A SUPERFICIAL CUTANEOUS DRESSING INHIBITS PAIN, INFLAMMATION AND SWELLING IN DEEP TISSUES

Alan R. Kahn M.D.[a]*, Robert W. Sessions[b], and Elena V. Apasova B.S. [a]
Pain Medicine · June 2000; 1(2):187

[a]Experimental Surgical Services, Department of Surgery, University of Minnesota School of Medicine, Box #220 UMHC, 420 Delaware St., Minneapolis, MN 55455.
[b]Ferris Pharmaceuticals, 16W300 83rd St., Burr Ridge, IL 60521.

*Corresponding author. 1912 Irving Ave. South, Minneapolis, MN 55403.
Tel: (612) 377-6226; Fax: (623) 377-6446.
E-mail: AKAHN@VISI.COM

Data Presented at the World Pain Conference July 15-21, 2000

Abstract

This study is a consequence of a series of unexpected findings resulting from clinical experience with a commercial wound dressing. The *PolyMem*® family of dressings, provided by Ferris Manufacturing for the treatment of open ulcerative wounds, has been on the market for nine years. During this period, the manufacturer has received numerous communications from patients and wound care specialists describing instances in which the application of the dressing over traumatized areas helped to prevent the development of pain, inflammation, swelling, and bruising in the areas surrounding the wounds. Experiments revealed that, when applied to intact skin over a mechanically traumatized area, the dressing was effective in preventing the development of pain, bruising, swelling and inflammation in the deep tissues beneath the skin. Ferris then modified the formulation of the ingredients contained within the dressing to enhance its effects on pain and inflammation.

This background of anecdotal data has been reinforced by more objective evidence. For example, a case study is reported here in which the application of the dressing to the knee area immediately after arthroscopic surgery prevented the anticipated post-operative pain and swelling and eliminated the need for medications and a rehabilitation program.

A controlled animal study was performed to investigate the effects of the application of the new Ferris pain dressing on the response of deep tissues to mechanical trauma. Controlled mechanical impact, using a calibrated device, was applied to the gastrocnemius areas of both hind legs of 14 rabbits. Immediately after application of the trauma, one leg of each rabbit was wrapped with the Ferris pain dressing covered by an elastic bandage and the other leg was simply wrapped with the elastic bandage and served as a control. The differences in the degree of swelling observed between the treated and untreated legs were large and easily observed on gross inspection. The swelling was graded by two independent observers and scored on a scale of 1 to 4, 4 being the most severe. 24 hours after the experimental procedure, the treated legs exhibited either a low level or a total absence of swelling (mean=0.71±0.83), while the swelling was pronounced in all of the untreated legs (mean=3.29±0.73). 48 hours after the trauma was applied, 11 of the 14 subjects exhibited no swelling at all in the treated legs (mean=0.29±0.61) while the untreated legs continued to be inflamed and swollen (mean=2.36±1.15). While pain was not measured directly in this study, the substantial effects on swelling and inflammation are strongly inferential, especially in light of the coupling of pain with swelling and inflammation which is reviewed in the Discussion section of this manuscript.

These various reports, observations, and data on the effects of treatment of deep tissue trauma with the Ferris pain dressing point towards the suppression of the nociceptive nervous system as a likely mechanism. If more extensive clinical studies confirm these initial observations, this could generate a variety of potential therapeutic applications in areas such as plastic and orthopedic surgery, emergency trauma, sports medicine, and chronic neuromuscular pain.

Introduction

This study began as an investigation of a series of anecdotal communications describing the effects of applying a commercially available wound dressing to suppress pain, swelling, and inflammation in deep tissue structures well below the skin surface. The Polymem™ family of dressings, provided by Ferris Manufacturing for the treatment of open ulcerative wounds, (Blackman et. al., 1994; Fowler and Papen, 1991; Carr et. al., 1990) has been on the market for nine years. During this period, the manufacturer has received numerous communications from patients and wound care specialists indicating that the application of a Polymem™ dressing over a portion of the body which has sustained injury due to surgery, mechanical trauma, neuromuscular irritation, etc. has reduced or prevented subsequent pain, inflammation and swelling. Relief of pain was typically reported within 15 to 30 minutes after application of the dressing. Experiments performed in the Ferris laboratory revealed that, when applied to intact skin over a mechanically traumatized area, the dressing was effective in preventing the development of pain, bruising, swelling and inflammation in the deep tissues beneath the skin. Ferris then modified the formulation of the ingredients contained within the dressing to enhance its effects on pain and inflammation. We will refer to the new dressing as the Ferris pain dressing.

The aforementioned communications were anecdotal, poorly documented, and not placebo-controlled, and it was our initial tendency to ignore them on that basis. However, the growing number of these communications and observations warranted scientific investigation.

In addition, there were several instances in which we directly observed that placing a sheet of the dressing over an area that had recently suffered blunt trauma, on human patients, prevented the development of the expected tenderness, swelling, and discoloration. This was especially apparent when the traumatized area extended beyond the boundaries of the dressing. In these cases the area beneath the dressing was not tender and appeared normal while the area outside the dressing was typically discolored and tender. Figure 1 illustrates such a case.

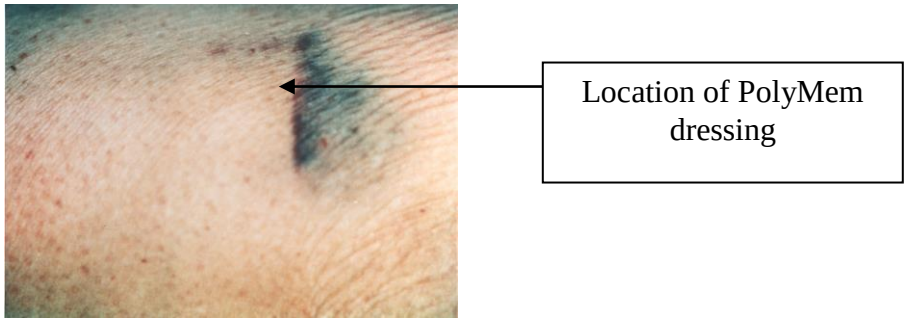

Figure 1. Photograph of a traumatized area of human skin**.** The central area previously covered by the Polymem™ dressing did not become tender or swollen and shows no signs of bruising. The traumatized area was somewhat larger than

the dressing. The untreated area exhibits a bruise which was indurated and tender.

Subsequently, we had the opportunity to interview 24 patients, who were suffering from persistent chronic lower back pain, immediately after a 10 day treatment with a Ferris pain dressing applied to the lower back area. Previously, these patients had not responded successfully to other therapies and did not expect relief from the current trial. 21 of the 24 patients reported significant improvement during the study.

We had the opportunity to observe the results of the treatment of a young woman with numerous lesions of Morphea spread across her back. These lesions were characterized by areas of dry, nonviable skin, each surrounded by a border of raised, inflammatory tissue. One side of the back was treated with the dressing. Observations after 3 days of treatment revealed that, on the treated side, the inflammatory borders were absent and the pathologic process appeared to be quiescent, while the untreated side continued to exhibit the characteristic lesions.

As a result of these additional observations, a prospective clinical study was performed on a surgical patient. The results of that study were so positive that a controlled animal study was initiated. At the same time, a literature review revealed a physiological mechanism which potentially can explain the results of the anecdotal reports and the subsequent studies. This paper will present the case history of the surgical patient and the results of the follow-up animal study, as well as a discussion of potential mechanisms of action.

Surgical Patient Prospective Case

The patient is a 65 your old white male physician who presented with complaints of acute pain and a "clicking" sensation upon motion of his right knee. Physical and x-ray examinations resulted in a preoperative diagnosis of a medial meniscus tear.

His past history revealed a similar pathology in his left knee diagnosed and treated with arthroscopic surgery ten years previously. At the time of that surgery, moderate degeneration was noted in the articular surfaces, and debridement of the degenerative portion of the medial meniscus was performed. His post-operative recovery included a period of several weeks in bed with significant pain at rest and during knee flexion, followed by a period of several months of gradually increasing ambulation accompanied by exercise and physical therapy. The tenderness and swelling of the left knee gradually subsided but was still evident several months after surgery.

On the basis of the current diagnosis, the past history, and the patient's more advanced age, we might expect a recovery period as long, or longer than that which he experienced after a similar surgical procedure ten years ago. Arthroscopic surgery was performed on the right knee and, again, a degenerative medial meniscus tear and partial thickness changes to the articular surfaces were observed. Debridement of the

degenerative portion of the medial meniscus was performed. At the end of the procedure, excess fluid was removed from the knee and a single suture of 4-0 nylon closed each of the three portals. The entire right knee was then wrapped with a Ferris pain dressing, covered by a lightly wrapped Ace bandage. The patient was then sent home with the usual pain medications, crutches, etc. and instructed to return in two weeks to begin a rehabilitation program.

The patient returned home and, in the absence of any pain, went to his home office and spent several hours working at his desk. Again without pain, he went to sleep and on the next morning discovered he was able to walk comfortably without the aid of a cane or crutches. On the second day after surgery he was able to maintain a normal gait including walking up-and-down the stairs from the first to the third-floor in his home. He then removed the dressing and noted that there was no evidence of swelling, inflammation, or bruising of the right knee and, with the exception of the three tiny portal incisions, the operated knee looked like the normal left knee. Furthermore, the ranges of motion of both knees were the same and the operated knee exhibited no limitations. He then resumed his normal daily activities and subsequently never experienced any pain, swelling, limitations of the range of motion, or any other disability associated with the surgery. On the third day after surgery he returned to the clinic, had the three sutures removed, returned the unused crutches, and canceled future appointments for the scheduled rehabilitation program.

This case history does not describe an incidental finding. The Ferris pain dressing was applied on the basis of a prior hypothesis that it could suppress the inflammatory process resulting from the arthroscopic procedure. This is a prospective experiment in which the patient provided the history of a similar operative procedure on the other knee as a control. The results of this clinical trial are totally unexpected and dramatically different from the usual course of recovery of this kind of patient from this surgery. While this represents a single trial on one patient, it is more than anecdotal and provides justification for serious consideration. As a consequence, we decided to undertake a controlled animal study to test the effects of the Ferris pain dressing on the response of deep tissues to mechanical trauma.

Randomized Controlled Animal Study

Methods

Subjects

A total of 14 male 6-7 lb. New Zealand White rabbits were used. The animals were housed 1 to a cage, maintained on a 12 hour light/dark cycle, and given food and water ad libitum. The protocol was approved by the Animal Care Committee of the University of Minnesota.

Ferris Pain Dressing

The Ferris pain dressing as used in these experiments was made up of a urethane membrane matrix containing moisturizers and copolymers. At this time we do not know

what specific roles these ingredients play in the capability of the dressing to control pain, inflammation and swelling in deep tissues.

Mechanical Trauma

Mechanical trauma was applied to the gastrocnemius area of each of the hind legs of all rabbits using an apparatus specially constructed for that purpose. This device provided the means for dropping a shaft one cm in diameter onto the target area. Calibrated weights could be affixed to the top of the shaft, the initial height of the shaft above the tissues could be adjusted, and precise means were available for positioning the leg of the animal. During initial pilot experiments, we were able to determine that applying a single weight of 4 lbs., falling a distance of 30 cm. produced repeatable bruising in the muscles of these animals without breaking the overlying skin.

Immediately prior to the experimental procedure, each rabbit received an injection of a mixture of 10 mg of acepromazine tranquilizer, 10 mg of butorphanol analgesic, and 1 mg of ketamine anesthetic. Each hind leg was then shaved to remove all of the fur from the ankle to well above the knee. The mechanical stimulus described above was then applied to each leg in the area of the gastrocnemius muscle. One leg was then wrapped loosely with a strip of Ferris pain dressing and the other leg was used as a control. Both legs were then wrapped loosely with an elastic, lightweight Ace bandage. For each of the two days following the procedure, each rabbit received subcutaneous injections of 0.5 ml of buprenorphine twice daily.

The hind legs of each of the rabbits were examined 24 hours and again 48 hours after the trauma procedure. The dressings were removed and the gastrocnemius areas were inspected and palpated independently by two members of the laboratory. The swelling was graded on a scale of 0 to 4, wherein 0 indicated no observable swelling, 1 indicated that a trace could be palpated, 2 indicated mild established swelling, 3 indicated moderate swelling with deformity through which the anatomical structures could be palpated, and 4 indicated severe deformity with no palpable anatomy. For statistical analysis, the assessments of the degree of swelling in the treated legs vs. the untreated control legs were compared using Paired T tests to determine the significance of the differences between the two groups.

Results

Table 1 presents the data derived from the 14 subjects. Mechanical trauma produced clear swelling and bruising in all control legs. After 24 hours, the mean degree of swelling, based on the 0 to 4 grading system described above, was 3.29 ±0.83. In contrast, the legs treated with the Ferris pain dressing exhibited significantly less swelling (mean=0.71±0.83, $p<.001$). After 48 hours the swelling in the control legs persisted (mean=2.36±1.15) while the treated legs improved (mean=0.29±0.61, $p<.001$), 11 of the 14 treated legs showing no swelling at all.

	POST-TRAUMATIC SWELLING (scale = 1 to 4)			
	1 DAY POST-OP		2 DAYS POST-OP	
RABBIT #	**treated**	**untreated**	**treated**	**untreated**
1	1	3	0	3
2	1	4	0	4
3	0	2	0	1
4	0	4	0	3
5	2	3	2	3
6	0	3	0	2
7	0	3	0	2
8	0	4	0	3
9	2	4	0	4
10	1	3	0	2
11	1	3	0	0
12	2	4	1	2
13	0	4	0	3
14	0	2	1	1
AVERAGE	0.71	3.29	0.29	2.36
T TEST	p<.001	(0.0000001)	p<.001	(0.0000582)

Table 1. Data on the post-traumatic swelling in the treated legs and the untreated legs in fourteen rabbits. The data was derived from examinations on the first day after the traumatizing procedure, and again on the second day.

Figure 2 is a photograph of the legs of one of the subjects after 24 hours and Figure 3 is a photograph of the same subject on after 48 hours.

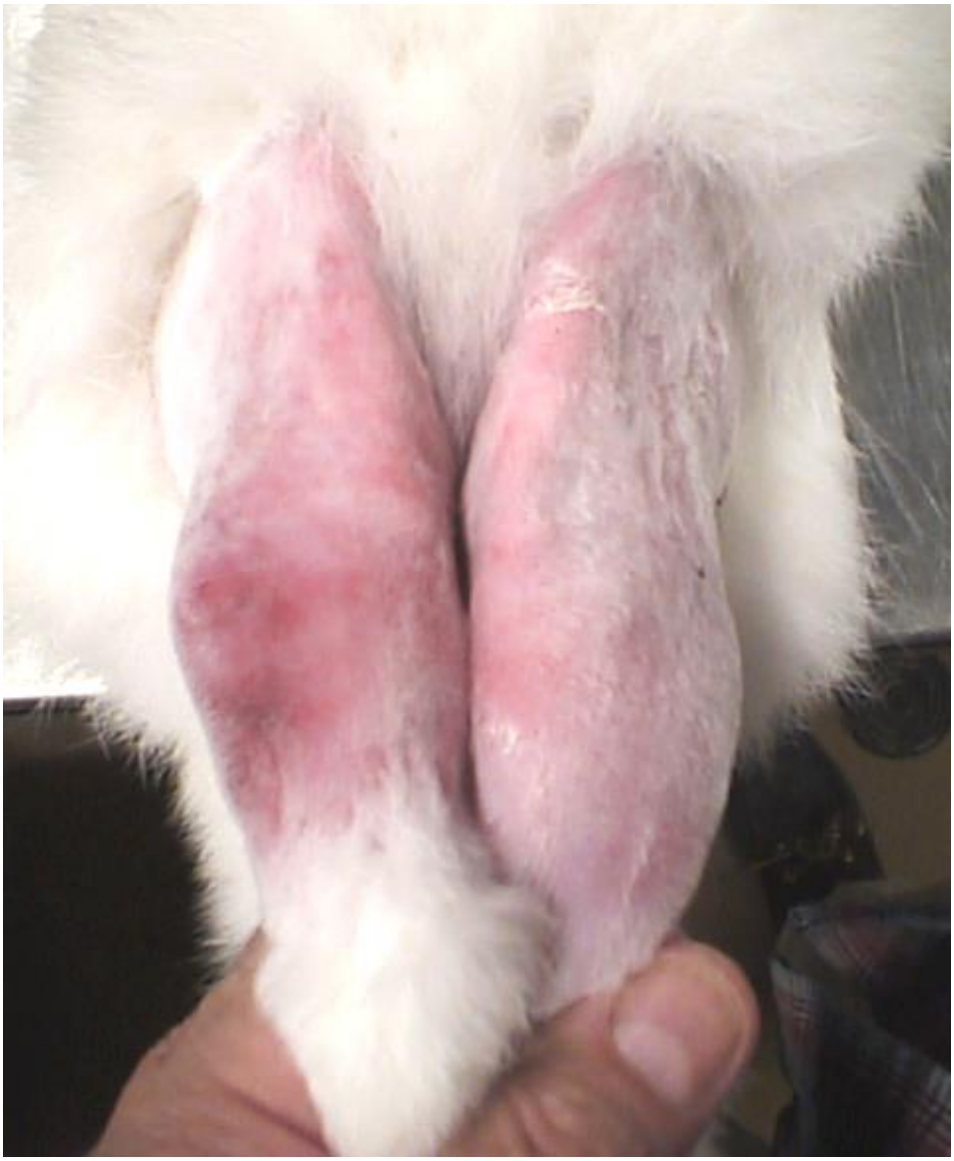

Figure 2. Photograph of both hind legs of rabbit #4. The legs were shaved and traumatized on the previous day. The left leg (on your right) was wrapped with a Ferris pain dressing and now appears normal (swelling score=0). The untreated right leg is inflamed and swollen (score=4). The dressing was reapplied after this examination.

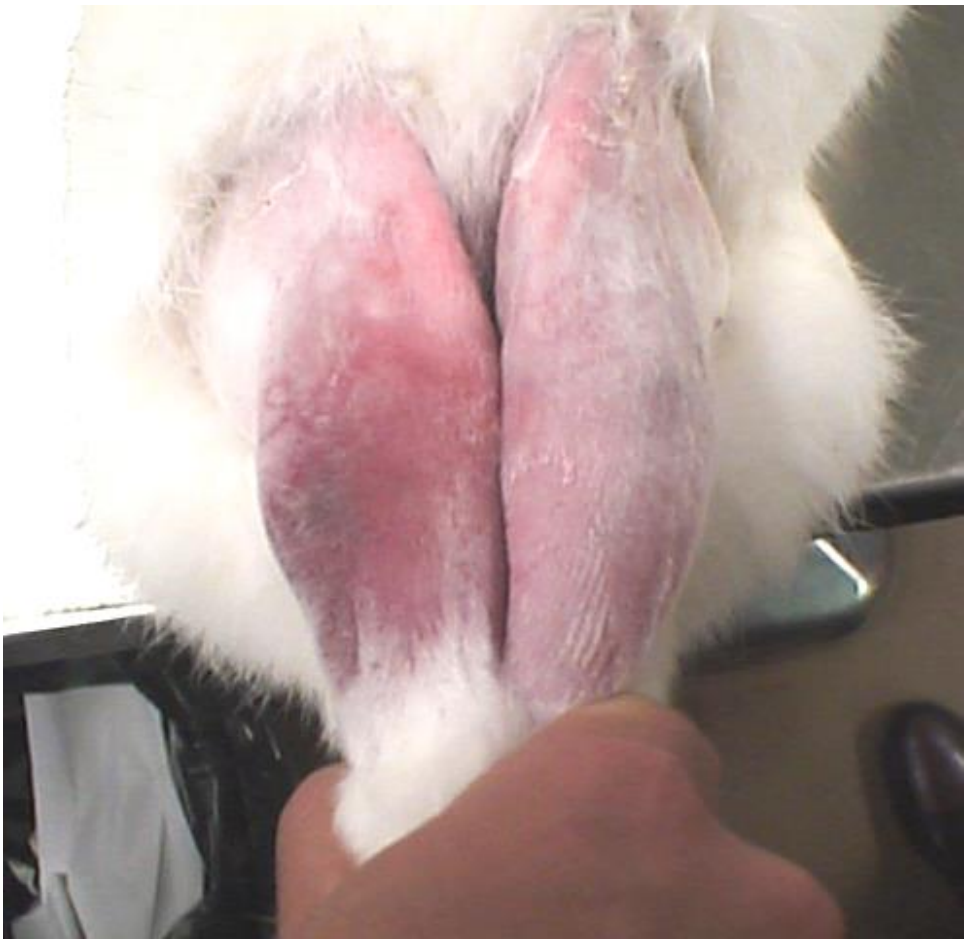

Figure 3. Photograph of both hind legs of the same rabbit as in Figure 2, taken the following day (2 days after traumatization). The treated leg continues to appear normal (score=0) and the swelling and inflammation have improved only slightly in the untreated leg (score=3).

Figure 4 is a graph of the results of the swelling in all subjects after 24 hours, illustrating that, in the treated legs, half of the subjects exhibited no swelling at all and the remainder of the subjects exhibited minimal swelling. The swelling was much more pronounced in all of the untreated legs. Figure 5 is a graph of the results of the swelling after 48 hours, showing that the treated legs of 11 of the subjects exhibited no swelling at all while the untreated legs continued to be inflamed and swollen.

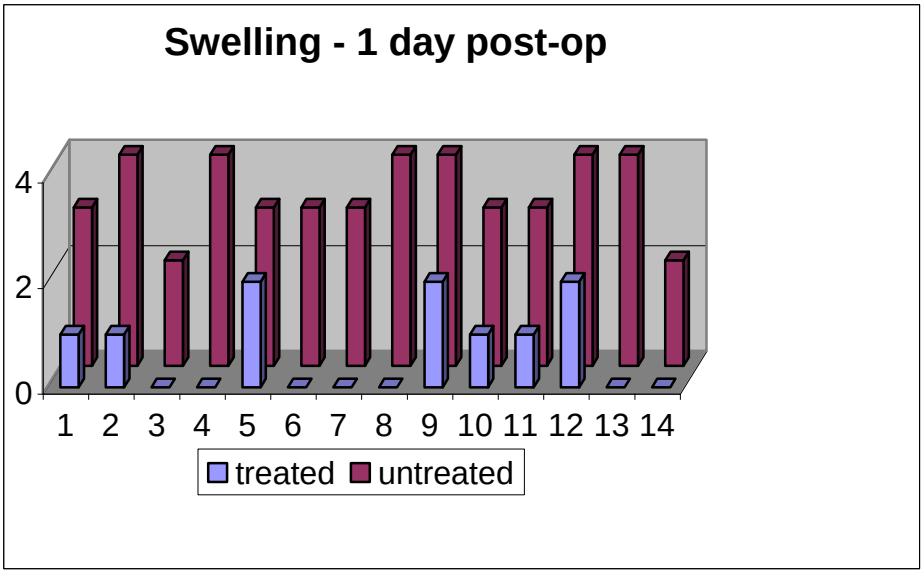

Figure 4. Graphical representation of the data on the swelling in the treated legs and the untreated legs one day after the bruising procedure. Seven of the fourteen subjects exhibited no swelling in the treated legs and the other seven showed only mild swelling. All of the untreated legs developed more severe swelling.

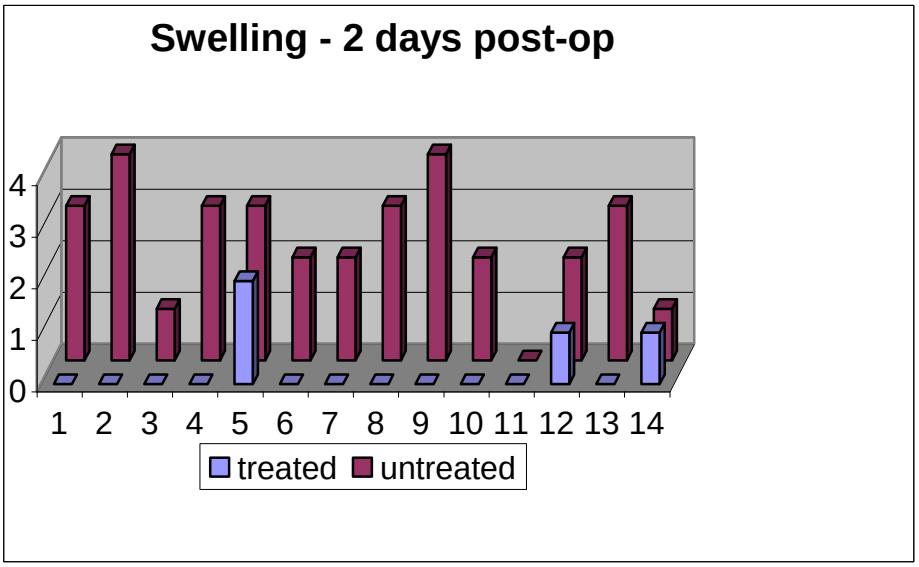

Figure 5. Graphical representation of the data on the swelling in the treated legs and the untreated legs two days after the bruising procedure. Eleven of the fourteen subjects exhibited no swelling in the treated legs. One of the untreated legs returned to normal but the rest of the group continued to show various degrees of swelling.

Discussion

The anecdotal and experimental data presented here suggest that the application of a Ferris pain dressing to intact skin over traumatized areas inhibits the development of pain, inflammation, swelling, and bruising in the deeper tissues. While it is easy to dismiss the earlier results as anecdotal, the photographs of bruises and the surgical case history are more substantial. Finally, our firsthand observations of the patients and experimental animal subjects were more convincing than the descriptions in this paper are able to present. Initially, it is difficult to envision physiological mechanisms which could be responsible for these results. There now remains a requirement to provide a scientific explanation of the effects of treatment with a Ferris pain dressing on the development of pain, inflammation, and swelling in the deep tissues.

Prior to beginning the animal study we performed a search of the literature, which pointed to the nociceptive nervous system as a possible source responsible for mediating the experimental observations. We discovered a long history of publications describing this key physiological system which apparently mediates pain, inflammation, and swelling in most of the tissues of the body. The nociceptive system is an archaic nervous system which has been well described in animals as primitive as the leech.(Johansen et. al., 1984; Pastor et. al., 1996) Its primary function appears to be a reaction to noxious stimuli by generating tissue responses which protect against invasion by foreign materials, organisms, etc.(Kumazawa, 1996; Bessou and Perl, 1969) Most nociceptive neurons (nociceptors) are unmyelinated C-fibers which are peptigergic neurons releasing tachykinins (notably Substance P), calcitonin gene-related peptide (CGRP), and other neuroactive peptides.(Lawson, 1996) The peripheral C-fiber termini responsible for the initial detection of noxious stimuli lie throughout the body in cutaneous, subcutaneous and visceral organs and tissues.(Dubner and Bennett, 1983) The cell bodies of these neurons are located within the dorsal root ganglia (DRG) lying within the spinal cord at the same segmental level as the innervated tissues.(Blackshaw et. al., 1982)

The nociceptive neurons contain fibers within the skin whose sensory endings protrude well into the epidermis. (Treede, 1992) These fibers are not specialized sensory structures, but rather are raw nerve endings which respond to all sorts of noxious stimuli which cause tissue destruction, including mechanical, chemical, and thermal sources of trauma. Once stimulated, these neurons conduct information back to the spinal DRG wherein they send pain signals to the brain and also synapse with other nociceptors and transmit signals in a retrograde fashion back into the general area of the trauma. The recruitment of these additional fibers provides enough activity to liberate substantial amounts of neural peptides into these tissues. Specifically, the release of CGRP causes vasodilatation of the pre-capillary arterioles,(Brain et. al., 1985; Gamse and Saria, 1985) thereby generating tissue inflammation. The release of Substance P causes the post-capillary venules to mediate plasma extravasation,(White and Helme, 1996) liberating various white blood cells, mast cells, and, in severe trauma, red blood cells as well.(Reeh et. al., 1986; Hanesch, 1996; Katz, 1996) The release of these substances causes degranulation of mast cells and the release of histamine. As a result of retrograde conduction along the network of axons, the area of the tissue affected is typically larger

than the actual trauma site. We can easily observe this phenomenon in what we call the "triple response" (Lewis, 1927) to local injury. A surprising correlate of this scenario is demonstrated by experiments which block the spinal reflex by the application of bicuculline to the dorsal surface of the spinal cord or by cutting the peripheral nerves leading to the spinal cord. (Lin et. al., 1997) In both instances, trauma to the denervated tissues does not produce inflammation, swelling, or the "triple response".

Pain is another consequence of stimulation of the peripheral nociceptive system. Within the spine, afferent C-fiber neurites run from the DRG to synapse with neurons ascending into the contralateral spinothalmic tract, through the thalamus, and ultimately to the cerebral cortex. The role of the nociceptive system in activating these pain pathways is currently the subject of extensive research interest. (Kruger and Liebeskind, 1984)

Evidence supports the fact that inhibition of nociceptive activity in a peripheral area can block the development of inflammation, swelling, and pain which would otherwise result from local trauma. Experiments using capsaicin (a hot pepper extract) have confirmed that its application to the skin surface can inhibit inflammation and swelling in joints and muscles beneath.(Jancso et. al., 1967; Colpaert et. al., 1983; Levine et. al., 1984; Levine et. al., 1985) Capsaicin acts specifically on the cutaneous nociceptors, over-stimulating them and rendering them inoperative for a period of time. That this can affect deep tissues is not surprising in that the nociceptive fibers form a network which includes cutaneous as well as deep tissue connections. (Weike et. al., 1991)

The various reports, observations, and data on the effects of treatment of trauma with the Ferris pain dressing point to the suppression of nociceptive activity as a likely mechanism. The suppression of pain and inflammation produced by this dressing closely match the results generated by the application of capsaicin, albeit without the discomfort and transient activity of capsacian therapy.

If we suspect that the application of a Ferris pain dressing to the skin surface somehow inhibits the activity of the nociceptors, we are faced with the question of how that happens. We surmise that the application of the dressing creates a surface condition which inhibits the activity of the C-fibers in the superficial epithelium which, in turn, blocks the axon reflexes, and prevents notification of the DRG. Preliminary data indicate that the Ferris pain dressing substantially modifies the concentration of electrolytes in the epithelium.

The implication of suppression of the nociceptive nervous system as a mechanism of action of the Ferris pain dressing appears probable but is not yet supported by direct experimental evidence. We are currently testing this hypothesis using biochemical stimulation of the nociceptive system in the skin and muscles of experimental animals. The effects of the use of this dressing on the biochemical and the electrophysiological responses will be investigated.

The results reported here are preliminary and encouraging. We expect that more extensive clinical studies are likely to confirm these initial observations and generate a variety of potential therapeutic applications in pain management in areas such as plastic and orthopedic surgery, emergency trauma, sports medicine, chronic neuromuscular pain, and other conditions in which pain, inflammation, and swelling are important components.

Acknowledgement - This study was supported by a grant from Ferris Pharmaceuticals, Inc.

Reference List

Bessou, P. and Perl, ER., Responses of cutaneous sensory units with unmyelinated fibers to noxious stimuli, J. Neurophysiology, 32 (1969) 1025-43.

Blackman, J.D., Senseng, D., Quinn, L. and Mazzone T., Clinical evaluation of a semipermeable polymeric membrane dressing for the treatment of chronic diabetic foot ulcers, Diabetes Care, 17 (1994) 322-5.

Blackshaw, S.E., Nicholls, J.G. and Parnas, I., Physiological responses, receptive fields and terminal arborizations of nociceptive cells in the leech, J. of Physiol, (Cambridge) 326 (1982) 251-60.

Brain, S.D., Williams, T.J., Tippins, J.R., Morris, H.R. and MacIntyre I., Calcitonin gene-related peptide is a potent vasodilator, Nature, 313 (1985) 54-56.

Carr, R., Lalagos, D. and Upman, P., Comparative studies of occlusive wound dressings on full thickness wounds in domestic pigs, Wounds, 3 (1990) 38-42.

Colpaert, F.C., Donnerer, J. and Lembeck, F., Effects of capsaicin on inflammation and on the substance P content of nervous tissues in rats with adjuvant arthritis, Life Sciences, 32 (1983) 1827-34.

Dubner, R. and Bennett G.J., Spinal and trigeminal mechanisms of nociception, Annual Review of Neuroscience, 6 (1983) 381-418.

Fowler, E. and Papen, J., Clinical evaluation of a polymeric membrane dressing in the treatment of dermal ulcers, Ostomy/Wound Management, 35 (1991) 35-44.

Gamse, R. and Saria, A., Potentiation of tachykinin-induced plasma protein extravasation by calcitonin gene-related peptide, Eur. J. Pharmacology, 114 (1985) 61-66.

Hanesch, U., Neuropeptides in dural fine sensory nerve endings-involvement in neurogenic inflammation, Progress in Brain Res., 113 (1996) 299-317.

Jancso, N., Jancso-Gabor, A. and Szolcsanyi, J., Direct evidence for neurogenic inflammation and its prevention by pretreatment with capsaicin, Br. J. of Pharmacology and Chemotherapy, 31 (1967) 138-51.

Johansen, J., Hockfield, S. and Mckay, R.D.G., Distribution and morphology of nociceptive cells in the central nervous system of leeches, J. of Comparative Neurology, 226 (1984) 263-73.

Katz, W.A., Approach to the management of nonmalignant pain, Amer. J. Med., 101 (1996) 54S-63S.

Kruger, L. and Liebeskind, J.C., Neural Mechanisms of Pain, Raven Press, New York, 1984.

Kumazawa, T., The polymodal receptor: bio-warning and defense system, Progress in Brain Res., 113 (1996) 3-18.

Lawson, S.N., Peptides and cutaneous polymodal nociceptor neurones, Progress in Brain Res., 113 (1996) 369-86.

Levine, J.D., Clark, R., Devor, M., Helms, C., Moskowitz, M. and Basbaum, A., Intraneuronal substance P contributes to the severity of experimental arthritis, Science, 226 (1984) 547-9.

Levine, J.D., Moskowitz, M. and Basbaum, A., The contribution of neurogenic inflammation in experimental arthritis, J. Immunology, 135 (1985) 843S-847S.

Lewis, T., The Blood Vessels of the Human Skin and Their Responses, Shaw & Sons Ltd., London, 1927, Chap. 5.

Lin, Q., Wu, J. and Willis, W.D., Dorsal root reflexes are involved in the development of central sensitization of the spinal cord following intradermal injection of capsaicin, Proc. 16th Annual Meeting of the Amer. Pain Soc., 1 (1997) 187.

Pastor, J., Soria, B. and Belmonte, C., Properties of the nociceptive neurons of the leech segmental ganglion, J. of Neurophysiology, 75 (1996) 2268-79.

Reeh, P.W., Kocher, L. and Jung, S., Does neurogenic inflammation alter the sensitivity of unmyelinated nociceptors in the rat? Brain Research, 384 (1986) 42-50.

Treede, R.D., Vasodilator flare due to activation of superficial cutaneous afferents in humans: heat-sensitive versus histamine-sensitive fibers, Neuroscience Letters, 141 (1992) 169-72.

Weike, E., Nohr, D., Muller, S., Buchler, M., Friess, H. and Zentel, H.J., The tachykinin neuroimmune connection in inflammation, Ann. N.Y. Acad. Sci., 632 (1991) 283-95.

White, D.M. and, Helme, R.D., Release of substance P from peripheral nerve terminals following electrical stimulation of the sciatic nerve, Progress in Brain Res., 113 (1996) 27-31.