International Journal of Advanced Engineering Research and Science (IJAERS)
Peer-Reviewed Journal
ISSN: 2349-6495(P) | 2456-1908(O)
Vol-9, Issue-9; Sep, 2022
Journal Home Page Available: https://ijaers.com/
Article DOI: https://dx.doi.org/10.22161/ijaers.99.69

Sympathetic ablation combined to dorsal ganglion modulation was cost-effective for Complex Regional Pain Syndrome-1

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Received: 26 Aug 2022,
Received in revised form: 20 Sep 2022,
Accepted: 26 Sep 2022,
Available online: 30 Sep 2022

***Keywords*— Complex Regional Pain Syndrome-1, sympathetic block, dorsal ganglion, radiofrequency, central pain sensitization.**

Abstract *— Sympathetic ablation combined to dorsal ganglion modulation was cost-effective for Complex Regional Pain Syndrome-1. Background: In Complex Regional Pain Syndrome-1 (CRPS), sympathetic ganglion block followed by radiofrequency (RF) is the treatment of choice. However, data suggest that dorsal ganglion (DG) is partly responsible for its central pain sensitization. The study aimed to evaluate the cost-effectiveness of central desensitization combined to either blocks or RF at the same levels. Methods: 36 patients with lower extremity CRPS-1 were randomly assigned to 1 of 2 Treatments (n=18). After effects of the first selected treatment receded, patients were crossed over to the second treatment. The treatments were : 1) test blocks followed by 4-weekly L3 sympathetic block + epidural sacral block or 2) test blocks followed by L3-L4-L5 sympathetic ablation + L3-L4-L5 DG modulation RF. Time of analgesia was defined as VAS>3cm. Patients acted as their own control related to analgesia, routine activities, sleep pattern and costs. Results: 24 patients completed the study. The analgesia time after the 4-weekly blocks were 5±1 months and the annual costs USA$5000. Analgesia time after RF was 15±2 months ($p<0.001$) and costs reduced by 23% in the first year and 32%-36% in the following years extrapolation. Quality of life and sleep pattern improved during the analgesia period ($p> 0.05$). Discussion: Sympathetic ganglion combined to DR RF at the same levels (L3-L4-L5) resulted in 15-month compared to 5-month analgesia after the classical 4-weekly blocks, and improved physical capacity and sleep pattern. It was cost-effective, and reduced rates by 23% during the first-year evaluation, followed by 32%-36% cost reduction in following years, by extrapolation.*

I. INTRODUCTION

When conservative pain management and physical rehabilitation fails in Complex Regional Pain Syndrome (CRPS)-1, the sequence of sympathetic block is the interventional treatment is part of treatment. For a lasting effect, sympathetic radiofrequency (RF) treatment is elected (2B+),[1] and the benefit of an early intervention is renowned in order to prevent long-term incapacity.[2] Inappropriately, RF is not included in all Health Systems,

mainly because the government authority's belief is that the higher costs would not justify its implementation.

Although CRPS-1 classically implies in autonomic dysfunction,[3,4] central pain sensitization also develops with the disease,[5,6] and suggests evidence of pivotal inflammation.[7] Central sensitization has been included in the guidelines for back pain classification and may require specific treatment targeting the mechanisms underlying the hyper excitability of the central nervous system,[8] and epidural sacral block could be used for this purpose, as in turn it reaches dorsal ganglions (DG). The DG has been suggested participating in the central pain sensitization,[9,10] and its modulation maintained substantial pain relief over time.[11]

The aim of this study was to evaluate the cost-effectiveness of: a) the routinely applied sequence of sympathetic block combined with epidural sacral block, with b) RF ablation of sympathetic ganglion combined to RF modulation of DG at the same lumbar levels in CRPS-1 patients, being either the epidural sacral block or the DG modulation involved in central pain desensitization.

II. METHODS

This clinical protocol and patient consent forms were designed in accordance with the revised Declaration of Helsinki and the Good Clinical Practice of the International Conference on Harmonization and approved by the Ethics Committee of the School of Medicine of Ribeirão Preto, University of São Paulo (USP) (Reg 14302010). All blocks were performed under conscious sedation with 2-4 mg midazolam + alfentanil 500-750 mcg by one anesthesiologist. Monitoring of the patient included continuous pulse oximetry and electrocardiography and non-invasive blood arterial pressure at 5 min interval, combined to nasal 0^2 at 3 $Lmin^{-1}$. All blocks were performed under fluoroscopy after adequate asepsis in operating room. The correct position of each needle was verified with 0.5 ml injection of Omnipaque 300 contrast (non-ionic, iohexol). The blocks and RF were performed by the same double anesthesiologists.

Diagnosis of CRPS-I was made on the basis of the proposed modified Budapest Criteria.[12] Subjects had to be willing and able (e.g. mental and physical condition) to participate in all aspects of the study, including use of medications, completion of evaluations, attending the scheduled clinic visit and compliance with protocol requirements. Patients were excluded from the study for the following reasons: clinically unstable disease, psychiatric disease other than depression, refusal or known allergy to the devices used, diabetes, previous cardiac infarction or angina, infection or coagulation disturbance.

Thirty six patients with lower extremity CRPS-I were computer randomly assigned to 1 of 2 interventional treatments (n=18) (Figure 1). After effects of the first selected treatment receded, patients were crossed over to the second treatment. The test blocks in all patients were: a) epidural sacral block with 40 mg lidocaine + 10 mg dexamethasone + 15 mcg clonidine, diluted to 10 ml volume with saline and b) sympathetic Lumbar L3 block at the affected side with 80 mg lidocaine + 5 mg dexamethasone + 15 mcg clonidine. The test blocks aimed at least 50% of pain relief in order the patient could carry on in the proposed protocol of the study.

The 2 Treatments are described as follows (Figure 1): 1) test blocks followed by 4-weekly Lumbar L3 sympathetic block + epidural sacral block or 2) test blocks followed by L3, L4 and L5 sympathetic ganglion ablation + L3, L4 and L5 DG modulation by RF. Time of analgesia was defined as VAS>3-cm. Patients acted as their own control related to analgesia, routine activities, sleep pattern and costs.

For the sympathetic block, a 15 cm 22 gauge needle was inserted under tunnel vision anterolateral to each vertebral body, and the proper positioning was checked by administration of 1-2 ml contrast. Following, it was administered a total 10 ml solution containing 5 mg dexamethasone + 15 mcg clonidine + 80 mg lidocaine.

For the L3, L4 and L5 DG modulation, sensitive test was performed in order to get stimulus < 0.7 mV, and absence of motor stimulus no less than 1.4 mV. The 10 cm needle was positioned at the superior posterior area of each foramen, just posterior to the "safe triangle", and modulation was performed during 120 sec, 45 V, 42ºC, and thereafter, o total of 3.3 ml of the final solution containing total of 10 mg dexamethasone + 30 mcg clonidine + 80 mg lidocaine (final 10 ml volume) was injected.

For the RF ablation of L3, L4 and L5 sympathetic ganglions, sensitive and motor tests were performed in order to get negative results up to 1 mV sensitive test and 2 mV motor tests. The 15 cm needle was positioned anterolateral to each vertebral body, using tunnel vision technique with needle insertion just lateral to the superior vertebral plate in oblique view. The amount of 3.3 ml of the final solution containing total of 10 mg dexamethasone + 30 mcg clonidine + 80 mg lidocaine (final 10 ml volume) was then injected followed by RF ablation 80ºC, 80 sec.

Demographics characteristics were described. Time of analgesia was defined as the time after the 4-weekly sequence, and from the RF treatment until pain (Visual numerical scale (VNS-pain) was classified as > 3

cm (VNS 0-10 cm) and rescue tramadol consumption. Rescue analgesics consisted of oral 50 mg tramadol up to 4 times daily. Any adverse effects were noted and treated as necessary.

Weekly Global Perceived Effect after the procedures, such as quality of sleep and quality of daily activities were evaluated by the 10 cm VNS scales, where zero meant comfortable sleep or the best capacity for routine activities up to 10 cm which meant worst and most uncomfortable sleep or most difficulties to perform routine activities.

Statistics

The power of the study was based upon preliminary data. We hypothesised that the RF technique would increase analgesia by 100% compared to the routine 4-weekly sequence of blocks in the population studied. With a beta value of 80% and an alpha value of 0.05, these assumptions would require at least 12 patients. $P<0.05$ was considered significant. Data are expressed as mean±SD, unless otherwise stated.

The normality of the data was evaluated by the Shapiro Wilkings test. Demographic data was described. Quality of sleep, daily activities and analgesia time was evaluated by t-student for dependent groups (analgesia) and Wilcoxon Matched Pairs test (sleep and capacity). $P<0.05$ was considered significant. Adverse effects were described.

III. RESULTS

The final data set included 24 subjects (Figure 2). Related to initial Treatment 1, two of the patients had incomplete data, while 3 of them could not be submitted to the treatment due to inadequate transportation back home. Regarding patients form initial Treatment 2, two of them did not have adequate transportation back home, while 5 of them did not respond to the first test block and were treated with implantation spinal cord stimulation device.

Related to demography of the 24 patients, mean age was 46±9.6 years; 72±15.8 kg; 166± 7.8 cm. Sixteen patients were Catholics, while 8 were Presbyterians. They were 12 male and 13 female, 16 white and 8 black people, and all of them were routinely taking antidepressants (amitriptyline, sertraline or duloxetine); Twelve of them were taken methadone, 2 gabapentin and finally 8 of them were taking carbamazepine.

The time of analgesia defined as time since the end of the 4-weekly block sequence and since RF until time when pain VNS> 3 cm is described in Table 3 ($p<0.001$). When patients were submitted to a 4-week sequence of blocks, the time of analgesia was around 15 months (Table 1, $p<0.001$).

The sleep pattern and the physical routine activities were quantified by patients using the VNS (0-10 cm) and were equally improved during controlled pain for both techniques, as quantified by the VNS scale by the patients ($p>0.05$). Related to the night sleep quality, patients referred that when pain was under control, the night sleep was equally nice and comfortable for both groups (Table 2, $p>0.05$), however uncomfortable during the periods of stronger pain with many times of arousal ($p<0.05$). Similarly, the routine physical capacity was also equally improved for both treatments when pain was under control (Table 4, $p<0.05$ when compared to the uncontrolled pain period).

Regarding costs, annual money savings was 23% when RF was applied, compared to the sequence of 4-blocks during the same period (Table 6). From the second year forward, money saving increased to 32% and this improvement was gradually increased until the 5th year, by extrapolation data, as in the following years the test block would not be necessary to be performed, but only the RF (Figure 3).

Related to adverse effects, all patients referred difficulty to sleep during the first 2-3 nights when each block was performed, however, the following day was not tiring, and all patients referred good disposition for activities. Patients complained of pain during 3-4 days after RF technique, and all of them used oral 100 mg tramadol for 2-3 days after RF.

IV. DISCUSSION

In the present study we have demonstrated that in CRPS-1, when ablation by RF of L3-L4-L5 sympathetic ganglions associated to L3-L4-L5 DG modulation was compared to the classical 4-weekly blocks, the time of analgesia was threefold longer (15 months) for the RF, added to a better capacity for routine physical activities, improved sleep pattern and mean of 30% annually lesser costs. As described, we kept all poly pharmacy during the conduction of the study. However, 17% of patients were refractory and benefit from spinal cord stimulation implantation. Searching the literature, we could not compare this incidence of miscarriage with other publications, as the data related to the incidence of test block failure in CRPS-1 is missing.

While Treatment 1 included epidural sacral block, Treatment 2 included RF modulation of DG of the affected region (L3-L4-L5), procedures used in order to reverse central pain sensitization. The central sensitization is partly

explained by DG hyper excitability demonstrated in CRPS. DG perineuronal glial cells produce diverse proinflammatory mediators, including microglia-derived IL-1β.[13] In addition, the microglia expressing cannabinoid receptor-2 and the chemokine fractalkine receptor (CX3CR1) plays a substantial role in microglial activation and neuroinflammation.[14] The induction of spinal adenosine could also participate.[15] This hyper excitability drives the immune response to more rostrally and caudally located DG and other spinal cord sites explaining the development of widespread pain and autonomic dysfunction.[16]

Inflammatory mechanisms activate the central pain sensitization.[17] The inflammatory process that contributes to CRPS results from two inflammatory sequences. Firstly, the classic inflammatory mechanisms through immune cells. After trauma, soft tissue, mast cells and lymphocytes release proinflammatory cytokines, including tumor necrosis factor -α, interleukin-1β, -2, and 6.[18] Secondly, neurogenic inflammation mechanisms through the direct release of neuropeptides mediators (calcitonin gene-related peptide, substance P, and bradykinin) and inflammatory cytokines from nociceptive fibers.[19] Both inflammatory cascades activate central sensitization.[17] In addition, expression of adrenergic receptors on nociceptive fibers after tissue damage might provide sympathetically induced pain n CRPS patients.[20] Also, there is a compensatory up regulation mechanism at peripheral adrenergic receptors that may lead to higher sensitivity to circulating catecholamines.[21]

Successful treatment for CRPS involving the lower limb was described after continuous epidural bupivacaine,[22] putting a role for epidural local anesthetics in central pain sensitization. In the epidural sacral block, we used the 40 mg lidocaine. However, the efficacy of this low dose could be that the DG as a prime interventional target for pain control DG ectopia and allodynia was selectively suppressed with lidocaine at concentrations too low to block only axonal impulse propagation, without blocking normal sensation or motor function.[23]

Apart from lidocaine, dexamethasone was the non-particulate steroid of choice,[24] and combining clonidine and dexamethasone for epidural injection did not form precipitates of non-aggregated smaller particles compared to dexamethasone alone, proving to be a useful combination.[25,26] While dexamethasone reversed central sensitization and hyperalgesia induced by L-glutamate and substance P in rats, an action dependent on the intracellular messengers nitric oxide, arachidonic acid and protein kinase C,[27] perineural clonidine reduced local cytokine expression by actions on alpha2 adrenoceptors, reduced hypersensitivity in established nerve injury, likely by an immunomodulatory mechanism.[28] The neuroprotective effect of clonidine during ischemia may be ascribed to both a sensitization of central sympathetic activity and a reduced release of glutamate thereby reducing NMDA receptor activation.[29]

In the present study, when one considers that patients submitted to Treatment 1 received the total amount of 360 mg lidocaine, 30 mg dexamethasone and 75 mcg clonidine; while in Treatment 2 they received the total amount of 200 mg lidocaine, 30 mg dexamethasone and 75 mcg clonidine. However, the time elapsed until each patient was crossed to the following Treatment was always superior to 3 months (3-8 months; minimum-maximum) which would be enough for avoiding any systemic action of lidocaine,[30] dexamethasone,[31] or clonidine.[32] Consequently, the results obtained in the actual study would imply that all analgesia benefit observed in this study was secondary of the central action of each block or RF.

Regarding quality of life, the 4-weekly intervention technique resulted in 5-month analgesia while RF resulted in 15-month analgesia accompanied of improved capacity of daily activities and better sleep pattern, which certainly reflected a better quality of life during the controlled analgesia period,[33] and a decreased waiting list for treatment. Imani F et al (2016) described 5-6 months of analgesia after stellate ganglion block in CRPS,[34] what would be similar to our findings in the classical sequence of sympathetic ganglion, however in lower extremities. In our study, RF modulation of GD combined to the classical ablation of sympathetic ganglions at the same levels (L3-L4-L5) resulted in 15-month analgesia. However, a third group of study where patients would be submitted to only classical L3-L4-L5 sympathetic ganglion ablation was missing. We did not intend at the time to do a threefold cross-match study, and also could not to carry on a double blind three independent groups which would be subject to bias.

Importantly, the costs were reduced since the first year of treatment, reflecting that when the traditional 4-weekly treatment for CRPS-I was applied, each patient came 8-9 times per year to the hospital, meaning personal costs apart the government costs. In addition, more patients per year would have the opportunity to be treated, and each patient would be less expense for the Public Health System if RF was adopted as part of public health treatment.

As conclusions, the RF technique of the same levels for both sympathetic ablation and DR modulation (L3-L4-L5) was cost-effective and resulted in 15-month

analgesia compared to 5-month for the traditional sequence of blocks. Also, patients described better sleep pattern and improved routine physical capacity during the period of analgesia. The data suggest that treating the central pain sensitization should be evaluated in this population.

ACKNOWLEDGMENTS

The authors thank the Foundation Coordination of the Improvement of Higher Level Personnel (CAPES-Brazil) for financial support regarding radiofrequency apparatus, to make possible this project.

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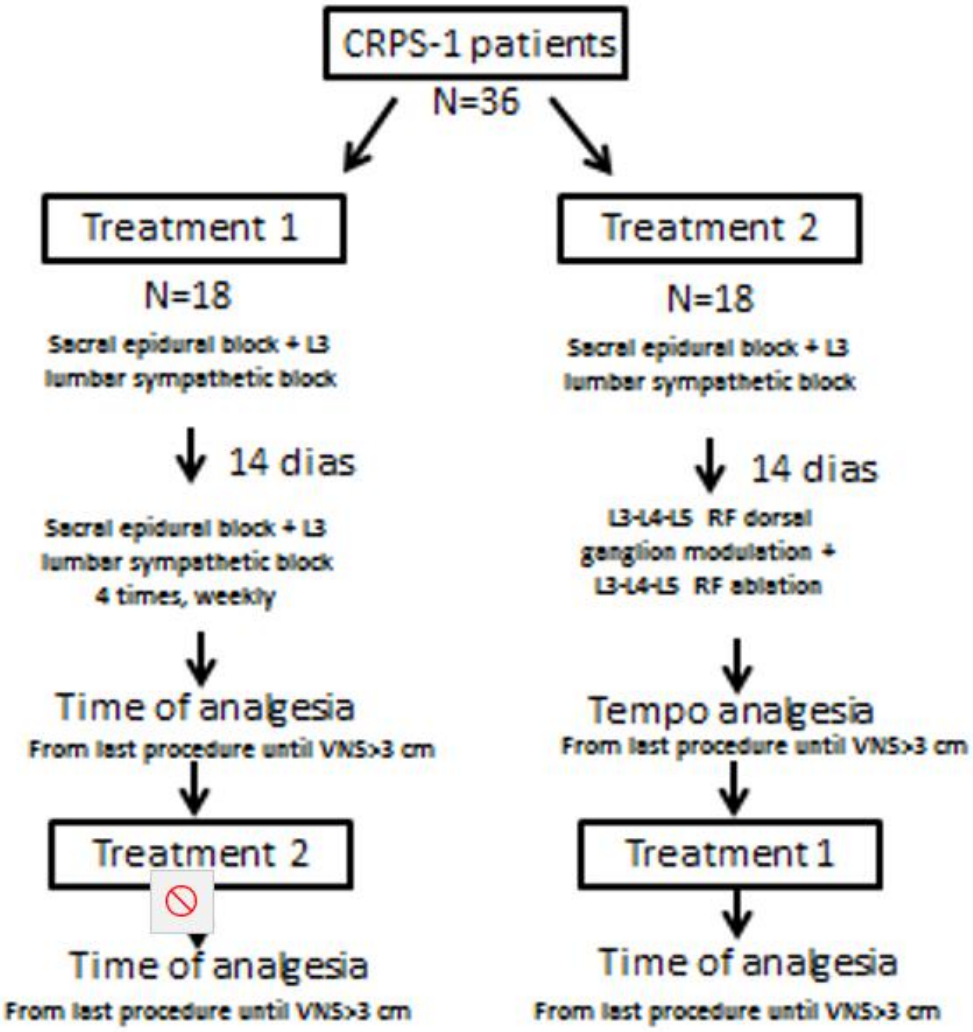

Fig. 1. Chart of the study.

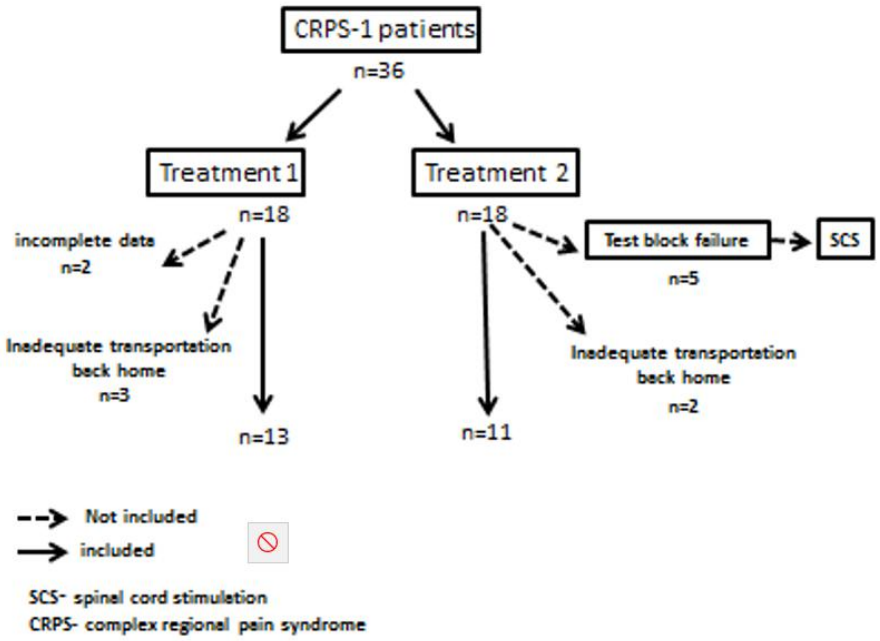

Fig.2. Flowchart of the study.

Treatment 1- test block + 4-weekly blocks; Treatment 2- test blocks + RF.

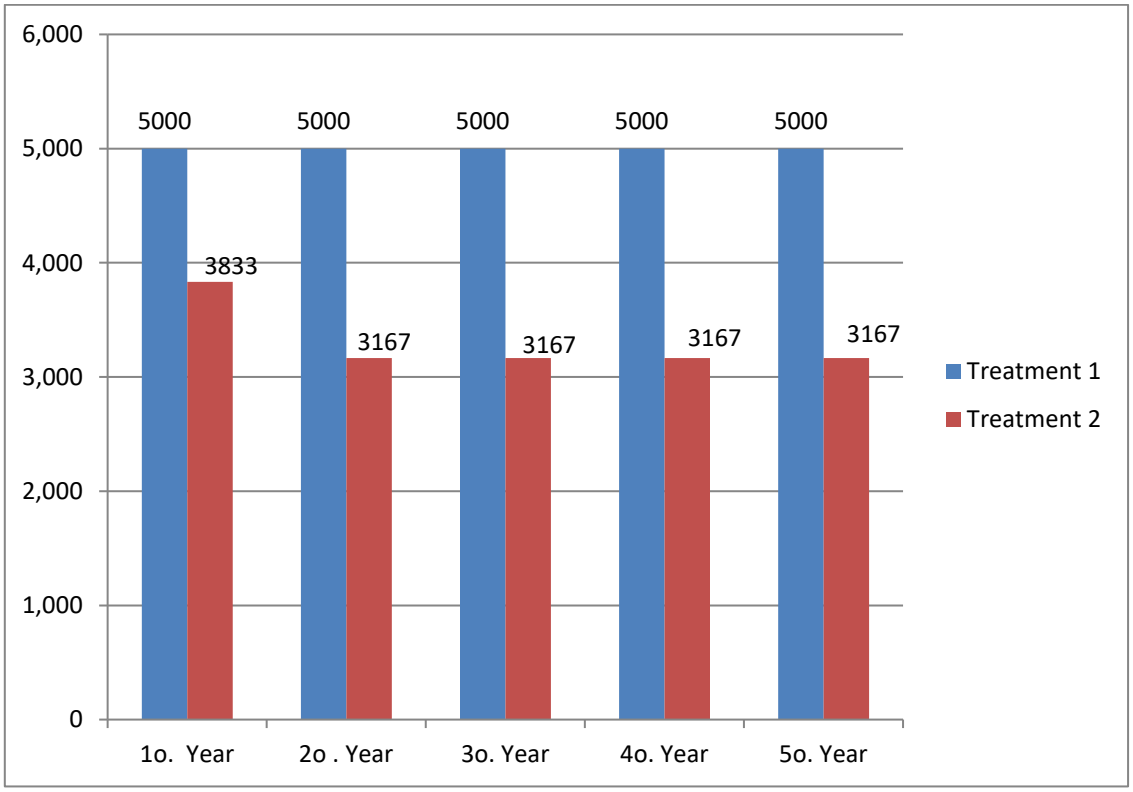

Fig.3. Annual cots (USA$ dollars) during five-years extrapolation for Treatment 1 and 2. Treatment 1- test block + 4-weekly blocks; Treatment 2- test blocks + RF.

Table 1. Time of analgesia (until VNS > 3 cm).

	Time of analgesia Treatment 1 (months)	**Time of analgesia Treatment 2 (months)**
Mean	5.5	15.5
STD	1.47442	2.340568

Treatment 1- test block + 4-weekly blocks

Treatment 2- test blocks + RF

Wilcoxon test, P<0.001, STD- Standard deviation.

Table 2. Sleep pattern graded by patients during the period of adequate analgesia and inadequate analgesia.

	Sleep pattern Inadequate analgesia (VNS 0-10 cm)	**Sleep pattern Adequate analgesia (VNS- 0-10 cm)**
Mean	6.208333	2.916667
STD	1.841058	0.974308

Wilcoxon rank test, P<0.05

STD- standard deviation

VNS 0-10 cm- zero meant comfortable sleep up to 10 cm which meant worst, uncomfortable sleep.

Table 3. Capacity of performing routine activities during adequate analgesia and inadequate analgesia.

	Capacity for activities Adequate analgesia	**Capacity of activities Inadequate analgesia**
Mean	6.375	3.5
STD	1.714706	0.978019

Wilcoxon rank test P<0.05

STD- standard deviation

ENV 10 cm- zero meant the best capacity to perform routine activities up to 10 cm which meant worst most difficulties to perform routine activities.