Effects of Transdermal Application of Steroids in Radiculitis

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Abstract:
Iontophoresis is used as a means of delivering drugs across the skin for the management of a variety of medical conditions, most often, for localized inflammation and pain. There are many previous studies indicating that this mode of drug delivery can be useful, and iontophoresis with dexamethasone phosphate (DEX-P), sodium diclofenac, and acetic acid appears to be effective in treating inflammations in several areas of the body. The objectives of such research explorations were to see if local iontophoretic administration of an antiinflammatory drug to patients with tendonitis at the shoulder joint would achieve results similar to those obtained by local injection of the drug. Results were positive for iontophoretic delivery. Transdermal application of the steroids (iontophoresis) in addition to medical and physical therapy treatment was done in 36 patients with cervical & lumbar radiculitis. The protocol was followed for 1 week with outcome measures of VAS score, Dallas Pain Questionnaire score, Neck Pain & Disability Index score, and Modified Oswestry Disability Index score. The mean, standard deviations were calculated for all variables. Further Willcoxon Signed Rank Test was used within the group and Kruskalwallis Test & Jonkheere-Terpstra were applied between the groups to find the most effective one. On analysis test results were found significant within the group and between all the three groups. It was concluded that on comparison between the groups, the third group in which iontophoresis was used along with medication and other physical therapy modalities showed the best results.

Key words: Iontophoresis, Cervical & Lumbar Radiculitis

Introduction

Radiculitis is also termed as radicular pain syndrome, which means alterations of sensation or of muscle power which show that the primary disease-process producing them is in the spinal roots and not in the tracts and nuclei of the spinal cord *(Hubeny, 1933)*. Cervical radiculopathy is a common condition that usually results from compression and inflammation of the cervical nerve root or roots in the region of the neural foramen. It is frequently caused by cervical disc herniation and cervical spondylosis. It occurs annually in 85 out of 100,000 people *(Khalid et al., 2007)*. Clinical symptoms of cervical radiculopathy include pain and paresthesias radiating along the distribution of a nerve root, often associated with sensory loss and motor dysfunction *(Kyoung & Young 2010)*. Lumbar radiculopathy is a condition in which disease process affects the function of one or more lumbosacral nerve roots *(Taruli et al, 2007)*. The nerve root pathology arises primarily from direct neural compression irrespective of whether the etiology is an acute herniated or displaced disc, bony spurs, foraminal stenosis, central stenosis, or hypermobil ity of a vertebral segment. The prevalence of lumbar radiculopathy varies from about 2.2% to 8% and the incidence ranges from 0.7% to 9.6%. However in patients with radiculopathy and stenosis usually present with low back pain and unilateral more than bilateral leg pains, numbness, and

weakness *(Ayse & Aaron, 2010).* Diagnostic imaging (Magnetic Resonance Imaging) and electrophysiological tests (Nerve Conduction Velocity, Electromyography) are commonly used to confirm a diagnosis of Cervical Radiculitis. Provocative maneuvers may be observed that stretch the nerve root, such as coughing, sneezing, Valsalva, cervical distraction, and the Spurling's maneuver *(Whalen, 2007).* In lumbar radiculitis the most applied investigation is the straight leg raising test or Lasegue's sign. Patients with sciatica may also have low back pain but this is usually less severe than the leg pain *(Koes et al, 2007).*

Main objectives of treatment are to relieve pain and improve neurologic function and prevent recurrences *(Simon Fehlings, 2005).* Initially patients were treated conservatively, which generally includes nonsteroidal anti-inflammatory medication, activity modification, traction, epidural injections, and physical therapy modalities *(Whalen, 2008).* Superficial heat therapy is used to relieve muscular and joint pain, either alone or as an adjunct to other pain treatments *(Meryl, 2004).* The main action of AL-TENS is extra segmental analgesia mediated by ergo receptor activity *(Kitchen, 2008).* Continuous or intermittent traction has been regarded as an effective treatment for herniated cervical disks (HCDs) because it facilitates widening of the disk spaces. The traction induces pain relief and regression of the herniated disks *(Tae-Sub Chung et al., 2002).*

Current treatment strategies typically involve a gradual progression in the aggressiveness of intervention, progressing from less to more invasive interventions only in refractory cases *(Christopher, 2009).* Iontophoresis is the application of an electrical potential that maintains a constant electric current across the skin or barrier that enhances the delivery of ionized as well as unionized moieties. Iontophoresis increases the absorption of EMLA (eutectic mixture of local anaesthetics) and renders it effective for analgesia within five to fifteen minutes *(Miller et al., 2001).* Anti-inflammatory drugs used to treat tendinitis and bursitis when delivered by iontophoresis was described as successful by several workers *(Cummings, 1987).* The advantages of this method of delivery over conventional injection are the painless and sterility of the treatment: absolute sterility is clearly very important for the introduction of anti-inflammatory agents, prevents the variation in the absorption and metabolism seen with oral administration. The objectives of the present study are to evaluate the effectiveness of transdermal administration of mixture of 0.4% dexamethasone and 4% lidocaine in patients of radiculitis along with medication and other physical therapy modalities. This study also puts efforts to compare its effects with the other treatment protocols which include medication and physical therapy modalities.

Materials and Methods:-

This study was performed on 36 radiculitis patients in the outpatient department of SBSPGI, Dehradun. This is an experimental randomized control trial study, which is comparative in nature. Prior to the study, an approval was taken from the subjects included for conducting the study. Patients were taken on first

come first basis and randomly by using lottery method; they were divided into three groups: (a) 36 subjects (18 patients of lumbar radiculitis & 18 patients' cervical radiculitis), (b) 12 patients (6 lumbar & 6 cervical radiculitis each) in each group. On the basis of inclusion and exclusion criteria patients were chosen for the study. Inclusion criteria was; Patients with acute neck and low back pain persisting for less than 3 months, Unilateral or bilateral radiating type of pain till hands in UL and toes in LL. In UL (upper limb), distraction test, quadrant test, spurling's test was positive and SLR positive in lower limb. If any one of the ULTT or LLTT is positive. Exclusion Criteria includes; any deformity/contracture of LL and UL, any previous surgical procedures of spine. Patients with major psychiatric disorder, neurological disorders, or any other chronic muscle wasting or weakness were also excluded. Subjects who are on narcotics, neurodepressants or are under current use of any steroidal medication prescribed for radiculopathy symptoms and use of steroidal injections (in spine) in the past 2wk.

The subjects in the first group were only on medication. In the second group along with medication other treatment was given which included hot pack, traction and tens. In the third group along with medication and above treatment iontophoresis was given. Iontophoresis was done using electrical stimulator with dose current of 2mA for 5 minutes. It was increased progressively to 3mA for next 5 mins and then increased to 4mA for the remaining 10 minutes, giving a total treatment time of 20 minutes. Treatment was continued for one week. Outcome measures were taken on pre (0 day) and on post treatment day (8^{th} day). For patients with low back pain modified Oswestry Disability Index was used and for patients with neck pain, Neck Pain Disability Index was administered. Dallas Pain Questionnaire and VAS score was also administered. Readings were taken on the 0 day and 8^{th} day. Data was collected and analyzed.

Results

Table1: Comparison of means of pre and post protocol readings of Visual Analog Scale (VAS) score, Dallas Pain Questionnaire(DPQ), Neck Pain Disability Index score(NPDI), Modified Oswestry Disability Index score(MODI) of each group.

Variables	Pre protocol 0-day	Post protocol 8^{th} day	Z-value	t-value	Significance
Group A					
VAS	7.35 ± 1.204	5.8 ± 1.33	-	2.75	S
DPQ-A	69.25±16.43	60 ± 15.08	-3.078	-	S
DPQ-B	61.25± 19.08	52.50± 20.83	-2.831	-	S
DPQ-C	49.58±18.52	39.58±15.44	-2.737	-	S
DPQ-D	44.58±19.75	37.91±18.022	-1.847	-	S
NPDI	66.33±11.82	50±9.71	-2.226	-	S
MODI	75.33±8.91	63±8.60	-2.207	-	S
Group B					
VAS	7.51 ± 1.314	4.69 ± 1.09	-	8.08	S
DPQ-A	62.25±11.59	35.25 ± 12.80	-3.066	-	S
DPQ-B	59.16±15.05	31.66±15.12	-3.086	-	S
DPQ-C	43.33±18.25	20.41±12.14	-3.076	-	S
DPQ-D	32.08±14.37	15.41±11.95	-2.968	-	S
NPDI	70.33±6.50	49.33±5.31	-2.214	-	S
MODI	60.66±11.77	37±11.22	-2.207	-	S
Group C					
VAS	8.25 ± 0.70	3.51 ± 0.5	-	2.62	S
DPQ-A	63.75±12.54	25±8.70	-3.084	-	S
DPQ-B	62.91±12.14	20.16±9.96	-3.077	-	S
DPQ-C	47.08±16.57	10.41±8.64	-3.072	-	S
DPQ-D	44.58±17.89	10.83±8.48	-3.070	-	S
NPDI	67.66±4.96	26.33±7.31	-2.201	-	S
MODI	73.33±8.16	34.33±5.85	-2.207	-	S

Table 2: Table showing Mean difference, Standard deviation, One Way Anova test & Significance values of VAS on 0 day & 8^{th} day.

Visual Analog Scale	0 day	8^{th} day
GROUP-A	7.35 ± 1.204	5.8 ± 1.33
GROUP-B	7.51 ± 1.314	4.69 ± 1.09
GROUP-C	8.25 ± 0.70	3.51 ± 0.5
F VALUE	2.258	14.492
SIGNIFICANT	NS	S

Table 3: Table showing Mean difference & Standard deviation values of Kruskal Wallis Test and Significance of values of Dallas Pain Questionnaire Scores on 0 day.

Kruskal Wallis	DPQ-A	DPQ-B	DPQ-C	DPQ-D
GROUP-A	9.25±16.43	61.25± 19.08	49.58±18.52	44.58±19.75
GROUP-B	62.25±11.59	59.16±15.05	43.33±18.25	32.08±14.37
GROUP-C	63.75±12.54	62.91±12.14	47.08±16.57	44.58±17.89
Chi.Square	3.110	.385	1.044	3.709
Asymp. Sig.	.211	.825	.593	.157

Table 4: Table showing Mean difference & Standard deviation values of Kruskal wallis Test And Significance & Jonkheere-Terpstra Test And Significance Of Values Of Dallas Pain Questionnaire Scores Post 1 week (on 8th day).

Kruskal Wallis	DPQ-A	DPQ-B	DPQ-C	DPQ-D
GROUP-A	60 ± 15.08	52.50± 20.83	39.58±15.44	37.91±18.022
GROUP-B	35.25 ± 12.80	31.66±15.12	20.41±12.14	15.41±11.95
GROUP-C	25±8.70	20.16±9.96	10.41±8.64	10.83±8.48
Chi.Square	18.982	13.076	17.056	14.537
Asymp. Sig.	0.000	0.001	0.000	0.001
Jonkheere-Terpstra	DPQ-A	DPQ-B	DPQ-C	DPQ-D
STD.J-T Value	-4.565	-3.759	-4.304	-3.729
Asymp. Signi.	0.000	0.000	0.000	0.000

Table 5: Table showing Mean difference & SD values of Kruskal Wallis Test and Significance & Jonkheere-Terpstra and Significance of Neck Pain Disability Index on 0day & Post 1 week (on 8th day).

NPDI	0-day	8th –day
GROUP-B	70.33±6.50	49.33±5.31
GROUP-C	67.66±4.96	26.33±7.31
Chi- SQUARE	4.813	10.434
Asymp. Significance	0.09	0.005
Std.J-T	-	-3.137
Asymp. Significance	-	0.002

Table 6 : Table showing Mean difference & Standard deviation values of Kruskal Wallis Test And Significance & Jonkheere-Terpstra and Significance and Modified Oswestry Disability Index on 0 day & Post 1 week (on 8th day).

MODI	1. Day	□ 8th day
GROUP-A	75.33±8.91	63±8.60
GROUP-B	60.66±11.77	37±11.22
GROUP-C	73.33±8.16	34.33±5.85
Chi- SQUARE	0.8	10.827
Asymp. Significance	0.668	0.004
Std. J-T	-	-2.814
Asymp. Significance	-	0.004

Discussion:-

In the current study the result showed reduction in pain and related disability, within all the three groups. However, on comparing the three groups, group C (ie the group that received transdermal application of drugs (iontophoresis) alongwith medication, heat therapy, TENS, traction,) showed the most significant results.

In the group that was on medication which included NSAID's (Voveron SR 100) along with antacid (Rentac 100mg) and neural vitamin tablets (Neurobion Forte). On analysis a significant reduction

in pain was found. *Sara Brown (2009)* also support that NSAIDs are effective to control acute pain and if the pain is severe then opioids are given. *Ross et al (2009)* said that anti-inflammatory medications and oral corticosteroids can decrease nerve inflammation thus help in immediate pain reduction. There are various side effects of NSAID's so antacids are preferably given along with them. NSAIDs exert an immediate analgesic effect; however their anti-inflammatory effect, which is related to the achievement of steady state, is only evident after dosing for three to five half-lives. This means that NSAIDs with shorter half-lives, such as ibuprofen and diclofenac, should be prescribed in preference to those with longer half-lives, such as piroxicam and sulindac, for non-specific low back pain due to acute injury. Although COX-2 selective inhibitors (eg Celecoxib, Rofecoxib) may reduce the risk of side effects but are less effective than NSAID's some are only preferred in high risk cases.

The group that received Conservative Treatment (Medication+Moist Heat+ Tens +Traction) also showed significant result from the 0 day to 8th day. On comparison between groups-A and group-B, group-A showed more significant difference in pain reduction, as this included other conservative treatment modalities along with medication. This group had heat therapy as an adjunct applied before Traction and TENS was applied. Moist heat has been a recommended therapy aid for many years. A report by *Meryl (2004)* says Heat, cold, and physical pressure sensations are transmitted by larger nerve fibers. When the large neurons are stimulated, by applying heat for example, they inhibit the pain transmission and close the gate to further travel of pain impulses, leading to a reduction of pain. Heat therapy can help to relieve pain by closing the gating system in the spinal cord. According to *McCaffery & Wolff (1992),* heat reduces muscle spasm by reducing tension in muscle trigger points, and it increases the ability of the muscle tendon unit to relax and stretch. The application of heat lowers the viscosity of collagen, softening muscle and tendon, enabling muscles to relax and extend more easily. In this way heat therapy had additive effects on relieving pain, and it also helps other modalities to work more efficiently and give beneficial outcomes.

According to *White et al (2001),* the purported mechanism of action of TENS invokes both spinal (i.e., gate-control, frequency-dependent blockade) and supraspinal theories (i.e., release of endogenous neuromediators). It has also been suggested that TENS involves activation of the body's pain modulation system and increases in the release of endogenous opioids within the central nervous system, thereby suppressing the transmission and perception of noxious stimuli from the periphery. *Mannheimer and Lampe (1984)* suggested that acute pain of superficial nature, including causalgia, responds best to conventional TENS whereas longstanding deep aching pain responds best to low frequency TENS, however *Johnson et al (1991)* found that there was no relation between the cause of pain and the pulse frequency or pattern used by their patients. Another study explains the purpose of AL-TENS, which is to selectively activate small diameter fibres (Aδ or group III) arising from muscles (ergoreceptors) by the induction of phasic muscle twitches. Evidence suggests that AL-TENS produces extra-segmental analgesia in a

manner similar to that suggested for acupuncture. TENS is delivered to selectively activate Aα afferents leading to inhibition of nociceptive transmission in the spinal cord. It is claimed that the mechanism of action and analgesic profile of AL-TENS and intense TENS differ from conventional TENS and they may prove useful when conventional TENS is providing limited benefit *(Kitchen, 2008)*. Traction is widely used modality for the cervical or lumbar spine disorder due to muscle spasm or intervertebral disc. *Moeti & Marchetti, (2001)* believed that it can reduce disk herniations, decompress the nerve root, or stretch ligaments and dural sheaths, thus reducing symptomatology. *Chung et al (2002)* reported that Cervical traction has been applied widely to relieve neck pain from muscle spasm or nerve compression in rehabilitation medicine settings. Continuous or intermittent traction has been regarded as an effective treatment for herniated cervical disks (HCDs) because it facilitates widening of the disk spaces. The traction induces pain relief and regression of the herniated disks. Several reports have described the regression of herniated disks either spontaneously or within the treatment period. The disk may be subject to desiccation and shrinkage from loss of hydrophilic proteoglycans, which leads to a loss of water content and, consequently, a decrease in disk size. Reports have suggested that traction therapy can induce HCD regression. In a report, it is stated that the length of a cervical disk increases during traction. *Krause et al (2000)* in their study concluded that traction is most commonly used for normalization of neurological deficits or painfully restricted neuromeningeal tension signs, relief of pain and for improving joint mobility. Evidence available suggests that traction is more effective for pain reduction and return to activity than infra-red radiation, corset and bed rest, hot pack and rest, hot pack, massage and mobilization and bed rest. Thus all these modalities are used under the conservative treatment protocol which proved to be more beneficial than giving medication alone.

Effect of Use of Transdermal Application (Iontophoresis) Of Steroids (In Addition To Conservative Management) In Reducing Pain and Disability

The group that received transdermal application (iontophoresis) of steroids in addition to conservative management showed the maximum significant results. In this group iontophoresis was included, which is one of the best noninvasive methods of drug delivery into the body. This route of drug delivery avoids all the systemic effects of drugs and first pass metabolism, thus this mode of drug delivery was chosen over other treatment techniques. Transdermal iontophoresis is the application of an electrical potential that maintains a constant electric current across the skin and enhances the delivery of ionized as well as unionized moieties *(Rashmi et al., 2005)*. It offers various advantages such as easier termination of therapy, better control of drug delivery, improving delivery of polar drugs as well as high molecular weight substances, benefits of bypassing hepatic metabolism and reducing considerably the inter and intra-individual variability *(Williams & Barry, 1991 & 1992)* and ability to be used for systemic delivery or local delivery of drugs *(Dehgan & Mouzam, 2008)*. Corticosteroids are widely used because they possess a profound anti-inflammatory effect and are available in

relatively inexpensive forms designed both for oral and topical administration. Several corticosteroids are available as water soluble salts, rendering the corticosteroid molecule negatively charged and therefore available to move under the influence of a negative current field *(Costello et al, 1995).* Corticosteroids inhibit the inflammatory process, in part by reducing the migration of neutrophils and monocytes into the inflamed area and reducing the activity of these white blood cells *(Wigard et al., 1991).* Corticosteroids have recently been shown to reduce "sprouting" that occurs in sensory nerves in association with tissue injury *(Hong et al, 1993).* Dexamethasone is often administered by iontophoresis, in combination with lidocaine, in the treatment of musculoskeletal disorders. This corticosteroid has frequently been administered from the positive electrode (it presumably comes through the skin by the electro osmotic effect, because it is a negatively charged ion) *(Costtelo et al., 1995).* Lidoaine is applied iontophoretically under the anode. When applied in this manner, lidocaine produces dilation of blood vessels and a rather profound topical anesthesia of the skin, to depths of several millimeters *(Gangarosa et al., 1981). DeLacerda (1982)* used dexamethasone (1mL of 0.4% dexamethasone mixed with **2**ml of 4% lidocaine in aqueous solution administered from the anode at a dosage of 5 mA for 10 minutes) to treat patients with myofacial shoulder girdle syndrome and found that iontophoresis produced the most rapid improvement in range of motion, compared with treatment with ultrasound or muscle relaxants. He used a current of 5mA for 15 minutes, applied over trigger points. *Bertolucci (1982)* reported reduction of pain and increased range of motion in a group of patients with shoulder tendinitis treated with the same mixture of dexamethasone and lidocaine iontophoresis, applied for 10 minutes at 2mA, for 5 minutes at **3**mA, and for 5 minutes at 4mA, compared with a control group. He reported that the results were similar to those seen with steroid injections. He used a current of 2 to 4mA, progressed over a 20-minute treatment period. Similarly, *Hasson and colleagues (1988)* reported a delay in the onset of post-acute exercise muscle soreness with the use of dexamethasone iontophoresis, and an improvement in knee joint range of motion and a reduction in knee circumference following dexamethasone iontophoresis, applied using the same protocol as Berto1ucci.

Thus from above studies and the results of the present study, conclusion is drawn that iontophoresis is very effective method to deliver drugs to suppress inflammation and pain. This suggests that the group which had iontophoresis as a treatment modality has to have extra effect to alleviate pain and disability in radiculitis compared to other groups.

Conclusion

On the basis of its results, the present study concluded that the third treatment protocol which includes medication, physiotherapy treatment and iontophoretic administration of mixture of anti-inflammatory (dexamethasone) & local anesthetic (lignocaine) showed the maximum positive effects. There was more relief in pain and the percentage of disability was also decreased, thus improving the activities of daily living.

References

Bertolucci, LE. 1982. Introduction of anti-inflammatory drugs by iontophoresis:

doubleblind study. *J Ortbop Sports Pbys Ther*. **4:**103-108.

Charles T Costello, Arthur H Jeske, 1995. Iontophoresis: Applications in transdermal medication delivery, *Phys. Therap.*, **75:** 554-563.

Dehghan, M.G.H., Mouzam, M.I. 2008. Advances in iontophoresis for drug delivery, *Int. J. Health Res.*, **1(3):** 115-127.

DeLacerda, F.G. 1982. A comparative study of three methods of treatment for shoulder girdle myofascial syndrome. *J Orthop. Sports Phys. Ther***., 4:**51-54.

Gangarosa, L.P. 1981. Defining a practical solution for iontophoretic local anesthesia of the skin. Methods *Find. Eq. Clin. Pharmacol.*, 3:83-94

Harris, P.R. 1982. Iontophoresis: clinical research in musculoskeletal inflammatory conditions, *J Orthop. Sports Phys. Ther***., 4:** 109-1 12.

Hasson SM. et. al. 1988. Effect of Iontophoretically Delivered Dexamethasone on Muscle Performance in a Rheumatoid Arthritic Joint. *Arthritis Care & Research*.; 1:177-182.

Koes, B. W. ,Van Tulder, M. W., Peul, W. C. 2007. Diagnosis and treatment of sciatica, *B.M.J.*, 334**:** 1313-7.

Krause, M., Refshauge, K.M., Dessen, M., Boland, R. 2000. Lumbar spine traction: evaluation of effects and recommended application for treatment, *Man. Therap.*, **5(2):**72-81.

Kyoung-Tae Kim, Young-Baeg Kim, 2010. Cervical Radiculopathy due to Cervical Degenerative Diseases: Anatomy, Diagnosis and Treatment, *J. Korean Neurosurg. Soc.*, **48:** 473-479.

McCaffery, M. and Wolff, M. 1992. Pain relief using cutaneous modalities, positioning and movement. *Hosp. J.*, 8(1-2): 121–153.

Meryl, R., 2004. Modern Heat Therapy: A Report, business briefing: *US Pharmacy Review*, 1-3.

Miller, K.A., Balakrishnan, G., Eichbauer, G., Betley, K. 2001. 1% lignocaine injection, EMLA cream or"numbing stuff" for topical analgesia associated with peripheral intravenous cannulation. *AANA J* **69:** 185-7.

Moeti, P., Marchetti, G.J. 2001. Clinical outcome from mechanical intermittent cervical traction for the treatment of cervical radiculopathy: a case series. *J. Orthop. Sports Phys. Ther***., 31:** 207-213.

Pearl, P., Law, W. and Gladys, L., Cheing, Y. 2004. Optimal Stimulation Frequency Of Transcutaneous Electrical Nerve Stimulation on people with Knee Osteoarthritis. *J. Rehabil. Med.*, **36:** 220-225.

Robinson, A.L. and Lee, A.T. (2010), Clinical and Diagnostic Findings in Patients withLumbar Radiculopathy and Polyneuropathy, *Am. J. Clin. Med.*, **7(2):** 80-85.

Ross, A. Hauser,Glen M. Batson,Chris Ferrigno. 2009. Non-Operative Treatment of Cervical Radiculopathy: A Three Part Article from the Approach of a Physiatrist, Chiropractor, and Physical Therapist, J. Prol., **4:** 217-231.

Tae- Sub Chung, Young- Jun Lee, Seong - Woong Kang, Chang – Jun Park, Won – Suk Kang,Yong – Woon Shim, (2002) , Reducibility of Cervical Disk Herniation : Evaluation at MR Imaging During Cervical Traction with a Nonmagnetic traction Device,Radiology;224:895-900.

Thakur, R., Yiping Wang, Y., Qiuxi Fan, Michniak, B. 2005. Transdermal iontophoresis: Combination strategies to improve transdermal iontophoretic drug delivery. *Eur. J. Pharm. Biopharm.*, **60(2):**179–191.

Wayne M. Whalen DC, (2007), Resolution of cervical radiculopathy in a woman after chiropractic manipulation, journal of chiropractic medicine ;7:17-23.

Williams AC, Barry BW. Skin absorption enhancers. Crit Rev Ther Drug Carrier Syst, 1992;9(3-4):305–353.

Wingard LB, Brody TM, Larner J. SchwartzA. Glucocorticoids and other adrenal steroids. In: Human Pbanacology. St Louis, Mo:Mosby-Year Book; 1991:484-493.