Intravenous Regional Block with Phentolamine in the Treatment of Complex regional Pain Syndrome

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Received: 20 Aug. 2010; Received in revised form: 17 Sep. 2010; Accepted: 28 Sep. 2010

Abstract- Complex regional pain syndrome (CRPS) is a variety of painful conditions following injury which appears regionally having a distal predominance of abnormal findings. This study, evaluate the use of phentolamine for sympathetic block and regional anesthesia in treatment of CRPS related pain. In this study, 68 patients with CRPS who were referred to pain clinics of Imam Hossein and Akhtar Hospitals and Gandy Center of Surgery between 2003-2008 were evaluated. Forty three of 87 patients finally undertaken intravenous regional sympatholytic block according to therapeutic protocol. 37 patients (86%) received one block, 2 of them (4.75%) received 2 repetitions of blocks and finally repeated block for three times occurred in 4 patients (9.3%). A week after block pain relief outcomes was recorded as following; excellent in 7 patients (16.3%), good in the 32 patients (74.4%) and moderate in the 4 patients (9.3%). After a month, 8 patients (18.5%) showed excellent relief and it was good and moderate in 32 (78%) and one case (2.4%), respectively. Pain relief after three months was excellent, good and moderate in the 13 patients (31.7%), 25 patients (61%) and 3 patients (7.3%), respectively. In this study level of pain relief was significant in various intervals and it showed significant difference in relief three months after block (P=0.04). CRPS due to SMP(sympathetically maintained pain) is thought to be alleviated by phentolamine. Intravenous phentolamine infusion is potentially a new significant option for the therapy of CRPS.

Acta Medica Iranica, 2011; 49(8): 523-526.

Keywords: Autonomic nerve block; Phentolamine; Complex regional pain syndrome

Introduction

Complex Regional Pain Syndrome (CRPS) still remains a medical challenge today. It is a chronic condition with recurring and relapsing bouts which may potentially results in considerable physical disability (1).

CRPS is a constellation of symptoms which occur commonly as a complication of surgery or trauma. The most recent definition from the International Association for the Study of Pain (IASP) is that CRPS is a collection of locally appearing painful conditions following a trauma, which chiefly occur distally and exceed in intensity and duration the expected clinical course of the original trauma, often resulting in considerably restricted motor function. Although this syndrome happens usually in a single extremity, involvement of more than one limb has been reported as well. Besides surgery and trauma as main causes of CRPS, spontaneous CRPS can occur (2). The estimated incidence varies from 5.46 to 26.2 per 100,000 person years. CRPS in adult populations occurs slightly more often in the upper extremities, where fracture is the common initial insult. Women are affected 3.4 to 4 times more often than men. The mean age at diagnosis does not differ between men and women and varies between 47 and 52 years (3,4). One of the drug regimens for treatment of CRPS is Phentolamine. Phentolamine is a competitive nonselective α_1- and α_2 -adrenergic receptor antagonist with an elimination half-life of 19 minutes after intravenous injection. Phentolamine also promotes histamine release from mast cells, antagonizes serotonergic receptors, and blocks potassium channels (5). The main adverse effects of phentolamine are hypotension caused by a direct vasodilatory effect on vascular smooth muscle and subsequent baroreceptor-mediated reflex tachycardia. However, intravenous

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infusion of phentolamine in patients suffering from neuroleptic pain has been reported to associate with cardiovascular safety (6). Since, to date, us study is available to evaluate the use of Phentolamine for sympathetic block and regional anesthesia in treatment of CRPS related pain, the present study was designed to evaluate this in a sample of CRPS patients.

Materials and Methods

This is a prospective interventional study (Before & after). The study was conducted with the full approval of the Institutional Review Board of our university. In this study 68 patients with CRPS who were referred to pain clinics of Imam Hossein and Akhtar Hospitals and Gandy center of surgery between 2003-2008 were evaluated. The patients with following features were included; traumatic damages, vascular problems, diabetes, post stroke sequels, unknown pains after other causes ruled out, edema, abnormal skin circulation and pseudo tumor.

Following cases were excluded; patients who didn't give consent to enter the study, pregnancy, myocardial infarction, subjects suspected to have pheochromocytoma, advanced neurologic disorders, psychiatric disorders, unstable angina, active peptic ulcer, ventricular arrhythmia, symptoms of hypovolumia, hypotension, heart failure, positive history of coagulapathy, contraindication of injection of phentolamin, sympathic bock contraindications, allergy to lidocaine, poor patient cooperation, taking drugs with anti sympatholytic effects, need for more than three blocks, stroke within six last months and addiction. Intravenous regional sympatholytic block was performed by fellow of pain subspecialty. Pain level was measured before block through Visual Analog Scale. This scale comprise zero to 10 divisions. Pain relief less than 30% was regarded as bad outcome, and 30-50%, 50-60%, 60-70% and higher than 70% of relief levels were regarded as mild, moderate, good and excellent outcomes, respectively. Patients' dystrophic changes (in nails, hair, and skin, joint range of motion, bone and muscles) were also evaluated. Presence of pain and less than 50% relief led to repetition of block for three times with an interval of one week maximally for 3 times. Patients were visited to assess the pain level and relief one week, one month and three months after block. It is noteworthy that blood pressure and pulse rate monitoring, pulse-oxymetry and ECG were performed during the procedure.

Therapeutic protocol

Dose of drug infusion was as following:

1-Upper limb

a- Whole upper limb: total volume of 40ml (30 mg phentolamin 0.075%, 100 mg lidocaine 2.5%). Tourniquet was consecutively being closed and opened at proximal part of limb.

b- Distal part of limb: total volume of 20 ml (15 mg phentolamin 0.075%, 50mg lidocaine 2.5%). Tourniquet was being closed under the elbow.

2- Lower limb:

a- Whole lower limb: total volume of 60 ml (45 mg phentolamin 0.075%, 150 mg lidocaine 2.5%). Tourniquet was being closed at the groin.

b- Above the Knee: total volume of 40 ml (30 mg phentolamin 0.075%, 100mg lidocaine 2.5%). Tourniquet was being closed above the knee.

c- Below the knee: total volume of 30 ml (22.5 mg phentolamin 0.075%, 75mg lidocaine 2.5%). Tourniquet was being closed under the knee.

d- Above the ankle: total volume of 20 ml (15 mg phentolamin 0.075%, 50 mg lidocaine 2.5%). Tourniquet was being closed above the ankle.

It should be noted that 5-10 minutes after drug infusion distal part was filled with tourniquet pressure equivalent to 2-2.5 times the limb's systolic pressure and proximal part was being emptied gradually. One hour after drug infusion distal tourniquet was also being emptied with control of vital signs.

Data were analyzed with SPSS V. 16 software. Comparison between quantitative variables of different times was performed by Wilcoxon test and $P<0.05$ was regarded as significant statistic results.

Results

Forty three of 87 patients studied received Intravenous regional sympathetic Block. Mean age of patients was 49.9 ± 10.3 (26-75) years old. 30 of them were male (69.8%) and 13 were female (30.2%). Patients with CRPS I, were 83.7% (36 cases) and CRPS II, 16.3% (7cases). From all studied population, 37 patients (86%) received one block, 2 of them (4.75%) received 2 repetitions of blocks and finally repeated block for three times occurred in 4 patients (9.3%). Site of pain was in the upper and lower limbs in the 19 patients (44.2%) and 24 patients (55.8%), respectively. A week after block pain relief outcomes was recorded as following; excellent in 7 patients (16.3%), good in the 32 patients (74.4%) and moderate in the 4 patients (9.3%). After a month, 8 patients (18.5%) showed excellent relief and it

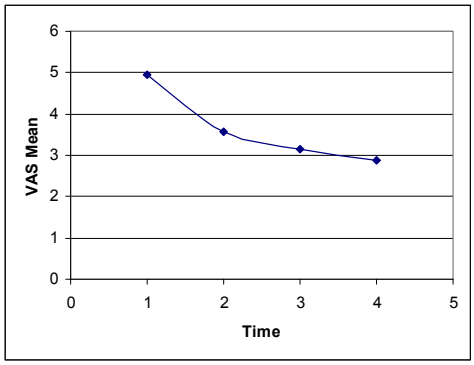

Figure 1. Comparison of pain relief between different periods of time
1: Before Block, 2: 1 week after block, 3: 4 weeks after block, 4: 12 weeks after block

was good and moderate in 32 (78%) and one case (2.4%), respectively. Pain relief after three months was excellent, good and moderate in the 13 patients (31.7%), 25 patients (61%) and 3 patients (7.3%), respectively. In this study level of pain relief was significant in various intervals and it showed significant difference in relief three months after block (P=0.04).
Comparison of pain relief between different periods of time has been shown in the Figure 1.

Discussion

It has been proposed that infusion of phentolamine intravenously potentially produces similar efficacy to that of sympathectomy. Raja et al. reported that using phentolamine as IV infusion (during a diagnosis test with total dosage of 25-35 mg) yielded pain relief which was closely correlated with the same level of pain relief achieved by local anesthetic sympathetic block in sympathetically maintained pain (SMP) (7). It was shown in our study that Intravenous Regional Block with phentolamine results in significant relief of pain in the lower and upper limbs. Drugs that decrease the norepinephrine content of sympathetic nerve terminals treat the sympathetically maintained pain in the CRPS.

Selective α_2 agonists are of drugs that provide successful treatment of SMP (8).

Intravenous Regional Block with phentolamine causes the SMP relief of CRPS. On the other hand α adrenergic block with Intravenous infusion of phentolamine is a sensitive test for determination of patients with SMP. Phentolamine is used as a predictor drug before more aggressive sympathetic block (7,9,10).

They suggested assessment of long-term therapeutic benefits of sympathetic block by pharmacologic agents such as phentolamine in SMP cases. Galer on his study on neuroleptic pain found that 35-mg intravenous phentolamine over 30 minutes produced pain relief which its peak clinical effect occurred most often at least 24 h after completion of the infusion and the pain relief itself sustained for more than 2 days (11).

It is generally accepted that the alpha adrenergic receptor (AR) plays a significant role in the maintenance of pain. The intravenous administration of the nonspecific alpha-blocker phentolamine can result in similar pain relief as that of blockade of the sympathetic ganglion (7) Hence, it was presumed that alpha-1 AR plays a major role in the SMP (12,13). However, in an animal model, following nerve injury, it appeared that an increase in alpha-2 like AR sites occurred at peripheral sensory neurons and cutaneous nociceptor in rabbit became sensitive to adrenergic agonist (14). Also, chronic inflammation produces conditions in which alpha- 2 AR-mediated sympathetic activities excites some nociceptor (15).

Some studies have shown that alpha-2 AR is more important in neuropathic pain (16-22). These results were similar to the extent that phentolamine reduced pain. Raja *et al.* demonstrated that intravenous phentolamine achieved pain relief in 20 patients with pain and hyperalgesia to mechanical and cooling stimuli in extremity and was a sensitive alternative test to identify sympathetic ganglion block (7). Tracey et al. found that subcutaneous injection of phentolamineinto affected hid paw eliminated mechanical hyperalgesia (20). But, Verdugo and Ochoa reported that rate of pain reduction was 9.2% (7 in 77) during phentolamine infusion (23). The pharmacological manipulation of the alpha-1 AR by either agonist or antagonist drugs does not influence neuropathic pain (23).

Due to the short half life of intravenous phentolamine, 60 minutes of post-infusion monitoring period is considered adequate.

Galer *et al.* described that phentolamine infusion has advantages over other sympathetic blocks. It is minimally invasive, is not technician-dependent, and has systemic activity that allows for treatment of multiple body regions in patients with SMP (24).

Neuropathic pain is often maintained or augmented by efferent activity in the sympathetic nervous system, and SMP is mediated largely through α-adrenergic mechanisms, so the intravenous infusion of phentolamine has been described as a reliable, specific, and easy-to-do carry out diagnostic test for SMP (25).

It is not completely understood that by which mechanism exactly sympathectomy with systemic phentolamine relieve CRPS.

Therefore, results of the present study indicate that CRPS due to SMP is thought to be alleviated by phentolamine. In conclusion, intravenous phentolamine infusion is potentially a new significant option for the therapy of CRPS.

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