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Multimodal cocktail analgesic injection in PIVD with lower limb radiculopathy – A mixed design cohart study

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ABSTRACT

Background: The role of Sodium Channel Blocker and steroid is well established for pain relief in neuropathic pain by reducing inflamation and desensitization of nerve roots. Our study aims at analyzing the effectiveness of multimodal cocktail injections for redicular pain relief & functional outcome in patients with intervertebral disc herniation.

Material and method: This was a Mixed design (prospective & retrospective) cohort study; we included 113 patients between the age group of 18–70 years, diagnosed with Prolapse of intervertebral disc (PIVD) with lower limb radiculopathy with MRI finding L4-L5/L5-S1 vertebral disc involvement. Patients were injected with total 15 ml of cocktail injection in 3 divided doses at 3 identified sites in affected lower limb. . Patient was examined & evaluated clinically for VAS pain score, SLRT, Sensory, Motor Examination on day 2, day 7, day 15 & after 1 month.

Result: We found that the mean pre-VAS score was 7.83 followed by the mean VAS score on post 2 days was 1.05, post 7 days was 3.47, post 15 days was 3.9 and post 30 days was 3.81. There was a statistically significant difference in the mean VAS score (p-value<0.0001). After one month majority of patients (54.62%) had comfortable painless walk and comfortable walking distance increased up to 1 km in 45.37% of them.

Conclusion: Use of cocktail multimodal injections for radiculopathy pain suggests that this non-operative,OPD based technique could be reasonable, efficient, and safe.

1. Introduction

Epidural injection (Lignocaine 3% + Triamcinolone 40 mg) accelerates pain relief in patients who eventually have natural resolution of radicular pain in a gradual delayed fashion.[1] The injection may give relief of pain of variable duration and confirms origin of pain, by relieving it. But Epidural injections are also associated with some adverse events & complications. Complications of Epidural SNRB are due to contaminated epidural steroid injections (mainly due to aspergilosis) resulting in meningitis, stroke, paralysis, and death. Other complications are also being reported with epidural SNRB as life-threatening infections, spinal fluid leaks (0.4–6%), positional headaches (28%), adhesive arachnoiditis (6–16%), hydrocephalus, air embolism, urinary retention, allergic reactions, intravascular injections (7.9–11.6%), stroke, blindness, neurological deficits/paralysis, hematomas, seizures, and death.[2]

Still there is current need of some other safe method of conservative management of PIVD radiculopathy. In different studies pain pathway is little bit different in PIVD radiculopathy as Primary afferent fibers of this pain have a unique morphology, called pseudo-unipolar, wherein both central and peripheral terminals have common axonal stalk. This distinguishes the primary afferent neuron from the typical neuron, where the recipient branch of the neuron (the dendrite) is biochemically distinct from the

Abbreviations: VAS, Visual Analogue Score; SLRT, Straight Leg Raising Test; SNRB, Selective Nerve Root Block.

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transmission branch (the axon). The biochemical functional similarity of central and peripheral terminals means that the nociceptor can send and receive messages from either end. This is a very significant functional characteristic.[3]

There is study to see effect of sodium channel blocker on sciatic pain and mechanosensitization of the nerve when injected at distal most part of the nerve. In that study there is good pain relief found with distal injection at the site of tender area found in limb at particular anatomical sites of distal nerves in symptomatic PIVD patients of sciatica.[20]As we found that the role of Sodium Channel Blocker and steroid is well established for pain relief in patients of PIVD to reduce inflammation and desensitization of nerve roots.

In this study we will be analyzing the effectiveness of these multimodal cocktail injections for pain relief & functional outcome of patients.

2. Material and method

This was an Mixed design (prospective & retrospective) cohort study conducted during September 2020 to December 2021 at Department of Orthopaedics & Traumatology, Dr S. N. medical college & attached hospitals, Jodhpur, Rajasthan.The study included all the patients between the age group of 18–70 years, attending opd with back pain with lower limb rediculopathy of duration up to 6 months, their MRI showing involvement of L4-L5/L5-S1 intervertebral disc prolapse, lumbar canal stenosis, ligamentum flavum hypertrophy with VAS score more than 5 and also who had undertaken conservative management in form of NSAID/Gabapantoids/opiods/steroids etc. Patients having listhesis, osteoporotic vertebral body fracture, tubercular and pyogenic infection, known hypersensitivity history to Drug used in cocktail Injection and those who have Cardiac Arrhythmia, were excluded. Informed consent was obtained from all participants and institutional review board approval was obtained before initiating the study.

All the patients were assessed for standard neurological examination which included,duration of symtoms, walking pattern, comfortable walking distance,SLRT, VAS score, sensory and motor examination. Area of pain was marked to see if it fell in specific dermatome. If symptoms were present in bilateral lower limb then injection was given in more affected side. VAS for pain was marked as numeric and compared in follow up.

Three main specific injection sites were marked anatomically in affected lower limb as shown in Figs. 1–3.

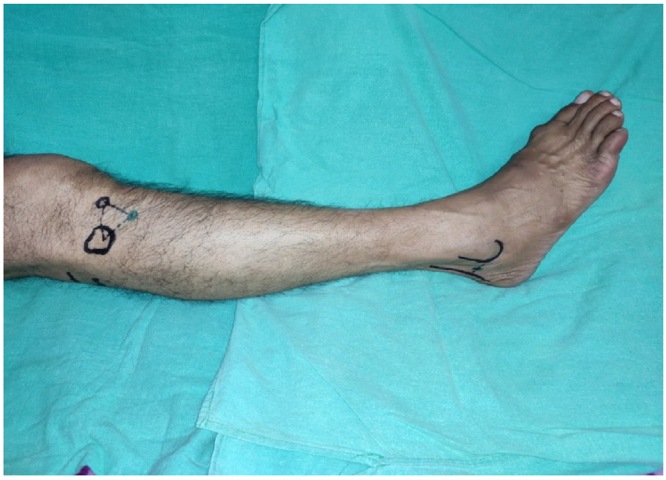

Fig. 1. The sites of injection of Deep peroneal nerve & Sural nerve for Cocktail solution.

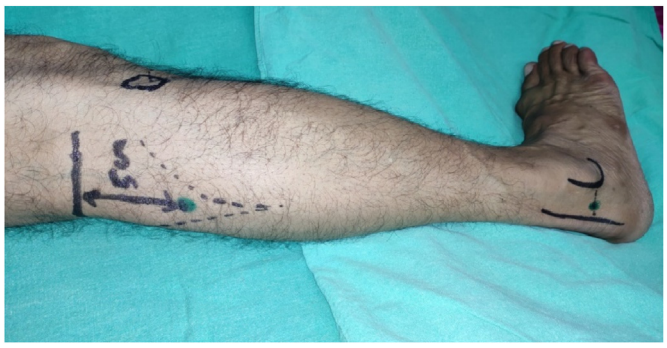

Fig. 2. The site of injection of Tibial nerve.

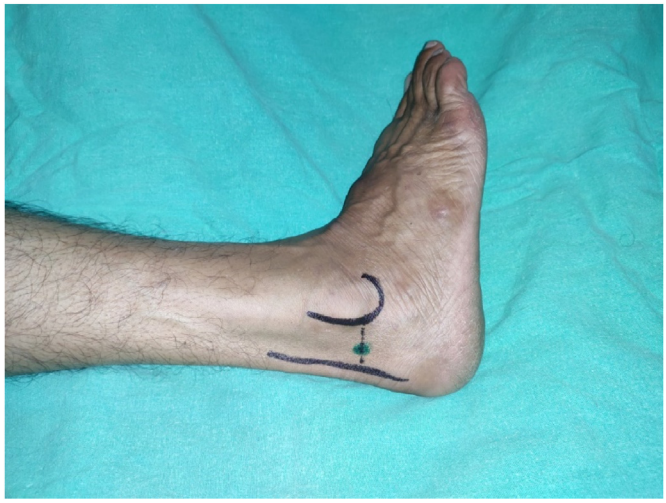

Fig. 3. The site of injection for sural nerve.

1 Deep peroneal nerve near origin: 1.5 cm antero medial to anterior border of head of fibula or Inferio-Medial angle of a triangle made between Gerdy tubercle of tibia & Centre of head of fibula.
2 Tibial nerve: 5 cm just distal to popletial crease in midline between medial & lateral Gastronemius muscle head.
3 Sural Nerve: A midpoint between posterior inferior border of lateral malleoli and lateral border of Tendo Achillis.

All these points were anatomically easy and were confirmed from anatomical books to be commonest part where these nerves will lay. (see anatomical diagrams).

Patients were injected with total 15 ml of cocktail injection in 3 divided doses at 3 identified sites of mentioned composition and dilution. The Needle will be pierced perpendicular to skin while giving injection & drug will be injected as deep as possible.

3. Composition detail

DRUG	DOSE
Inj. Lignocaine 2% (without Adrenaline & without preservatives)	4.5 ml
Inj. Triamcinolone	80 mg (2 ml)
Inj. Clonidine	150 μg (1 ml)
Distilled Water	7.5 ml
Total dose	15 ml

After injection patient was kept under observation for 30 min in OPD. After 30 min vitals of patients were evaluated, if any adverse event found patient was managed accordingly.

In further follow up there was no neuropathic or analgesic drug given after injection and patients were evaluated clinically for VAS pain score, SLRT, Sensory, Motor Examination & for any adverse event on day 2, day 7, day 15 & after 1 month.

4. Results

In this study we analyzed 113 patients in OPD at Department of Orthopaedics, Dr S. N. medical college & attached hospitals. 5 patients had lost the followup. The mean age of patients is 42.43 years. There was 55% males with mean age is 40.06 years and 45% females with mean age is 45.29 years.

In our study majority of patients (51%) had injection on left side; followed by 49% had injection on right side. Seven (6.19%) patients had shown no improvement in pain VAS score,comfortable walking distance after one week of post injection. They were labeled as a failed block, and repeat cocktail injection was given on day 7,after they all were responded.

Complain of all patients had Dryness of mouth up to 24 h; followed by 4% had Dizziness within 30 min and 90% had Abnormal tingling sensation up to 24 h 30% had local injection site bruise or ecchymosis which resolved spontaneously in three to five days. Out of 113 patients,fifteen (13.27%) patients had diabetes or HTN or both,out of those fifteen patients Only one patient with uncontrolled diabetes developed cellulitis of leg,which was managed with Magnesium sulfate (su-mag) dressing and oral antibiotics.

The mean pre-VAS score was 7.83 followed by mean VAS score post 2 days was 1.05, post 7 days was 3.47, post 15 days was 3.9 and post 30 days was 3.81. There was statistically significant difference in mean VAS score (p-value<0.0001) as shown in table-1.

Here, 13.90% patients came to us on wheel chair followed by 45.40% use support for walking and 40.74% had painful walking before start of treatment. But after 1 month only 1.85% were on wheel chair, 16.70% use support for walk, 26.85% had painful walk, majority (54.62%) had comfortable painless walk as shown in table-2.

Initially, 41.51% patients had comfortable walk up to 10 m, 24.53% had walk up to 100 m, 18.87% had walk up to 1 km and 15% had no comfortable walk. But after 1 month of injection only 2 patients had no comfortable walk, followed by 8.33% walk for only 10 m, 37.80% walk for 100 m and 45.37% patients walk for 1 km as shown in table-3.

Table 1
VAS score.

Follow up	VAS Score		t value	p value
	Mean ± SD	Mean difference		
Pre	7.83 ± 0.87	–	–	–
Post 2 days	1.05 ± 0.63	6.774	52.84	<0.0001
Post 7 days	3.47 ± 2.79	4.35	12.33	<0.0001
Post 15 days	3.9 ± 2.70	3.9	10.92	<0.0001
Post 30 days	3.81 ± 2.66	3.98	11.19	<0.0001

Table 2
Ambulatory method.

Ambulatory method	Pre	after 1 month
Wheel chair	15 (13.90%)	2 (1.85%)
Walk with support	49 (45.40%)	18 (16.70%)
Painful walking	44 (40.74%)	29 (26.85%)
Comfortable painless walking	0	59 (54.62%)
Total	108	108

Table 3
Comfortable walking distance.

Comfortable walking distance approx	Pre	after 1 month
10 m	45 (41.70%)	9 (8.33%)
100 m	28 (25.92%)	41 (37..80%)
1 km	20 (18.52%)	49 (45.37%)
>1 km	0	7 (6.50%)
Nill	15 (13.90%)	2 (1.85%)
Total	108	108

5. Discussion

In most cases of low back pain, radicular pain is easily diagnosed in clinical practice.[4] The primary pathophysiological mechanism for inducing radiculopathy was thought to be mechanical compression of a nerve root by a protruding disc, but new experimental studies[5] demonstrates that nerve inflammation is yet another, and possibly the more crucial pathophysiological mechanism for stimulating lumbar radiculopathy.[6]

For the vast majority of patients, non-operative management of radicular pain is the preferred therapeutic option. A multimodal approach to non-operative care should include anti-inflammatory drugs, education, and physical therapy.[7]

Injecting a multimodal cocktail is a safe, reliable and cost-effective treatment that may affect in reducing pain and suppressing inflammation. Although the analgesic efficacies of numerous therapeutic combinations for local injection following total knee arthroplasty have been widely studied, there is no standard approach for drug combinations. This injection combination typically has a multi-component composition based on local anesthetics and epinephrine, as well as other medications such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, opioids, and so on.[8]

In our study, we employed a multimodal cocktail injection of Lignocaine 2% (without Adrenaline and preservatives), Triamcinolone, and Clonidine for alleviating radicular pain as a non-operative treatment.

Allodynia (pain caused by ordinarily non-painful stimuli) and/or hyperalgesia are common symptoms of neuropathic pain. Neuropathic pain can develop as a result of an increase in intrinsic neuronal excitability, which is usually expressed in ectopically produced or minimally stimulated impulses. Changes in sodium channel trafficking, gene expression, and/or channel kinetics due to nerve injury can all contribute to the remodelling of neuronal membranes and hyperexcitability associated with neuropathic

pain.[9] As a result, voltage-gated sodium channels are promising targets for the production of new pain medicines. Tricyclic antidepressants (TCAs: amitriptyline and nortriptyline), local anesthetics (lignocaine, mexiletine) are currently used medications for the treatment of neuropathic pain that have proven actions against sodium channels.[10]

Triamcinolone, a corticosteroid had been used to eliminate inflammation. According to previous research studies, corticosteroid injections may provide short-term relief from leg discomfort and sensory impairments, but they may not lessen the need for surgery or provide significant functional benefit.[11] Infliximab, a TNF inhibitor, was reported to be beneficial in the treatment of sciatica in patients with radicular pain by **Korhonen et al.**[12] They found that 1-year response significantly improved with 3 mg/kg infliximab over periradicular saline in leg pain ($P = 0.005$) and disability ($P = 0.003$). Neurologic abnormalities normalized more comprehensively in the infliximab group ($P = 0.001$). But The results of this randomized trial do not support the use of infliximab for lumbar radicular pain in patients with disc herniation-induced sciatica**. Freeman et al.**[13] demonstrated a significant reduction in both worst leg pain (WLP) and worst back pain (WBP) scores. They examine the safety and efficacy of three different doses of the tumor necrosis factor alpha (TNF-α) inhibitor etanercept versus placebo for the treatment of symptomatic lumbar disc herniation. Patients receiving 0.5-mg etanercept showed a clinically and statistically significant ($P < 0.1$) reduction in mean daily WLP compared with the placebo cohort from 2 to 26 weeks for both the per protocol population (-5.13 vs. -1.95; $P = 0.066$) and the intention-to-treat population (-4.40 vs. -1.84; $P = 0.058$). Fifty percent of these subjects reported a 100% reduction in WLP 4 weeks post-treatment compared with 0% of subjects in the placebo cohort. In our study, mean pre-VAS score was 7.83, which was significantly improved (3.81) at the end of one month with p-value <0.0001, but there was no improvement in axial backache.

The mechanism of action of clonidine in the CNS for pain management is that many pain signals originate in the dorsal horn of the spinal cord and are transmitted to higher CNS centres. The descending inhibitory bulbospinal neurons release norepinephrine, which binds to alpha-2-receptors in the dorsal horn to reduce afferent pain transmission and generate analgesia.[16] As a result, medications that target alpha-2 receptors, such as clonidine, can significantly affect pain transmission.[14] B K Bral[15] et al. assess the effectiveness of epidural steroid injection for low back and radicular pain. They found that the functional status and pain response was improved in 81% of the patients during all the follow-up periods ($p < 0.001$). Lignocaine injection was delivered by Gore S[16] et al. to all pain points (50 at sinus tarsi for lateral terminal deep peroneal nerve (LTDPN), 30 at the lateral wall for sural nerve pain) by. At 10 min postinjection, relief of pain is noted. Average VAS scores decreased from 7 preinjection to 1 for patients in the LTDPN group; for patients in the sural nerve treatment group, average VAS scores decreased from 8 to 2. At 30 min posttreatment, no patients in the LTDPN group reported any pain; only 3 of the 24 patients in the sural nerve treatment group reported a VAS greater than 0 (1 in all cases) and duration of relief averaged 8 h (range 3–36 h). In a Case series which was published in 1960, where distal to lesion block was studied to relieve pain from a large area supplied by the nerve by blocking the afferent from that area. “Evidence that local anesthetic injections of the afferent pathway, distal to the site of the lesion, may stop the pain or paraesthesia that may far outlast the duration of the anesthesia; and blocking a peripheral nerve supplying a large part but not the whole of the region where the pain or paraesthesia are felt may remove these sensations from the entire region.[17] Another study by Xavier et al. highlights peripheral inputs as a cause of pain during distal block study.[18,19] The effectiveness of common peroneal nerve block for lumbar disc herniation was evaluated in a double blind study by Tajiri et al.[20] Common peroneal nerve block was performed near the fibular head in nine patients using 2% lidocaine and in 10 patients using saline. The average pain scale score decreased from 3.1 to 0.6 in the lidocaine group, whereas it decreased from 3.0 to 2.6 in the placebo group. The average result in the straight leg raising test increased from 61° to 84° in the lidocaine group, but from 44° to 50° in the placebo group. Lower leg pain lessened more in the lidocaine group than in the placebo group. Selective Nerve Root Block (SNRB), injected with a combination of 40 mg of Methylprednisolone based suspension with local anesthetic over the affected nerve root to 40 patients with various grades of disc prolapse affecting a particular lumbar nerve root presenting with chronic radicular pain were identified irrespective of age and sex. All were and results were analyzed. Those graded mild had 4.3 months relief and those graded moderate had 2.5 months relief. Those with severe disc prolapse had no relief except for the immediate postprocedural relief. Only 20% patients had relief up to 6 months.[21] Ninja et al.[22] reported a case of 50 year old woman who was presented with neuropathic pain in the left lower limb after resection of a schwannoma on the left S1 nerve root, 20 ml of the anesthetic mixture were injected. The patient had immediate pain relief after the block (VAS 1/10). She remained pain free for 15 days after which pain reappeared but with less severity (3/10). Repetitive sciatic nerve block was performed in a progressive manner and was shown to be effective in managing neuropathic pain.

In this study, we investigated the efficacy of multimodal cocktail injections for pain management and patient functional outcomes as a conservative treatment option.

The mean age of patients was 42.43 years. There were 54.72% males with mean age of 40.06 years and 45.28% females with a mean age of 45.29 years. Majority of the patients (50.94%) had an injection on the left side followed by 49.06%, injection on the right side.

We found that, mean pre-VAS score was 7.83 followed by, the mean VAS score after 2 days was 1.05, after 7 days was 3.47, after 15 days was 3.9 and after 1month was 3.81. There was a statistically significant difference in the mean VAS score (p-value<0.0001).

At the time of presentation, 13.90% of patients were wheelchair bound, 45.40% needed walking assistance, and 40.74% had difficulty in walking. However, after one month, only 1.85% was wheelchair bound, 16.70% needed assistance to walk, 26.85% had a painful walk, and the majority (47.22%) had a pain-free walk. At the time of presentation, 41.70% of patients were able to walk comfortably for 10 m, 25.92% for 100 m, 18.52% for 1 km, and 13.90% had no comfortable walk. After cocktail injection, Only two patient had no comfortable walk after one month, followed by 8.33% who could only walk 10 m, 37.80% who could walk 100 m, and 45.37% who could walk up to 1 km without pain. **Manchikanti et al.**[4] conducted a study that was similar to this study. They evaluated the efficacy of caudal epidural injections with or without steroids in treating chronic low back and lower extremity pain caused by disc herniation or radiculitis, as well as the differences between local anesthetics with and without steroids in providing efficient and long-lasting pain relief. At the end of a year's follow-up, their study found significant pain relief (50%) in 79%–81% of patients, as well as significant improvement in functional status (40% or greater reduction in Oswestry scores) in 83–91% of patients, with no major differences noted with or without steroids. Opioid consumption and employment both improved significantly. Both groups had significant reductions in opioid intake, as well as pain alleviation and improved functional status. Furthermore, when compared to baseline employment, Group II saw a considerable increase in employment.

In a randomized trial of 84 patients with lumbosacral radiculopathy of less than 6 months duration, Cohen et al.[23] reported that Subjects who received 2 epidural injections of corticosteroids, etanercept (4 mg) or saline, mixed with bupivicaine. A greater reduction in leg pain 1 month after the second injection was observed with corticosteroids than etanercept or saline. Despite its extensive use and numerous publications, there is much debate on the medical necessity and criteria for lumbar epidural injections4. In positive reports for treating radicular pain from herniated lumbar intervertebral discs and radiculitis, multiple systematic reviews, guidelines and other evaluations have revealed indications for caudal epidural injections.

In the past, study shown serious systemic complications of epidural corticosteroid[2] but here We discovered that patients had a mild complication like Dryness of mouth for up to 24 h in all, 3.77% had a complication of Dizziness within 30 min, and 84.91% had a condition of Abnormal tingling sensation for up to 24 h, no serious systemic side effect was noted.

Patients undergoing discectomy for lumbar disc herniation often report a prompt reduction in leg pain, but many complain of persistent or in some cases worse low back pain after surgery.[24] Moreover, long-term outcomes of conservative management have been reported to be better than surgical intervention in several studies.[25,26] Additionally, surgical intervention is not available for everyone who is symptomatic and may lead to failure in approximately 25% of carefully selected cases[27]

Hence we tried to resort to an alternative method of treatment that entailed only non-operative treatment of the prolapse intervertebral disc based on this concept of multimodal cocktail injection. We discovered that injecting a mixture of multimodal injections into the affected spinal segments without attempting to “decompress” the bones, soft tissues, or disc is an effective nonsurgical therapeutic strategy. However axial backache was not improved but leg pain,comfortable walking distance improved significantally.

LIMITATION - In this study, patient were assessed for short period of time, long term follow-up will require for further evaluation.

6. Conclusion

Although the direct surgical excision of the herniated disc material is widely acknowledged for the treatment of PIVD, the use of cocktail multimodal injections for radiculopathy pain suggests that this non-operative, OPD based technique could be reasonable, efficient, and safe.

FIGURES- Three main specific injection sites were marked anatomically in affected lower limb as shown in Figs. 1–3.

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