Hospital and General Electric resulted in the world's first iMRI system in 1994 at Brigham and Women's Hospital in Boston, Massachusetts[17]. Since then, several types of iMRI units have been developed that can be classified as low or high-field systems based on the magnetic field strength ranging from 0.12 and 3 Tesla (T)[18]. Low-field magnets (0.15-0.2 T) have the advantage of providing good surgical access to the patient; however, they have the disadvantage of lower resolution. High-field magnets (1.5-3 T) have the advantage of providing better resolution but may limit access to the patient during imaging. The recent high field iMRI system, constructed by the cooperation of Siemens and Brain Lab (Brain Suite), consists of a standard 1.5 T magnet scanner, implemented in a dedicated operating room (OR) with a computer-assisted neuronavigation system, and digitized image transfer and projection system to form a comprehensive unit (Figure 1).

DESIGN OF THE IMRI SUITE

The incorporation of MRI technology into the OR requires special considerations. In this setting, the respective role and communication among team members (*e.g.*, surgeons, radiologists, MR technologists, nurses, anesthesiologists, computer scientists, and engineers) is of paramount importance. The design of the OR must allow adequate anesthesia monitoring and care. Room size must be significantly larger than a standard operating room to allow enough space to install an MRI machine, to move the patient into and out of the MRI core. The monitoring equipment has to be MR safe as well as MR conditional. MR Safe indicates an item that poses no known hazards in all MRI environments and is non-conducting, nonmetallic, and non-magnetic. MR Conditional indicates an item that has been demonstrated to pose no known hazards in a specified MR environment with specified conditions of use. An example of this would be an MRI conditional anesthesia machine (Datex-Ohmeda Aestiva; GE Healthcare, Waukesha, WI, United States) that is

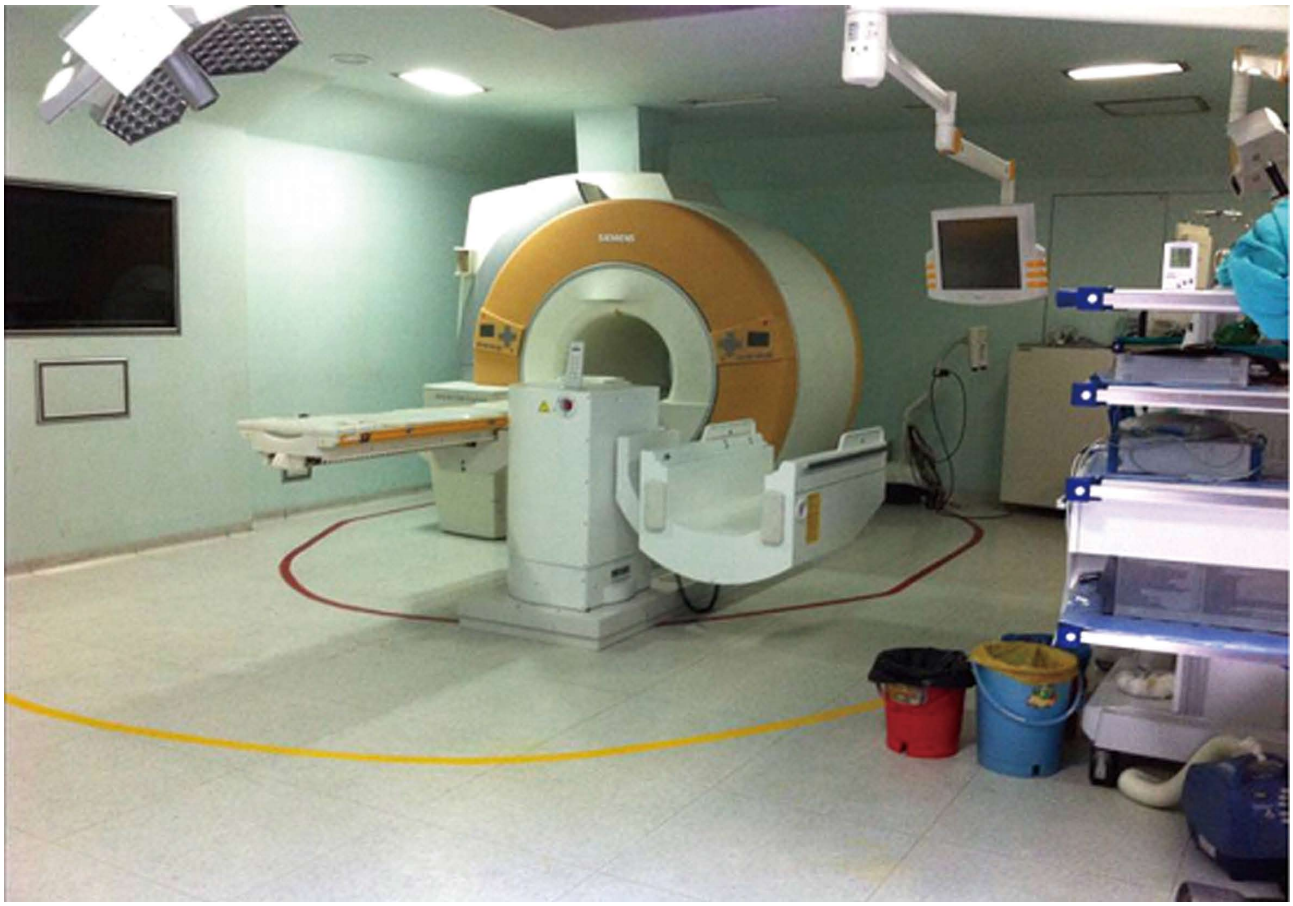

Figure 1 Brain suite with magnet scanner and computer-assisted, ceiling-mounted navigation system.

conditional to 100 Gauss (G) in a 1.5 T magnet. MR unsafe indicates an item that is known to pose hazards in all MRI environments[19].

Another important consideration is to assure adequate distance between equipment with ferromagnetic properties and the location where the magnetic field is the strongest. A red line (inner) represents the region where the magnetic field is 50 G and higher, and the yellow line (outer) demarcates the region beyond which the magnetic field strength is less than 5 G. Any ferromagnetic object within 5 G line can be attracted to the magnet and act as a missile with devastating consequences. Since the areas for imaging and surgery are separate in many clinical circumstances using iMRI, either the patient is transferred to the MRI, or the MRI is brought to the patient.

Brain suite has 180° rotating dedicated table (modified Angio DIAGNOST 5 Syncra Tilt Patient Support, Philips Medical Systems) and the surgery is carried out under standard operating environment, with conventional ferromagnetic instruments and microscope as patient is placed outside 5 G line (Figure 2). This area is equipped with a ceiling-mounted navigation system (BrainLab Vector Vision), which allows conventional neuronavigation with preoperative and updated navigation with intraoperatively acquired images. For intraoperative imaging, the patient is transferred from the primary microneurosurgical operating site to the scanner (imaging site) using the rotating table, which is returned to the MR- axis, connected, and the patient is transferred into the magnet. For this transfer, every ferromagnetic item is removed and the surgical field is covered with additional sterile drapes. MRI images are obtained and loaded into the navigation system while the patient is transferred back to the surgical area. If residual tumor is identified, resection is continued, using the updated image data for continued neuronavigation. Biopsies can be performed outside the 5 G line, using standard frame-based or frameless systems. Both of these methods employ standard neurosurgical techniques and equipments.

ANESTHETIC CHALLENGES IN IMRI

Introducing the MRI technology into the OR-setting presents unique challenge in a trans-disciplinary environment[20]. The American College of Radiologists has developed practice guidelines for personnel working in an MRI environment[21]. These guidelines extend to nurses, surgeons, and anesthesia providers in an iMRI setting.

Anesthetic considerations in the iMRI may include various aspects such as transport, remote location anesthesia, strong electromagnetic field, use of approved items, equipment counts, MRI periods, possible emergencies, and surgery in awake patients[22]. The anesthesiologist mediates safe conduct of neurosurgical procedure

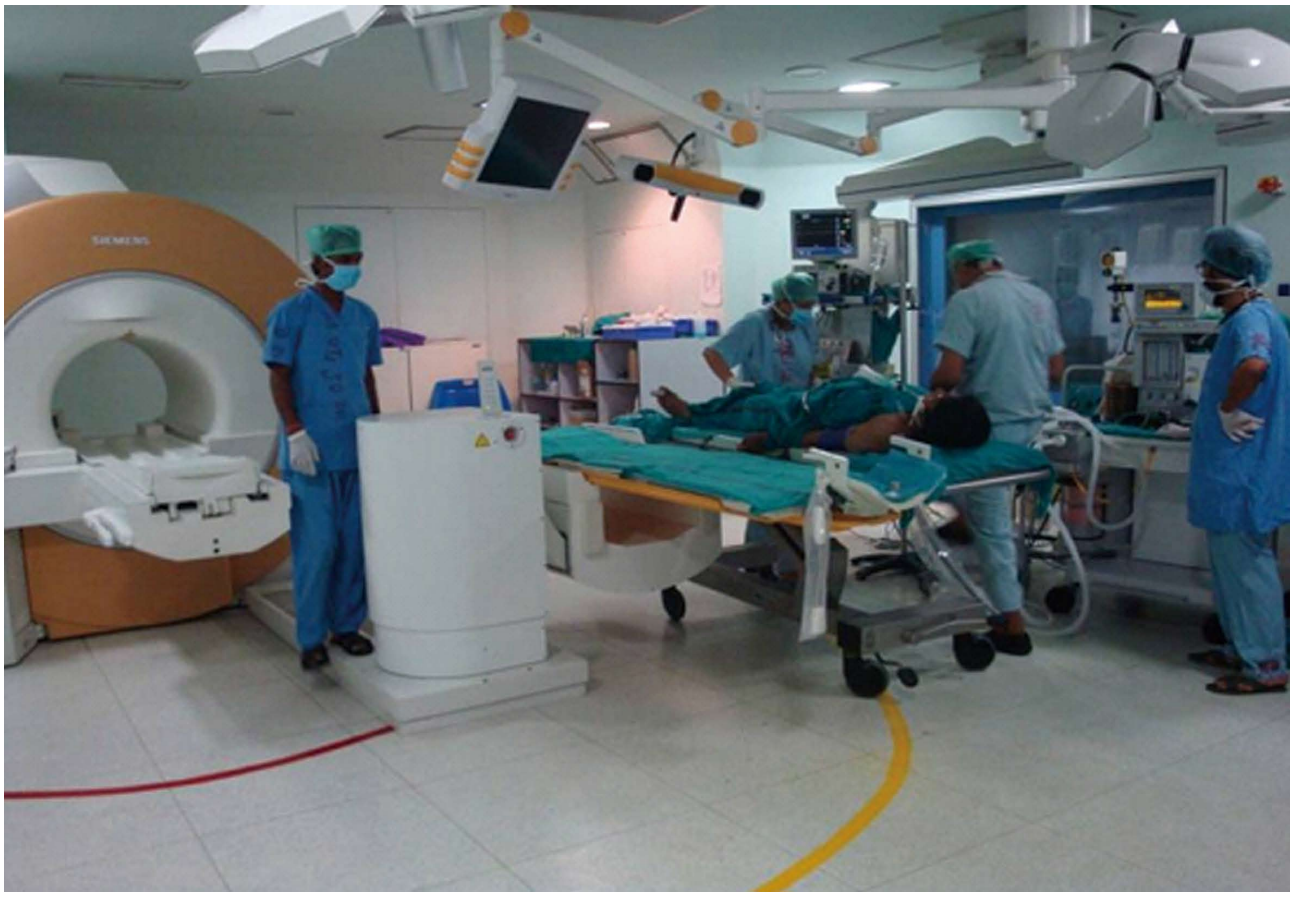

Figure 2 Procedure are being performed outside the 5-Gauss line in the brain suite.

by minimizing or eliminating iMRI associated accidents, while assuring optimal patient vigilance. Patient safety may be compromised by health-related, equipment-related, and procedure-related risks.

Preoperative evaluation is aimed for identifying functional limitations and patient risks associated with the iMRI technology. This examination should include history of implanted metallic devices, such as cardiac defibrillators or pacemakers, cerebrovascular clips, cochlear implants, vagal nerve stimulators, deep brain stimulators, other steel metallic implants, intravascular wires, stents, bullets, extensive tattoos, or permanent eye make-up. These devices may be ferromagnetic and lead to dislodgment[23]. Patients who have braces or dentures may generate artifacts that may significantly degrade iMRI images. The heating of metallic implants can lead to severe burns. The function of pacemakers, cardiac catheters and insulin pumps can be altered with exposure to the magnetic field.

Direct patient observation may be compromised by acoustic noise, darkened environment, obstructed line of sight, and distractions along with difficult access to the patient for airway management. Most often, the patient's head will be 180° away from the anesthesiologist during the procedure. The actual distance may be 10-15 feet from the anesthesia workstation, limiting access to the patient. A magnetic field is constantly present and extends beyond the magnet. This source of the electromagnetic force attracts any ferromagnetic object or instrument, such as glasses, pens, stethoscopes, scissors, intravenous (IV) stands, gas cylinders, laryngoscopes, and anesthesia machines. This ferromagnetic attraction poses potential injury to patients or staff in the OR. In general, no metallic object should be allowed in the OR.

Several monitors exist that are designed for conditional use in a MR environment. The general design criterion in these monitors is to eliminate conductors that carry electrical signals for monitoring physiologic parameters of the patient. These conductors can function as receiving antenna on which the pulsating electrical and magnetic energy can induce spurious electric noise (EN) that distorts and corrupts the physiologic waveforms displayed on the monitor. The two general approaches currently used to achieve this criterion are the use of fiberoptics and wireless technology. When metal objects and electronic monitors are introduced into the MR environment, they may interact with the images produced by the MRI scanner by reflecting or generating radiofrequency (RF) waves. These may result in distorted MR images that are unreliable for diagnostic purposes.

There is negligible ferromagnetic material in vaporizers and mechanical ventilators, and with the exception of desflurane, these devices behave properly when introduced into MR environments[24]. Isoflurane and sevo-

flurane vaporizers are MR safe and cleared for use in the low- and high-field MR environments. The desflurane vaporizer is not MR safe. MRI compatible anesthesia machines and ventilators are also available.

The RF signal and the magnetic gradients of an iMRI system are pulsed during a scan at a frequency dependent on the specific imaging pulse sequence type and the parameters used. The sequences used for iMRI typically apply gradient and RF pulses at rates less than 100 Hz[25]. These high-energy pulsations can generate a significant second EN component in the frequency bandwidth of most monitored physiologic signals. The most vulnerable signal is the electrocardiogram (ECG), with masking of virtually all details of the ECG waveform. Specialized equipment compatible with MRI is currently available for monitoring of ECG, non-invasive blood pressure, oxygen saturation (SpO_2), end-tidal CO_2, invasive blood pressure and central venous pressure, and Doppler. Both audio and visual alarms are necessary because the loud noise generated by the scanner may mask the sound of the audio alarms. Necessary monitoring equipments that do not have MRI conditional counterparts include defibrillators, fluid-warming devices, forced air warming devices, peripheral nerve stimulators, and temperature probes. The MRI unsafe monitoring can be used during the non-imaging portions of the case, with the equipment tethered to the wall of the MRI suite with the help of cables to prevent them from ever being inadvertently moved within the 5 G line. Before transferring the patient to the imaging area, a checklist is used to assure all MRI unsafe items are counted and moved beyond the 5 G line.

Most monitors have ECG filters that can be adjusted to minimize the noise while maintaining as much of the rhythm information as possible. The ECG electrodes and cables should be MR safe and contain minimal metal components. Cables should be well padded to avoid direct contact with the skin.

Standard blood pressure monitoring techniques may be used with minimal adaptations. A mercury manometer, sphygmomanometer, or automated oscillometric blood pressure recording device may still be used as long as they are kept away from the scanner[24]. For major craniotomies invasive blood pressure monitoring is done. MRI compatible anesthesia monitors with invasive monitoring are now available.

Cold temperature is required in the room to keep the magnet super cooled with liquid helium or nitrogen in an effort to maintain a pristine magnetic field, which may decrease body temperature. Active heating with forced hot air warmers is essential in maintaining proper patient temperature during the non-imaging phases of the procedure. Covering the patient with impermeable sterile drapes during the imaging phase prevents most radiant heat loss by the patient. Again, perioperative hypothermia is of greater concern in pediatric patients than adults[26], given the relatively cool iMRI environment. However, studies have shown that RF waves emitted from the magnet may produce heat and increase body temperature in pediatric patients, despite minimal efforts to reduce passive heat loss under sedation and without the use of warming devices[27,28].

Heating of devices used in the OR, such as pulse oximeters and temperature probes, may cause local burn injuries. MR safe pulse oximeters are available for use in MR environments to measure SpO_2. Anesthesiologists may benefit by using an end-tidal CO_2 monitor with elongated sampling tube in anesthetized patients.

Another safety consideration for high-field MR environments is the acoustic noise generated from the MR machine during a scan, which can exceed 100 dB[29]. Exposure to high noise levels can lead to hearing loss, making hearing protection essential[30]. An effective barrier against patient and operator injury from this sound is the use of foam earplugs. It is important that the use of earplugs by iMRI staff does not interfere with the ability to hear physician commands or respond to emergencies.

General anesthesia requires an extended anesthetic circuit for ventilation maintenance and drug administration because the patient is located farther from the anesthesia machine than in traditional OR settings. Dead space creates a time delay before the volatile anesthetic and drugs are administered and when expected effects can be observed. A combination of IV anesthetic with volatile agents is preferred. The intravenous extension lines must be long, properly arranged, color-coded, and positioned along the patient's body to extend caudally.

AWAKE CRANIOTOMY IN HIGH-FIELD INTRAOPERATIVE MRI

Combination of brain tumor surgery under local anesthesia with iMRI is a demanding procedure mostly because of procedural limitations in the form of prolonged duration and subsequent patient exhaustion. The patients should be carefully selected with regard to neurological status, cognitive, and mental resilience. However, the procedure seems to be tolerable and reasonable for most patients from a psychological point of view[31]. Standard draping protocols in high-field iMRI units make awake craniotomies challenging due to issues with both patient comfort (claustrophobia for alert patients) and safety (airway protection for sedated patients). Nabavi *et al*[32] suggest uncovering the patient's face and Weingarten *et al*[33] described trimming drapes hanging below the operating table. During the procedure, the patient is transferred between operating and imaging area with a rotating table. The scanning procedure adds extra 45-60 min to the surgery time. Earplugs are placed during the scans and sedation may be increased to help tolerate immobility and noise.

Gadolinium-based contrast agents are approved by the United States Food and Drug Administration for use in MRI. There is a finite risk of moderate-to-severe acute adverse reaction to IV gadolinium chelates (0.01%)[34], but until recently there was no evidence for late adverse reaction to MR contrast agents. However, gadolinium chelate is now the suspected trigger for development of a rare

debilitating syndrome termed as nephrogenic systemic fibrosis (NSF). This syndrome occurs in patients with renal insufficiency. To date, NSF has not been reported in patients with normal renal function.

CONCLUSION

The incorporation of MRI technology into the operating room requires special anesthetic considerations. The patient safety may be compromised by health, equipment and/or procedure-related risks. In this context, the role of anesthesiologists in mediating the safe conduct of neurosurgical procedures by minimizing MRI associated accidents, while assuring optimal patient vigilance, may not be overemphasized.

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ORIGINAL ARTICLE

Paroxetine *vs* pregabalin for the management of neuropathic pain in multiple sclerosis

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Abstract

AIM: To compare the effectiveness and tolerability of paroxetine *vs* pregabalin for the management of multiple sclerosis (MS)-induced neuropathic pain (NPP).

METHODS: A randomized, flexible-dose open-label 8-wk study involving 21 relapsing-remitting MS patients with MS-induced NPP was conducted to evaluate the effectiveness and tolerability of pregabalin versus paroxetine for pain management. The trial included a 3-wk dose titration phase followed by a 5-wk stable dose phase. Primary outcome measures included daily patient-reported pain intensity as measured using a 100 mm visual analogue scale (VAS_{pain}) and daily impact of pain on daily activities (VAS_{impact}). Hierarchical regression modeling was conducted on each outcome to determine if within person VAS trajectory for pain and impact differed across study groups, during 56 d follow-up.

RESULTS: Attrition rates were significantly greater ($P < 0.001$) in the paroxetine versus pregabalin study group (70% *vs* 18.2%, respectively). Average study duration between study groups also significantly differed ($P < 0.001$). Paroxetine participants completed an average of 27.3 d of treatment *vs* 49.5 d in the pregabalin group, with the majority of patients withdrawing due to adverse events. Due to the high attrition rates in the paroxetine study arm, the investigators stopped the study prior to achieving complete recruitment. As such, no significant differences between pregabalin and paroxetine study arms were noted for the primary outcome measures (VAS_{pain}, VAS_{impact}). Comparative assessment of baseline patient characteristics also revealed no significant differences between the study arms.

CONCLUSION: High attrition rates associated with paroxetine use suggest that it be used with caution for MS-induced NPP. Efficacy outcomes could not be assessed due to attrition.

Key words: Multiple sclerosis; Neuropathic pain; Paroxetine; Pregabalin; Clinical trial

Core tip: The high attrition rates identified in the paroxetine study arm suggest that it be used with caution for multiple sclerosis (MS)-induced neuropathic pain (NPP). Although analysis of the primary endpoint measures revealed no significant differences, there was a trend toward marked improvement for visual analogue scale and daily impact of pain on daily activities in favor of pregabalin. However, due to the premature study cessation, definitive confirmation of pregabalin's enhanced efficacy was not possible. These results reinforce the recognized challenges clinicians encounter in drug selection for MS-induced NPP. Due to the lack of well-designed controlled NPP trials in this population, effective and well-tolerated treatment selection poses a significant clinical challenge.

Turcotte DA, Doupe M, Torabi M, Gomori AJ, Ethans K, Esfahani F, Galloway K, Namaka MP. Paroxetine *vs* pregabalin for the management of neuropathic pain in multiple sclerosis. *World J Anesthesiol* 2014; 3(2): 181-188 Available from: URL: http://www.wjgnet.com/2218-6182/full/v3/i2/181.htm DOI: http://dx.doi.org/10.5313/wja.v3.i2.181

INTRODUCTION

Multiple sclerosis (MS) is a chronic, neurodegenerative disease that affects over two million people world-wide[1]. Pain is recognized as one of the most significant MS-induced symptoms. It has been reported that up to 80% of MS patients experience some form of chronic pain[2-5]. MS-induced neuropathic pain (NPP) is a chronic pain syndrome caused by damage to the nerve fibers involved in the synaptic transmission of pain. Hallmark clinical symptoms include sensory abnormalities such as: numbness, burning, feeling of pins and needles, tingling sensations and shock-like pain[6,7].

At present, there is no cure for MS-induced NPP. Henceforth, treatment goals are focused primarily on reducing pain to a more tolerable level. Patients with NPP often suffer other co-morbidities such as mood and sleep disorders[8,9]. Clinicians are therefore faced with the additional challenge of selecting a therapeutic option capable of managing all these domains associated with chronic pain. For example, antidepressant medications possess a distinct advantage of having analgesic and antidepressant/sedative properties that assist with both pain, mood and sleep issues. As such, tricyclic antidepressants (TCAs), such as amitriptyline and nortriptyline, are recommended as first-line agents for NPP[10]. TCAs elicit their analgesia through the pre-synaptic reuptake inhibition of serotonin (5-HT) and norepinephrine (NE), thereby enhancing descending pain modulating pathways[11]. In addition, TCAs have also been shown to exhibit sodium and calcium channel blockade, resulting in decreased neuronal hyperexcitability[11]. Despite documented effectiveness in various NPP conditions, the usefulness of TCAs in MS is often limited due to poor tolerability[11]. MS patients often suffer a variety of disease-induced symptoms that include: dizziness, ataxia, bladder/bowel retention, drowsiness and fatigue. These underlying disease induced symptoms can all be potentially intensified by the addition of a TCA to their medication regimen. As such, it many cases, it is difficult to attain therapeutic dosages to successfully control their pain.

Selective serotonin reuptake inhibitors (SSRIs) are antidepressant medications that may be better tolerated in individuals with MS due, in part, to the lack of anticholinergic effects. SSRIs selectively block the pre-synaptic reuptake of 5-HT, resulting in an accumulation of 5-HT in synapses involved in the transmission of pain. As such, analogous to TCA's, SSRIs are suggested to have an analgesic role via potentiating the descending pain inhibitory mechanisms[12]. Interestingly, a recent animal model evaluating the analgesic effects of the SSRI paroxetine suggests an additional mechanistic link to produce analgesia *via* opioid systems[13]. Although limited, there is some evidence supporting the analgesic efficacy of SSRIs in NPP. In two randomized, placebo controlled trials, citalopram[14] (n = 17) and paroxetine[15] (n = 20) were both found to be effective at reducing pain intensity associated with diabetic peripheral neuropathy (DPN) when comparatively assessed against placebo. Citalopram, dosed at 40 mg daily, was found to significantly reduce self-reported pain intensity (P = 0.007), and was well-tolerated with two individuals receiving active treatment withdrawing early due to adverse events (nausea and vomiting, gastric upset)[14]. Paroxetine evaluated for DPN in a placebo-controlled cross-over design at a dosage of 40 mg daily was found to be significantly better at reducing self-reported pain intensity than placebo (P = 0.012)[15]. No individuals receiving paroxetine in this trial withdrew early. Although, paroxetine has been evaluated for depression in MS[16], to the best of our knowledge, it has not been evaluated for MS-induced NPP.

In addition to antidepressants, several other first-line agents have been used in the treatment of NPP, including pregabalin[10]. Pregabalin is an anticonvulsant medication thought to elicit analgesic effects through interaction with the $\alpha 2\delta$ subunit of N-type voltage-dependent Ca^{2+} channels, ultimately reducing overall neuronal excitability[17]. Several large controlled trials have demonstrated consistent efficacy results for use in post-herpetic neuralgia (PHN) and diabetic peripheral neuropathy (DPN)[18-20]. Formal evaluation of pregabalin for use in MS-induced NPP, however, is limited. One open-label pilot study evaluating the effect of pregabalin (mean dosage 154 mg daily) on paroxysmal painful symptoms in MS (n = 16) found it to be both efficacious at reducing pain from time 0 to one month follow-up ($P < 0.05$) and well-tolerated[21].

At present, few drugs are approved specifically for MS-induced NPP[22]. In fact, MS-induced NPP is often managed by the off label use of medications. Hence, outcome measures of efficacy and tolerability in clinical trials focused on NPP resulting from diabetes, herpes zoster or injury, are often employed to drive therapeutic decision-

Table 1 Study eligibility requirements

Inclusion criteria	Exclusion criteria
Males and females 18-65 years old	Breastfeeding
Clinically definite RRMS	History of alcohol or other substance abuse
EDSS ≤ 6.5	Significant hepatic/renal insufficiency
VAS score for NPP symptoms > 5	Significant cardiac disease (CHF, arrhythmia); hypertension
Pain present for at least 3 mo	Hypersensitivity/allergy to study medications or their derivatives
Negative serum pregnancy test	No current therapeutic duplications
	No history of psychotic/non-psychotic emotional disorders

Inclusion and exclusion criteria for enrolment in the study are noted above. RRMS: Relapsing-remitting multiple sclerosis; EDSS: Expanded Disability Status Scale; NPP: Neuropathic pain; VAS: Visual analogue scale; CHF: Congestive heart failure.

making in the MS population. Due to the lack of focused research specifically evaluating therapies for MS-induced NPP, we have undertaken a study aimed to evaluate the efficacy and tolerability of paroxetine and pregabalin for the management of NPP in individuals with relapsing-remitting MS (RRMS). We hypothesize that pregabalin would significantly reduce daily absolute pain when compared to paroxetine with similar tolerability. To our knowledge, this is the first study to formally compare these agents for the management of NPP in RRMS.

MATERIALS AND METHODS

A randomized, open-label, parallel pilot study was conducted at the MS clinic of the Health Sciences Centre in Winnipeg, Manitoba, Canada over a 4-year-period. Ethical approval for this study was obtained by the Biomedical Research Ethics Board of the University of Manitoba. Study procedures adhered to practices outlined in Good Clinical Practice Guidelines. Based on stringent enrolment criteria, eligible patients providing written informed consent were enrolled for participation into the trial. Eligibility inclusion criteria comprised: (1) males and females between the ages of 18-65 years old, (2) clinically definite RRMS, as defined by the McDonald Criteria[23], (3) expanded Disability Status Scale (EDSS) score of < 6.0 (*i.e.*, not restricted to a wheelchair)[24], (4) no concurrent MS relapse at time of enrolment, and (5) Visual Analogue Scale (VAS) score for NPP symptoms ≥ 5 with pain symptoms present for at least 3 mo prior to enrolment. Eligibility exclusion criteria comprised: (1) pregnancy or breastfeeding, or immediate conception plans; (2) known history of alcohol and/or substance abuse; (3) history of non-psychotic emotional disorders; (4) significant hepatic and/or renal insufficiency that would require dose adjustments of study medications; (5) significant cardiovascular disease (congestive heart failure, cardiac rhythm abnormalities) and/or uncontrolled hypertension (systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg); (6) documented hypersensitivity to paroxetine or pregabalin or any of their derivatives; and (7) current medications with potential significant interactions with study meds (as determined by clinical pharmacist). In addition, patients were allowed to remain on current pain medications provided medications have been at stable dosages for at least 6 mo and must not interact with study medications. Please refer to Table 1 for a complete summary list of all the inclusion and exclusion criteria.

All eligible, consenting patients were randomized to receive treatment with either paroxetine or pregabalin. Randomization assignments, completed by an individual independent of the study, were generated using pre-programmed computer software (Microsoft Excel®) employing a random permuted blocks approach[25]. To minimize the ability to predict subsequent treatment assignments, it was selected to also randomize the block sizes, varying them as either 2 or 4 patients per block. Results of the randomization generation were placed within opaque envelopes numbered sequentially. After all pre-screening and consenting procedures were done, the subsequent treatment assignment envelope was opened and randomization result provided.

Once randomized to drug treatment, patients completed a physician-conducted baseline screening (Baseline Assessment), during which they underwent baseline physical and neurological examinations. Additionally, patients were provided with a daily pain diary (DPD), required for daily self-completion to monitor the intensity and impact of pain. Patients were instructed to record their daily pain score upon waking each morning in the DPD provided to them. The DPD was comprised of a vertical VAS scale of 0 mm (no pain) to 100 mm (worst pain imaginable) and patients were required to record their daily pain score (intensity) over the previous 24 h (VAS_{pain}). In addition, the DPD contained a second identical vertical VAS scale to evaluate the impact of daily pain on their daily activities (VAS_{impact}), anchored this time with 0 mm (no effect) to 100 mm (incapacitating). At the end of the baseline assessment, patients were provided with dosing instructions for the subsequent three-week "titration period".

Dosing instructions were dependent on treatment assignment, and included three possible weekly increases. Patients were contacted by phone prior to the initiation of the subsequent dosage step. If patients were experiencing significant adverse events or ≥ 50% pain relief at the current dose, in collaboration with the patient, it was within the clinician's discretion to halt dosage increases and instruct individuals accordingly. Please refer to Table 2 for a summary of the suggested dosage schedule.

Patients were required to return to the clinic for an adverse event assessment at the end of the "titration phase" (Post-Titration Assessment). At this time, patients completed a standardized "Adverse Event Checklist" containing a word-list of possible side effects to document any current or previously experienced symptoms since beginning the study. To minimize prompting, passive collection of adverse events was facilitated through the inclusion of adverse event descriptors of known association to the study drugs and those of less common

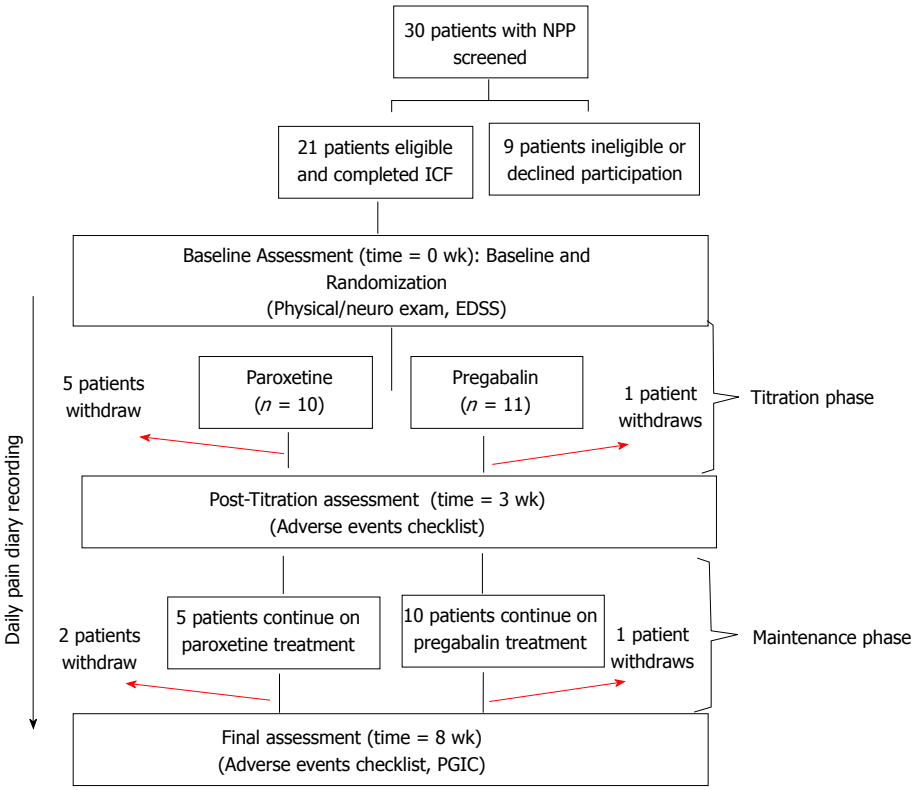

Figure 1 Study schedule summary. Patient screening outcomes and visit schedule summaries are provided. Bracketed information on specified "Assessment" lines indicates evaluations conducted at each visit. NPP: Neuropathic pain; ICF: Informed consent form; EDSS: Expanded disability status scale; PGIC: Patient rated global Impression of change.

Table 2 Paroxetine/pregabalin flexible-dose titration schedule

Schedule	Dosage	
	Paroxetine	Pregabalin
Day 1	20 mg once daily	75 mg twice daily
Day 8	40 mg once daily	150 mg twice daily
Day 15	50 mg once daily	300 mg twice daily

Flexible-dose titration schedule for each group is presented. Assuming therapy was well-tolerated patients were instructed to increase dosages as indicated above. If, however, at any point patients experienced intolerable side effects they were instructed to contact study investigators for tailored dosing instructions.

or unknown association, in random order. At the end of the post-titration assessment the current dose that the patient was able to attain by the end of the titration phase was entered as their stable dose for the subsequent 5-wk "maintenance phase". DPD recording continued over the 5-wk maintenance phase. At the end of the maintenance phase patients returned to clinic for one final visit (Final Assessment) where they completed the same Adverse Event Checklist. Additionally at this time, patients were required to complete the Patient-Rated Global Impression of Change (PGIC). This tool is used to evaluate the patient's perception of their assigned treatment on their pain symptoms. Patients were asked to rate their overall pain at this time point in comparison to their pain at the baseline assessment. Selection options included: (1) very much improved; (2) much improved; (3) minimally improved; (4) no change; (5) minimally worse; (6) much worse; and (7) very much worse. The PGIC is well-validated for assessing patient perception on clinical treatment outcomes[26]. Please refer to Figure 1 for a summary of the clinical trial timeline.

Statistical analysis

Baseline patient covariates were compared for group differences using either an independent t test for continuous measures or a chi-squared test for the categorical measure (patient sex). Daily VAS_{pain} and VAS_{impact} data exist at two levels (time and person), therefore a hierarchical model was used to assess the rate of within person change in these outcomes, differences in these outcomes across study groups collapsed across all times, and most importantly, group × time interactions to determine if the rate of change in VAS_{pain} and VAS_{impact} differed significantly by group[27]. All data analyses were conducted using R Software (2013)[28].

Sample size calculation

The required sample size in each treatment group was calculated based on the procedure outlined by Diggle *et al*[29]. It was assumed that the treatment allocation and baseline differences accounted for at least 13% of the total variation in daily VAS, which corresponds to a medium effect size defined by Cohen[30]. As well, there were 56 repeated measures for each subject with alpha set at 0.05 and the power was set at 0.8. Predicted drop-out was determined from results of previous clinical trials (pregabalin average 15.5%[31,32], paroxetine 19%[33]). The drop-out rates were accounted for using the method described by Sakpal (2010)[34]. Therefore, it was found that there should be a sample size of approximately 24 subjects would be required (12 in each study arm).

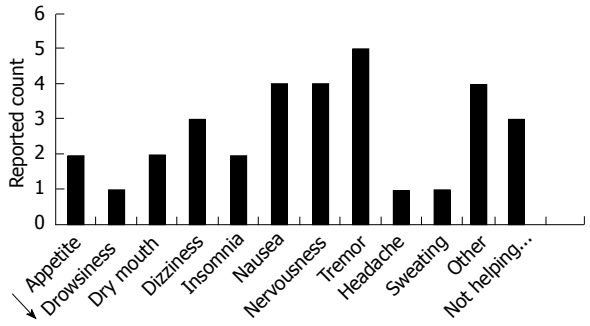

Figure 2 Patient-reported reasons for study attrition: paroxetine arm. Patient-reported reasons for attrition are presented (n = 7). Patients were permitted to cite multiple reasons for treatment discontinuation. "Other" included complaints of feeling "shaky", "caffeinated", "jittery" and "anxious".

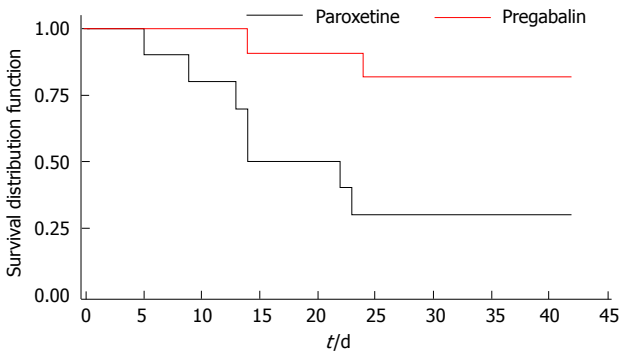

Figure 3 Attrition by study group. Attrition rates (shown in the format of survival distribution by study day) for each group (paroxetine and pregabalin) are presented. The average study duration (days) for paroxetine = 27.3 and for pregabalin = 49.5.

RESULTS

Collectively, 30 patients were screened for enrolment into the trial, prior to early closure of the study due to high drop-out rates. Of these patients, 7 were found to be ineligible based on inclusion/exclusion criteria (Table 1) and two were eligible but elected not to participate. Ultimately, 21 patients consented and were enrolled for participation in the study (10 randomized to paroxetine and 11 to pregabalin). No significant differences were noted between the groups on any of the baseline cohort characteristics collected. This information is summarized in Table 3.

Significant differences ($P < 0.001$) in attrition rates were identified between the two study groups that favored the pregabalin treatment arm. Specifically, in the pregabalin study arm, a total of 2 patients (18.2%) did not complete the entire 8-wk duration of the study. Conversely, assessment of the paroxetine study arm identified 7 patients (70%) that were not able to complete the study. The average percentage of maximum dosage was compared by study arm and did not differ significantly. This information is summarized in Table 3. Both patients who withdrew early in the pregabalin study arm did so as a result of intolerable sedation and dizziness. Attrition reasons for the paroxetine arm are summarized in Figure 2, with the most commonly reported attrition reasons being tremor, nausea and feelings of nervousness. Figure 3 illustrates drop-out as a survival plot. In comparing the average study duration (days) by study group, paroxetine was found to have a significantly lower mean than pregabalin (27.3 d *vs* 49.5 d, respectively, $P < 0.01$). This information is presented in Table 4.

Primary outcome measures were compared between the groups, with univariate modeling for VAS_{pain} and VAS_{impact} demonstrating all non-significant findings. These results are presented in Table 5. Comparative assessment of 8 wk trial data involving patient-perceived treatment effect, (evaluated using the PGIC), revealed no statistically significant differences between treatment arms.

DISCUSSION

Individuals with MS can be plagued by many unique disease-induced symptoms not commonly seen in other NPP conditions, including: ataxia, dizziness, cognitive impairment, imbalance, bladder/bowel dysfunction and visual disturbances. Many of the current first-line treatment recommendations from general NPP guidelines have the potential to induce drug-related adverse effects that can mimic and worsen MS disease symptoms. As such, tolerability limitations must be considered when translating general NPP guideline recommendations to MS-induced NPP clinical management. This is made evident by the outcomes of the current trial, which indicated a significantly high attrition rate in those patients treated with paroxetine versus pregabalin ($P < 0.001$). The results of our study in this specific patient population contradicts the favorable tolerability of paroxetine in reported in other clinical pain trials, such as burning mouth syndrome[33] and DPN[15]. Our results suggest that due to other underlying disease induced symptoms commonly associated with MS, paroxetine may not be the most suitable choice for this patient population. Furthermore, the combination of stringent enrollment criteria and recognized high attrition rates hindered patient enrollment for this study. As result, the reduced sample size prevented optimal assessment of the proposed primary study aims developed to assess efficacy.

Irrespective of these challenges, the primary outcome measures (VAS_{pain} and VAS_{impact}) were compared univariately revealing no significant difference between groups. In addition, patient-perceived treatment benefit–as determined by the PGIC at the Final Assessment–did not differ significantly between the groups, reinforcing the equivocal results of this trial. Due to the high attrition rate in the paroxetine study arm, comparison of primary outcomes between the groups is compromised due to small numbers of patients remaining after the mid-point of the study. As such, comparison results must be interpreted cautiously as the ability to detect any potential differences is greatly restricted.

In addition to the high attrition and resultant reduced study power, our study is not without further limitations that may impact interpretation of results. Our study was developed as an open-label design. As a result of patient's

Table 3 Study patient characteristics

	Total	Paroxetine	Pregabalin	*P* value
n	22	10	11	N/A
Demographic				
Age: mean (SD)	45.7(12.49)	43.1(12.85)	48.1(12.28)	0.374
Sex: % female	81	90	72.7	NS
Clinical				
EDSS: mean (SD)	2.3(1.44)	2.6(1.29)	1.9(1.57)	0.34
Baseline pain: mean (SD)	71.5(10.66)	68.3(10.11)	74.7(10.73)	0.19
Duration of pain (mo): mean (SD)	25.75(19.77)	22.5(19.72)	29(20.31)	0.48
Time since MS diagnosis (yr): mean (SD)	9.39(8.63)	7.8(8.79)	11.38(8.57)	0.4
Analysis				
% withdrawal from study	40.9	70	18.2	< 0.001
Average final daily dose (mg) attained (% of maximum possible)	N/A	31 (62)	422.7 (70.5)	N/A

Baseline characteristics–categorized as either "demographic" or "clinical" are presented collectively for all patients combined (n = 22) as well as individually for paroxetine (n = 10) and pregabalin (n = 11) patient groupings. Where appropriate, mean and SD are provided. "Analysis" subheading provides information on the number of patients who withdrew prematurely from the study ("% withdrawal from study") by group as well as the final average daily dose attained in each group. *P* values have been provided to estimate equivalence of groups. EDSS: Expanded disability status scale; NS: No significant; N/A: Not available.

Table 4 Average study duration (d) by study group

	Average study duration by group (d)				
	n	Mean days in study	SD	Range of values	
				Lower	Upper
Paroxetine	10	27.3	21.6	5	58
Pregabalin	11	49.5	15.7	14	63

The mean duration of participation in the study by group is presented, with associated SD and range; Independent *t* test between groups, $P < 0.01$.

Table 5 Univariate comparison results: VAS_{pain} and VAS_{impact}

	VASpain	VASimpact
	RR	RR
Group	8.7270	3.4270
Day	0.5036	0.5065
Group × day	0.1513	0.1918

Univariate comparison results are presented on data from study participants completing the study. No significant findings were noted between comparisons. RR: Relative risk.

awareness of active treatment, psychosomatic contributions may have contributed to any primary outcome effects. Although blinding and controlling for bias through inclusion of a placebo arm would have undoubtedly strengthened the power of the study ethical restraints prevented study blinding as neither of the comparative agents selected for the study had approved indication from Health Canada for MS-induced NPP. As a result, this aspect of study design was not incorporated to ensure complete transparency in that the enrolled patients were fully informed of the use of an off-label medication to manage their pain.

MS presents an especially challenging disease to effectively manage NPP. This in part is not only due to confounding disease-induced symptoms, but also due to the polypharmacy that is often observed in this population. Individuals with MS are often on multiple medications to manage the multifaceted nature of their primary disease. As such, NPP treatment options are further limited due to potential drug interactions and/or therapeutic class duplication issues. These unique treatment considerations make simply applying current general NPP guidelines directly to MS care inappropriate. Most guidelines for NPP are created based on large-scale studies in various other NPP conditions, such as DPN and post-herpetic neuralgia. Although, mechanistically, it is likely that current first-line agents for NPP would target the underlying pain mechanisms of MS-induced NPP, the inability to tolerate these medications and achieve therapeutic dosages can be significantly hindered. The only way to appropriately apply guideline recommendations to this unique patient population is by first validating their efficacy and tolerability in these patients in accordance with a randomized, controlled setting. Unfortunately, data from randomized clinical trials (RCTs) for MS-induced NPP is significantly lacking. Until the need for well-designed RCTs in MS-induced NPP is met, clinicians managing pain in this patient population must first consider tolerability issues of therapy rather than relying solely on the general NPP guidelines that encompass all patients with NPP irrespective of origin. In order to optimize treatment success, careful review of patient-reported disease-induced symptoms must be completed to determine which medications being considered for NPP would have the lowest likelihood of aggravating these underlying complaints. Additionally, a thorough review of concomitant medications would also be of benefit. Once an appropriate treatment is selected, a conservative dosage titration schedule should be followed in order to minimize adverse events and prevent drug interactions with existing therapy. Frequent follow-up to facilitate communication between clinician and patient should be established to ensure that realistic treatment goals as well as realistic timelines for these outcomes are met.

In summary, due to the high attrition rates observed

in this study resulting in premature closure, primary pain outcomes could not be appropriately assessed. Paroxetine, which has been found to be well-tolerated and effective for other chronic pain conditions, has been found poorly tolerated in this study. These results suggest that paroxetine should be used cautiously in those with MS-induced NPP. The unique tolerability issues observed in individuals with MS-induced NPP make the application of general therapeutic NPP guidelines inappropriate for many in this population, without consideration of additional disease-induced factors that may affect drug safety. Available guidelines are helpful tools for clinicians, however cannot be considered absolute due to unique needs of individuals in an MS population. Expert clinical judgement appropriately considering the therapeutic requirements of this population along with evidence-based data from other NPP states is therefore required, as it is unlikely that evidence-based guidelines specific to MS-induced NPP will be developed due to the lack of RCTs in this population. Collaborative communication between clinicians specialized in both MS care and pain management would ultimately improve therapeutic selection, implementation and follow-up resulting in improved tolerability and efficacy outcomes.

COMMENTS

Background

Neuropathic pain is a painful condition that can result from a number of different pathophysiological and disease-induced causes, and can be significantly challenging to control for many individuals. The majority of neuropathic pain management guidelines available to guide patient care are based upon larger scale pharmacotherapeutics trials in the more prevalent neuropathic pain conditions, including diabetic peripheral neuropathy, post-herpetic neuralgia and trigeminal neuralgia. Multiple sclerosis (MS) is a chronic, progressive neurological condition that can frequently result in the development of neuropathic pain. Due to the often complicated presentation of co-morbid disease-induced symptoms, treatment of neuropathic pain in individuals with MS can be challenging due to poor tolerability of first-line agents. Clinical trials specific to the MS population with neuropathic pain are rare, however they are essential in order to better understand safety and efficacy in this unique patient population. Both the antidepressant and antiepileptic classes of medication are used as first-line agents for many neuropathic pain conditions, however their efficacy and tolerability in individuals with MS-induced neuropathic pain are not well-studied.

Research frontiers

Paroxetine is a selective serotonin reuptake inhibitor antidepressant. Antidepressants are currently touted as first-line agents for the management of painful neuropathies not only based on their analgesic effects but also their effect on co-morbid mood and sleep issues often associated with chronic pain. Pregabalin is an antiepileptic and antineuralgic medication that is relatively new to the market and is also recommended as a first-line agent for the management of neuropathic pain.

Innovations and breakthroughs

Most clinical trials evaluating the efficacy and tolerability of specific medications for effects in various neuropathic pain conditions look at the effect of a specific agent against a placebo comparator. Although this is important to establish treatment effect, it does not allow us to differentiate between the various first-line agents. Additionally, very few clinical trials evaluating therapy for neuropathic pain in individuals with MS have been conducted. In an attempt to provide some initial information on the management of neuropathic pain in this patient population the authors have conducted a head-to-head clinical trial comparing paroxetine *vs* pregabalin to assess both efficacy and tolerability in this understudied patient group.

Applications

The results of this study provide us initial insight regarding the use of "first-line" agents in the management of neuropathic pain. The high rate of intolerability in the paroxetine treatment arm was surprising based on literature use in other patient populations. This reinforces to clinicians that individuals with MS present unique and complex clinical cases that may limit the use of agents considered "first-line" in other painful neuropathies.

Terminology

MS-induced neuropathic pain (NPP) is a chronic pain syndrome caused by damage to the nerve fibers involved in the synaptic transmission of pain. Pregabalin is an anticonvulsant medication thought to elicit analgesic effects through interaction with the $\alpha 2\delta$ subunit of N-type voltage-dependent Ca^{2+} channels, ultimately reducing overall neuronal excitability. Paroxetine is a selective serotonin reuptake inhibitor that selectively blocks the pre-synaptic reuptake of 5-HT, resulting in an accumulation of 5-HT in synapses involved in the transmission of pain.

Peer review

The primary aim was to compare the analgesia effect and improve of quality of daily life quality by the administration of Paroxetine and Pregabalin in neuropathic pain patients with MS. The study was well designed and written given the consideration of various factors confounding in this particular patients population.

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CASE REPORT

Anesthesia for ambulatory surgery in a child with hyposensitivity to pain

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Abstract

Congenital hyposensitivity to pain is a condition with predisposition to injury. In these patients, knowledge regarding anesthetic requirements and complications derives from individual case reports, or small case series. Different categories have been described. In patients with hyposensitivity to pain, preventing and treating anxiety as well as insuring immobilization, avoidance of triggering of autonomic reflexes, and sedation are integral aspects for a safe and adequate anesthetic management.

Key words: General anesthesia; Child; Pain; Hyposensitivity; Surgery

Core tip: Congenital hyposensitivity to pain is a condition with predisposition to injury. In patients with congenital hyposensitivity to pain/Hereditary sensory and autonomic neuropathy (HSAN), knowledge regarding anesthetic requirements and complications derives from individual case reports, or small case series. Different categories of HSAN have been described. Complications in the immediate perioperative period have been described such as mild hypothermia and cardiovascular events, mostly bradycardia and hypotension. The majority of patients with hyposensitivity to pain reported in the literature have received standard anesthesia for surgery. Immobilization, prevention of autonomic reflexes, anxiolysis, and sedation are equally important aspects of the anesthetic management in patients with hyposensitivity to pain.

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INTRODUCTION

Congenital hyposensitivity to pain is a condition with predisposition to injury, often associated with a delay and difficulty in diagnosis. Anesthesia care of these children may pose a challenge secondary to the rarity of the disease, the presence of unclassified congenital variants of pain hyposensitivity, and the limited information regarding anesthetic management.

CASE REPORT

The following is a description of a case of a 2-year-old patient, female gender, with mild developmental delay, who presented as a same day case for ear surgery. The duration of the surgery was expected to be 90 min. During the process of the interview, the mother revealed that her daughter is insensitive to pain, no further details were available. Otherwise the review of systems was negative. Premedication with oral midazolam 0.5 mg/kg was administered. Patient received general anesthesia with endotracheal intubation [Sevoflurane mask induction in

O_2/N_2O followed by propofol (3 mg/kg Ⅳ)], and narcotics were titrated to maintain spontaneous ventilation for a total dose of Fentanyl of 1 mcg/kg. No fluctuations in temperature were noticed during the case. Vital signs were stable. There was no delay in emergence from general anesthesia. Recovery room stay was not prolonged and was uneventful. Patient was discharged the same day without further need for narcotics postoperatively.

DISCUSSION

In patients with congenital hyposensitivity to pain/hereditary sensory and autonomic neuropathy (HSAN), knowledge regarding anesthetic requirements and complications derives from individual case reports, or small case series. Different levels and modalities of autonomic dysfunction and sensory loss have been described[1]. Some patients do have tactile hyperesthesia, or partially preserved nociception with sometimes preserved mechanoreceptor, cooling, and warming sensations. Five types of HSAN have been categorized. HSAN Ⅰ is inherited with autosomal dominance. The age of onset of HSAN Ⅰ is between the 2nd and 4th decade of life while the other types are autosomal recessive with an earlier age of onset, usually at birth in type Ⅲ (familial dysautonomia) or in infancy. HSANs Ⅱ, Ⅳ and Ⅴ usually present with a profound reduction of pain perception, while HSAN Ⅰ has as a milder manifestation. Patients with HSAN Ⅲ's may have intact visceral and peritoneal pain sensation with profound dysautonomia. Thermal perception is severely impaired in all HSAN types. Mild hyperhidrosis is associated in HSAN type Ⅴ, hypohidrosis in type Ⅰ and Ⅱ, while severe anhidrosis with recurrent episodes of severe hyperpyrexia is associated to HSAN type Ⅳ. Type Ⅴ may present with unaffected sensitivity to touch, pressure and vibration. Mutilations may be common in all types of HSAN. The requirements for volatile anesthetics have been described as being within the range of standard population. Intraoperative opioids dosage has been reported to be less than standard, if not negligible. Because some HSAN patients may have anhidrosis, intraoperative hyperthermia cases have been reported[2]. There is no description of malignant hyperthermia in association with the different HSAN types. Patients usually do not require opioids postoperatively. Complications in the perioperative care have been described as cardiovascular, such as bradycardia and hypotension and mild hypothermia. A cardiac arrest following management of a patient with HSAN Ⅳ has been published[3]. Although there is report of an adult patient diagnosed with profound congenital insensitivity to pain who has undergone a major orthopedic surgery without receiving general anesthesia and narcotics; in the literature, patients with hyposensitivity to pain, have been documented to receive standard anesthesia for surgery. In patients with hyposensitivity to pain, preventing and treating anxiety as well as insuring immobilization, avoidance of triggering of autonomic reflexes, and sedation are integral aspects for a safe and adequate anesthetic management.

COMMENTS

Case characteristics

Pediatric patient with hyposensitivity to pain.

Clinical diagnosis

Anesthesia management of a pediatric patient with hyposensitivity to pain.

Differential diagnosis

Different categories of hereditary sensory and autonomic neuropathy are described.

Experiences and lessons

Immobilization, prevention of autonomic reflexes, anxiolysis, and sedation are equally important aspects of the anesthetic management in patients with hyposensitivity to pain.

Peer review

The author described anesthesia management in a child with congenital hyposensitivity to pain. The diagnosis is based on the history and clinical findings. The paper is good for publication.

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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